Annual Report 2015

National Cancer Center

Hospital, Hospital East, Research Institute,
Exploratory Oncology Research & Clinical Trial Center,
Research Center for Cancer Prevention and Screening,
Center for Cancer Control and Information Services,
Japan

Annual Report 2015

National Cancer Center

Hospital, Hospital East, Research Institute,
Exploratory Oncology Research & Clinical Trial Center,
Research Center for Cancer Prevention and Screening,
Center for Cancer Control and Information Services,
Japan

CONTENTS

Hospital East

Research Institute

Exploratory Oncology Research & Clinical Trial Center

Research Center for Cancer Prevention and Screening

Center for Cancer Control and Information Services

Greeting from the President

Founded in 1962 as a hub for cancer treatment and research in Japan, the National Cancer Center has since become a strong leader in the field. The Center was reborn as an Independent Administrative Institution in April 2010, and designated a National Research and Development Agency in April 2015, giving it the role of an agency to handle those issues that are difficult for universities or private enterprises. At the same time, there is a need to produce research results and optimize research and development results on a global level. In August 2015, the Hospital (Tsukiji campus) was designated a core hospital for clinical research, followed by the Hospital East (Kashiwa campus) in September of the same year. It is hoped that we will take on the central role of international standard clinical research and investigator-initiated trials. Especially from both basic and clinical viewpoints, it is essential to be significant as a facility that can practice cancer control from both sides (research as well as treatment to contribute to control over cancer), and that can propose these strategies to Japan and the Japanese people.

Currently, one in every two Japanese people will contract cancer in their lifetime. Nearly one million people are newly diagnosed with cancer in a year; and as the population is aging, we can expect the number of cancer-affected patients to increase in the future. The mission of the National Cancer Center is not only to provide the best possible care for each individual cancer patient based on genomic and other information, but we must also prevent the onset of cancer by identifying high-risk groups and developing and implementing appropriate prevention measures. In other words, this is the same as practicing precision medicine on a patient-by-patient basis. To achieve these objectives, as a foundation of research to elucidate traits and diversity of cancer in individuals, it is essential to plan forceful promotion of integrated omics research including genomic analysis, and optimize individual treatment and prevention methods based on the results. Understanding the localized immune response in tumor tissue is also an urgent issue.

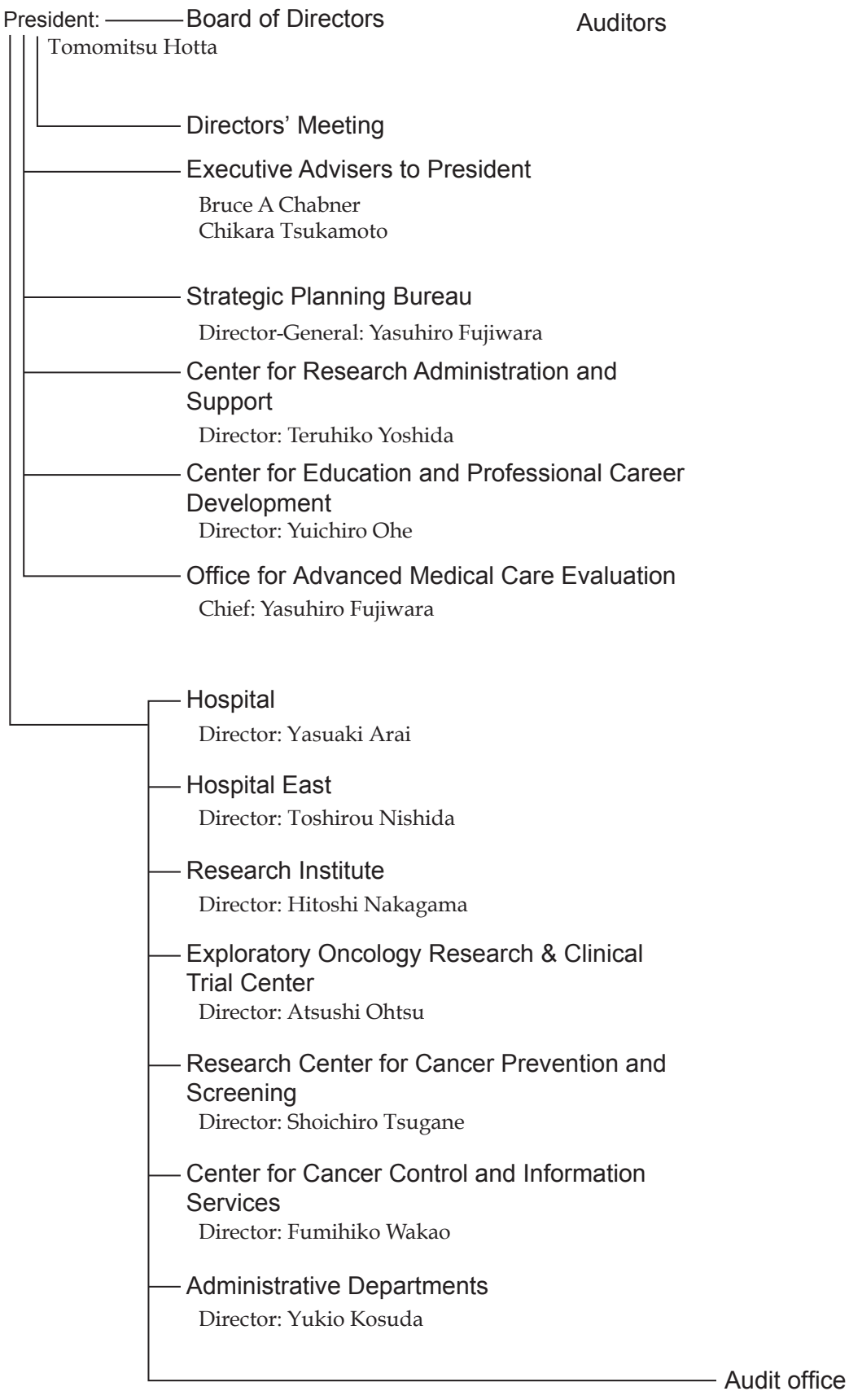
In view of these points, I present the following points as issues that must be handled as priorities in the slogan "Cancer cure and prevention, symbiosis with cancer" of the 10-year Cancer Control Strategy (a new national project for cancer strategy, started in 2014), and even in the National Cancer Center's planned course of action.

- Strengthening the research and clinical systems to resolve the issue of unmet medical needs
- Maintaining a system and proposing policies to provide optimized treatment and proactive medical care for individual patients based on genomic information

In addition to these important issues, experts at both campuses must combine their wisdom and experience and act as a single unit in order to take on the issues of promoting new cancer control strategies and policies. Furthermore, it is essential to coordinate with industrial, academic, and governmental researchers and research institutions, and to build a cooperative relationship that will be effective in gaining control over cancer. The wishes and hopes of Japan's people (including cancer patients and their families) are broadly reflected as issues, and we must work toward solutions for these. I want to develop a system for providing medical care (and a foundation for research for such system) that will allow all cancer patients and their families to always remain hopeful.

Hitoshi Nakagama, M.D., D.M.Sc.
President
National Cancer Center

Organization of National Cancer Center



Sections Directed by President

Office of Public Relations, Strategic Planning Bureau

Hiroshi Nokihara, Miyako Horikoshi, Mari Hatakeyama, Toru Kishida, Hironobu Ohmatsu, Rika Kojima, Kajitsu Ogawa, Rey Yoshida

Introduction

The Office of Public Relations has been organized as one branch of the Strategic Planning Bureau, which was assigned as a public section under the supervision of the president of the National Cancer Center (NCC) in April 2013. A full-time staff member was newly assigned to the Office of Public Relations in April 2014. Our task is management of the NCC homepage (http://www.ncc.go.jp/), publication of reports, coverage and delivery of press conferences and press releases. By sharing the mission and vision between staff members throughout the NCC, we provide information about NCC's most outstanding activities in cancer care, research, screening, prevention, and policy making.

Activities

During the weekly meetings of the Office of Public Relations, we performed prompt decision making regarding the public relations policy and shared information about our tasks by using a TV conference system between Tsukiji and Kashiwa campuses. We received information on the publicity work from each department, and drafted the publication plan. Also, by distribution of the intramural information for staff members in the NCC, we shared vital messages via e-mail, a bulletin board and/or an information magazine to facilitate communication between the staff and the executive. We distributed information promptly by publishing and sharing press releases, press conferences and seminars about novel treatments, research activities and notable accomplishments within the NCC and elsewhere.

- Homepage improvement and updates
- Public information magazine "The National Cancer Center News": for external hospitals, academia, research institutions, administrative agencies
- Public information magazine "hibiho": for patients in center Hospital and east Hospital
- Intramural information brochure "challenge": for staff members and their families in the NCC Hospitals
- Support of the event, seminar and public information
- Media support at press conferences, press releases and media coverage

We held six press conferences (projected cancer statistics in 2015, development of a novel nucleic acid drug discovered by the NCC, genetic testing lab established within the NCC Hospital, etc.) and published 38 press releases.

The future direction

We need to renew the NCC homepage into a more attractive, informative, and accessible page for users to be informed about NCC's activities in cancer care, research, screening, prevention, and policy making. We also feel it is important to move forward public relations activities towards expansion to overseas media via our homepage and press releases. We hope that all staff members in the NCC share their information and thoughts and will move in the same direction to execute NCC's mission.

Office of International Affairs, Strategic Planning Bureau

Seiichiro Yamamoto, Sakiko Suzuki, Mitsuko Otani

The main strategy of the international activities of the National Cancer Center (NCC) is as follows:

1) Develop human resources to work in the fields of oncology practice and research, and build networks through exchanges of personnel with world-leading oncology centers.
2) Contribute scientifically through international collaborative studies, and enhance our international presence,
3) Contribute medically to Asian countries as a responsibility for leadership.

The Office of International Affairs supports the NCC's activities with these goals as its aim, and supports other international activities and those related with foreign countries and people.

As for 1. above, the NCC has dispatched a nurse to Massachusetts General Hospital, a prestigious hospital in the USA. The nurse stayed four weeks and exchanged information about cancer nursing, nursing education, cancer survivorship, support for clinical trials, etc.

In May, the embassies of the USA, the UK, France and Korea and the NCC co-organized an international symposium on cancer clinical trials, where attendees shared updated information about development of precision medicine and established platform for future collaboration.

The NCC has a lot of collaborative work projects that have been completed or are currently on-going, and some of them have achieved major accomplishments. See the details in the reported activities of each department.

Visiting fellowship (mainly observership)

One of the NCC's longstanding medical contributions is to accommodate medical professionals around the globe as visiting fellows. The NCC began this fellowship just after its establishment. In 2015, the NCC had 159 visiting fellows (at both campuses of Tsukiji and Kashiwa). The number of visitors keeps rising. As for the few-day visitors, the NCC had 121. (See the table below for details.) Including the few-hour visitors, the NCC has had over 400 in total. The majority of visitors come from Asian countries, followed by European countries. As a recent trend, visitors from the Middle East are also on the rise. In order for continuous support, an international party was held to interact with employees from foreign countries, international temporary visitors, and Japanese staff. In addition, the Office continues to support former fellows through the alumni organization to keep in touch with them.

As another important topic, the NCC has made donations for earthquake victims in Nepal through the Embassy of Nepal. The donation was collected from employees and totaled one million yen.

The NCC works closely with the ministries of Japan. In 2015, the NCC was involved in a project supported by the Ministry of Economy, Trade and Industry. This project was led by FUJIFILM Corporation, aiming to establish a cancer screening center in Brazil. The NCC's endoscopists fully cooperated.

Fellowship (with and without fees)…4 days or more
Short-term visit…Within 3 days

Table 1. Visiting fellows (with and without fees) of the hospital

Visitors by region		Country of home organization	Hospital																				
			Head & Neck Surg.	Plastic & Reconstructive Surg.	Breast and Medical Oncology	Thoracic Oncology	Esophageal Surg.	Gastric Surg.	Colorectal Surg.	Gastrointestinal Medical Oncology	Gastrointestinal Endoscopy	Respiratory Endoscopy	HPB Surg.	Urology	Hematology	Diagnostic Radiology	Radiation Oncology	Pathology	Thoracic Surg.	Nursing	Total # by division*	Total (Actual #)
Asia		India														2					2	2
		Singapore							1				1								2	1
		Thailand									2			1							3	5
		Korea						2	3		3	1	1							2	12	10
		China				1	3		1		12	1	2					1	3		24	19
		Taiwan			1				2	1	14	13			1	9				3	44	40
		Hong Kong							2		3										5	3
		Philippines	1				1	1	2			1	2								8	5
		Vietnam									3					1**					4	4
		Malaysia														2					2	2
	92	Myanmar															1				1	1
Oceania	1	Australia						1													1	1
N America	6	USA									5							1			6	6
L America		Colombia						1													1	1
		Brazil											1								1	1
		Peru		1																	1	1
	8	Mexico	1								3		1						1		6	5
M East		UAE									3										3	3
		Iran									1										1	1
		Saudi Arabia									1										1	1
	7	Turkey									2										2	2
Europe		Italy									3										3	3
		UK						1			2										3	3
		Austria									1										1	1
		Netherlands									1										1	1
		Georgia						1	1		1		1								4	1
		Spain					1	4			8					1					14	13
		Germany						1													1	1
		Poland									1										1	1
		Portugal									1										1	1
		Romania						1													1	1
	27	Russia									1										1	1
		Total	2	1	1	1	5	13	12	1	71	16	9	1	1	14	1	2	4	5	161	141

* Total number by division (Some visitors rotate between multiple divisions)
** A Vietnamese citizen, enrolled in a university in Japan, is counted as Vietnam because they may return to their home country one day.

Fellowship (with and without fees)…4 days or more
Short-term visit…Within 3 days

Table 2. Visiting fellows (with and without fees) of all centers except the hospital

Visitors by region		Country of home organization	Hospital East								Research Institute						Cntr. for Cancer Control & Info. Services	Research Cntr. for Cancer Prevention & Screening	Exploratory Oncology Research & Clinical Trial Cntr.			Cntr. for Research Administration & Support
			Head & Neck Surg.	Plastic & Reconstructive Surg.	Esophageal Surg.	Gastric Surg.	HPB Surg.	Radiation Oncology	Total # by division*	Total (Actual #)	Molecular and Cellular Medicine	Rare Cancer Research	Genome Biology	Cancer Genomics	Total # by division*	Total (Actual #)	Total (Actual #)	Total (Actual #)	Developmental Therapeutics	Total # by division*	Total (Actual #)	Total (Actual #)
Asia		Indonesia																	1	1	1	
		China				6	2		8	8												
		Taiwan						1	1	1												
		Hong Kong	1						1	1												
	12	Philippines			1	1			2	1												
N America	1	USA												1	1	1						
L America	1	Peru		1					1	1												
Europe		Switzerland									1				1	1						
		Sweden									1				1	1						
		Spain			1	1		1	3	2												
		Germany										1	1		2	2						
	7	Portugal							1	1												
Other**	1	Japan									1				1	1						
		Total	1	1	3	8	2	2	17	15	3	1	1	1	6	6	0	0	1	1	1	0

* Total number by division (Some visitors rotate between multiple divisions)
** A Malaysian citizen, enrolled in a university in Japan, is counted as Japan

Fellowship (with and without fees)…4 days or more
Short-term visit…Within 3 days

Table 3. Short-term (within three days) visitors of the hospital

Visitors by region	Country of home organization	Hospital																	
		Head & Neck Surg.	Gastrointestinal Endoscopy	Respiratory Endoscopy	Gastric Surg.	Colorectal Surg.	HPB Surg.	Esophageal Surg.	Thoracic Surg.	Hematopoietic Stem Cell Transplantation	Dermatologic Oncology	Anesthesia and Intensive Care	Diagnostic Radiology	Radiation Oncology	Pathology	Nursing	Pharmacy	Clinical Trial Coordination (& Support) Office	Total
Asia	Indonesia		1																1
	Singapore												1						1
	Thailand		1					1							4				6
	China		11			1				5		6		6					29
	Taiwan	4						3	7							3			17
	Korea		1																1
	Philippines			1															1
	Vietnam																3		3
62	Malaysia												3						3
Oceania	New Zealand		1																1
1																			
N America	USA		1								2		15				2		20
21	Canada							1											1
S America	Brazil		3					1											4
4																			
Europe	Sweden		3																3
8	Russia		3			2													5
M East	Israel		1																1
3	Kuwait				1		1												2
Unknown*	Unknown							1		1					1			2**	5
5																			
	Total	4	26	1	1	3	1	7	7	6	2	6	19	6	5	3	5	2	104

* Because an application for a short-term visit does not require the country of the home organization of applicants, it is unknown, unless otherwise declared by the applicant

** Same visitors as the visitors at the Research Coordination of Control for Research Administration & Support

Fellowship (with and without fees)…4 days or more
Short-term visit…Within 3 days

Table 4. Short-term (within three days) visitors of all centers except the hospital

Visitors by region	Country of home organization	Hospital East		Research Institute	Cntr. for Cancer Control & Info. Services		Research Cntr. for Cancer Prevention & Screening			Exploratory Oncology Research & Clinical Trial Cntr.		Cntr. for Research Administration & Support	
		Radiation Oncology	Total	Total	Health Services Research	Total	Screening Practice	Floor for Screening	Total	Cancer Immunotherapy	Total	Research Coordination	Total
Asia	China	2	2				10	2	12				
2	Korea				5	5							
N America	USA									1	1		
1													
Europe	Russia	1	1										
1													
Unknown*	Unknown											2**	2
2													
	Total	3	3	0	5	5	10	2	12	1	1	2	2

* Because an application form for a short-term visit does not require the country of the home organization of applicants, it is unknown, unless otherwise declared by the applicant

** Same visitors as the visitors at Clinical Trial Coordination (& Support) Office of Hospital

Center for Research Administration and Support (CRAS)

See the CRAS Organization Chart for Division Chiefs and Section Heads.

Introduction

The Center for Research Administration and Support (CRAS) was established on July 16, 2014. At that time, CRAS started with approximately 160 staff members, who together offer diverse functions and specialties, ranging from research fund administration, alliances with the private sector, intellectual properties, clinical research coordinators and data managers, monitoring and audit, biostatistics support, offices for research ethics (IRB) and COI committees.

Dr. Hotta, President of the National Cancer Center (NCC), explained the reason and the purpose of the creation of CRAS in NCC News 2014 Vol. 5/ No. 3 (in Japanese). NCC was founded in 1962, and since then, it has added several new segments and organizations to evolve as a comprehensive cancer center. Because each segment needed its own research infrastructure, support activities in NCC had become fragmented and scattered with the possibility of gaps and redundancies. Dr. Hotta approached the Strategic Planning Bureau and put together the "NCC New Vision" in 2014, in which he proposed integration and communication of various research support functions in NCC.

The NCC Hospital and Hospital East have been certified as the Core Clinical Research Hospital based on the Medical Care Acts of August and September 2015, respectively. It is then required that the support functions for clinical research, especially those concerning clinical trials, need to be operated under the responsibility of a hospital director. As a result, the governance of the Research Coordination Division, Research Promotion Division and Regulatory Science Section of CRAS have now been moved to the Clinical Research Support Office, which belong to the common departments of each hospital. The annual report of the activities of the three divisions and the section will be found in the respective hospital sections.

(Future Prospects)

The mission of CRAS is to enhance the research support and administration capabilities of NCC based on the "NCC New Vision". It entails well-functioning integration and interaction of both campuses, Tsukiji and Kashiwa, as a solid and efficient NCC system. However, the integration should not necessarily mean homogenization but should respect differences in roles and various characteristics of each NCC campus to make the most of their strong points. Similar to last year, CRAS will keep evolving through a further trial-and-error process to find the best-fit system, with bridging both campuses being its fundamental spirit and agenda.

Activities and Future Prospects of each Division/Section

1. Research Administration Division

1) Research Administration Section

The Research Administration Section is a central office in charge of various administrative work related to research funding including application and reporting. The major external funding sources of NCC are competitive grants from the government and government-supported agencies, such as the Ministry of Health, Labour and Welfare (MHLW), Japan Science and Technology Agency (JST) and Japan Agency for Medical Research and Development (AMED). The Section also serves as an administrative office for the NCC Research and Development Fund, which is provided directly from the government to NCC for fulfillment of its mission as the national core institute of cancer control. The Section organized seminars regarding research funding and its rules to prevent financial misconduct.

(Future Prospects)

The Guidelines for Managing and Auditing Public Research Funds at Research Institutes was updated by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in February 2014 and adopted by MHLW in March 2014. The Section serves as a compliance promotion office of the Guidelines and has established a new system for research fund administration, which is fully compatible with the new Guidelines.

2) Research Administrators

Research administrators (RA) helped the Director of the Research Institute to review the research achievements in 2015 and to develop research plans in 2016. RA also offered to undertake administrative office work for the NCC Seeds Selection Committee, which was established in 2015 to identify promising research and development seeds of cancer diagnostics and therapeutics in NCC; in 2015, 11 seeds were selected to be funded for 1 year by the NCC in-house grant.

RA has supported the promotion of the commercial viability of research outcomes based upon three main pillars: a comprehensive alliance with companies, academic drug discovery research supported by the Drug Discovery Support Network, and establishment of NCC-launched venture companies. Candidate compounds for clinical development have been provided by collaboration with business enterprises, and four themes are in progress as a Drug Discovery Support Network. In 2015, one venture company was established as an NCC-spin off.

(Future Prospects)

RA promotes translation of innovative research in NCC to clinical diagnostic and therapeutic development and to patient care through four major mechanisms: the NCC Seeds Selection Committee, comprehensive alliances with leading companies, participation in the academic Drug Discovery Network, and establishment of NCC spin-off venture companies.

3) Research Auditor

For clinical studies led by the National Cancer Center's (NCC's) investigator, thirteen audits were conducted on GCP trials, and internal audits were conducted on departments in the NCC conducting clinical research. Other activities included GCP-related training and consultation as well as support of regulatory inspection management.

(Future Prospects)

Audit and its related activities will be continued to boost the quality of NCC's clinical research. In addition, as clinical interventional studies with invasive procedures will come into audit targets along with the implementation of "Ethical Guidelines for Medical and Health Research Involving Human Subjects", preparation of processes and techniques will be critical for the new type of audit. Moreover, building a risk-based audit plan will be effective for improvement of our research process.

4) Research Alliance Section and Intellectual Property Section

To make the NCC research outcomes clinically useful products available to cancer patients, the Research Alliance Section promotes collaborative research arrangements with the private sector. The number of collaborative research projects and their funds has been increasing each year (Figure. 1). As of December 31, 2015, the number of collaborations was 199, and their research funds amount to approximately 1.0 billion yen, which exceeded those of 2014. NCC has developed a comprehensive collaboration research system with companies and academic institutions. With the addition of a new collaborative framework this year, NCC has eight comprehensive collaborative alliances (Figure. 2). The section supported a nationwide genomic screening project with the participation of major pharmaceutical companies and institutions across Japan (SCRUM-Japan "Cancer Genome Screening Project for Individualized Medicine in Japan"), which was launched in March 2015. Currently, 14 pharmaceutical companies have registered (Figure. 3). The section has also assisted regional alliances with medium-sized medical device companies.

The Intellectual Property (IP) Section constantly reviews IPs and declines those that cannot find a business sponsor within a certain period; the limited budget can then be focused

on IPs that are commercially viable. The number of patent licensing agreements in recent years is shown in Figure. 4.

Staff members actively participate in seminars with regard to IP laws and regulations to update their knowledge and elevate their skills to promote academic-industrial alliances. Their competency in problem solving gained through OJT and effective consultation with experts will enable them to face new challenges in innovative fields.

(Future Prospects)

In the trend of Open Innovation, the Section will keep supporting the creation of systemic and effective collaborative research frameworks. It also foresees the possibility of a new laboratory setup where research is being performed by researchers from both industry and NCC, and should lead to more functional collaboration.

As to IP management, NCC employs patent strategies to protect the potential value of the invention for industry, through which the translation of academic science and technology is made to the patient's bedside. The IP section plays an important role in assisting NCC's comprehensive decision making, taking various aspects into consideration such as incubation of innovative technologies, cost and effect balance, and risk management.

2. Biostatistics Division

The Biostatistics Division has a responsible role in study design, analysis, interpretation and publication, especially in the Japan Clinical Oncology Group (JCOG) and the Exploratory Oncology Research & Clinical Trial Center (EPOC) clinical trials. We have also committed to support the investigator-initiated clinical trials led by investigators in the NCC Hospitals.

We provided introductory biostatistics lectures (10-part series) for investigators in NCC to learn and review the elementary aspects of biostatistics. We had a cumulative total of 447 participants. In addition, we newly launched advanced biostatistics lectures to cover the important biostatistical side of various application fields. We hosted 7 lectures and a cumulative total of 418 investigators participated.

Furthermore, we have provided biostatistical consultation and expertise, which supports NCC investigators working on basic, translational, clinical and epidemiological research. We offered advice regarding 117 problems (74 in the Tsukiji campus and 43 in the Kashiwa campus) for which biostatistical consultation was requested.

(Future Prospects)

NCC has a critical role for providing clinical service, education, conducting research and making policy recommendations/proposals, which all need decisions on the basis of solid and scientific evidence from reliable data and information. The mission of the Biostatistics Division is to contribute to providing the best evidence and the improvement of clinical practices and public health through the development and application of statistical methods. The Biostatistics Division is expanding its independent and collaborative research within a range of areas, including prevention and policy recommendations/proposals, as well as treatment development. We are also opening up a new methodological research area in which a mathematical approach will serve as a solid basis.

3. Human Research Protection Section

The major role of the Human Research Protection Section has been its function as a secretariat for various research ethics committees (IRBs) in NCC for human subject research. In 2015, the Section led efforts involving various sections in NCC to overhaul the NCC codes, rules and Standard Operating Procedures to adapt the newly enforced Ethical Guidelines for Medical and Health Research Involving Human Subjects in April 2015. Moreover, the Section has revised and developed the system to accept the ethics review requests from other institutions including those protocols that do not include NCC researchers; this will be an important step forwards to the future evolution to the Central IRB.

On the other hand, however, one major issue in the Section has been the long review waiting list fueled partly by the review complexities introduced by the new Ethics Guidelines and by an increase in the ethics review requests from other institutions. However, the more fundamental problem is the

paucity of human resources in the field of the research ethics review.

(Future Prospects)

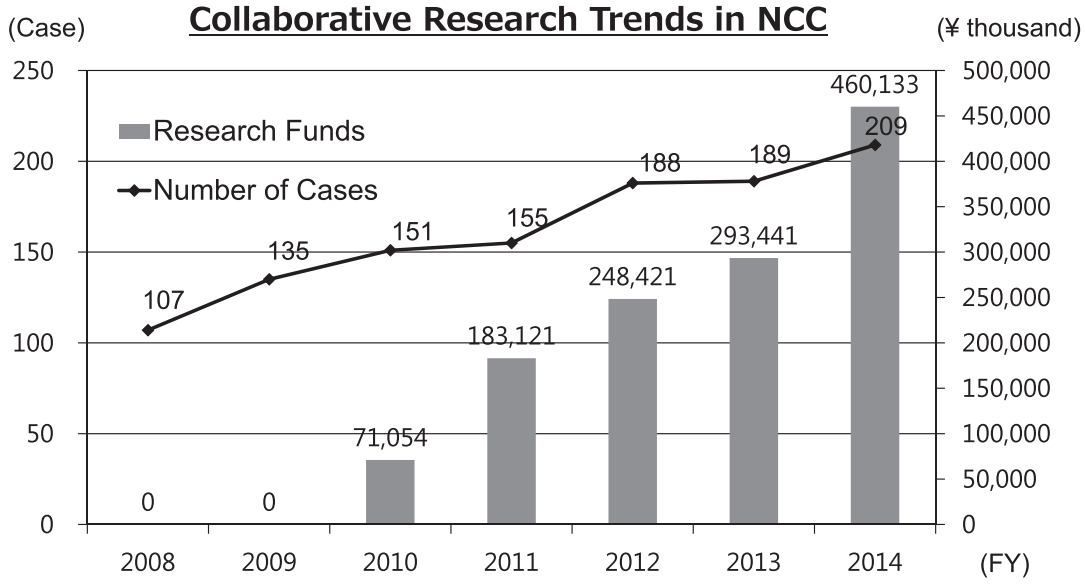
The CRAS and Clinical Research Support Offices in both hospitals keep working to further update the research support system in NCC, which will enable the IRB to concentrate more on its core responsibility of ethics reviews. Sometime in 2016, the Human Research Protection Section is planning to call regular IRB meetings twice a month and in both campuses alternatively, to respond to the increasing demands for ethics reviews and to enhance the equal participation and communication of both campuses in the process.

4. Bioethics Section

The Bioethics Section provides research ethics consultation service to researchers/research support staff, IRB members/staff, and other stakeholders in research enterprises throughout the lifecycle of a study. The research ethics consultation service plays a strictly advisory role and is independent from IRB decisions. The Bioethics Section started providing an ethics consultation service from 2015 and received about 100 calls a year. Also, this Section provides ethics education to researchers and IRB members/staff.

(Future Prospects)

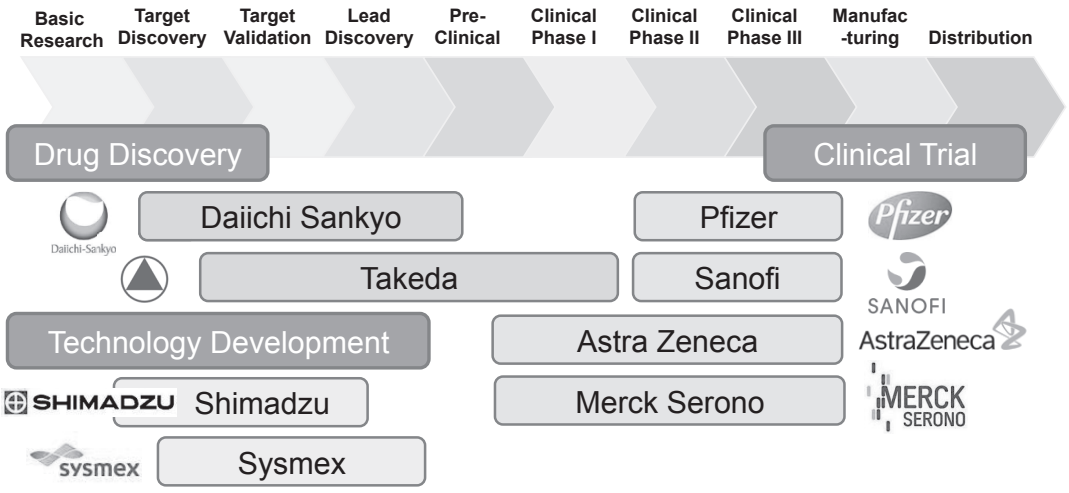
The Bioethics Section will produce a standard format for requesting a consultation service and improve quality of the consultation service. Also, the Section will provide advanced education on research ethics as well as basic education.



Collaborative Research Funds from industry have increased each year since the IP and Research Alliance Division was set up in 2010.

Figure 1. Collaborative Research (FY 2008-2014)

Major Industry Partners of NCC



NCC has concluded a number of partnership agreements with Pharma-, Diagnostic- and Med-Device Industries at various R&D stages.

Figure 2. NCC-Industry Partnership

The Screening Project for Precision Medicine as Academic-Industrial Collaboration

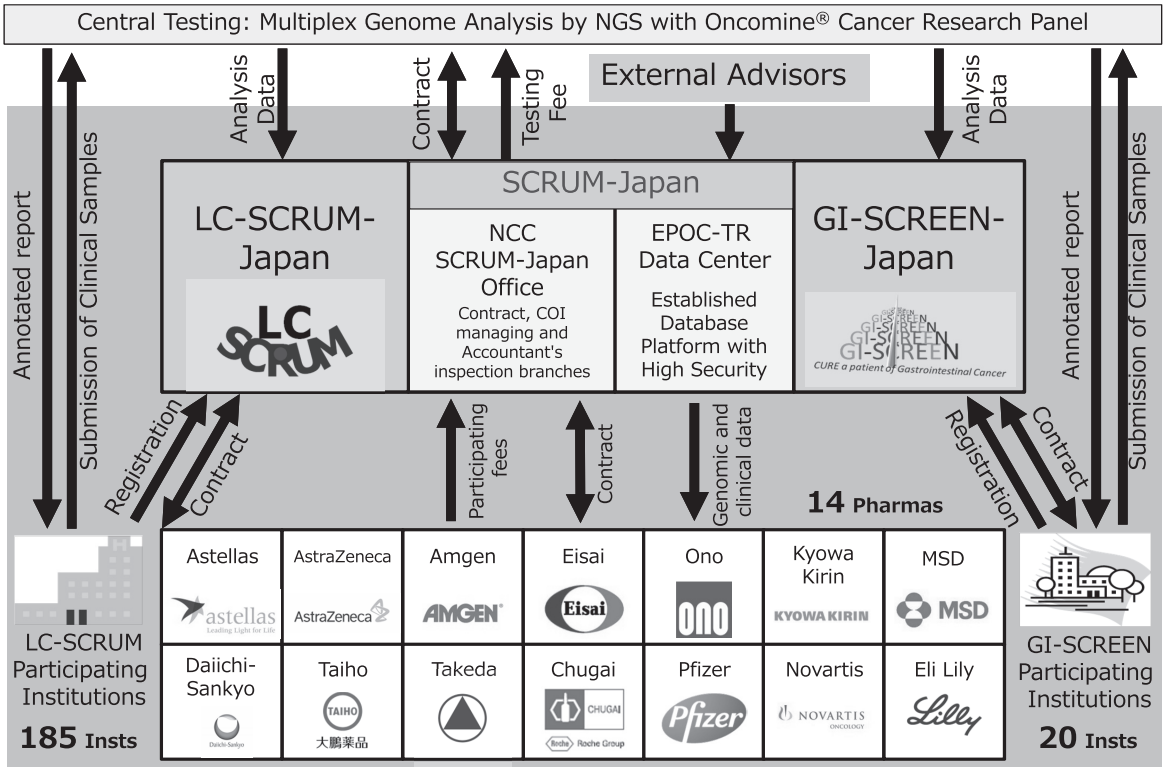
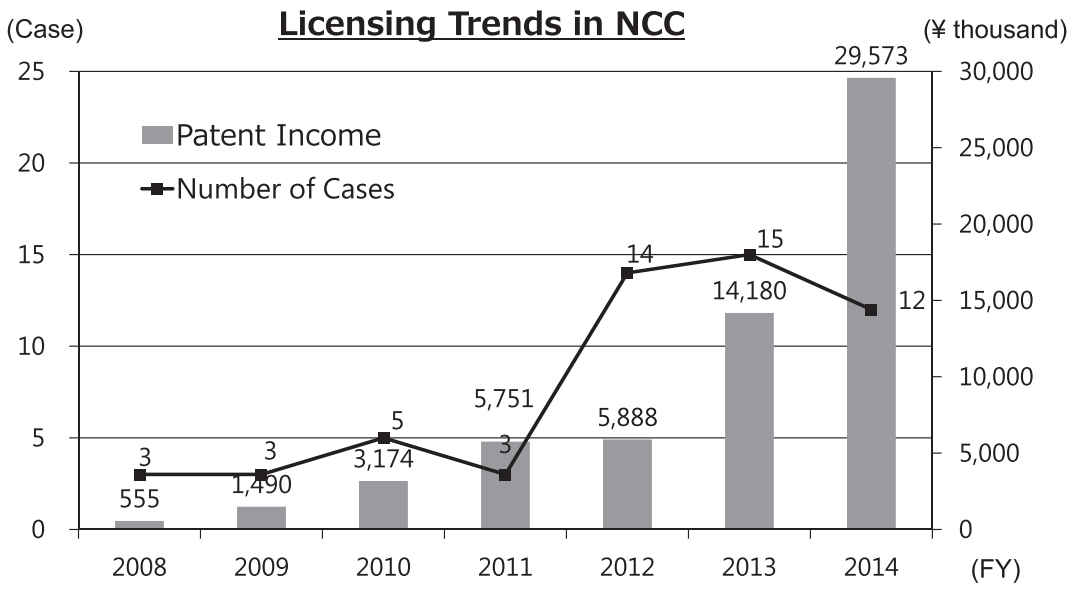


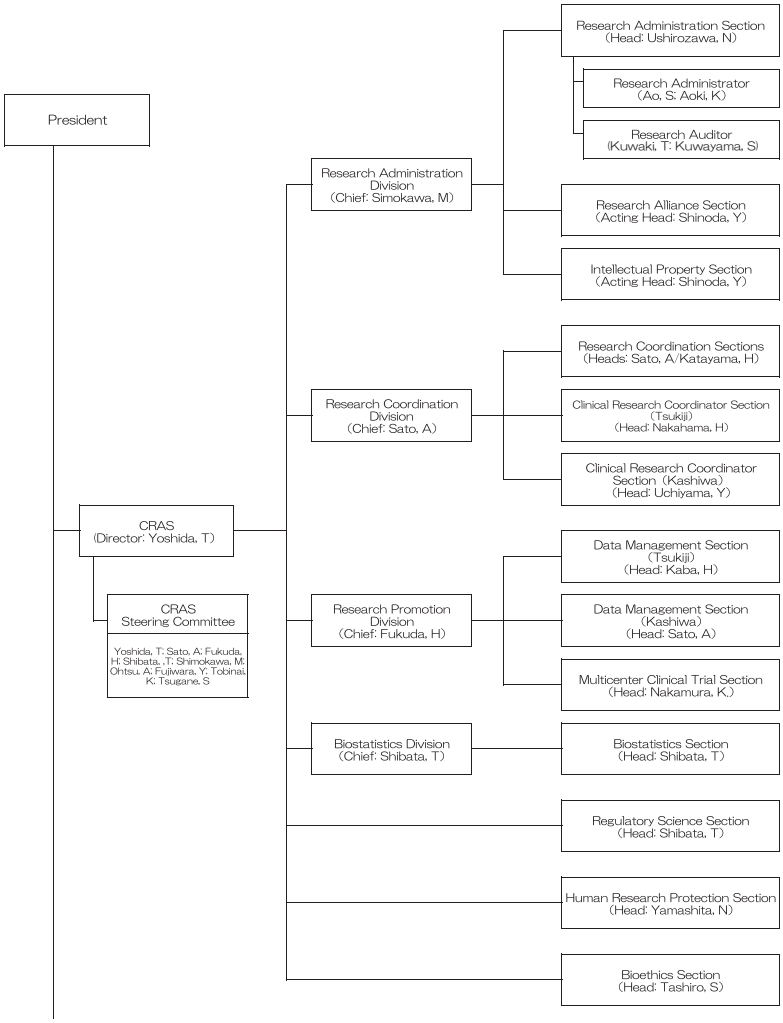
Figure 3. SCRUM-Japan (established in February 2015)



Patent income has increased each year, especially in later years.

Figure 4. Licensing Deals (FY2008-2014)

Organization of Center for Research Administration and Support (CRAS) (as of June 20, 2015)



List of papers published in 2015

Journal

1. Kataoka K, Aoyama I, Mizusawa J, Eba J, Minashi K, Yano T, Tanaka M, Hanaoka N, Katayama H, Takizawa K, Fukuda H, Muto M, Gastrointestinal Endoscopy Study Group (GIESG) of the Japan Clinical Oncology Group. A randomized controlled Phase II/III study comparing endoscopic balloon dilation combined with steroid injection versus radial incision and cutting combined with steroid injection for refractory anastomotic stricture after esophagectomy: Japan Clinical Oncology Group Study JCOG1207. Jpn J Clin Oncol, 45:385-389, 2015

2. Tsukada H, Yokoyama A, Goto K, Shinkai T, Harada M, Ando M, Shibata T, Ohe Y, Tamura T, Saijo N, Lung Cancer Study Group of the Japan Clinical Oncology Group (JCOG). Randomized controlled trial comparing docetaxel-cisplatin combination with weekly docetaxel alone in elderly patients with advanced non-small-cell lung cancer: Japan Clinical Oncology Group (JCOG) 0207†. Jpn J Clin Oncol, 45:88-95, 2015

3. Kurokawa Y, Sasako M, Sano T, Yoshikawa T, Iwasaki Y, Nashimoto A, Ito S, Kurita A, Mizusawa J, Nakamura K, Japan Clinical Oncology Group (JCOG9502). Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia. Br J Surg, 102:341-348, 2015

4. Tahara M, Kiyota N, Mizusawa J, Nakamura K, Hayashi R, Akimoto T, Hasegawa Y, Iwae S, Monden N, Matsuura K, Fujii H, Onozawa Y, Homma A, Kubota A, Fukuda H, Fujii M. Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). Cancer Sci, 106:726-733, 2015

5. Kato T, Takashima A, Kasamatsu T, Nakamura K, Mizusawa J, Nakanishi T, Takeshima N, Kamiura S, Onda T, Sumi T, Takano M, Nakai H, Saito T, Fujiwara K, Yokoyama M, Itamochi H, Takehara K, Yokota H, Mizunoe T, Takeda S, Sonoda K, Shiozawa T, Kawabata T, Honma S, Fukuda H, Yaegashi N, Yoshikawa H, Konishi I, Kamura T, Gynecologic Oncology Study Group of the Japan Clinical Oncology Group. Clinical tumor diameter and prognosis of patients with FIGO stage IB1 cervical cancer (JCOG0806-A). Gynecol Oncol, 137:34-39, 2015

6. Satoh T, Tsuda H, Kanato K, Nakamura K, Shibata T, Takano M, Baba T, Ishikawa M, Ushijima K, Yaegashi N, Yoshikawa H, Gynecologic Cancer Study Group of the Japan Clinical Oncology Group. A non-randomized confirmatory study regarding selection of fertility-sparing surgery for patients with epithelial ovarian cancer: Japan Clinical Oncology Group Study (JCOG1203). Jpn J Clin Oncol, 45:595-599, 2015

7. Tanaka K, Mizusawa J, Fukuda H, Araki N, Chuman H, Takahashi M, Ozaki T, Hiruma T, Tsuchiya H, Morioka H, Hatano H, Iwamoto Y. Perioperative chemotherapy with ifosfamide and doxorubicin for high-grade soft tissue sarcomas in the extremities (JCOG0304). Jpn J Clin Oncol, 45:555-561, 2015

8. Suzuki K, Watanabe S, Mizusawa J, Moriya Y, Yoshino I, Tsuboi M, Mizutani T, Nakamura K, Tada H, Asamura H, Japan Lung Cancer Surgical Study Group (JCOG LCSSG). Predictors of non-neoplastic lesions in lung tumours showing ground-glass opacity on thin-section computed tomography based on a multi-institutional prospective study†. Interact Cardiovasc Thorac Surg, 21:218-223, 2015

9. Etoh T, Inomata M, Watanabe M, Konishi F, Kawamura Y, Ueda Y, Toujigamori M, Shiroshita H, Katayama H, Kitano S. Success rate of informed consent acquisition and factors influencing participation in a multicenter randomized controlled trial of laparoscopic versus open surgery for stage II/III colon cancer in Japan (JCOG0404). Asian J Endosc Surg, 8:419-423, 2015

10. Onimaru R, Shirato H, Shibata T, Hiraoka M, Ishikura S, Karasawa K, Matsuo Y, Kokubo M, Shioyama Y, Matsushita H, Ito Y, Onishi H. Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer with PTV<100 cc using a continual reassessment method (JCOG0702). Radiother Oncol, 116:276-280, 2015

11. Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, Shioyama Y, Onimaru R, Kozuka T, Kunieda E, Saito T, Nakagawa K, Hareyama M, Takai Y, Hayakawa K, Mitsuhashi N, Ishikura S. Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. Int J Radiat Oncol Biol Phys, 93:989-996, 2015

12. Foster NR, Renfro LA, Schild SE, Redman MW, Wang XF, Dahlberg SE, Ding K, Bradbury PA, Ramalingam SS, Gandara DR, Shibata T, Saijo N, Vokes EE, Adjei AA, Mandrekar SJ. Multitrial Evaluation of Progression-Free Survival as a Surrogate End Point for Overall Survival in First-Line Extensive-Stage Small-Cell Lung Cancer. J Thorac Oncol, 10:1099-1106, 2015

13. Wang M, Kuchiba A, Ogino S. A Meta-Regression Method for Studying Etiological Heterogeneity Across Disease Subtypes Classified by Multiple Biomarkers. Am J Epidemiol, 182:263-270, 2015

14. Kojima M, Puppa G, Kirsch R, Basturk O, Frankel WL, Vieth M, Lugli A, Sheahan K, Yeh M, Lauwers GY, Risio M, Shimazaki H, Iwaya K, Kage M, Akiba J, Ohkura Y, Horiguchi S, Shomori K, Kushima R, Nomura S, Ajioka Y, Adsay V, Ochiai A. Blood and lymphatic vessel invasion in pT1 colorectal cancer: an international concordance study. J Clin Pathol, 68:628-632, 2015

15. Yamada M, Sakamoto T, Otake Y, Nakajima T, Kuchiba A, Taniguchi H, Sekine S, Kushima R, Ramberan H, Parra-Blanco A, Fujii T, Matsuda T, Saito Y. Investigating endoscopic features of sessile serrated adenomas/polyps by using narrow-band imaging with optical magnification. Gastrointest Endosc, 82:108-117, 2015

16. Sugiyama E, Umemura S, Nomura S, Kirita K, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Ohe Y, Goto K. Impact of single nucleotide polymorphisms on severe hepatotoxicity induced by EGFR tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring EGFR mutations. Lung Cancer, 90:307-313, 2015

17. Guidance Development Review Committee, Working Group for Clinical Studies of Cancer Immunotherapy, Working Group for Effector Cell Therapy, Working Group for CMC/Non-clinical Studies, Working Group for Cancer Vaccines and Adjuvants, Working Group for Anti-immune Checkpoint Therapy and Comprehensive Cancer Immunotherapy, Biostatistics Subcommittee. 2015 Guidance on cancer immunotherapy development in early-phase clinical studies. Cancer Sci, 106:1761-1771, 2015

18. Hojo T, Masuda N, Mizutani T, Shibata T, Kinoshita T, Tamura K, Hara F, Fujisawa T, Inoue K, Saji S, Nakamura K, Fukuda H, Iwata H. Intensive vs. Standard Post-Operative Surveillance in High-Risk Breast Cancer Patients (INSPIRE): Japan Clinical Oncology Group Study JCOG1204. Jpn J Clin Oncol, 45:983-986, 2015

19. Homma A, Nakamura K, Matsuura K, Mizusawa J, Onimaru R, Fukuda H, Fujii M. Dose-finding and efficacy confirmation trial of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer (JCOG1212, RADPLAT-MSC). Jpn J Clin Oncol, 45:119-122, 2015

20. Tsukada H, Yokoyama A, Goto K, Shinkai T, Harada M, Ando M, Shibata T, Ohe Y, Tamura T, Saijo N. Randomized controlled trial comparing docetaxel-cisplatin combination with weekly docetaxel alone in elderly patients with advanced non-small-cell lung cancer: Japan Clinical Oncology Group (JCOG) 0207. Jpn J Clin Oncol, 45:88-95, 2015

21. Abe T, Takeda K, Ohe Y, Kudoh S, Ichinose Y, Okamoto H, Yamamoto N, Yoshioka H, Minato K, Sawa T, Iwamoto Y, Saka H, Mizusawa J, Shibata T, Nakamura S, Ando M, Yokoyama A, Nakagawa K, Saijo N, Tamura T. Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Intergroup Trial JCOG0803/WJOG4307L. J Clin Oncol, 33:575-581, 2015

22. Eba J, Shimokawa T, Nakamura K, Shibata T, Misumi Y, Okamoto H, Yamamoto N, Ohe Y, Lung Cancer Study Group of the Japan Clinical Oncology Group. A Phase II/III study comparing carboplatin and irinotecan with carboplatin and etoposide for the treatment of elderly patients with extensive-disease small-cell lung cancer (JCOG1201). Jpn J Clin Oncol, 45:115-118, 2015

23. Kitagawa R, Katsumata N, Shibata T, Kamura T, Kasamatsu T, Nakanishi T, Nishimura S, Ushijima K, Takano M, Satoh T, Yoshikawa H. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III trial JCOG0505. J Clin Oncol, 33:2129-2135, 2015

24. Kunieda F, Kasamatsu T, Arimoto T, Onda T, Toita T, Shibata T, Fukuda H, Kamura T, Gynecologic Cancer Study Group of the Japan Clinical Oncology Group. Non-randomized confirmatory trial of modified radical hysterectomy for patients with tumor diameter 2 cm or less FIGO Stage IB1 uterine cervical cancer: Japan Clinical Oncology Group Study (JCOG1101). Jpn J Clin Oncol, 45:123-126, 2015

25. Matsumoto K, Katsumata N, Shibata T, Satoh T, Saitou M, Yunokawa M, Takano T, Nakamura K, Kamura T, Konishi I. Phase II trial of oral etoposide plus intravenous irinotecan in patients with platinum-resistant and taxane-pretreated ovarian cancer (JCOG0503). Gynecol Oncol, 136:218-223, 2015

26. Yokota M, Kobayashi A, Nomura S, Nishizawa Y, Ito M, Nagai K, Saito N. Patterns and treatment of recurrence following pulmonary resection for colorectal metastases. World J Surg, 39:1758-1766, 2015

27. Nozaki I, Kato K, Igaki H, Ito Y, Daiko H, Yano M, Udagawa H, Mizusawa J, Katayama H, Nakamura K, Kitagawa Y. Evaluation of safety profile of thoracoscopic esophagectomy for T1bN0M0 cancer using data from JCOG0502: a prospective multicenter study. Surg Endosc, 29:3519-3526, 2015

28. Sasaki T, Fuse N, Kuwata T, Nomura S, Kaneko K, Doi T, Yoshino T, Asano H, Ochiai A, Komatsu Y, Sakamoto N, Ohtsu A. Serum HER2 levels and HER2 status in tumor cells in advanced gastric cancer patients. Jpn J Clin Oncol, 45:43-48, 2015

29. Fujiwara Y, Yonemori K, Shibata T, Okita N, Ushirozawa N. Japanese universal health care faces a crisis in cancer treatment. Lancet Oncol, 16:251-252, 2015

30. Yokota T, Ando N, Igaki H, Shinoda M, Kato K, Mizusawa J, Katayama H, Nakamura K, Fukuda H, Kitagawa Y. Prognostic Factors in Patients Receiving Neoadjuvant 5-Fluorouracil plus Cisplatin for Advanced Esophageal Cancer (JCOG9907). Oncology, 89:143-151, 2015

31. Shinoda M, Ando N, Kato K, Ishikura S, Kato H, Tsubosa Y, Minashi K, Okabe H, Kimura Y, Kawano T, Kosugi S, Toh Y, Nakamura K, Fukuda H, Japan Clinical Oncology Group. Randomized study of low-dose versus standard-dose chemoradiotherapy for unresectable esophageal squamous cell carcinoma (JCOG0303). Cancer Sci, 106:407-412, 2015

32. Kataoka K, Nakamura K, Mizusawa J, Fukuda H, Igaki H, Ozawa S, Hayashi K, Kato K, Kitagawa Y, Ando N. Variations in survival and perioperative complications between hospitals based on data from two phase III clinical trials for oesophageal cancer. Br J Surg, 102:1088-1096, 2015

33. Kataoka K, Tsushima T, Mizusawa J, Hironaka S, Tsubosa Y, Kii T, Shibuya Y, Chin K, Katayama H, Kato K, Fukuda H, Kitagawa Y, Japan Esophageal Oncology Group/Japan Clinical Oncology Group. A randomized controlled Phase III trial comparing 2-weekly docetaxel combined with cisplatin plus fluorouracil (2-weekly DCF) with cisplatin plus fluorouracil (CF) in patients with metastatic or recurrent esophageal cancer: rationale, design and methods of Japan Clinical Oncology Group study JCOG1314 (MIRACLE study). Jpn J Clin Oncol, 45:494-498, 2015

34. Tahara M, Fuse N, Mizusawa J, Sato A, Nihei K, Kanato K, Kato K, Yamazaki K, Muro K, Takaishi H, Boku N, Ohtsu A. Phase I/II trial of chemoradiotherapy with concurrent S-1 and cisplatin for clinical stage II/III esophageal carcinoma (JCOG 0604). Cancer Sci, 106:1414-1420, 2015

35. Kataoka K, Tokunaga M, Mizusawa J, Machida N, Katayama H, Shitara K, Tomita T, Nakamura K, Boku N, Sano T, Terashima M, Sasako M, Stomach Cancer Study Group/Japan Clinical Oncology Group. A randomized Phase II trial of systemic chemotherapy with and without trastuzumab followed by surgery in HER2-positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1301 (Trigger Study). Jpn J Clin Oncol, 45:1082-1086, 2015

36. Nakamura K, Kuwata T, Shimoda T, Mizusawa J, Katayama H, Kushima R, Taniguchi H, Sano T, Sasako M, Fukuda H. Determination of the optimal cutoff percentage of residual tumors to define the pathological response rate for gastric cancer treated with preoperative therapy (JCOG1004-A). Gastric Cancer, 18:597-604, 2015

37. Mizutani T, Tanaka M, Eba J, Mizusawa J, Fukuda H, Hanaoka N, Takeuchi M, Aoyama I, Kojima T, Takizawa K, Ono H, Muto M, Gastrointestinal Endoscopy Study Group of the Japan Clinical Oncology Group (JCOG). A Phase III study of oral steroid administration versus local steroid injection therapy for the prevention of esophageal stricture after endoscopic submucosal dissection (JCOG1217, Steroid EESD P3). Jpn J Clin Oncol, 45:1087-1090, 2015

Center for Education and Professional Career Development

Yuichiro Ohe, Hidehito Horinouchi, Tomonori Yano, Ayako Mori, Mayumi Tsukagoshi, Naoko Nishikimi, Hironobu Hashimoto, Tomohiko Aso, Yuzuru Kouno, Yoshihisa Abe, Satoshi Nakajima, Mayumi Miyauchi, Noriko Kobayashi, Miki Ito, Miho Kurihara, Kazue Hayasaka, Yasuhiko Ichida, Tetsuo Akimoto, Yoshihisa Muramatsu, Mitsuhiro Yoshida, Eichi Yoshikawa, Haruka Chitose, Miki Fukutani, Tosikazu Usijima, Gen Fujii, Takahiro Ochiya, Akihiro Sato, Noriko Yamashita, Taro Shibata, Hatoe Sakamoto, Kayoko Miyata, Kazuyuki Fukuda, Hiroji Yamakabe, Masaru Furuichi, Hideyuki Yoshizumi, Shinichi Kouno, Rie Nakashima, Namiko Aoshima, Miyoko Tanaka, Mika Asari, Yukiyo Fujita

Introduction

The Center for Education and Professional Career Development was established in July 2014. The purposes of the Center are nurturing and securing of able human resources, clarification of career paths in each type of job, and improvement of systematic educational programs. Under the director of the center and two vice-directors, the Office for Career Management, the Office for Graduate Medical Education, and the Office for Professional Education Management are placed.

Routine activities

The Office for Career Management conducts career path development of each professional, strategic securing of able professionals, and management of the information about alumnus. The Office for Graduate Medical Education conducts the promotion of the cooperative post-graduate school and management of the education program for residents. The Office for Professional Education Management conducts the planning of education programs for all the center staff, the planning and implementation of common training programs at the time of adoption, the planning and implementation of the individual education program for each professional field, and the management of attendance on various lectures.

The resident educational program of the National Cancer Center has a history of nearly 50 years, and has started the re-examination of the resident educational program to effectively produce more able cancer specialists. We carry out discussions to build a new resident educational program that can cope with the change of a new board certification system that will start in 2017.

Education

The cooperative post-graduate school program with Keio University and Juntendo University were started in 2012. In 2015, 16 and 55 post-graduate students, 71 in total, were registered at the cooperative post-graduate school program with Keio University and Juntendo University, respectively. Among them, 23 post-graduate students received a PhD.

Future prospects

The National Cancer Center has to nurture experts in a variety of job types to engage in medical treatment and cancer research, support cancer patients and provide such experts throughout Japan. It is also expected that we nurture able professionals who should be leaders in their field in the near future. We want to aim at the construction of a system performing personnel training by all types of jobs about medical treatment and cancer research, and support of cancer patients including office workers as well as doctors.

Innovation Center for Supportive, Palliative and Psychosocial Care

Yosuke Uchitomi, Yutaka Matsuoka, Takuhiro Yamaguchi, Kyoko Akutsu

Introduction

The scientific background about supportive, palliative and psychosocial care to reduce both physical and mental distress caused by cancer treatment and/or cancer itself is insufficient. In particular, the development of new medical interventions regarding symptom control in the progressive period and the end-of-life period are insufficient worldwide. We have many experience-based guidelines for pain, vomiting, fatigue, numbness, dysgeusia, insomnia, depression, anxiety and delirium, but said guidelines are not well supported by evidence. Developing a standard treatment based on scientific evidence for supportive, palliative and psychosocial care is our responsibility as a developed country. However, there isn't a secure base for conducting clinical research and developing a support organization in Japan. First, we made preparations to establish the Innovation Center for supportive, palliative and psychosocial care at the National Cancer Center Hospital Japan in 2015. Second, we are building J-SUPPORT [Japan Supportive, Palliative and Psychosocial Oncology Group] as an open hub for multi-institute collaborative clinical research for supportive, palliative and psychosocial care.

Routine activities

We cooperate in providing consultation services and expert advice on clinical research design and statistics to investigators as they launch new research projects in the field of supportive, palliative and psychosocial care. This service includes face-to-face clinical design and biostatistics consultation. In addition, we adjust collaborative studies with other study groups or institutions.

Research activities

We have made preparations to start J-SUPPORT. In particular, we organize operating structures, basic constitutions, and procedures to review study protocol. We classified a study implementing group into five regions: 1) medicine and device development, 2a) supportive care, 2b) palliative care, 3) psychosocial and behavioral care, 4) research methodology, 5) needs survey and implementation. First, we launched a protocol review committee, which was held in August and October 2015.

Future prospects

We plan to hold the protocol review committee regularly and are going to launch the J-SUPPORT website in spring 2016. According to a roadmap (Figure 1), we plan to expand J-SUPPORT as an open hub to contribute to the development of supportive, palliative and psychosocial care for cancer patients.

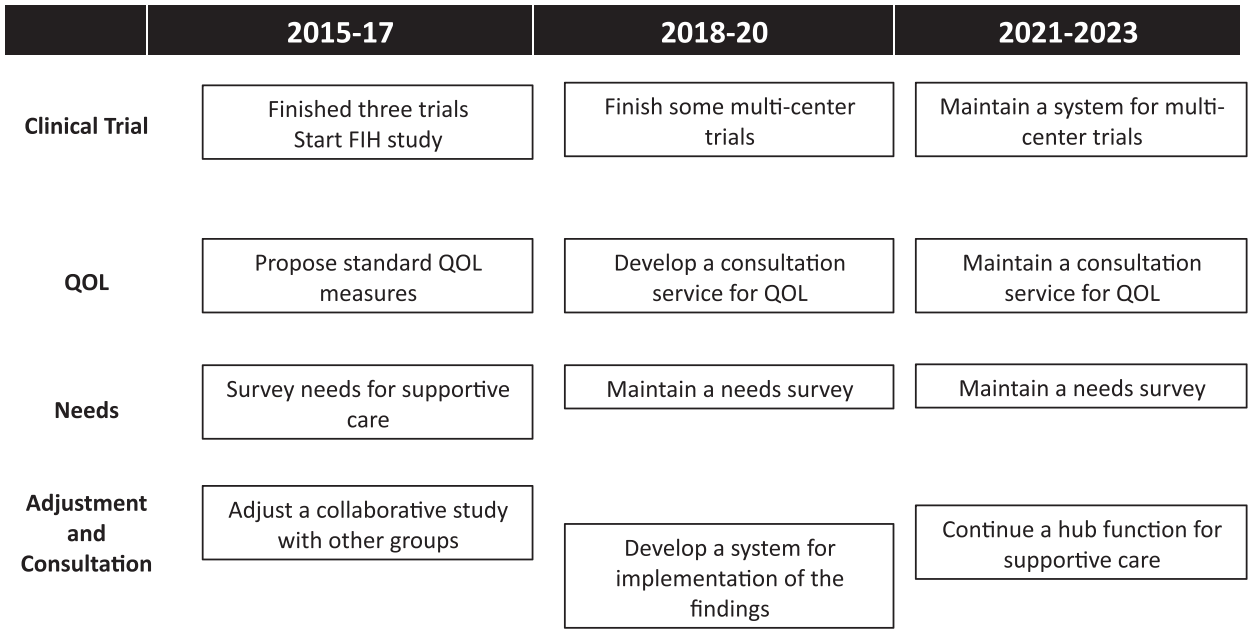


Figure 1. Roadmap of J-SUPPORT

List of papers published in 2015

Journal

1. Wada S, Shimizu K, Inoguchi H, Shimoda H, Yoshiuchi K, Akechi T, Uchida M, Ogawa A, Fujisawa D, Inoue S, Uchitomi Y, Matsushima E. The Association Between Depressive Symptoms and Age in Cancer Patients: A Multicenter Cross-Sectional Study. J Pain Symptom Manage, 50:768-777, 2015

2. Higuchi Y, Uchitomi Y, Fujimori M, Koyama T, Kataoka H, Kitamura Y, Sendo T, Inagaki M. Exploring autistic-like traits relating to empathic attitude and psychological distress in hospital pharmacists. Int J Clin Pharm, 37:1258-1266, 2015

3. Ishida M, Onishi H, Toyama H, Tsutsumi C, Endo C, Tanahashi I, Takahashi T, Uchitomi Y. Missing memories of death: Dissociative amnesia in the bereaved the day after a cancer death. Palliat Support Care, 13:1787-1790, 2015

4. Umezawa S, Fujimori M, Matsushima E, Kinoshita H, Uchitomi Y. Preferences of advanced cancer patients for communication on anticancer treatment cessation and the transition to palliative care. Cancer, 121:4240-4249, 2015

Office for Advanced Medical Care Evaluation

Yasuhiro Fujiwara, Kan Yonemori, Nobuko Ushirozawa, Seiichiro Yamamoto, Taro Shibata, Aya Kuchiba, Shogo Nomura, Natsuko Okita

Introduction

In November 2013, our Office was established by the NCC as a secretariat to "evaluate advanced medical treatments involving anti-cancer drugs due to high unmet medical needs", a project commissioned by the Health Policy Bureau of the Ministry of Health, Labour and Welfare (MHLW).

Our Office's mission is to provide support for institutions, including the "core clinical research hospitals", that are going to conduct clinical studies of anti-cancer drugs identified as potential treatments for diseases with high unmet medical needs by the Evaluation Committee on Unapproved or Off-label Drugs with High Medical Needs, within the framework of the Advanced Medical Care B program of the MHLW.

Routine activities

We assist institutions by 1) preparing their study plans, 2) supporting their application procedures, e.g., facilitating discussions with regulatory authorities, and 3) reviewing the technical adequacy of the applications and the content of the study implementation plans by establishing and operating the Assessment Committee on Advanced Medical Care. We also report the assessment results to the Advanced Medical Care meeting.

As of now, the anti-cancer drugs expected to be covered by this system include 131I-MIBG (pheochromocytomas, neuroblastoma, medullary thyroid cancer, etc.). We are currently discussing their development strategy in coordination with clinical experts, the pharmaceutical industry, and regulatory authorities.

We also make a list of unapproved anticancer drugs (i.e., those approved in the United States and/or the European Union, but not in Japan) for the understanding of drugs as a target of this system.

Hospital

Preface

The National Cancer Center Hospital (NCCH) was established in 1962, as a hub for cancer therapy in Japan. Cooperating with patients and society, the Hospital has been providing the best medical treatment, undertaking high-quality clinical research to develop brand new medicines, and nurturing many outstanding healthcare providers, including physicians, nurses, and pharmacists in the oncology field. The NCCH has profound expertise in cancer research including drugs, devices and cell therapy from FIH to global Phase three trials, which are supported by world-class diagnosis capabilities, such as IVR, PET imaging, and by full-spec intensive care units and an ISO15189-certified laboratory. Based on the achievements in clinical research activities, the NCCH was selected as the Core Hospital for Clinical Research in August 2015. We will contribute to Japan's innovative development of medical treatments and to their dissemination across Japan, as well as around the globe.

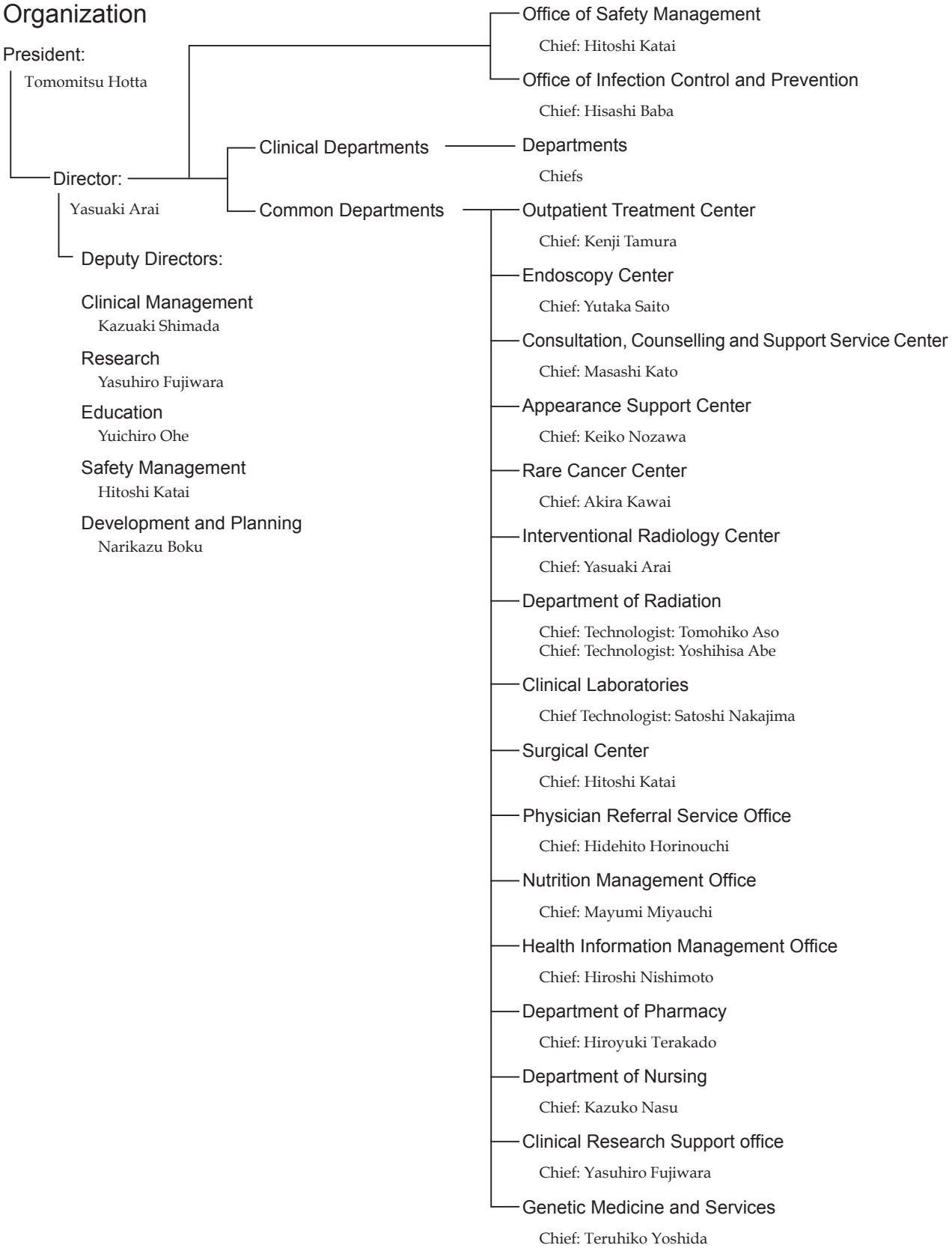
In the last year, the outpatient chemotherapy has been powered up by increasing the bedspace for chemotherapy, and the Department of Genetic Medicine and Service has been launched as common departments. These facilitate future medical practice including precision medicine and clinical research together with the CLIA-compatible NGS Lab (SCI-Lab), where clinical sequencing is conducted. In addition, we redesigned our healthcare safety system to reduce medical errors and provide safe and qualified medical treatment.

There is more to cancer patients than just being "sick." Patients may suffer from other diseases, and may have anxiety and various problems arising and affecting daily activities and employment. With the aging of the population, the number of cancer patients with comorbid diseases increases. The NCCH, a cancer-specialized facility, has been working in cooperation with Saiseikai Central Hospital and the nearby Jikei University School of Medicine since 2015 in a system in which these patients could receive secure and optimal treatment and care for cancer. Furthermore, we have provided a free-WiFi service for inpatient amenity, and the Supportive Care Development Center has been established on the 8th floor to improve the quality of life of cancer patients and to promote research of supportive care for cancer.

Over the past year, we have redesigned our system for future clinical practice and development in cancer and we appreciate your understanding and cooperation.

Toshirou Nishida, MD, PhD
Director of the Hospital
National Cancer Center Hospital

Organization



Clinical Departments

Director:
Yasuaki Arai

Deputy Directors:

Clinical Management
Kazuaki Shimada

Research
Yasuhiro Fujiwara

Education
Yuichiro Ohe

Safety Management
Hitoshi Katai

Development and Planning
Narikazu Boku

- Department of Neurosurgery and Neuro-Oncology
  Chief: Yoshitaka Narita
- Department of Ophthalmic Oncology
  Chief: Shigenobu Suzuki
- Department of Head and Neck Oncology
  Chief: Seiichi Yoshimoto
- Department of Plastic and Reconstructive Surgery
  Chief: Shimpei Miyamoto
- Department of Breast Surgery
  Chief: Takayuki Kinoshita
- Department of Breast and Medical Oncology
  Chief: Kenji Tamura
- Department of Thoracic Surgery
  Chief: Shun-ichi Watanabe
- Department of Thoracic Oncology
  Chief: Yuichiro Ohe
- Department of Esophageal Surgery
  Chief: Yuji Tachimori
- Department of Gastric Surgery
  Chief: Hitoshi Katai
- Department of Colorectal Surgery
  Chief: Yukihide Kanemitsu
- Department of Gastrointestinal Medical Oncology
  Chief: Narikazu Boku
- Department of Endoscopy
  Chief: Yutaka Saito
- Department of Hepatobiliary and Pancreatic Surgery
  Chief: Kazuaki Shimada
- Department of Hepatobiliary and Pancreatic Oncology
  Chief: Takuji Okusaka
- Department of Urology
  Chief: Hiroyuki Fujimoto
- Department of Gynecology
  Chief: Tomoyasu Kato
- Department of Musculoskeletal Oncology and Rehabilitation
  Chief: Hirokazu Chuuman
- Department of Dermatologic Oncology
  Chief: Naoya Yamazaki
- Department of Hematology
  Chief: Kensei Tobinai
- Department of Hematopoietic Stem Cell Transplantation
  Chief: Takahiro Fukuda
- Department of Blood Transfusion and Cellular Therapy
  Chief: Ryuji Tanosaki
- Department of Pediatric Oncology
  Chief: Chitose Ogawa
- Department of General Internal Medicine, Dentistry, Oncologic Emergencies
  Chief: Ken Ohashi
- Department of Anesthesia and Intensive Care
  Chief: Tetsufumi Sato
- Department of Palliative Medicine
  Chief: Eriko Satomi
- Department of Psycho-Oncology
  Chief: Ken Shimizu
- Department of Diagnostic Radiology
  Chief: Yasuaki Arai
- Department of Radiation Oncology
  Chief: Jun Itami
- Department of Pathology and Clinical Laboratories
  Chief: Nobuyoshi Hiraoka
- Department of Experimental Therapeutics
  Chief:Noboru Yamamoto

Activities of the Departments

Department of Neurosurgery and Neuro-Oncology

Yoshitaka Narita, Yasuji Miyakita, Makoto Ohno, Masamichi Takahashi, Takahiro Ogawa, Shunicihro Miki, Sakura Kuzuoka

Introduction

Patients with primary and metastatic brain tumors are treated by four neurosurgeons and three senior residents in the Department of Neurosurgery and Neuro-Oncology. A total of 327 patients were admitted and 121 craniotomies for tumor removal were carried out in 2015 including 38 gliomas, 49 brain metastases, six primary central nervous system (CNS) lymphomas, and 12 meningiomas (Table 1). The site of the craniotomy and the extent of tumor removal were visualized on the intraoperative magnetic resonance imaging (MRI) in real time, contributing to safer and more precise surgery. Intraoperative monitoring with motor- and sensory-evoked potential (MEP and SEP) recording as well as preoperative functional MRI and magnetic resonance (MR) tractography were also used to preserve patient neurological functions. Nine awake surgeries were also performed, particularly for removal of gliomas near the speech center. Patients with malignant brain tumors were treated with postoperative radiotherapy and chemotherapy. In order to design a more effective chemotherapy regimen, molecular biological studies for drug resistance, growth factors, cell kinetic studies on individual tumors and several clinical trials are ongoing.

Routine activities

A weekly conference of treatment of patients with brain tumors is held with doctors of the Department of Radiation Oncology and of the Division of Brain Tumor Translational Research. Usually 15-20 patients are hospitalized and two or three of them undergo surgical treatment every week. The patients with malignant brain tumors receive postoperative radiotherapy and chemotherapy. Statistical analysis revealed that surgical removal of as much of the tumor as possible yielded better survival rates even for the most malignant glioblastomas, which usually recur soon after surgery without radiotherapy. Concomitant use of chemotherapy is considered to enhance the anti-tumor effect of radiotherapy. Temozolomide has been given to all malignant glioma patients during radiotherapy and repeated every month for two years. The five-year survival rates of the patients with anaplastic astrocytomas and glioblastomas were 66.1% and 10.1%, respectively, which were better than those recorded in the Brain Tumor Registry of Japan (BTRJ). High dose methotrexate is administered to the patients with primary CNS lymphoma before radiotherapy.

The decision on the indication for surgery of metastatic brain tumors is not simple. Multiplicity of brain metastasis, the stage of the primary malignancy and the patient performance status should be taken into careful consideration.

Research activities

Patients with brain tumors have been registered in the BTRJ since 1969. More than 100,000 patients have been registered and followed up. The Department of Neurosurgery and Neuro-Oncology, the National Cancer Center Hospital, contributes as a managing office of the BTRJ and established on-line registration using the University Hospital Medical Information Network (UMIN) system in 2009. Clinical data during 2005 and 2008 were collected and the report will be published in 2016 as a supplement of the official journal of the Japan Neurosurgical Society.

An analysis of gene expression profiles in malignant gliomas is being carried out in order to determine specific genes that have an influence on the effects of chemotherapy and radiation therapy in cooperation with the Division of Brain

Tumor Translational Research, the National Cancer Center Research Institute. The determination of the methylation status of O6-methylguanine-DNA methyltransferase (MGMT) and the mutation of IDH1/2 and TERT are also carried out to predict the prognosis of patients with malignant gliomas.

Clinical trials

The Japan Clinical Oncology Group (JCOG) – Brain Tumor Study Group was organized in 2002 and a multi-institutional randomized controlled trial is performed. "A randomized controlled phase II/III study of chemoradiotherapy using nimustine hydrochloride (ACNU) versus procarbazine and ACNU for astrocytoma grade 3 and 4 (JCOG0305)" was published. "A multicenter randomized phase II trial of Interferon-beta and Temozolomide combination chemoradiotherapy for newly diagnosed glioblastomas (JCOG 0911)" and "A Randomized phase III trial of postoperative whole brain radiation therapy compared with salvage stereotactic radiosurgery in patients with one to four brain metastasis (JCOG 0504)" was finished.

These studies, under the surveillance of JCOG, aim to set a standard protocol for treating malignant brain tumor patients. Moreover, a proper methodology for performing randomized studies will be established in the field of neuro-oncology. "Phase III randomized Study in patients with anaplastic glioma of radiotherapy with temozolomide versus ACNU followed by temozolomide (JCOG1016)," "Phase III Study of High-dose Methotrexate and Whole Brain Radiotherapy With or Without Concomitant and Adjuvant Temozolomide in Patients with Primary CNS Lymphoma (JCGO1114)," "Randomized phase III study for unresectable WHO Grade II astrocytoma with radiotherapy alone or chemoradiotherapy with temozolomide (JCOG1303)," and "a multicenter randomized phase III study for recurrent glioblastoma comparing bevacizumab alone with dose-dense temozolomide followed by bevacizumab (JCOG1308)" are now ongoing.

Education

Our Department plays the roles of the office of the general secretary of the JCOG – Brain tumor study group and the brain tumor registry of Japan; we have conducted many clinical trials and brain tumor registries. We educate many neurosurgeons and oncologists about surgical techniques of awake craniotomy and intraoperative MRI and the effective usage and adverse effects of many chemotherapeutic agents for malignant brain tumors.

Future prospects

Malignant brain tumors, especially glioblastoma, still have worse prognosis among cancers. We always make an effort to defeat these brain cancers through various clinical works and research.

Table 1. Number of patients

	2011	2012	2013	2014	2015
Surgeries	123	132	140	128	153
Craniotomy/Biopsy	92	98	106	96	121
Glioma	35	47	39	34	38
Brain metastases	39	33	40	42	49
Meningioma	5	7	12	7	12
Lymphoma	6	4	7	5	6
Spinal tumors		2	4	1	3
Others	7	5	8	7	13
Neuroendoscope, shunt	31	34	34	32	32

List of papers published in 2015

Journal

1. Arita H, Narita Y, Matsushita Y, Fukushima S, Yoshida A, Takami H, Miyakita Y, Ohno M, Shibui S, Ichimura K. Development of a robust and sensitive pyrosequencing assay for the detection of *IDH1/2* mutations in gliomas. Brain Tumor Pathol, 32:22-30, 2015

2. Takami H, Yoshida A, Fukushima S, Arita H, Matsushita Y, Nakamura T, Ohno M, Miyakita Y, Shibui S, Narita Y, Ichimura K. Revisiting *TP53* Mutations and Immunohistochemistry-A Comparative Study in 157 Diffuse Gliomas. Brain Pathol, 25:256-265, 2015

3. Fukushima S, Yoshida A, Narita Y, Arita H, Ohno M, Miyakita Y, Ichimura K, Shibui S. Multinodular and vacuolating neuronal tumor of the cerebrum. Brain Tumor Pathol, 32:131-136, 2015

4. Narita Y, Shibui S, Committee of Brain Tumor Registry of Japan Supported by the Japan Neurosurgical Society. Trends and outcomes in the treatment of gliomas based on data during 2001-2004 from the Brain Tumor Registry of Japan. Neurol Med Chir (Tokyo), 55:286-295, 2015

5. Narita Y. Bevacizumab for glioblastoma. Ther Clin Risk Manag, 11:1759-1765, 2015

6. Okita Y, Narita Y, Miyahara R, Miyakita Y, Ohno M, Shibui S. Health-related quality of life in long-term survivors with Grade II gliomas: the contribution of disease recurrence and Karnofsky Performance Status. Jpn J Clin Oncol, 45:906-913, 2015

7. Arita H, Narita Y, Yoshida A, Hashimoto N, Yoshimine T, Ichimura K. *IDH1/2* mutation detection in gliomas. Brain Tumor Pathol, 32:79-89, 2015

8. Takami H, Fukushima S, Fukuoka K, Suzuki T, Yanagisawa T, Matsushita Y, Nakamura T, Arita H, Mukasa A, Saito N, Kanamori M, Kumabe T, Tominaga T, Kobayashi K, Nagane M, Iuchi T, Tamura K, Maehara T, Sugiyama K, Nakada M, Kanemura Y, Nonaka M, Yokogami K, Takeshima H, Narita Y, Shibui S, Nakazato Y, Nishikawa R, Ichimura K, Matsutani M. Human chorionic gonadotropin is expressed virtually in all intracranial germ cell tumors. J Neurooncol, 124:23-32, 2015

9. Ichimura K, Narita Y, Hawkins CE. Diffusely infiltrating astrocytomas: pathology, molecular mechanisms and markers. Acta Neuropathol, 129:789-808, 2015

10. Iwakawa R, Kohno T, Totoki Y, Shibata T, Tsuchihara K, Mimaki S, Tsuta K, Narita Y, Nishikawa R, Noguchi M, Harris CC, Robles AI, Yamaguchi R, Imoto S, Miyano S, Totsuka H, Yoshida T, Yokota J. Expression and clinical significance of genes frequently mutated in small cell lung cancers defined by whole exome/RNA sequencing. Carcinogenesis, 36:616-621, 2015

Department of Ophthalmic Oncology

Shigenobu Suzuki, Yukiko Aihara, Shuichi Sano

Introduction

Our Department is one of the rare groups specializing in ocular tumors, especially intraocular tumors. Recently, more than 70% of patients nationwide with retinoblastoma, which is the most frequent intraocular malignancy in childhood, and more than 50% of patients with choroidal melanoma, which is the most frequent primary intraocular malignancy in adults, have been referred to our department.

Routine activities

Our outpatient service is open four days a week. Every week, eight operations under general anesthesia are performed in our department. Our treatment strategies for ocular tumors are as follows:

1) Retinoblastoma

Unless the patient's family has concerns about preserving the affected eye, if the eye has already suffered from complications such as secondary glaucoma or severe hemorrhage, or if extraocular extension of the retinoblastoma is strongly suspected, we can offer the family eye-preserving treatment. Initial systemic chemotherapy and additional local therapies, called "chemoreduction therapy", comprise the main strategy. If the tumor is localized in the peripheral retina, plaque radiotherapy using ruthenium-106 is also available. Transpupillary thermotherapy or cryotherapy is also used in cases with localized small tumors. Patients with extraocular extension, recurrence or metastasis who need intensive systemic chemotherapy are treated with dedicated support from the Department of Pediatric Oncology.

2) Choroidal melanoma

Choroidal melanoma is a rare disease in Asians. Recent reports from Western countries have demonstrated that the prognosis of eye-preserving treatment with plaque radiotherapy is equivalent to that of enucleation (COMS, medium-sized tumor study). For localized tumors up to 5 mm thick, ruthenium-106 plaque radiotherapy is the first choice. In Japan, plaque radiotherapy is only available in our institute. Patients with much larger tumors are treated by radiotherapy: CyberKnife Robotic Radiosurgery in our institute or carbon ion therapy in the National Institute of Radiological Science, Research Center for Charged Particle Therapy. Choroidal melanomas often metastasize to the liver and this is invariably fatal. Life-long follow-up with liver imaging is routinely conducted for our patients. Patients with liver and systemic metastases are treated by the Department of Dermatologic Oncology.

3) Orbital tumors

Whereas most orbital tumors in childhood are benign, rhabdomyosarcoma is a malignant tumor that requires systemic chemotherapy and radiation after biopsy. The most common orbital tumors in adults include cavernous hemangioma, lacrimal gland tumor, lymphoma, metastatic tumor, and orbital inflammatory disease. Patients with a biopsy-confirmed orbital lymphoma are referred to the Department of Hematology, and Hematopoietic Stem Cell Transplantation. Total resection by orbitotomy, or sometimes orbital exenteration, is used for lacrimal gland tumors. Recurrent lacrimal gland cancers are referred to the National Institute of Radiological Science, Research Center for Charged Particle Therapy, for carbon ion therapy.

4) Eyelid tumors

The most common malignant eyelid tumors include basal cell carcinoma, sebaceous carcinoma, and squamous cell carcinoma. They are treated by excisional resection with reconstruction.

Radiotherapy using electrons is another strategy. Orbital exenteration is selected in cases of orbital invasion.

5) Conjunctival tumors

Conjunctival malignant tumors are treated by excisional resection with a safety margin combined with cryotherapy at the resection margin. Diffuse conjunctival tumors or tumors with orbital invasion are treated with orbital exenteration.

Research activities

One of the unique techniques in our department is local chemotherapy for retinoblastoma via selective ophthalmic artery infusion using a balloon catheter. This procedure was developed in our hospital from 1987, and has been modified and performed after 2009 in more than 20 countries. We are planning a clinical trial on selective ophthalmic artery injection therapy for initial treatment methods.

Direct injection of diluted melphalan into the vitreous cavity is performed for retinoblastoma eyes with vitreous seeding. Vitreous seeding can be cured for eyes with vitreous seeds after other treatment modalities, and about 65% of eyes were rescued using this strategy.

The National Registry of Retinoblastoma in Japan was organized in 1975, and more than 3,000 patients are registered. We contribute to this registry as an administrator of personal data and check overlapping. This registry now covers almost all patients in Japan, and provides epidemiological data.

A clinical study concerning the development of retinoblastoma patients with visual disturbance, and maternal psychological burden, is now ongoing. The result will be helpful for a social and psychological approach for retinoblastoma patients and their families.

We are now investigating the specific marker or genetic change for eye tumors, especially retinoblastoma, choroidal melanoma, and ciliary body tumors.

We also contribute to the international registry system, as the AJCC Ophthalmic Expert Panel, to advise and reflect the Asian data in the TNM system.

Ocular adverse events caused by anti-cancer drugs used for systemic disease have been recently recognized, and ocular examinations are included in clinical trials, especially for molecular targeted drugs. Serous retinal detachment (SRD), retinal vein occlusion (RVO), and ocular surface complications are major adverse events caused by kinase inhibitor drugs, stenosis or occlusion of lacrimal drainage systems are common events caused by S-1, and cystoid macular edema (CME) caused by some drugs. We examine and follow these adverse events, with or without additional treatment, to support clinical trials, to contribute to establishing protocols, and to enlighten general ophthalmologists about these events.

Future prospects

We plan to establish the multicenter study group for eye tumors to employ clinical studies, confirm the diagnostic criteria and guidelines, and clarify the carcinogenesis for eye tumors.

Table 1. Number of patients

Retinoblastoma	53
Choroidal melanoma	26
Other intraocular tumors	39
Eyelid tumor	11
Conjunctival tumor	7
Orbital tumor	19
Ocular adnexal lymphoma	14
Other	2
Total	181

Table 2. Type of procedure

Retinoblastoma	
Selective ophthalmic arterial injection	131
Laser and/or vitreous injection	142
Ruthenium brachytherapy	14
Enucleation	10
Examination under general anesthesia	1
Choroidal melanoma	
Ruthenium brachytherapy	4
Enucleation	2
Resection of ciliary body tumor	2
Resection of eyelid tumor	7
Resection of conjunctival tumor	2
Resection of orbital tumor	14
Total	329

List of papers published in 2015

Journal

1. AJCC Ophthalmic Oncology Task Force. International Validation of the American Joint Committee on Cancer's 7th Edition Classification of Uveal Melanoma. JAMA Ophthalmol, 133:376-383, 2015

2. Goto H, Takahira M, Takahira M, Azumi A, Japanese Study Group for IgG4-Related Ophthalmic Disease. Diagnostic criteria for IgG4-related ophthalmic disease. Jpn J Ophthalmol, 59:1-7, 2015

3. Suzuki S, Aihara Y, Fujiwara M, Sano S, Kaneko A. Intravitreal injection of melphalan for intraocular retinoblastoma. Jpn J Ophthalmol, 59:164-172, 2015

4. Fujiwara T, Fujiwara M, Numoto K, Ogura K, Yoshida A, Yonemoto T, Suzuki S, Kawai A. Second primary osteosarcomas in patients with retinoblastoma. Jpn J Clin Oncol, 45:1139-1145, 2015

5. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Fujiwara Y, Tamura Y, Wakui H, Honda K, Mizugaki H, Kitazono S, Tanabe Y, Asahina H, Yamazaki N, Suzuki S, Matsuoka M, Ogita Y, Tamura T. Phase I and pharmacokinetics/pharmacodynamics study of the MEK inhibitor RO4987655 in Japanese patients with advanced solid tumors. Invest New Drugs, 33:641-651, 2015

Department of Head and Neck Oncology

Seiichi Yoshimoto, Fumihiko Matsumoto, Kenya Kobayashi, Daisuke Maki, Masanori Teshima, Masahiko Fukazawa

Introduction

The treatment strategy for head and neck cancer is to improve survival rates while preserving the significant functions including speech, mastication, swallowing and cosmetic appearance. In order to achieve this strategy, our department has tried to select the best treatment modality and devise new surgical procedures based on clinic-pathological findings and our large database of patients with head and neck cancer.

Our department has developed and performed original surgical procedures of partial or subtotal laryngectomy for newly diagnosed and radiation-failed laryngeal cancer, partial pharyngectomy for hypopharyngeal cancer and total glossectomy for advanced tongue cancer. These surgical approaches can be performed without sacrificing the larynx. Compared with the results of conventional surgery, there are apparently fewer wound complications. Patients can resume social activities more easily when they maintain their ability to communicate vocally.

Routine activities

The Department of Head and Neck Oncology at NCCH consists of six head and neck surgeons. Many operations are performed under general and local anesthesia with or without microsurgical reconstructive surgery. In addition to radiotherapy, concurrent chemo-radiotherapy is performed with the Department of Radiation Oncology.

In 2015, 403 patients with head and neck tumor underwent surgery under local or general anesthesia: 127 and 276, respectively, including 78 patients with major ablation and reconstructive surgery. Table 1 shows the number of surgical cases with each primary site. Table 2 shows the number of each surgical procedure.

Research activities

We have been taking part in multi-institutional studies of sentinel lymph node navigation surgery for oral cavity cancer using RI and laryngopharyngeal cancer using ICG. We are also taking part in a multi-institutional study of intra-arterial chemo-radiotherapy for maxillary cancer.

Clinical trials

We are participating in a few clinical trials about immune checkpoint inhibitors.

Education

We provide plenty of educational opportunities for resident doctors, especially focusing on acquiring operative techniques. They can learn everything about perioperative management, such as physical examination, image diagnosis, informed consent, preoperative preparation and postoperative management.

Future prospects

We have recently started trans-oral resection for superficial laryngopharyngeal cancer. Trans-oral resection will be indicated for more patients. Cetuximab is used for many patients with recurrent or metastatic tumors. We will be able to get useful information about the response rate of Cetuximab for Japanese patients. The number of patients with HPV-related oropharyngeal cancer has increased. The treatment strategy for this disease should be discussed.

Table 1. Number of patients

Tongue	41
Oral cavity (without tongue)	53
Nasal and paranasal cavity	14
Nasopharynx	1
Oropharynx	50
Hypopharynx	79
Cervical esophagus	9
Larynx	30
Salivary gland	16
Thyroid	29
Parathyroid	0
Neck	57
Others	24
Total	403

Table 2. Type of procedure

Skull base (+ reconstruction)	3(3)
Maxillectomy (+ reconstruction)	16(4)
Glossectomy (+ reconstruction)	37(8)
Resection of Oral cavity (+ reconstruction)	47(18)
Nasopharyngectomy	1
Oropharyngectomy (+ reconstruction)	37(14)
Endoscopic resection of hypopharynx	7
Trans-oral resection of hypopharynx	23
Partial pharyngectomy (+ reconstruction)	7(1)
Total laryngopharyngectomy (+ reconstruction)	22(22)
Trans-oral resection of larynx	6
Partial or supracricoid laryngectomy	2
Total laryngectomy (+ reconstruction)	10(1)
Thyroidectomy (+ reconstruction)	24(1)
Parotidectomy (+ reconstruction)	12(2)
Neck dissection (+ reconstruction)	28(2)
Resection of parapharyngeal tumor	2
Voice prosthesis	12
Lymphadenectomy	68
Others (+ reconstruction)	39(2)
Total	403(78)

List of papers published in 2015

Journal

1. Murakami N, Yoshimoto S, Matsumoto F, Ueno T, Ito Y, Watanabe S, Kobayashi K, Harada K, Kitaguchi M, Sekii S, Takahashi K, Yoshio K, Inaba K, Morota M, Sumi M, Saito Y, Itami J. Severe gastrointestinal bleeding in patients with locally advanced head and neck squamous cell carcinoma treated by concurrent radiotherapy and Cetuximab. J Cancer Res Clin Oncol, 141:177-184, 2015

2. Kinjo Y, Nonaka S, Oda I, Abe S, Suzuki H, Yoshinaga S, Maki D, Yoshimoto S, Taniguchi H, Saito Y. The short-term and long-term outcomes of the endoscopic resection for the superficial pharyngeal squamous cell carcinoma. Endosc Int Open, 3:E266-E273, 2015

3. Wakisaka N, Hasegawa Y, Yoshimoto S, Miura K, Shiotani A, Yokoyama J, Sugasawa M, Moriyama-Kita M, Endo K, Yoshizaki T. Primary Tumor-Secreted Lymphangiogenic Factors Induce Pre-Metastatic Lymphvascular Niche Formation at Sentinel Lymph Nodes in Oral Squamous Cell Carcinoma. PLoS One, 10:e0144056, 2015

4. Kobayashi K, Ando M, Saito Y, Kondo K, Omura G, Shinozaki-Ushiku A, Fukayama M, Asakage T, Yamasoba T. Nerve Growth Factor Signals as Possible Pathogenic Biomarkers for Perineural Invasion in Adenoid Cystic Carcinoma. Otolaryngol Head Neck Surg, 153:218-224, 2015

Department of Plastic and Reconstructive Surgery

Shimpei Miyamoto, Masahide Fujiki, Masaki Arikawa, Yu Kagaya

Introduction

The Department of Plastic and Reconstructive Surgery has mainly focused on surgical reconstruction after cancer ablation. In our institution, reconstructive procedures using free flap transfer with microvascular anastomosis are the most important operations. In addition, several methods such as tissue transfer with pedicled flaps, local flaps, skin grafts, and so forth, are used for reconstructive surgery. The objectives of reconstructive surgery are not only morphological reconstruction, but also restoration of postoperative functions after ablative surgery. The quality of life (QOL) of the patient can be improved by functional and morphological reconstruction.

Routine activities

Two plastic surgeons cover reconstructive operations. Every week, five to ten reconstructive operations are performed. These reconstructive surgeries are performed in cooperation with the surgeons from other divisions of the hospital, such as Head and Neck Surgery, Breast Surgery, Orthopedic Surgery, Esophageal Surgery, and Dermatology. The number of patients who receive immediate breast reconstruction is increasing. Most patients undergo breast reconstruction with a silicone implant. Limb reconstruction after limb preservation surgery has increased.

Research activities

Multi-institutional analysis of postoperative functions after microvascular tongue reconstruction is ongoing. Also, laboratory research of flow-through flaps using a rat model is ongoing.

Table 1. Reconstructive procedures

Free flap	123
ALT	39
Jejunum	23
DIEP	13
RAMC	13
LDMC	11
TAP	8
SIEA	6
Fibula	4
Others	5
Other microsurgical procedures	11
Supercharge	1
Extremity revascularization	5
LVA	4
Others	1
Total (Microsurgery)	134
Pedicled flap	53
LD (TAP)	14(4)
Pectoralis Major	8
ALT	6
RAMC (DIEP)	5(1)
Others	20

Table 2. Breast reconstruction

Tissue expander	111
Silicone implant	56
DIEP	14
LD	5

List of papers published in 2015

Journal

1. Miyamoto S, Kayano S, Fujiki M, Kamizono K, Fukunaga Y, Sakuraba M. Flow-through divided latissimus dorsi musculocutaneous flap for large extremity defects. Ann Plast Surg, 74:199-203, 2015

2. Miyamoto S, Fukunaga Y, Fujiki M, Nakatni F, Tanzawa Y, Sakuraba M. Accompanying artery of sciatic nerve as recipient vessel for free-flap transfer: a computed tomographic angiography study and case reports. Microsurgery, 35:284-289, 2015

3. Fujiki M, Miyamoto S, Arikawa M, Sakuraba M. Combined Use of Anterolateral Thigh and Gluteal Fold Flaps for Complex Groin Reconstruction. Plast Reconstr Surg Glob Open, 3:e541, 2015

4. Fujiki M, Miyamoto S, Sakuraba M. Flow-through anastomosis for both the artery and vein in leg free flap transfer. Microsurgery, 35:536-540, 2015

5. Miyamoto S, Fujiki M, Sakuraba M. Clinical analysis of 33 flow-through latissimus dorsi flaps. J Plast Reconstr Aesthet Surg, 68:1425-1431, 2015

6. Fujiki M, Miyamoto S, Nakatani F, Kawai A, Sakuraba M. Rotationplasty with vascular reconstruction for prosthetic knee joint infection. Case Rep Orthop, 2015:241405, 2015

7. Miyamoto S, Fujiki M, Nakatani F, Sakisaka M, Sakuraba M. Free flow-through anterolateral thigh flap for complex knee defect including the popliteal artery. Microsurgery, 35:485-488, 2015

Department of Breast Surgery

Takayuki Kinoshita, Shin Takayama, Sota Asaga, Kenjiro Jimbo, Eriko Iwamoto, Sho Shiino

Introduction

The Breast Surgery Department deals with treatment of breast cancer through surgeries, as well as diagnosis of breast diseases and assessment of lymph nodes in the axillary and clavicular regions that are suspected of harboring metastases. The trend in surgical procedures has been changing year by year. Although breast-conserving therapy (BCT) accounted for 40% of the total surgeries in our division in 2015, BCT is on the decline in recent years. One of the reasons for such decline is increasing needs of immediate reconstruction surgery. In 2010, immediate breast reconstruction became one of the choices for patients in whom breast preservation was impossible, and a total of 130 immediate breast reconstructions were performed in 2015, comprising more than 20% of all the cases. The number of cases of immediate breast reconstruction has gradually increased year by year to match the increase in needs of patients. Sentinel lymph node (SLN) biopsies (SLNB) were performed in 83% of the cases. Following SLNB, axillary lymph node dissection (ALND) could be avoided when the SLNB was negative. One-step nucleic acid amplification (OSNA) assay, that quantitatively measures CK19 mRNA detects sentinel lymph node metastases even in molecular levels, in conjunction with this assay and conventional microscopic method, we began to be able to evaluate the SLN more precisely. Further, by comparing the OSNA results with that of conventional histological diagnosis, we try to search for the possibility of omitting axillary lymph node dissection by using two methods. Thus, we are striving continuously to meet the diverse needs of breast cancer patients.

Routine activities

Our division comprises of four staff surgeons, one chief resident, and three or four rotating residents. From 7:20 every morning, all the staff and the residents perform in-patient rounds together. The journal club and research conference are scheduled on every Tuesday morning after rounds. Weekly conferences are held on Monday and Wednesday from 17:00 to 18:00 for shared discussions with surgeons, medical oncologists, radiologists, and radiology and sonography technicians. The diagnostic images of pre-operative patients are reviewed and compared to pathological reports for every postoperative patient. A breast pathology/imaging conference is held on the second Wednesday of each month from 19:00 to 20:00 to discuss problems with diagnostic imaging, and with pathologically interesting cases. A conference about studies, institutional treatment guidelines and recent topics regarding breast cancer is held on the last Wednesday of each month by a multidisciplinary team. Treatment Guidelines for primary and metastatic breast cancer have been updated regularly through this multidisciplinary discussion since 2003.

Surgery

We perform surgeries from Monday to Friday; there are generally 13 to 15 cases of breast cancer in a week.

Table 1 shows the total number of patients with primary breast cancer (including breast primary sarcoma) and other breast disease. The types and number of operative procedures are shown in Table 2. The rate of mastectomy was 55% (340/614), including 130 cases of immediate reconstruction. SLNB was performed in 331 patients, and 251 patients were spared from ALND in 2014.

Research activities and Clinical trials

1) Radiofrequency ablation therapy for early breast

cancer as local therapy (RAFAELO study)

The trial of image-guided radiofrequency ablation (non-surgical therapy) has been accomplished for early-stage breast carcinomas of less than 1.0 cm in diameter (Phase I/II study; Kinoshita et al.). After years of trial, the indication has just been expanded up to 1.5 cm in diameter and this technique has been certified as an advanced medical treatment by the Ministry of Health, Labour and Welfare. Our secondary goals are to determine the size, configuration and pathological features of acute RFA treatment of breast cancers, and we have conducted clinical studies to evaluate the oncologic safety of RFA in terms of local recurrence.

2) Intensive vs. standard post-operative surveillance in high risk breast cancer patients (JCOG1204, INSPIRE Trial)

This is a multi-center randomized phase 3 trial that started in 2012. This clinical trial is to prove the hypothesis that postoperative intensive follow-up of patients with breast cancer is good for a standard follow-up.

3) Denosumab adjuvant treatment (D-CARE)

This phase 3 multi-center, randomized, double blind, placebo controlled study is continuing, designed to compare the treatment effect of denosumab with that of a placebo on prolonging bone metastasis-free survival in subjects with early-stage breast cancer at high risk of disease recurrence.

4) Scalp-cooling device during chemotherapy

A feasibility study to test the use of a scalp-cooling device that breast cancer patients will wear while undergoing chemotherapy treatment has started and continued in order to slow or halt hair loss during chemotherapy.

5) Postoperative Therapy with Endocrine and TS-1 (POTENT study)

This multi-center randomized trial has continued from 2012. This study compares invasive disease-free survival in patients with or without TS-1 administration together with adjuvant endocrine therapy in hormone positive and HER2 negative high recurrence risk patients.

6) Registration database system for breast cancer patients who had lymph node metastasis diagnosis by the OSNA® method (LynoLog Database)

The aim of this study is to accumulate the administrative data on cases with the OSNA method in a common database, the LynoLog Database, and to evaluate the clinical significance of intraoperative SLN metastases detected by OSNA.

7) Olaparib as adjuvant treatment in patients with germline BRCA mutated high risk HER2 negative primary breast cancer (OlympiA)

A randomized, double-blind, parallel group, placebo-controlled multi-center phase III study started in 2014. The aim of the study is to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.

Table 1. Number of patients

		2012	2013	2014	2015
Primary breast cancer (or sarcoma)		494	555	514	625
cStage	0	76	99	106	141
	Ⅰ	199	215	184	230
	Ⅱ	194	203	189	196
	Ⅲ	17	33	27	40
	Ⅳ	8	5	3	1
unknown or others		2	0	6	18

bilateral breast cancer was culculated as two cases.

Table 2. Type of procedure

	2011		2012		2013		2014		2015	
Total number of operations	577		589		618		582		679	
Total number of Primary breast cancer	526		502		560		530		625	
Mastectomy (%)	250	(48)	234	(45)	263	(47)	262	(51)	340	(55)
Breast-conserving surgery (%)	269	(51)	275	(53)	283	(51)	222	(43)	242	(40)
Radiofrequency ablation (%)	6	(1)	6	(1)	9	(2)	30	(6)	32	(5)
Axillary lymph node dissection (ALND) (%)	205	(33)	188	(15)	93	(21)	83	(20)	103	(17)
Sentinel lymph node biopsy (SLNB) (%)	402	(67)	409	(85)	347	(79)	331	(80)	501	(83)
Immediate breast reconstruction (%)	74	(14)	62	(13)	65	(12)	75	(14)	130	(20)
Secondory breast reconstruction (%)	1	0	8	(2)	5	(1)	16	(3)	11	(2)
Neoadjuvant therapy	57	(11)	45	(8)	38	(7)	36	(7)	64	(10)

Table 3. Survival (2006.1-2007.12)

		No. of patients	5-yr survival (%)
Total			92
stage	0	150	100
	Ⅰ	303	95
	Ⅱ	381	93
	Ⅲ	28	73

List of papers published in 2015

Journal

1. Jimbo K, Kinoshita T, Asaga S, Hojo T. Oncological safety of breast-conserving surgery after primary systemic chemotherapy in cT3-4 breast cancer patients. Surg Today, 45:1255-1262, 2015

2. Ono M, Tsuda H, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Kinoshita T, Fujiwara Y. Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers. Breast Cancer, 22:141-152, 2015

3. Hojo T, Masuda N, Mizutani T, Shibata T, Kinoshita T, Tamura K, Hara F, Fujisawa T, Inoue K, Saji S, Nakamura K, Fukuda H, Iwata H. Intensive vs. Standard Post-Operative Surveillance in High-Risk Breast Cancer Patients (INSPIRE): Japan Clinical Oncology Group Study JCOG1204. Jpn J Clin Oncol, 45:983-986, 2015

4. Yoshida M, Ogawa R, Yoshida H, Maeshima A, Kanai Y, Kinoshita T, Hiraoka N, Sekine S. TERT promoter mutations are frequent and show association with MED12 mutations in phyllodes tumors of the breast. Br J Cancer, 113:1244-1248, 2015

5. Asaga S, Kinoshita T, Hojo T, Jimbo K, Yoshida M. Predictive Factors for Non-Sentinel Lymph Node Metastasis in Patients With Clinically Node-Negative Ipsilateral Multiple Breast Cancer Treated With Total Mastectomy. Clin Breast Cancer, 15:362-369, 2015

6. Shiino S, Tsuda H, Yoshida M, Jimbo K, Asaga S, Hojo T, Kinoshita T. Intraductal papillomas on core biopsy can be upgraded to malignancy on subsequent excisional biopsy regardless of the presence of atypical features. Pathol Int, 65:293-300, 2015

7. Kikuyama M, Akashi-Tanaka S, Hojo T, Kinoshita T, Ogawa T, Seto Y, Tsuda H. Utility of intraoperative frozen section examinations of surgical margins: implication of margin-exposed tumor component features on further surgical treatment. Jpn J Clin Oncol, 45:19-25, 2015

8. Ono M, Tsuda H, Kobayashi T, Takeshita F, Takahashi RU, Tamura K, Akashi-Tanaka S, Moriya T, Yamasaki T, Kinoshita T, Yamamoto J, Fujiwara Y, Ochiya T. The expression and clinical significance of ribophorin II (RPN2) in human breast cancer. Pathol Int, 65:301-308, 2015

Department of Breast and Medical Oncology

Kenji Tamura, Chikako Shimizu, Kan Yonemori, Mayu Yunokawa, Makoto Kodaira, Tatsunori Shimoi, Akihiko Shimomura, Shinsuke Sasada, Aiko Maejima, Atsuko Kitano, Tadaaki Nishikawa, Emi Noguchi, Yasuhiro Fujiwara

Introduction

The Department of Breast and Medical Oncology provides the most effective treatment by the use of chemotherapy, and works on the establishment of new standard care for adult malignancies including breast cancer, gynecologic cancer, soft-tissue sarcoma, extragonadal germ cell tumors, primary unknown tumors and other rare types of solid tumors.

We envision becoming a premier medical oncology department, which leads cancer care in Japan and in the world. Our mission is to provide patient-centered, state-of-the-art medical care to cancer patients, to develop new effective cancer treatment through clinical and translational research, and to nurture medical oncologists. An evidence-based, research-oriented and multi-disciplinary approach is the core value of our practice.

Routine activities

1) Setup

Our Department consists of eight full-time attending physicians, four chief residents (fellows), and two to three clinical residents. We also provide educational opportunities to short-term (a half year) residents. Full-time attending physicians are on duty at the outpatient clinic two to three days per week. The management of hospitalized patients is undertaken by clinical teams, which consist on attending physicians and residents. A Grand Round is scheduled every Wednesday and Friday.

2) Performance

There were 1,423 first visits of new patients including second opinions in 2016 (Table 1). Approximately two thirds of the new patients were referred from other divisions of the National Cancer Center Hospital (NCCH). About half of the new patients are breast cancer patients, but it is noteworthy that there was an approximate 30% increase in patients with adult sarcoma this year because of our work with the Rare Cancer Center. The number of outpatient who received chemotherapy delivered by our Department delivered by our division was 8,580, which accounts for 27.3% of the total number and ranks first in the number of treatments delivered at the Outpatient Treatment Center.

We have approximately 32 (range 30-40) inpatients daily. Terminally ill patients are transferred to palliative care units or in-home care clinics outside the NCCH, whereas 33 patients of our Department passed away in the NCCH in 2016. Autopsies were undertaken on five patients.

3) Conference

The one-hour briefing medical conferences are held every morning to discuss the evidenced-based care for individual patients. The phase 1 conference is held on Monday, Journal Club on Wednesday, Clinical trial conference on Thursday, and Weekend and Outpatient follow-up conference on Friday. Multidisciplinary Case Conferences with diagnostic radiologists, surgeons, and pathologists are held with members of the Department of Breast Surgery, Gynecology, Musculoskeletal Oncology and Rehabilitation, Radiation Oncology and Division of pathology once or twice (Breast) per week, respectively.

The Monthly Breast Cancer Conference is held with the participation of multidisciplinary specialists to discuss recent topics in breast oncology and to update institutional treatment guidelines. This year, we published "Nyugan-shinnryou Application Notebook" from Nankodo based on this guideline, which reflects the consensus of the breast team on the body of evidence on breast

cancer management.

4) Coordination of care

Three board-certified Breast Cancer Specialist Nurses help provide seamless and comprehensive care to breast cancer patients. Group-assigned pharmacists support patients in the ward and in the clinic. Most patients are supported by the Consultation, Counseling and Support Service Center for coordination of care. Post-operative breast cancer patients without disease recurrence are referred to local breast cancer specialists participating in the Tokyo Breast Consortium network (http://breastcons.com/).

Research activities

Our research interest extends across a wide range of topics related to treatment and clinical program development. A lot of our research is secured by public and consignment research grants. In 2015, we conducted many research programs as the primary investigator and participated in additional research programs as the co-investigator secured by competitive public research funds. We published 29 international manuscripts. We value cancer survivorship as a research theme in order to develop a patient-centered comprehensive care program. In 2015, we published a guideline on fertility and fertility preservation for young breast cancer patients in cooperation with gynecologists and reproductive specialists. In addition, we took the lead in a multidisciplinary collaborative study group on End-of-life decision support for patients with advanced cancer.

Clinical trials

In 2015, we actively enrolled patients in phase I studies (including the first in human or global) as well as national and international phase II and III studies (Table 2). Of note, we launched a pharmacokinetic and dose-finding study of eribulin/olaparib, and a phase II study of eribulin in a neoadjuvant setting in triple negative breast cancer and phase I of Ribophorin (RPN)2 (first in human) as an investigator-initiated clinical trial (IIT in Table 2). New molecular imaging studies are launched in cooperation with research institutes. We also conducted many types of prospective cohort translational studies to find novel biomarkers.

Education

We provide rich educational opportunities to both residents and chief residents through clinical experience as well as research activities. Residents are encouraged to make presentations at local and national conferences. We vigorously support basic, clinical, or translational research conducted by postgraduate students.

Future prospects

We will continue to establish new standard treatments and propose a near-future model of clinical management of adult solid tumors, including breast cancer and gynecologic cancer. Moreover, we aim to build a comprehensive program, which includes a tumor registry, translational research, clinical trials and patient care in rare adult tumors based on our rich clinical experience. We would also like to improve the efficiency of anti-cancer drug development by coordinating basic and translational research in early-phase clinical trials.

Table 1. 1st Visiting Patients to the Department of Breast and Medical Oncology (Jan. – Dec. 2015)

No. of 1st Visits	n	%
Total	1,000	100
Breast	426	42.6
GYN	151	15.1
Cancer of primary unknown	207	20.7
Sarcoma	141	14.1
Others	75	7.5
Purpose of consultation		
Total	1,423	
2nd opinion	423	
Total No. of 1st visits	1,000	
2nd opinion as 1st visits	26	2.6
Treatment at NCCH	51	5.1
Referrals from other hospitals	286	28.6
Referrals from other divisions in the NCCH	634	63.4 (100)
Breast surgery	299	(47.2)
GYN	89	(14.0)
Urology	19	(3.0)
Orthopedics	24	(3.8)
Others	50	(7.9)
Rare Cancers Hotline	153	(24.1)
Others	3	0.3

Table 2. Active Clinical Trials (Jan. 2015-Dec. 2015)

Disease	Clinical setting	Phase	Protocol	Regimen	Status
Breast	Neo-adjuvant	II (IIT*)	Neo-Eribulin (TNBC)	Eribulin followed by FEC	Active, not recruiting
		II	Neo-Peaks	T-DM1 neoadjuvant	Active
	Follow-up	III	JCOG1204	Intensive follow-up vs. standard follow-up	Active
		II	POSITIVE	Pregnancy during hormonal therapy	Active
	Adjuvant	III	BEATRICE (TNBC)	CTx vs. CTx + Bevacizumab	Active, not recruiting
		III	ALTTO (HER2)	Lapatinib vs. HCN vs. Lapa/HCN	Active, not recruiting
		III	CREATE-X (JBCRG04)	Capecitabine vs. none post-NAC	Active, not recruiting
		III	D-CARE	Denosumab vs. placebo	Active, not recruiting
		III	APHINITY (HER2)	CTx+HCN/placebo vs. CTx/HCN/Pertuzumab	Active, not recruiting
		III	POTENT	HTx+S1 vs. HTx alone	Active, not recruiting
		III	KAITLIN (HER2)	Taxane/Trastuzumab/Pertuzumab vs. T-DM1/ Pertuzumab	Active, not recruiting
		III	OlympiA (BRCA+)	Olaparib vs. placebo	Active
			HOPE	Frozen Cap	Active
	Metastatic	III	JCOG1017	Surgery vs. no surgery for primary Stage IV BC	Active
		III	MARIANNE (HER2)	RO5304020+/- RO4368451 vs. HCN/PTX	Active, not recruiting
		III	NK105	NK105 vs. Paclitaxel	Active, not recruiting
		III	PALOMA-2 (HR+)	Letrozole +/- PD0332991	Active, not recruiting
		III	ELTOP (WJOG)	Lapa/Capecitabine vs. HCN/Capecitabine	Active, not recruiting
		III	OlympAD (BRCA+)	Olaparib vs. TPC	Active, not recruiting
		III	Monach2	Fulvestrant +/- Abemaciclib	Active, not recruiting
		III	Monach3	Letrozole +/- Abemaciclib	Active, not recruiting
		II	CAPTURE (HR+)	Paclitaxel/Bevacizumab vs. maintenance endocrine therapy	Active
		II	BEECH	AZD5363+PTX	Active, not recruiting
		II	TARGET (HR+)	Tamoxifen vs. high-dose Tamoxifen /CIP2D6	Active
		II	lapaHER (HER2)	Lapatinib/HCN	Active, not recruiting
		II	CBDCA/S1 (TNBC)	CBDCA/S1	Active
		II	KEYNOTE-086	MK3475	Active
		I/II	CAPIRI	Capecitabine/CPT-11	Active
		I/II	S1/docetaxel	S1/docetaxel	Terminated
		I/II	Lapa/eriburin (HER2)	Lapatinib/eriburin	Terminated
		I/II (*IIT)	EO (TNBC)	Eribulin/AZD2281	Active, not recruiting
		I/II	PD0332991	Letrozole +PD0332991	Active, not recruiting
		I (exp)	AZD5363 (AKT+ or PIK3CA+)	AZD5363	Active

Disease	Clinical setting	Phase	Protocol	Regimen	Status
Metastatic		I	RPN2siRNA	RPN2siRNA	Active
		I	KHK2375	KHK2375/Exemestane	Active
		PK/PD/ PGx	Eriburin PK	Eriburin	Active
		PK/ADCC	T-DM1 PK/ADCC	T-DM1	Active
		Cohort	Nursing intervention for oral chemotherapy	Oral chemotherapy	Active
Ovary	Adjuvant	III	AZD2281	Chemotherapy+/-Olaparib	Active, not recruiting
	Advanced	III	JCOG0602	Primary surgery vs. NAC	Active, not recruiting
		III	JGOG3017	TC vs. CDDP/CPT-11	Active, not recruiting
		III	GOG213	TC +/- bevacizumab	Active
		III	GOG218	TC +/- bevacizumab	Active, not recruiting
		III	AMG386	PTX+/-AMG386	Active, not recruiting
		III	GW786034	Pazopanib	Active, not recruiting
		II	MORAb-003	MORAb	Active
		II	GOG268	TC+Temsirolimus	Active, not recruiting
		II	ONO-4538	Nivolumab vs. GEM or Doxil	Active
Cervical cancer	Advanced	I	S1/CDDP	S1/CDDP chemoradiation	Active, not recruiting
		III	JCOG1311	ddTC vs TC	Active
Ovary/Endometrial/Cervical		II	Perifosine (PIK3CA+)	Perifosine	Active, not recruiting
Primary unknown cancer		II	CBDCA/S1	CBDCA/S1	Active
PNET/Ewing's sarcoma		II	CDDP/CPT-11 for refractory PNET	CDDP/CPT-11	Active
Solid tumor		I	AZD5363	AZD5363	Active, not recruiting
		I	PD0332991	PD0332991	Active, not recruiting
		I	Veriparib (BRCA+)	Veriparib	Active, not recruiting
		I	BAY1179470 (FGFR+)	BAY1179470	Active, not recruiting
		I	KEYNOTE-028	MK3475	Active, not recruiting
		I	GDC0032	GDC0032	Active, not recruiting
		I	Ds5573a (FIH)	Ds5573a	Active
		I	DS8201a (FIH)	DS8201a	Active
Soft tissue sarcoma		III	Olaratumab (PDGFRi)	Olaratumab + DXR	Active
		II	ET-743	ET-743	Active, not recruiting
		I	Olaratumab (PDGFRi)	Olaratumab + DXR, mono	Active, not recruiting
CIPN SNPs		TR	Paclitaxel induced peripheral neuropathy	Paclitaxel	Active, not recruiting
Molecular Imaging		TR	Cu^{64}-trastuzumab/PET	Nano-dose, radio-labeled trastuzumab as PET probe	Active
		TR	Cu^{64}- cetuximab/PET	Nano-dose, radio-labeled trastuzumab as PET probe	Active
		TR	MAS- imaging	MAS-imaging for solid tumor	Active
Liquid Biopsy		TR	CTC	CTC/breast, gynecologic (blood)	Active, not recruiting
		TR	ADCC	Quantitative ADCC (blood)	Active, not recruiting
		TR	miRNA in exosome	miRNA in exosome (blood)	Active
		TR	ctDNA	ctDNA (blood) Sequenom	Not yet recruiting
Genomic test		TR	TOP-GEAR (NGS) TOPICS-1	Genome screening for phase I	Active, not recruiting
(NGS, Sequencing at hot spots, Whole Exon Sequence)		TR	TOP-GEAR (NGS)	SCI lab	Active
		TR	HER-Antibody induced heart failure	HER-Antibody	Active
		TR	Sequencing	Methylation of promoter BRCA	Active, not recruiting
		TR	Sequencing	Methylation of promoter TERT	Active
		TR	Sequencing	AKT1P, PIK3CA	Active

*IIT; investigator-initiated clinical trial, TNBC; triple negative breast cancer, CTx; chemotherapy, HTx; hormonal therapy, HR; hormone receptor, dd; dose-dense, FIH; First in Human TR; NAC; neoadjuvant chemotherapy, translational, NGS; next generation sequence

List of papers published in 2015

Journal

1. Ono M, Tsuda H, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Kinoshita T, Fujiwara Y. Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers. Breast Cancer, 22:141-152, 2015

2. Yamamoto H, Ando M, Aogi K, Iwata H, Tamura K, Yonemori K, Shimizu C, Hara F, Takabatake D, Hattori M, Asakawa T, Fujiwara Y. Phase I and pharmacokinetic study of trastuzumab emtansine in Japanese patients with HER2-positive metastatic breast cancer. Jpn J Clin Oncol, 45:12-18, 2015

3. Mori M, Shimizu C, Ogawa A, Okusaka T, Yoshida S, Morita T. A National Survey to Systematically Identify Factors Associated With Oncologists' Attitudes Toward End-of-Life Discussions: What Determines Timing of End-of-Life Discussions? Oncologist, 20:1304-1311, 2015

4. Doi T, Tamura K, Tanabe Y, Yonemori K, Yoshino T, Fuse N, Kodaira M, Bando H, Noguchi K, Shimamoto T, Ohtsu A. Phase 1 pharmacokinetic study of the oral pan-AKT inhibitor MK-2206 in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:409-416, 2015

5. Davies BR, Guan N, Logie A, Crafter C, Hanson L, Jacobs V, James N, Dudley P, Jacques K, Ladd B, D'Cruz CM, Zinda M, Lindemann J, Kodaira M, Tamura K, Jenkins EL. Tumors with AKT1E17K Mutations Are Rational Targets for Single Agent or Combination Therapy with AKT Inhibitors. Mol Cancer Ther, 14:2441-2451, 2015

6. Hojo T, Masuda N, Mizutani T, Shibata T, Kinoshita T, Tamura K, Hara F, Fujisawa T, Inoue K, Saji S, Nakamura K, Fukuda H, Iwata H. Intensive vs. Standard Post-Operative Surveillance in High-Risk Breast Cancer Patients (INSPIRE): Japan Clinical Oncology Group Study JCOG1204. Jpn J Clin Oncol, 45:983-986, 2015

7. Yasui N, Yoshida A, Kawamoto H, Yonemori K, Hosono A, Kawai A. Clinicopathologic analysis of spindle cell/sclerosing rhabdomyosarcoma. Pediatr Blood Cancer, 62:1011-1016, 2015

8. Kondo S, Shiba S, Udagawa R, Ryushima Y, Yano M, Uehara T, Asanabe M, Tamura K, Hashimoto J. Assessment of adverse events via a telephone consultation service for cancer patients receiving ambulatory chemotherapy. BMC Res Notes, 8:315, 2015

9. Kurihara H, Hamada A, Yoshida M, Shimma S, Hashimoto J, Yonemori K, Tani H, Miyakita Y, Kanayama Y, Wada Y, Kodaira M, Yunokawa M, Yamamoto H, Shimizu C, Takahashi K, Watanabe Y, Fujiwara Y, Tamura K. ^{64}Cu-DOTA-trastuzumab PET imaging and HER2 specificity of brain metastases in HER2-positive breast cancer patients. EJNMMI Res, 5:8, 2015

10. Guo J, Yonemori K, Le Marchand L, Turesky RJ. Method to Biomonitor the Cooked Meat Carcinogen 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine in Dyed Hair by Ultra-Performance Liquid Chromatography-Orbitrap High Resolution Multistage Mass Spectrometry. Anal Chem, 87:5872-5877, 2015

11. Hara M, Nakashima T, Harashima H, Ryushima Y, Shimizu C, Kodaira M, Yunokawa M, Yamamoto H, Hashimoto J, Tanabe Y, Bun S, Makino Y, Iwase H, Fujiwara Y, Tamura K, Hayashi Y. Efficacy and safety of aprepitant and dexamethasone in the prevention of nausea and vomiting from neoadjuvant or adjuvant anthracyclines and cyclophosphamide combination therapy in patients with breast cancer. J Pharm Health Care Sci, 41:603-611, 2015

12. Blake EA, Kodama M, Yunokawa M, Ross MS, Ueda Y, Grubbs BH, Matsuo K. Feto-maternal outcomes of pregnancy complicated by epithelial ovarian cancer: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol, 186:97-105, 2015

13. Matsumoto K, Katsumata N, Shibata T, Satoh T, Saitou M, Yunokawa M, Takano T, Nakamura K, Kamura T, Konishi I. Phase II trial of oral etoposide plus intravenous irinotecan in patients with platinum-resistant and taxane-pretreated ovarian cancer (JCOG0503). Gynecol Oncol, 136:218-223, 2015

14. Yunokawa M, Tsuta K, Tanaka T, Nara E, Koizumi F, Ito J, Sekine S, Fujiwara Y, Tamura K. Back with a vengeance: microvascular tumor embolism. Am J Med, 128:834-836, 2015

15. Tominaga N, Kosaka N, Ono M, Katsuda T, Yoshioka Y, Tamura K, Lötvall J, Nakagama H, Ochiya T. Brain metastatic cancer cells release microRNA-181c-containing extracellular vesicles capable of destructing blood-brain barrier. Nat Commun, 6:6716, 2015

16. Takahashi RU, Miyazaki H, Takeshita F, Yamamoto Y, Minoura K, Ono M, Kodaira M, Tamura K, Mori M, Ochiya T. Loss of microRNA-27b contributes to breast cancer stem cell generation by activating ENPP1. Nat Commun, 6:7318, 2015

17. Ono M, Tsuda H, Kobayashi T, Takeshita F, Takahashi RU, Tamura K, Akashi-Tanaka S, Moriya T, Yamasaki T, Kinoshita T, Yamamoto J, Fujiwara Y, Ochiya T. The expression and clinical significance of ribophorin II (RPN2) in human breast cancer. Pathol Int, 65:301-308, 2015

18. Tamura K. Development of cell-cycle checkpoint therapy for solid tumors. Jpn J Clin Oncol, 45(12):1097-1102, 2015

19. Sasaki Y, Miwa K, Yamashita K, Sunakawa Y, Shimada K, Ishida H, Hasegawa K, Fujiwara K, Kodaira M, Fujiwara Y, Namiki M, Matsuda M, Takeuchi Y, Katsumata N. A phase I study of farletuzumab, a humanized anti-folate receptor α monoclonal antibody, in patients with solid tumors. Invest New Drugs, 33:332-340, 2015

20. Fujiwara Y, Yonemori K, Shibata T, Okita N, Ushirozawa N. Japanese universal health care faces a crisis in cancer treatment. Lancet Oncol, 16:251-252, 2015

21. Shimizu C, Kato T, Tamura N, Bando H, Asada Y, Mizota Y, Yamamoto S, Fujiwara Y. Perception and needs of reproductive specialists with regard to fertility preservation of young breast cancer patients. Int J Clin Oncol, 20:82-89, 2015

Department of Thoracic Surgery

Shun-ichi Watanabe, Hiroyuki Sakurai, Kazuo Nakagawa, Keisuke Asakura, Kyohei Masai, Shigeki Suzuki

Introduction

The Department of Thoracic Surgery deals with various kinds of neoplasms and allied diseases in the thorax, with the exception of the esophagus. These include both primary and metastatic lung tumors, mediastinal tumors, pleural tumors (mesotheliomas), and chest wall tumors. The surgical management of lung cancer patients has been the main clinical activity of the division, as well as the subject of most of its research activities. In addition to continuing to improve procedures, such as the combined resection of neighboring vital structures and minimally invasive techniques (video-assisted thoracic surgery, VATS), it has become increasingly important to define the role of surgery in multimodality treatment for patients with a poor prognosis.

Routine activities

The Department has four attending surgeons. Attending surgeons and residents perform all of the inpatient care, operations, examinations, and outpatient care. In 2015, we performed a total of 664 operations; for lung cancer in 492 patients, metastatic tumor in 82, mediastinal tumor in 24, and others in 66.

The treatment strategy for patients with lung cancer is based on tumor histology (non-small cell vs. small cell), extent of disease (clinical stage), and physical status of the patient. In lung cancer patients, surgical resection is usually indicated for clinical stages I, II, and some IIIA with non-small cell histology and clinical stages I with small cell histology. However, to improve the poor prognosis of patients with clinically and histologically proven mediastinal lymph node metastasis or with invasion to the neighboring vital structures, optimal treatment modalities are sought in a clinical trial setting. Recently, adjuvant chemotherapy is often given to the patient with advanced lung cancer even after complete pulmonary resection.

For metastatic lung tumors, resection has been attempted on the basis of Thomford's criteria: eligible patients are those who are at good risk, with no extrathoracic disease, with the primary site in control, and with completely resectable lung disease. Metastasis from colorectal carcinomas is the most common disease.

For mediastinal tumors, thymic epithelial tumors are most commonly encountered for resection. In the mediastinum, where a variety of tumor histologies can arise, the treatment must be carefully determined by the cytologic/histologic diagnosis before surgery. For this purpose, CT-guided needle biopsy is replacing the formerly common biopsy under X-ray fluoroscopy. For patients with thymoma, we have already adopted video-assisted resection (VATS) of the tumor. VATS resection of mediastinal tumor is indicated exclusively for small thymomas.

As for meetings, there are two division meetings. One is for the preoperative evaluation and postoperative inpatient review on Friday and the other is for the journal club on Tuesday. In addition, on Thursday the chest group has a plenary meeting to share basic information about the current issues for diagnosis and treatment of patients with lung malignancy.

Research activities

Lymph node dissection for lung cancer has been a major issue in lung cancer treatment, and has been extensively studied in our division. We continue to improve the surgical technique of dissection based on oncological and surgical considerations: a more effective and less invasive lymph node dissection called "selective mediastinal/hilar dissection" according to the location of the primary tumor by the lobe.

Minimally invasive surgery with the thoracoscope for thoracic malignancies is also an important challenge in our division. In particular, the indications and surgical techniques of video-assisted surgery for early lung cancer are of special interest because of the increased incidence of such minute tumors due to improvements in CT devices and CT screening.

Clinical trials

Due to the advent of new technologies in CT scanning, small-sized lung cancers are being found in a screening setting and also by chance. They are usually present as "ground-glass opacity (GGO)" on CT, and pathologically they are considered early adenocarcinoma. The surgical management of such GGO-type lung cancer remains undetermined in terms of the extent of pulmonary parenchymal resection and lymph node dissection. Some cases might be followed up with careful monitoring by CT, since indolent tumors are known to exist. We are seeking the appropriate way to manage these patients. A clinical trial to determine the appropriateness of limited resection for early adenocarcinoma had been planned in the Japan Clinical Oncology Group (JCOG) – Lung Cancer Study Group, and two clinical trials (a phase III trial, JCOG 0802; a phase II trial, JCOG 0804) have been conducted since the end of 2009. In addition, another phase II trial (JCOG1211), a confirmatory trial of segmentectomy for clinical T1N0 lung cancer dominant with GGO, was started in 2013. The accrual for JCOG 0804 trial has already closed. The accrual for JCOG0802 was closed in 2014. The accrual for JCOG 1211 was closed in November 2015.

As for postoperative adjuvant therapy, a phase III clinical trial to compare the effectiveness of UFT with that of TS-1 for stage IA of more than 2 cm and IB NSCLC planned in JCOG (JCOG 0707) has been conducted since 2008. This trial completed the full accrual of 960 patients in 2013. A phase III clinical trial (JCOG 1205) to compare Irinotecan/Cisplatin with Etoposide/Cisplatin for adjuvant chemotherapy of resected pulmonary high-grade neuroendocrine carcinoma was started in 2013.

Table 1. Number of patients in 2015

Primary lung cancer	492
Metastatic lung tumor	82
Mediastinal tumor	24
Pleural disease	11
Chest wall tumor	8
Benign lung nodule	28
Others	19
Total	664

Table 2. Type of procedure in 2015

Lung resection	587
Lobectomy	347
Pneumonectomy	11
Segmentectomy	101
Wedge resection	128
Tracheal resection	0
Surgery for mediastinal tumors	23
Surgery for pleural tumors	16
Surgery for chest wall tumors	8
Others	30
Total	664

Table 3. Survival rates for primary lung cancer patients after surgery

Pathological stage (TNM-7)	No. of pts	5-yr survival (%)
IA	1,902	94.2
IB	556	83.5
IIA	320	71.7
IIB	208	64.4
IIIA	453	48.3
IIIB	82	34.9
IV	30	26.8

Operation period: 2003.1-2011.12 Total 3,551

List of papers published in 2015

Journal

1. Suzuki K, Watanabe S, Mizusawa J, Moriya Y, Yoshino I, Tsuboi M, Mizutani T, Nakamura K, Tada H, Asamura H, Japan Lung Cancer Surgical Study Group (JCOG LCSSG). Predictors of non-neoplastic lesions in lung tumours showing ground-glass opacity on thin-section computed tomography based on a multi-institutional prospective study†. Interact Cardiovasc Thorac Surg, 21:218-223, 2015

2. Sakurai H. Reply. Ann Thorac Surg, 100:2413, 2015

3. Yoshida A, Kamata T, Iwasa T, Watanabe S, Tsuta K. Myocardial Sleeve Tissues in Surgical Lung Specimens. Am J Surg Pathol, 39:1427-1432, 2015

4. Sato T, Soejima K, Arai E, Hamamoto J, Yasuda H, Arai D, Ishioka K, Ohgino K, Naoki K, Kohno T, Tsuta K, Watanabe S, Kanai Y, Betsuyaku T. Prognostic implication of PTPRH hypomethylation in non-small cell lung cancer. Oncol Rep, 34:1137-1145, 2015

5. Katsuya Y, Yoshida A, Watanabe S, Tsuta K. Tumour-to-tumour metastasis from papillary thyroid carcinoma with BRAF mutation to lung adenocarcinoma with EGFR mutation: the utility of mutation-specific antibodies. Histopathology, 67:262-266, 2015

6. Kamata T, Yoshida A, Kosuge T, Watanabe S, Asamura H, Tsuta K. Ciliated muconodular papillary tumors of the lung: a clinicopathologic analysis of 10 cases. Am J Surg Pathol, 39:753-760, 2015

7. Sakurai H, Nakagawa K, Watanabe S, Asamura H. Clinicopathologic features of resected subcentimeter lung cancer. Ann Thorac Surg, 99:1731-1738, 2015

8. Katsuya Y, Fujita Y, Horinouchi H, Ohe Y, Watanabe S, Tsuta K. Immunohistochemical status of PD-L1 in thymoma and thymic carcinoma. Lung Cancer, 88:154-159, 2015

9. Hishida T, Tsuboi M, Shukuya T, Takamochi K, Sakurai H, Yoh K, Ohashi Y, Kunitoh H. Multicenter observational cohort study of post-operative treatment for completely resected non-small-cell lung cancer of pathological stage I (T1 >2 cm and T2 in TNM classification version 6). Jpn J Clin Oncol, 45:499-501, 2015

10. Kitazono S, Fujiwara Y, Tsuta K, Utsumi H, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Sasada S, Watanabe S, Asamura H, Tamura T, Ohe Y. Reliability of Small Biopsy Samples Compared With Resected Specimens for the Determination of Programmed Death-Ligand 1 Expression in Non--Small-Cell Lung Cancer. Clin Lung Cancer, 16:385-390, 2015

11. Kakinuma R, Moriyama N, Muramatsu Y, Gomi S, Suzuki M, Nagasawa H, Kusumoto M, Aso T, Muramatsu Y, Tsuchida T, Tsuta K, Maeshima AM, Tochigi N, Watanabe S, Sugihara N, Tsukagoshi S, Saito Y, Kazama M, Ashizawa K, Awai K, Honda O, Ishikawa H, Koizumi N, Komoto D, Moriya H, Oda S, Oshiro Y, Yanagawa M, Tomiyama N, Asamura H. Ultra-high-resolution computed tomography of the lung: image quality of a prototype scanner. PLoS One, 10:e0137165, 2015

12. Kakinuma R, Moriyama N, Muramatsu Y, Gomi S, Suzuki M, Nagasawa H, Kusumoto M, Aso T, Muramatsu Y, Tsuchida T, Tsuta K, Maeshima AM, Tochigi N, Watanabe SI, Sugihara N, Tsukagoshi S, Saito Y, Kazama M, Ashizawa K, Awai K, Honda O, Ishikawa H, Koizumi N, Komoto D, Moriya H, Oda S, Oshiro Y, Yanagawa M, Tomiyama N, Asamura H. Correction: Ultra-high-resolution computed tomography of the lung: image quality of a prototype scanner. PLoS One, 10:e0145357, 2015

13. Saito M, Shimada Y, Shiraishi K, Sakamoto H, Tsuta K, Totsuka H, Chiku S, Ichikawa H, Kato M, Watanabe S, Yoshida T, Yokota J, Kohno T. Development of lung adenocarcinomas with exclusive dependence on oncogene fusions. Cancer Res, 75:2264-2271, 2015

14. Ito J, Yoshida A, Maeshima AM, Nakagawa K, Watanabe S, Kobayashi Y, Fukuhara S, Tsuta K. Concurrent thymoma, thymic carcinoma, and T lymphoblastic leukemia/lymphoma in an anterior mediastinal mass. Pathol Res Pract, 211:693-696, 2015

Department of Thoracic Oncology

Yuichiro Ohe, Noboru Yamamoto, Hiroshi Nokihara, Yutaka Fujiwara, Hidehito Horinouchi, Shintaro Kanda, Yasushi Goto, Tetsuhiko Asao, Shinsuke Kitahara, Kouta Itahashi

Introduction

Lung cancer is the leading cause of cancer death in Japan and worldwide. The incidence of lung cancer in Japan is still increasing, especially in elderly people. The Department of Thoracic Oncology provides care for patients with primary lung cancer, mediastinal tumors, and pleural tumors. The goals of the department are to provide the highest quality treatment and establish new effective treatments against lung cancer and other thoracic malignancies through innovative clinical and translational research. To provide assistance to our patients through multidisciplinary care, the staff members of the department work closely with thoracic surgeons, radiation oncologists, pharmacists, clinical research coordinators, and psychiatrists who have expertise in these areas. The department includes seven staff physicians. Moreover, residents and trainees from other institutions have joined the Thoracic Oncology Program.

Routine activities

The staff physicians attend outpatient services for thoracic diseases, and the department has approximately 60 beds in the hospital. Inpatient care is carried out by five teams. Each team consists of one staff physician and one or two residents and/or trainee doctors. Protocol and case conferences are scheduled every Monday morning and afternoon, respectively. The journal club is scheduled on Thursday mornings.

A total of 413 new patients were admitted in 2015, and the backgrounds and initial treatments of these patients are shown in tables 1 and 2. The initial treatments were chemotherapy in 230, adjuvant chemotherapy after surgery in 44, chemoradiotherapy in 62, curative radiotherapy in 5, and supportive care including palliative radiotherapy in 49. Survival of lung cancer patients treated in 2006-2010 in our department is shown in Table 3.

Research activities

Research activities of the department can be classified into four categories: (1) multi-institutional phase III studies to establish new standard treatments against lung cancer; (2) phase I and phase II studies to evaluate new anticancer drugs, (3) pharmacokinetic and pharmacodynamic (PK/PD) studies to investigate interpatient variability, optimal administration schedules and drug-drug interactions; and (4) translational research using clinical samples from bench to bed-side or from bed-side to bench for the development of innovative treatment strategies.

Clinical trials

The department is currently conducting and participating in multi-institutional phase III studies to establish new standard treatments against lung cancer such as the Japan Clinical Oncology Group (JCOG) trials and global trials conducted by pharmaceutical companies. Three JCOG phase III studies, JCOG1201 for elderly ED-SCLC, JCOG1206 for high-grade neuroendocrine carcinoma and JCOG1210/WJOG7813L for elderly non-squamous NSCLC are ongoing. In addition to these studies, JCOG1404 (AGAIN), a phase III study for EGFR mutation positive NSCLC, was started in December. The department is also participating in a nationwide screening project of lung cancer with rare driver mutation (LC-SCRUM) and phase II studies targeting rare driver mutation. The department carried out many clinical trials using 3rd generation EGFR-TKIs, anti-PD-1Ab, and anti-PD-L1Ab.

Education

In 2015, three chief residents, 16 residents and two research residents joined the department. A monthly research conference is held to discuss clinical and translational research conducted by young doctors.

Future prospects

The recent progression of lung cancer treatment is very rapid. Driver gene alteration targeted therapy such as EGFR-TKIs and ALK inhibitors are already established as a standard treatment for lung cancer patients with EGFR mutation and ALK fusion gene. Other rare driver gene alterations such as ROS1 fusion, RET fusion, and "BRAF mutation can be good targets for treatment of lung cancer." Immunotherapy using anti-PD-1Ab has been established as a standard 2nd or 3rd line treatment for NSCLC. Anti-PD-L1Ab will also be established as a standard treatment of lung cancer in the near future. These immunotherapies could provide a durable response for some lung cancer patients. Establishment of good biomarkers to identify the patients who respond to the immunotherapy is very important.

Table 1. Number of new inpatients in 2015

Thoracic malignancies total	413
NSCLC	350
Adenocarcinoma	261
Squamous cell carcinoma	54
Others	35
SCLC	49
Mesothelioma	7
Thymic cancer	5
Thymoma	2

Table 2. Initial treatments for new inpatients with lung cancer in 2015

Chemotherapy	230
Chemoradiotherapy	62
Adjuvant chemotherapy after surgery	44
Chemoradiotherapy followed by surgery	8
Curative radiotherapy	5
Supportive care including palliative radiotherapy	49

Table 3. Survival of lung cancer patients treated in 2006-2010

Disease	Stage	Treatment	N	Survival rate (%)				
				1y	2y	3y	4y	5y
NSCLC	IIIB, IV, recurrence	chemotherapy	601	64	39	22	13	8
NSCLC	IIIA,IIIB	chemoradiotherapy	187	84	61	44	34	30
SCLC	ED	chemotherapy	133	58	23	5	5	5
SCLC	LD	chemoradiotherapy	60	87	65	38	32	28

List of papers published in 2015

Journal

1. Tsukada H, Yokoyama A, Goto K, Shinkai T, Harada M, Ando M, Shibata T, Ohe Y, Tamura T, Saijo N, Lung Cancer Study Group of the Japan Clinical Oncology Group (JCOG). Randomized controlled trial comparing docetaxel-cisplatin combination with weekly docetaxel alone in elderly patients with advanced non-small-cell lung cancer: Japan Clinical Oncology Group (JCOG) 0207†. Jpn J Clin Oncol, 45:88-95, 2015

2. Yoshida T, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Ohe Y, Goto K. RECIST progression patterns during EGFR tyrosine kinase inhibitor treatment of advanced non-small cell lung cancer patients harboring an EGFR mutation. Lung Cancer, 90:477-483, 2015

3. Nakata A, Yoshida R, Yamaguchi R, Yamauchi M, Tamada Y, Fujita A, Shimamura T, Imoto S, Higuchi T, Nomura M, Kimura T, Nokihara H, Higashiyama M, Kondoh K, Nishihara H, Tojo A, Yano S, Miyano S, Gotoh N. Elevated β-catenin pathway as a novel target for patients with resistance to EGF receptor targeting drugs. Sci Rep, 5:13076, 2015

4. Jänne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, Ahn MJ, Kim SW, Su WC, Horn L, Haggstrom D, Felip E, Kim JH, Frewer P, Cantarini M, Brown KH, Dickinson PA, Ghiorghiu S, Ranson M. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med, 372:1689-1699, 2015

5. Sekiguchi M, Sekine S, Sakamoto T, Otake Y, Nakajima T, Matsuda T, Taniguchi H, Kushima R, Ohe Y, Saito Y. Excellent prognosis following endoscopic resection of patients with rectal neuroendocrine tumors despite the frequent presence of lymphovascular invasion. J Gastroenterol, 50:1184-1189, 2015

6. Yoshida T, Ishii G, Goto K, Neri S, Hashimoto H, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Iida S, Niimi A, Nagai K, Ohe Y, Ochiai A. Podoplanin-positive cancer-associated fibroblasts in the tumor microenvironment induce primary resistance to EGFR-TKIs in lung adenocarcinoma with EGFR mutation. Clin Cancer Res, 21:642-651, 2015

7. Yagishita S, Horinouchi H, Katsui Taniyama T, Nakamichi S, Kitazono S, Mizugaki H, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. Int J Radiat Oncol Biol Phys, 91:140-148, 2015

8. Sugiyama E, Umemura S, Nomura S, Kirita K, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Ohe Y, Goto K. Impact of single nucleotide polymorphisms on severe hepatotoxicity induced by EGFR tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring EGFR mutations. Lung Cancer, 90:307-313, 2015

9. Udagawa H, Ishii G, Morise M, Umemura S, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A, Ohe Y. Comparison of the expression levels of molecular markers among the peripheral area and central area of primary tumor and metastatic lymph node tumor in patients with squamous cell carcinoma of the lung. J Cancer Res Clin Oncol, 141:1417-1425, 2015

10. Matsumura Y, Umemura S, Ishii G, Tsuta K, Matsumoto S, Aokage K, Hishida T, Yoshida J, Ohe Y, Suzuki H, Ochiai A, Goto K, Nagai K, Tsuchihara K. Expression profiling of receptor tyrosine kinases in high-grade neuroendocrine carcinoma of the lung: a comparative analysis with adenocarcinoma and squamous cell carcinoma. J Cancer Res Clin Oncol, 141:2159-2170, 2015

11. Morise M, Hishida T, Takahashi A, Yoshida J, Ohe Y, Nagai K, Ishii G. Clinicopathological significance of cancer stem-like cell markers in high-grade neuroendocrine carcinoma of the lung. J Cancer Res Clin Oncol, 141:2121-2130, 2015

12. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Fujiwara Y, Tamura Y, Wakui H, Honda K, Mizugaki H, Kitazono S, Tanabe Y, Asahina H, Yamazaki N, Suzuki S, Matsuoka M, Ogita Y, Tamura T. Phase I and pharmacokinetics/pharmacodynamics study of the MEK inhibitor RO4987655 in Japanese patients with advanced solid tumors. Invest New Drugs, 33:641-651, 2015

13. Asao T, Nokihara H, Yoh K, Niho S, Goto K, Ohmatsu H, Kubota K, Yamamoto N, Sekine I, Kunitoh H, Fujiwara Y, Ohe Y. Phase II study of amrubicin at a dose of 45 mg/m2 in patients with previously treated small-cell lung cancer. Jpn J Clin Oncol, 45:941-946, 2015

14. Fujiwara Y, Kobayashi S, Nagano H, Kanai M, Hatano E, Toyoda M, Ajiki T, Takashima Y, Yoshimura K, Hamada A, Minami H, Ioka T. Pharmacokinetic Study of Adjuvant Gemcitabine Therapy for Biliary Tract Cancer following Major Hepatectomy (KHBO1101). PLoS One, 10:e0143072, 2015

15. Fujiwara Y, Nokihara H, Yamada Y, Yamamoto N, Sunami K, Utsumi H, Asou H, TakahashI O, Ogasawara K, Gueorguieva I, Tamura T. Phase 1 study of galunisertib, a TGF-beta receptor I kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1143-1152, 2015

16. Horinouchi H, Yamamoto N, Fujiwara Y, Sekine I, Nokihara H, Kubota K, Kanda S, Yagishita S, Wakui H, Kitazono S, Mizugaki H, Tokudome T, Tamura T. Phase I study of ipilimumab in phased combination with paclitaxel and carboplatin in Japanese patients with non-small-cell lung cancer. Invest New Drugs, 33:881-889, 2015

17. Kanai M, Hatano E, Kobayashi S, Fujiwara Y, Marubashi S, Miyamoto A, Shiomi H, Kubo S, Ikuta S, Yanagimoto H, Terajima H, Ikoma H, Sakai D, Kodama Y, Seo S, Morita S, Ajiki T, Nagano H, Ioka T. A multi-institution phase II study of gemcitabine/cisplatin/S-1 (GCS) combination chemotherapy for patients with advanced biliary tract cancer (KHBO 1002). Cancer Chemother Pharmacol, 75:293-300, 2015

18. Kanda S, Horinouchi H, Fujiwara Y, Nokihara H, Yamamoto N, Sekine I, Kunitoh H, Kubota K, Tamura T, Ohe Y. Cytotoxic chemotherapy may overcome the development of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) therapy. Lung Cancer, 89:287-293, 2015

19. Katsuya Y, Fujiwara Y, Sunami K, Utsumi H, Goto Y, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Takashima Y, Osawa S, Ohe Y, Tamura T, Hamada A. Comparison of the pharmacokinetics of erlotinib administered in complete fasting and 2 h after a meal in patients with lung cancer. Cancer Chemother Pharmacol, 76:125-132, 2015

20. Kitazono S, Fujiwara Y, Nakamichi S, Mizugaki H, Nokihara H, Yamamoto N, Yamada Y, Inukai E, Nakamura O, Tamura T. A phase I study of resminostat in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 75:1155-1161, 2015

21. Kitazono S, Fujiwara Y, Tsuta K, Utsumi H, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Sasada S, Watanabe S, Asamura H, Tamura T, Ohe Y. Reliability of Small Biopsy Samples Compared With Resected Specimens for the Determination of Programmed Death-Ligand 1 Expression in Non--Small-Cell Lung Cancer. Clin Lung Cancer, 16:385-390, 2015

22. Mizugaki H, Yamamoto N, Fujiwara Y, Nokihara H, Yamada Y, Tamura T. Current Status of Single-Agent Phase I Trials in Japan: Toward Globalization. J Clin Oncol, 33:2051-2061, 2015

23. Mizugaki H, Yamamoto N, Nokihara H, Fujiwara Y, Horinouchi H, Kanda S, Kitazono S, Yagishita S, Xiong H, Qian J, Hashiba H, Shepherd SP, Giranda V, Tamura T. A phase 1 study evaluating the pharmacokinetics and preliminary efficacy of veliparib (ABT-888) in combination with carboplatin/paclitaxel in Japanese subjects with non-small cell lung cancer (NSCLC). Cancer Chemother Pharmacol, 76:1063-1072, 2015

24. Motonaga M, Yamamoto N, Makino Y, Ando-Makihara R, Ohe Y, Takano M, Hayashi Y. Phase I dose-finding and pharmacokinetic study of docetaxel and gefitinib in patients with advanced or metastatic non-small-cell lung cancer: evaluation of drug-drug interaction. Cancer Chemother Pharmacol, 76:713-721, 2015

25. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Honda K, Tamura Y, Wakui H, Sasaki T, Yusa W, Fujino K, Tamura T. A phase 1 study of lenvatinib, multiple receptor tyrosine kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1153-1161, 2015

26. Nishio M, Horiike A, Murakami H, Yamamoto N, Kaneda H, Nakagawa K, Horinouchi H, Nagashima M, Sekiguchi M, Tamura T. Phase I study of the HER3-targeted antibody patritumab (U3-1287) combined with erlotinib in Japanese patients with non-small cell lung cancer. Lung Cancer, 88:275-281, 2015

27. Nishio M, Horiike A, Nokihara H, Horinouchi H, Nakamichi S, Wakui H, Ohyanagi F, Kudo K, Yanagitani N, Takahashi S, Kuboki Y, Yamamoto N, Yamada Y, Abe M, Tahata T, Tamura T. Phase I study of the anti-MET antibody onartuzumab in patients with solid tumors and MET-positive lung cancer. Invest New Drugs, 33:632-640, 2015

28. Abe T, Takeda K, Ohe Y, Kudoh S, Ichinose Y, Okamoto H, Yamamoto N, Yoshioka H, Minato K, Sawa T, Iwamoto Y, Saka H, Mizusawa J, Shibata T, Nakamura S, Ando M, Yokoyama A, Nakagawa K, Saijo N, Tamura T. Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Intergroup Trial JCOG0803/WJOG4307L. J Clin Oncol, 33:575-581, 2015

29. Eba J, Shimokawa T, Nakamura K, Shibata T, Misumi Y, Okamoto H, Yamamoto N, Ohe Y, Lung Cancer Study Group of the Japan Clinical Oncology Group. A Phase II/III study comparing carboplatin and irinotecan with carboplatin and etoposide for the treatment of elderly patients with extensive-disease small-cell lung cancer (JCOG1201). Jpn J Clin Oncol, 45:115-118, 2015

30. Tamura Y, Fujiwara Y, Yamamoto N, Nokihara H, Horinouchi H, Kanda S, Goto Y, Kubo E, Kitahara S, Tsuruoka K, Tsuta K, Ohe Y. Retrospective analysis of the efficacy of chemotherapy and molecular targeted therapy for advanced pulmonary pleomorphic carcinoma. BMC Res Notes, 8:800, 2015

31. Yagishita S, Horinouchi H, Sunami KS, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T, Ohe Y. Impact of KRAS mutation on response and outcome of patients with stage III non-squamous non-small cell lung cancer. Cancer Sci, 106:1402-1407, 2015

32. Fujita Y, Yagishita S, Hagiwara K, Yoshioka Y, Kosaka N, Takeshita F, Fujiwara T, Tsuta K, Nokihara H, Tamura T, Asamura H, Kawaishi M, Kuwano K, Ochiya T. The clinical relevance of the miR-197/CKS1B/STAT3-mediated PD-L1 network in chemoresistant non-small-cell lung cancer. Mol Ther, 23:717-727, 2015

33. Takahashi A, Ishii G, Neri S, Yoshida T, Hashimoto H, Suzuki S, Umemura S, Matsumoto S, Yoh K, Niho S, Goto K, Ohmatsu H, Nagai K, Gemma A, Ohe Y, Ochiai A. Podoplanin-expressing cancer-associated fibroblasts inhibit small cell lung cancer growth. Oncotarget, 6:9531-9541, 2015

Department of Esophageal Surgery

Yuji Tachimori, Hiroyasu Igaki, Kazuo Koyanagi, Jun Iwabu

Introduction

More than 300 new patients with esophageal tumors are admitted to the National Cancer Center Hospital (NCCH) every year. The multidisciplinary treatment plans are determined by the stage of the tumor in close cooperation with other teams. The Department of Esophageal Surgery cooperates in particular with the Department of Gastrointestinal Medical Oncology and the Department of Radiation Oncology for preoperative chemotherapy and chemoradiotherapy and salvage surgery after definitive chemoradiotherapy, and the Department of Endoscopy for diagnosis and endoscopic resection. We also maintain close cooperation with the Department of Head and Neck Surgery for cervical esophageal carcinomas and with the Department of Gastric Surgery for adenocarcinomas in the esophagogastric junction. Patients who required a laryngectomy for resection of cervical esophageal cancer were operated on in the Department of Head and Neck Surgery. Most patients with Siewert Type III adenocarcinoma were operated on in the Department of Gastric Surgery. In our Department, squamous cell carcinomas still constitute the largest proportion of esophageal tumors, and 11 patients with adenocarcinomas of the esophagogastric junction underwent an esophagectomy in 2015.

Routine activities

The Department of Esophageal Surgery consists of three staff surgeons, one chief resident and 1-2 rotating senior residents. A multidisciplinary conference (Esophageal Tumor Board) is held weekly in which surgeons, medical oncologists, radiation oncologists, endoscopists, radiologists, and pathologists who are involved in the treatment of esophageal diseases meet and discuss the diagnosis, staging, and treatment plans for patients with esophageal tumors. Every week, 2-3 patients with esophageal cancer undergo surgery. One hundred and four patients underwent esophagectomy including four patients with cervical esophageal cancer, three with carcinosarcoma, six with malignant melanoma, three with neuroendocrine tumors, and one with large Schwannoma. Two patients with gastric cancer after esophagectomy underwent gastric conduit resection and reconstruction. Preoperative chemotherapy was recommended for 56 patients and preoperative chemoradiotherapy was recommended for 4 patients with resectable Stage II-IV esophageal squamous cell cancer. A three-field dissection, including the whole upper mediastinum and supraclavicular area in addition to the lower mediastinum and abdomen, was performed on 72 patients as our standard procedure. Video-assisted thoracic surgery was introduced for esophagectomy as minimally invasive surgery in 44 patients. Two hospital deaths occurred due to postoperative complications including postoperative pneumonia and cardiac attack after esophagectomy.

In a paradigm shift toward organ-sparing therapy, the number of patients who receive definitive chemoradiotherapy as their primary treatment for resectable tumors is increasing. A persistent or recurrent loco-regional disease is not infrequent after definitive chemoradiotherapy. Nineteen patients underwent salvage esophagectomy after the failure of definitive chemoradiotherapy in 2015. A three-field dissection is avoided for salvage esophagectomy.

Research activities

Several translational studies are being carried out in cooperation with the National Cancer Center Research Institute. A study of DNA methylation in biopsied specimens is also ongoing to estimate the efficacy of preoperative chemotherapy in patients

with advanced esophageal cancer.

Clinical trials

A multi-institutional randomized controlled trial comparing standard preoperative chemotherapy (5FU and cisplatin), an intensive one (5FU and cisplatin plus docetaxel), and preoperative chemoradiotherapy (5FU and cisplatin plus 41.4 Gy irradiation) for Stage II-III esophageal cancer (JCOG1109) is ongoing. A new multi-institutional randomized controlled trial comparing minimally invasive esophagectomy versus open thoracic esophagectomy (JCOG1409) started registration in 2015. A Phase II trial for definitive chemoradiotherapy with or without salvage esophagectomy (JCOG0909) has finished registration. A new Phase II trial for a tri-modality strategy with docetaxel plus 5FU and cisplatin (DCF) induction chemotherapy for locally advanced unresectable esophageal cancer followed by conversion surgery for responders and chemoradiotherapy for non-responders (COSMOS) launched in 2013 and has finished registration.

Education

We accepted many surgeons from foreign countries, especially from Asia. A dramatic increase in the incidence of adenocarcinoma has been seen in Western patients. However, in Asian patients, including Japanese patients, squamous cell carcinoma remains the predominant type of esophageal cancer. Japanese strategies and surgical techniques for esophageal squamous cell carcinoma are instructive for Asian surgeons.

Table 1. Number of patients

Thoracic esophageal squamous cell carcinoma	78
Cervical esophageal squamous cell carcinoma	4
Adenocarcinoma of esophagogastric junction	11
Carcinosarcoma	3
Malignant melanoma	6
Neuroendocrine tumor	3
Large Schwannoma	1
Gastric cancer of gastric conduit after esophagectomy	2

Table 2. Type of surgical procedure

Open thoracic esophagectomy	53
Video-assisted esophagectomy	44
Transhiatal esophagectomy	1
Transhiatal esophagectomy with pharyngo-laryngectomy	3
Lower esophagectomy for esophagogastric junction cancer	5
Gastrectomy for gastric conduit cancer after esophagectomy	2
Esophageal bypass	1
Salvage lymph node dissection	7
Exploratory thoracotomy	2

List of papers published in 2015

Journal

1. Takahashi T, Yamahsita S, Matsuda Y, Kishino T, Nakajima T, Kushima R, Kato K, Igaki H, Tachimori Y, Osugi H, Nagino M, Ushijima T. *ZNF*695 methylation predicts a response of esophageal squamous cell carcinoma to definitive chemoradiotherapy. J Cancer Res Clin Oncol, 141:453-463, 2015

2. Koyanagi K, Igaki H, Iwabu J, Ochiai H, Tachimori Y. Recurrent Laryngeal Nerve Paralysis after Esophagectomy: Respiratory Complications and Role of Nerve Reconstruction. Tohoku J Exp Med, 237:1-8, 2015

3. Tachimori Y, Ozawa S, Numasaki H, Fujishiro M, Matsubara H, Oyama T, Shinoda M, Toh Y, Udagawa H, Uno T, The Registration Committee for Esophageal Cancer of the Japan Esophageal Society. Comprehensive registry of esophageal cancer in Japan, 2007. Esophagus , 12:101-129 , 2015

4. Tachimori Y, Ozawa S, Numasaki H, Fujishiro M, Matsubara H, Oyama T, Shinoda M, Toh Y, Udagawa H, Uno T, The Registration Committee for Esophageal Cancer of the Japan Esophageal Society. Comprehensive registry of esophageal cancer in Japan, 2008. Esophagus, 12:130-157, 2015

5. Tachimori Y, Ozawa S, Numasaki H, Matsubara H, Shinoda M, Toh Y, Udagawa H, Fujishiro M, Oyama T, Uno T, The Registration Committee for Esophageal Cancer of the Japan Esophageal Society. Efficacy of lymph node dissection for each station based on esophageal tumor location. Esophagus, 1-8, 2015

6. Nozaki I, Kato K, Igaki H, Ito Y, Daiko H, Yano M, Udagawa H, Mizusawa J, Katayama H, Nakamura K, Kitagawa Y. Evaluation of safety profile of thoracoscopic esophagectomy for T1bN0M0 cancer using data from JCOG0502: a prospective multicenter study. Surg Endosc, 29:3519-3526, 2015

7. Yokota T, Ando N, Igaki H, Shinoda M, Kato K, Mizusawa J, Katayama H, Nakamura K, Fukuda H, Kitagawa Y. Prognostic Factors in Patients Receiving Neoadjuvant 5-Fluorouracil plus Cisplatin for Advanced Esophageal Cancer (JCOG9907). Oncology, 89:143-151, 2015

8. Kataoka K, Nakamura K, Mizusawa J, Fukuda H, Igaki H, Ozawa S, Hayashi K, Kato K, Kitagawa Y, Ando N. Variations in survival and perioperative complications between hospitals based on data from two phase III clinical trials for oesophageal cancer. Br J Surg, 102:1088-1096, 2015

Department of Gastric Surgery

Hitoshi Katai, Takeo Fukagawa, Shinji Morita, Hisataka Fujiwara, Takeyuki Wada, Hiroshi Moro

Introduction

This department treats not only gastric adenocarcinoma but also sarcomas of gastric origin, such as malignant lymphomas or gastrointestinal stromal tumors (GISTs). Principally, we treat tumors of the esophagogastric junction.

Routine activities

The Department includes five staff surgeons, one chief resident and three or four rotating residents at any given time. Nine to eleven patients are operated upon every week. The Department shares a ward with the Departments of Hepatobiliary and Pancreatic Surgery and Oncology. Patients with stage I disease are followed-up without adjuvant chemotherapy. Adjuvant S-1 chemotherapy is used for patients with stage II and III disease. Adjuvant XELOX chemotherapy is applied for stage IIIC disease. Neoadjuvant chemotherapy is frequently used for patients with locally advanced tumors.

Patients with a superficial well-differentiated adenocarcinoma lesion are treated with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). Some undergo subsequent surgery based on the histological findings of the resected specimen. Every Tuesday from 6:15 to 7:00 P.M., a clinical conference is held for surgeons, a medical oncologist and endoscopists. All patients with gastric malignancies in the ward or on the waiting list for admission are briefly reviewed and those whose treatment is controversial are discussed in detail. Every Friday between 7:15 and 8:30 A.M., another clinical conference is held, in which endoscopists, radiologists, and pathologists present all candidates for surgical and endoscopic treatment for the following week, and the treatment strategy for each case is discussed in detail. These conferences are held in English whenever a foreign guest doctor is present.

We consider the education of foreign surgeons to be an important function. In 2015, more than 20 surgeons from various countries visited this division for 1 week to 6 months to learn about the management of gastric cancer patients, especially surgical techniques for lymph node dissection and postoperative care. All staff surgeons have sufficient experience in teaching in English.

Research activities

Several translational studies are being carried out in cooperation with the National Cancer Center Research Institute. Genomic scanning in gastric cancer is being carried out. DNA methylation as a gastric cancer metastasis risk factor has been investigated. A mini-chip assay of peritoneal washings for prediction of gastric cancer recurrence is being developed. Research on the detection of small amounts of cancer cells in peripheral blood and bone marrow of gastric cancer patients is being carried out.

Clinical trials

Our Department has been playing a central role in conducting multi-institutional clinical trials. H. Katai is a representative of the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG). Patients with gastric cancer are, when eligible, invited to participate in one of the ongoing clinical trials mentioned below. The JCOG 0501 phase III trial to evaluate the effect of neo-adjuvant (S-1 and CDDP) and adjuvant chemotherapy (S-1) for large type III and type IV tumors has been completed for accrual. JCOG 1001, which is designed to evaluate the significance of bursectomy for advanced cancer, has been completed for accrual. This trial includes the evaluation of long-term survival, postoperative morbidity, and mortality. The JCOG 0912 phase III

trial to prove the non-inferiority of laparoscopic gastrectomy over its open counterpart for patients with clinical stage IA and IB gastric cancer has also been completed for accrual. The JCOG 1104 phase III trial to evaluate the optimal period of adjuvant S-1 chemotherapy for pathological stage II gastric cancer patients who underwent D2 gastrectomy is ongoing. The JCOG1301C, a randomized phase II study of systemic chemotherapy with and without trastuzumab followed by surgery in HER2 positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis, just started. JCOG1302-A is a study to evaluate the accuracy of pre-operative staging for advanced tumors and has been completed for accrual and the results were reported. A phase II study to check the feasibility of Oxaliplatin, and S-1 neoadjuvant chemotherapy for stage III disease was carried out and the results were reported. We started a new phase II trial to prove the feasibility of laparoscopic total and proximal gastrectomy for stage IA and IB gastric cancer (JCOG 1401).

Education

Education of surgical operations has been introduced for chief and rotating residents throughout the perioperative management of more than 500 gastric cancer patients.

Future prospects

D2 gastrectomy is considered the standard surgical treatment for advanced gastric cancer but multi-modality treatments combined with surgery will further improve survival rates. There are several surgical options for early gastric cancer depending on the risk of nodal metastasis. The efficacy of laparoscopic surgery for early gastric cancer is being assessed. Moreover, robotic surgery is introduced as advanced medical care services and the safety and effectiveness has currently been evaluated. These procedures will require good quality control achieved through supervision and training by experienced surgeons in high volume centers.

Table 1. Number of Patients

Adenocarcinoma	447
GIST	18
Others	39
Total	504

Table 2. Operative morbidity and mortality after gastrectomy

	Number of patients	%
Major complications (Clavien-Dindo Grade 3-4)	43	11.9
Minor complications	76	21.1
Postoperative hospital deaths	1	0.3
Total number of gastrectomy	360	

Gastrectomy includes total, proximal, distal, and pylorus-preserving gastrectomy. Major complications include pancreatic fistulae, leakage, and intra-abdominal abscesses. Minor complications include wound infection, urinary tract infection, and line infection, etc.

Table 3. Operative Procedures

Distal gastrectomy	127
Total gastrectomy	78
Completion gastrectomy	13
Pylorus-preserving gastrectomy	32
Proximal gastrectomy	28
Pancreaticoduodenectomy	2
Wedge resection	21
Laparoscopic total gastrectomy	4
Laparoscopic distal gastrectomy	37
Laparoscopic pylorus preserving gastrectomy	39
Other (bypass, exploration, etc.)	123
Total	504

Table 4. Overall Survival Rates

Stage	No. of patients	5-yr survival
IA	1,920	94.8%
IB	396	92.6%
IIA	348	84.8%
IIB	316	78.6%
IIIA	242	64.0%
IIIB	214	57.7%
IIIC	195	38.6%
IV	644	11.9%
Total	4,275	74.2%

Stage: Japanese classification (14th ed.)
Period: 2000-2007

List of papers published in 2015

Journal

1. Sekiguchi M, Kushima R, Oda I, Suzuki H, Taniguchi H, Sekine S, Fukagawa T, Katai H. Clinical significance of a papillary adenocarcinoma component in early gastric cancer: a single-center retrospective analysis of 628 surgically resected early gastric cancers. J Gastroenterol, 50:424-434, 2015

2. Abe S, Oda I, Suzuki H, Nonaka S, Yoshinaga S, Nakajima T, Sekiguchi M, Mori G, Taniguchi H, Sekine S, Katai H, Saito Y. Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection. Endoscopy, 47:1113-1118, 2015

3. Yoda Y, Takeshima H, Niwa T, Kim JG, Ando T, Kushima R, Sugiyama T, Katai H, Noshiro H, Ushijima T. Integrated analysis of cancer-related pathways affected by genetic and epigenetic alterations in gastric cancer. Gastric Cancer, 18:65-76, 2015

4. Takeshima H, Niwa T, Takahashi T, Wakabayashi M, Yamashita S, Ando T, Inagawa Y, Taniguchi H, Katai H, Sugiyama T, Kiyono T, Ushijima T. Frequent involvement of chromatin remodeler alterations in gastric field cancerization. Cancer Lett, 357:328-338, 2015

5. Shirahige A, Suzuki H, Oda I, Sekiguchi M, Mori G, Abe S, Nonaka S, Yoshinaga S, Sekine S, Kushima R, Saito Y, Fukagawa T, Katai H. Fatal submucosal invasive gastric adenosquamous carcinoma detected at surveillance after gastric endoscopic submucosal dissection. World J Gastroenterol, 21:4385-4390, 2015

6. Hosoda F, Arai Y, Okada N, Shimizu H, Miyamoto M, Kitagawa N, Katai H, Taniguchi H, Yanagihara K, Imoto I, Inazawa J, Ohki M, Shibata T. Integrated genomic and functional analyses reveal glyoxalase I as a novel metabolic oncogene in human gastric cancer. Oncogene, 34:1196-1206, 2015

7. Ohashi M, Saka M, Katayama H, Okinaka K, Morita S, Fukagawa T, Katai H. A Prospective Cohort Study To Evaluate the Feasibility of Intraoperative Antimicrobial Prophylaxis in Open Gastrectomy for Gastric Cancer. Surg Infect (Larchmt), 16:833-839, 2015

8. Ohashi M, Morita S, Fukagawa T, Oda I, Kushima R, Katai H. Functional Advantages of Proximal Gastrectomy with Jejunal Interposition Over Total Gastrectomy with Roux-en-Y Esophagojejunostomy for Early Gastric Cancer. World J Surg, 39:2726-2733, 2015

9. Inada R, Sekine S, Taniguchi H, Tsuda H, Katai H, Fujiwara T, Kushima R. ARID1A expression in gastric adenocarcinoma: clinicopathological significance and correlation with DNA mismatch repair status. World J Gastroenterol, 21:2159-2168, 2015

10. Seishima R, Wada T, Tsuchihashi K, Okazaki S, Yoshikawa M, Oshima H, Oshima M, Sato T, Hasegawa H, Kitagawa Y, Goldenring JR, Saya H, Nagano O. Ink4a/Arf-Dependent Loss of Parietal Cells Induced by Oxidative Stress Promotes CD44-Dependent Gastric Tumorigenesis. Cancer Prev Res (Phila), 8:492-501, 2015

11. Katai H. Current status of a randomized controlled trial examining laparoscopic gastrectomy for gastric cancer in Japan. Asian J Endosc Surg, 8:125-129, 2015

12. Sasako M, Terashima M, Ichikawa W, Ochiai A, Kitada K, Kurahashi I, Sakuramoto S, Katai H, Sano T, Imamura H. Erratum to: Impact of the expression of thymidylate synthase and dihydropyrimidine dehydrogenase genes on survival in stage II/III gastric cancer. Gastric Cancer, 18:549, 2015

13. Umemura A, Koeda K, Sasaki A, Fujiwara H, Kimura Y, Iwaya T, Akiyama Y, Wakabayashi G. Totally laparoscopic total gastrectomy for gastric cancer: literature review and comparison of the procedure of esophagojejunostomy. Asian J Surg, 38:102-112, 2015

14. Ohashi M, Morita S, Fukagawa T, Kushima R, Katai H. Surgical treatment of non-early gastric remnant carcinoma developing after distal gastrectomy for gastric cancer. J Surg Oncol, 111:208-212, 2015

15. Sasako M, Terashima M, Ichikawa W, Ochiai A, Kitada K, Kurahashi I, Sakuramoto S, Katai H, Sano T, Imamura H. Impact of the expression of thymidylate synthase and dihydropyrimidine dehydrogenase genes on survival in stage II/III gastric cancer. Gastric Cancer, 18:538-548, 2015

16. Matsumoto T, Sasako M, Mizusawa J, Hirota S, Ochiai A, Kushima R, Katai H, Tanaka Y, Fukushima N, Nashimoto A, Tsuburaya A, Stomach Cancer Study Group of the Japan Clinical Oncology Group. HER2 expression in locally advanced gastric cancer with extensive lymph node (bulky N2 or paraaortic) metastasis (JCOG1005-A trial). Gastric Cancer, 18:467-475, 2015

17. Yamashita H, Katai H. Should adenocarcinoma of the esophagogastric junction be classified as esophageal cancer? Limited to Siewert type II, yes. Ann Surg, 261:e67, 2015

18. Abe S, Oda I, Nakajima T, Suzuki H, Nonaka S, Yoshinaga S, Sekine S, Taniguchi H, Kushima R, Iwasa S, Saito Y, Katai H. A case of local recurrence and distant metastasis following curative endoscopic submucosal dissection of early gastric cancer. Gastric Cancer, 18:188-192, 2015

19. Ichikawa H, Yoshida A, Kanda T, Kosugi S, Ishikawa T, Hanyu T, Taguchi T, Sakumoto M, Katai H, Kawai A, Wakai T, Kondo T. Prognostic significance of promyelocytic leukemia expression in gastrointestinal stromal tumor; integrated proteomic and transcriptomic analysis. Cancer Sci, 106:115-124, 2015

20. Fujita H, Yoshida A, Taniguchi H, Katai H, Sekine S. Adult-onset inflammatory myofibroblastic tumour of the stomach with a TFG-ROS1 fusion. Histopathology, 66:610-612, 2015

21. Yamanoi K, Arai E, Tian Y, Takahashi Y, Miyata S, Sasaki H, Chiwaki F, Ichikawa H, Sakamoto H, Kushima R, Katai H, Yoshida T, Sakamoto M, Kanai Y. Epigenetic clustering of gastric carcinomas based on DNA methylation profiles at the precancerous stage: its correlation with tumor aggressiveness and patient outcome. Carcinogenesis, 36:509-520, 2015

22. Suzuki M, Chiwaki F, Sawada Y, Ashikawa M, Aoyagi K, Fujita T, Yanagihara K, Komatsu M, Narita M, Suzuki T, Nagase H, Kushima R, Sakamoto H, Fukagawa T, Katai H, Nakagama H, Yoshida T, Uezono Y, Sasaki H. Peripheral opioid antagonist enhances the effect of anti-tumor drug by blocking a cell growth-suppressive pathway *in vivo*. PLoS One, 10:e0123407, 2015

23. Fujita T, Chiwaki F, Takahashi RU, Aoyagi K, Yanagihara K, Nishimura T, Tamaoki M, Komatsu M, Komatsuzaki R, Matsusaki K, Ichikawa H, Sakamoto H, Yamada Y, Fukagawa T, Katai H, Konno H, Ochiya T, Yoshida T, Sasaki H. Identification and Characterization of CXCR4-Positive Gastric Cancer Stem Cells. PLoS One, 10:e0130808, 2015

Department of Colorectal Surgery

Yukihide Kanemitsu, Dai Shida, Shunsuke Tsukamoto, Hiroki Ochiai, Masahiro Tanaka, Gouki Morizono

Introduction

The Department of Colorectal Surgery deals with colorectal cancer and allied malignancies in the colon and rectum. Liver metastasis from colorectal cancer is treated in cooperation with the Department of Hepatobiliary and Pancreatic Surgery. Lung metastasis from colorectal cancer is also treated in cooperation with the Department of Thoracic Surgery. Although surgery is still the main treatment modality for colorectal cancer, multi-disciplinary treatments including radiotherapy and chemotherapy are important in advanced cancer. We have multi-disciplinary meetings with the Department of Gastrointestinal Oncology, Endoscopy, Radiology and Pathology and Clinical Laboratories every week, and decide treatment strategy by a multi-disciplinary team (MDT) before treatment is held.

Routine activities

There are four staff surgeons, one chief resident, and three or four rotating residents. Every morning (7:30-8:30), we have a morning conference and rounds in wards 15A and B. MDT meeting is held for cancer patients as a form of institutionalized communication every Tuesday morning (7:15-8:00), and a conference is held for the diagnosis of colorectal cancer: colorectal surgeons, endoscopists, and radiologists discuss the diagnosis for preoperative patients every Tuesday evening (18:30-19:30). Every Wednesday morning (7:00-7:30), a conference is held for the treatment of colorectal cancer: colorectal surgeons discuss treatments for preoperative and postoperative patients. Ten to twelve operations are performed a week in our Department. Thus, we operate upon about 500 patients with colorectal cancers and allied diseases annually.

Research activities

Patients with advanced rectal cancers are treated with conventional surgery. Adjuvant chemotherapy is being used in stage III colorectal cancer patients in a clinical setting. Although preoperative radiotherapy is not performed routinely for advanced rectal cancer, patients with T4b rectal cancers or rectal cancers with multiple lymph node metastases are treated with preoperative chemoradiotherapy and surgery. Patients with symptoms caused by unresectable tumors are treated with palliative surgery including palliative resection, bypass, and stoma before chemotherapy. To evaluate the survival benefit and safety of primary resection plus chemotherapy compared to chemotherapy alone in asymptomatic stage IV colorectal cancer with synchronous unresectable metastatic disease, a randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable stage IV colorectal cancer is ongoing (The Japan Clinical Oncology Group (JCOG) 1007, iPACS). Another randomized controlled trial is ongoing to evaluate the non-inferiority of overall survival of laparoscopic surgery to open surgery for palliative resection of primary tumors in incurable stage IV colorectal cancer (JCOG1107, ENCORE). Symptomatic, stage IV colorectal cancer patients with non-curable metastasis are pre-operatively randomized to either open or laparoscopic colorectal resection. Patients with resectable liver metastasis are treated in cooperation with the Department of Hepatobiliary and Pancreatic Surgery and adjuvant chemotherapy regimens are being evaluated in a clinical trial (JCOG0603 study). To confirm the superiority of perioperative chemotherapy, a randomized phase II/III trial was started in May 2015 comparing perioperative versus postoperative chemotherapy with modified infusional fluorouracil and folinic acid with oxaliplatin (mFOLFOX6) for

lower rectal cancer patients with suspected lateral pelvic node metastasis (JCOG1310).

We also carry out basic research in cooperation with scientists at the National Cancer Center Research Institute and the identification of a suitable treatment based on such a prediction is one of our important goals.

Clinical trials

Our division plays a central role in conducting multi-institutional clinical trials in Japan. Y. Shimada is a representative of the Colorectal Cancer Group of the Japan Clinical Oncology Group (JCOG). Our Department is participating in nine phase III JCOG studies.

1) JCOG0212: A randomized study that compares mesorectal excision (ME) to ME with pelvic lateral lymph node dissection for clinical stage II or stage III lower rectal cancer patients. A total of 701 eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
2) JCOG0603: A randomized study that compares adjuvant modified FOLFOX (5-FU + l-LV +Oxaliplatin) to surgery alone after hepatic resection for liver metastasis from colorectal cancer. A total of 170 patients have been enrolled and recruitment continues.
3) JCOG1006: A randomized study that compares conventional techniques to the no-touch isolation technique for clinical T3 or T4 colon cancer. A total of 570 patients have been enrolled and recruitment continues.
4) JCOG1007: A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable stage IV colorectal cancer is ongoing.
5) JCOG1018: Randomized phase III study of mFOLFOX7 or CAPOX plus bevacizumab versus 5-Fluorouracil/leucovorin or capecitabine plus bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer is ongoing.
6) JCOG1107: A randomized controlled trial comparing laparoscopic surgery with open surgery in palliative resection of primary tumors in incurable stage IV colorectal cancer is ongoing.
7) JCOG1310: A phase II/III randomized controlled trial comparing perioperative versus postoperative chemotherapy with mFOLFOX6 for lower rectal cancer with suspected lateral pelvic node metastasis is ongoing.
8) JCOG1410A: Japanese Observational Study to Evaluate the Accuracy of Preoperative Imaging Diagnosis for Lateral Pelvic Lymph Node Metastasis in Rectal Cancer is ongoing.
9) JCOG1506A: Prognostic or predictive biomarker study in patients who underwent surgery with/without postoperative chemotherapy for stage II/III colorectal cancer is ongoing.

Table 1. Number of patients

Operative Procedures	Number of patients	
	Open	Laparoscopic
Colectomy	111	133
High anterior resection	12	29
Low anterior resection	33	17
Abdominoperineal resection	15	1
Hartmann's operation	3	
Intersphincteric resection	10	3
Robot-assisted surgery		18
Total extirpation of large intestine	1	2
Total pelvic exenteration	5	
Total pelvic exenteration with sacrectomy	2	
Bypass	4	
Colostomy or ileostomy	53	
Local excision	1	
Other	125	

List of papers published in 2015

Journal

1. Shinto E, Takahashi K, Yamaguchi T, Hashiguchi Y, Kotake K, Itabashi M, Yasuno M, Kanemitsu Y, Nishimura G, Akagi Y, Sato T, Kato T, Matsumoto H, Hase K, Sugihara K, Study Group for Liver Metastasis projected by the Japanese Society for Cancer of the Colon and Rectum (JSCCR). Validation and modification of the Japanese classification system for liver metastases from colorectal cancer: a multi-institutional study. Ann Surg Oncol, 22:3888-3895, 2015

2. Iwasa S, Souda H, Yamazaki K, Takahari D, Miyamoto Y, Takii Y, Ikeda S, Hamaguchi T, Kanemitsu Y, Shimada Y. Safety and efficacy of adjuvant therapy with oxaliplatin, leucovorin and 5-fluorouracil after mesorectal excision with lateral pelvic lymph node dissection for stage iii lower rectal cancer. Anticancer Res, 35:1815-1819, 2015

3. Kihara K, Fujita S, Ohshiro T, Yamamoto S, Sekine S. Spontaneous regression of colon cancer. Jpn J Clin Oncol, 45:111-114, 2015

4. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishihara S, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Boku N, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K, Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol, 20:207-239, 2015

Department of Gastrointestinal Medical Oncology

Narikazu Boku, Tetsuya Hamaguchi, Ken Kato, Satoru Iwasa, Yoshitaka Honma, Atsuo Takashima, Natsuko Okita, Naoki Takahashi, Yusuke Sasaki, Shoko Nakamura

Introduction

The Gastrointestinal Medical Oncology Division focuses on the development of new drugs and establishment of standard chemotherapy regimens including multi-modality treatment with surgery and/or radiotherapy for advanced esophageal/gastric/colorectal cancers, gastrointestinal stromal tumor and other gastrointestinal (GI) malignancies. From this year, we have started to handle induction chemotherapy or palliative chemotherapy for head and neck cancer.

Over recent years, a new generation of molecular-target agents has been developed for colorectal cancer, and bevacizumab (BV) directs against vascular endothelial growth factor (VEGF) and changes the microenvironment of the tumor by inhibiting angiogenesis. Two other molecular target-based drugs are the anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab, which were approved in 2008 and 2010. Thereafter, for colorectal cancer, the multi-kinase inhibitor regorafenib was approved in 2013, and a new cytotoxic agent, TAS-102 (TPI/FTD), was also approved in March 2014. For gastric cancer, an anti-HER2 monoclonal antibody, trastuzumab, was approved in 2011. And new anti-VEGF agent, ramucirumab, was also approved in March 2015 for gastric cancer based on the results of two randomized controlled trials. Moreover, in recent years, the efficacy of the immune-checkpoint inhibitor has also been evaluated for GI malignancies.

In the near future, we expect to develop other novel agents for the treatment of metastatic GI cancers that inhibit intracellular signal transduction and cellular interactions. However, many unusual adverse effects and a marked increase in medical costs have led to extensive discussion on more accurate targeting of the population using biomarkers. Although the response rates of monotherapy with these molecular-targeted drugs up to now have not been so high (about 5% to 20%) when used broadly in non-selected patients, there are a few new candidate biomarkers that may be useful for identifying patients for whom these molecular-targeted drugs will be remarkably beneficial. For example, all *RAS* mutation in tumor tissue is one of the negative predictive factors in the response to cetuximab/panitumumab. Accordingly, the identification of molecular markers that can be used to predict tumor shrinkage and/or prolong prognosis will be critical for further progress in the treatment of GI malignancies.

Routine activities

The staff of the GI Medical Oncology Division consist of seven medical oncologists, three chief residents, and three or four residents. We have a daily case conference together at 5 pm and also have a weekly research conference for sharing and discussing the progress of clinical trials or translational research with each other. Intergroup meetings with each surgical division (Colorectal, Gastric, and Esophageal Surgery Divisions) and the Radiation Oncology Division are held weekly to decide optimal treatment strategies for each individual case and to discuss treatment consensus for the disease. Palliative care considering the physical and psychological aspects of each case is another important issue discussed in staff meetings. The palliative care team and psycho-oncologists advise us on how to minimize patient discomfort and anxiety throughout end-of-life care. In 2015, we treated 1,946 hospitalized patients (649 of whom were newly diagnosed). Of these patients, 90 were enrolled into protocol studies.

Research activities

An endoscopic biopsy and blood sampling before and after chemotherapy provide an excellent opportunity to study biomarkers related to therapy-induced tumor response rates, overall survival, and time to progression or recurrence. We are collecting these fresh samples from patients with gastric cancer to evaluate the correlations between gene expression profiles and patients' outcomes by using genome sequencing, microarray or real time (RT) -PCR techniques.

We have also been measuring the gene expressions of possible predictive biomarkers by using paraffin-embedded GI cancer specimens obtained from surgical resection or endoscopic biopsy, and investigated the correlation between several candidates of related to anti-cancer drug metabolism and clinical outcomes with an RT-PCR assay. Some of these results on the correlation between gene mutation profile and cancer outcomes led to the clinical development of novel molecular targeted drugs, for example, an anti-FGF (fibroblast growth factor) antibody or FGF kinase inhibitor for gastric cancer.

These studies are being performed in collaboration with the Center for Medical Genomics, National Cancer Center Research Institute, or other institutions.

Clinical trials

We carried out several clinical trials in collaboration with the Surgery and Radiation Oncology Divisions in our hospital and other institutions. Details of clinical trials are summarized in the Table, including JCOG (Japan Clinical Oncology Group) trials, company initiated and investigator initiated registration trials and other collaborative investigator initiated trials.

1) Colorectal and Anal Canal Cancer

In first-line treatment, the phase III PARADIGM trial, comparing FOLFOX/panitumumab with FOLFOX/BV in all RAS-wild-type population, is ongoing. We are also investigating whether SIRB regimen is non-inferior to XELOX (capecitabine/oxaliplatin) plus BV in a multicenter phase III trial (TRICOLORE), and finished patient accrual on schedule. A randomized trial to investigate the superiority of fluoropyrimidine/oxaliplatin/BV to fluoropyrimidine/BV targeted at frail or elderly patients is also ongoing (JCOG1018).

In second-line treatment, we are investigating the non-inferiority of XELIRI (capecitabine/irinotecan) to FOLFIRI (5-FU/l-LV/irinotecan), for patients whose first-line treatment with FOLFOX or XELOX plus BV failed, in a multicenter phase III trial conducted in Asian countries (AXEPT), and finished patient accrual on schedule.

As an adjuvant treatment, JCOG0910, comparing S-1 with capecitabine, finished patient recruitment in 2013 on schedule, and the result was shown in ASCO 2015. Unfortunately, it could not show the non-inferiority of S-1 to capecitabine in terms of relapse free survival. A randomized trial comparing adjuvant mFOLFOX6 with observations after complete resection of liver metastasis from colorectal cancer is ongoing (JCOG0603).

The phase II part of JCOG0903, a phase I/II trial of definitive chemoradiotherapy with S-1/MMC for locally advanced anal canal squamous cell carcinoma finished patient accrual on schedule.

2) Gastric Cancer

In first-line treatment, a pivotal phase III trial comparing S-1/CDDP (CS) to S-1/CDDP/Docetaxel (DCS), patient enrollment was finished in March 2016. A new phase III trial comparing TAS-118 (S-1 plus l-LV)/oxaliplatin with CS has started from 2015. And a phase II/III study, comparing FLTAX with 5FU alone for patients who are inappropriate for CDDP usage or oral administration of S-1 due to severe peritoneal dissemination is also ongoing.

In second-line treatment, molecular-targeted drugs for advanced gastric cancer have been investigated. For HER2 negative gastric cancer, a phase III trial which will evaluate the additive effect of nimotuzumab, anti-EGFR antibodies, combined with irinotecan in second-line chemotherapy (ENRICH) is ongoing and is targeted at patients with high expression of EGFR. Two phase III trials which evaluate the additive effect of (i) Olaparib (PARP inhibitor), (ii) BBI608 (an inhibitor targeted at cancer stem cell), combined with paclitaxel finished patient accrual. Moreover, regarding the cases

inappropriate to the ENRICH trial, a feasibility study for a combination of weekly abraxane with ramcirumab started from the end of 2015.

For HER2 positive gastric cancer, a phase III trial which evaluates the additive effect of pertuzumab with capecitabine and cisplatin plus trastuzumab in first-line treatment (JACOB) finished patient accrual. A multi-center feasibility study of S-1/oxaliplatin plus trastuzumab in first-line treatment started from early 2015. A result of the phase II/III trial comparing TDM-1, ado-trastuzumab emtansine, with paclitaxel in second-line treatment (GATSBY) was reported to fail in showing superiority to paclitaxel at the ASCO-GI 2016 meeting. And a phase III trial comparing MK-3475, anti-programed cell death 1 (PD-1) immune-checkpoint inhibitor antibody, with weekly paclitaxel (KEYNOTE-061) is also ongoing.

In salvage-line treatment, a randomized trial to investigate the efficacy of ONO-4538, anti-PD-1 immune-checkpoint inhibitor antibody, compared with best supportive care (BSC) has completed patient recruitment.

3) Esophageal Cancer

Based on the results of JCOG9907 trial, in Japan, the standard care for stage IB/II/III esophageal cancer is preoperative 5-FU plus CDDP (CF) followed by surgery. The large pivotal trial JCOG1109, which compared DCF (Docetaxel plus CF) or CF plus radiotherapy (CF-RT, 41.4Gy) regimen with standard preoperative CF in stage IB/II/III esophageal cancer, started from 2012, and is progressing on schedule. A phase II study, JCOG0909 on the efficacy of CF-RT (50.4 Gy) regimen followed by salvage surgery or endoscopic resection in stage IB/II/III esophageal cancer, finished accrual in 2014.

In first-line treatment, a phase I/II study, JCOG0807 demonstrated the promising efficacy and feasibility of bi-weekly DCF regimen. According to this precedent study, a phase III trial comparing biweekly DCF with standard CF regimen started from September 2014 in JCOG.

In second-line treatment, two randomized controlled trials to investigate the efficacy of PD-1 immune-checkpoint inhibitor are ongoing; (i) Taxan versus ONO-4538 (OPERA) and (ii) paclitaxel versus MK-3475 (KEYNOTE-181).

In salvage-line treatment, two phase II studies (i) ONO-4538, and (ii) Sym004, a mixture of two synergistic full-length anti-EGFR antibodies, which bind to two separate non-overlapping epitopes on EGFR, finished patient accrual. A feasibility study to investigate the efficacy of MK-3475 is now ongoing. A multi-center feasibility study of TAS-102 has been also started.

4) Other

For metastatic neuroendocrine carcinoma (NEC) in GI-tract or hepato-billiary-Pancreatic field, a phase III trial comparing irinotecan plus CDDP with etoposide plus CDDP as first-line treatment (JCOG1213) is progressing faster than expected. And for metastatic head and neck squamous cell carcinoma, a phase III trial comparing MEDI-4736 (PD-L1 antibody) /Tremelimumab (anti-CTLA-4 antibody), MEDI-4736, and standard chemotherapy (Docetaxel or Cetuximab or S-1) in second-line treatment (EAGLE) is also ongoing, collaborating with doctors in the Department of Head and Neck Oncology. Several clinical trials have also been conducted and eligible patients have been enrolled as shown in the Table.

Table 1. Summary of newly diagnosed patients and number of patients enrolled to clinical trial

Clinical Trials	No. of pts. enrolled
1) Esophageal cancer (No. of newly diagnost pts=216)	
neo CF vs neoDCF vs neo CF-RT JCOG1109 (phase Ⅲ)	14
CF vs biweekly-DCF JCOG1314 (phase Ⅲ)	5
S-588410 for postoperative treatment (phase Ⅲ)	0
ONO-4538 vs taxan (phase Ⅲ)	0
MK-3475 vs paclitaxel (phase Ⅲ)	0
MK-3475 (phase Ⅱ)	0
TAS-102 (IIT-phase Ⅱ)	2
BKM120 (phase Ⅱ)	0
	subtotal 21
2) Gastric cancer (No.of newly diagnost pts=162)	
CS vs DCS JCOG1013 (phase Ⅲ)	22
TAS-118+Ox vs CS SOLAR (phase Ⅲ)	1
SOX+Tmab for HER2+(phase Ⅱ)	7
CPT-11±Nimotuzmab for EGFR++pts ENRICH (phase Ⅲ)	4
FL vs FLTAX for ascites++pts JCOG1108 (phase Ⅱ/Ⅲ)	1
MK-3475 vs paclitaxel (phase Ⅲ)	3
wAbraxan+ramucirumab (phase Ⅱ)	0
ONO4538 vs BSC (phase Ⅲ)	20
	subtotal 58
3) Colorectal cancer (No.of newly diagnost pts=223)	
FOLFOX+Pmab vs FOLFOX+BV for RAS-WT PARADIGM (phase Ⅲ)	2
mFOLFOX7/CAPOX+BV vs FL/Cape+BV for eldery pts JCOG1018 (phase Ⅲ)	6
	subtotal 8
4) Others (No. of newly diagnost pts=48)	
EP vs IP for GI & HBP-NEC TOPIC-NEC JCOG1213 (phase Ⅲ)	1
MEDI-4736+Tremelimumab vs MEDI-4736 vs CTx for 2nd-line HNC EAGLE (phase Ⅲ)	1
Regorafenib for imatinib-resistanrt GIST RESET (IIT-P Ⅱ)	1
ONO-4538 for virus related cancer (phase Ⅱ)	0
	subtotal 3
Total (n=649)	Total 90

※Abbreviation: No.; number, pts; patients, neo; neoadjuvant, CF; cisplatin plus fluorouracil, DCF; docetaxel plus CF, IIT; investigator initiated trial, CS; cisplatin plus S-1, DCS; docetaxel plus CS, Ox; oxaliplatin, SOX; S-1 plus Ox, Tmab; trastuzumab, FL; fluorouracil plus leucovorin, FLTAX; FL plus paclitaxel, BSC; best supportive care, FOLFOX; leucovorin, fluorouracil plus Ox, Pmab; panitumumab, BV; bevacizumab, WT; wild type, CAPOX; capecitabine plus Ox, EP; etoposide plus cisplatin, IP; irinotecan plus cisplatin, GI; gastrointestinal, HBP; hepato-biliary-pancreatic, NEC; neuroendocrine cell carcinoma, CTx; chemotherapy, HNC; head and neck cancer, GIST; gastrointestinal stromal tumor

List of papers published in 2015

Journal

1. Takahashi T, Yamahsita S, Matsuda Y, Kishino T, Nakajima T, Kushima R, Kato K, Igaki H, Tachimori Y, Osugi H, Nagino M, Ushijima T. *ZN*F695 methylation predicts a response of esophageal squamous cell carcinoma to definitive chemoradiotherapy. J Cancer Res Clin Oncol, 141:453-463, 2015

2. Utsumi H, Honma Y, Nagashima K, Iwasa S, Takashima A, Kato K, Hamaguchi T, Yamada Y, Shimada Y, Kishi Y, Nara S, Esaki M, Shimada K. Bevacizumab and postoperative wound complications in patients with liver metastases of colorectal cancer. Anticancer Res, 35:2255-2261, 2015

3. Chua C, Tan IB, Yamada Y, Rha SY, Yong WP, Ong WS, Tham CK, Ng M, Tai DW, Iwasa S, Lim HY, Choo SP. Phase II study of trastuzumab in combination with S-1 and cisplatin in the first-line treatment of human epidermal growth factor receptor HER2-positive advanced gastric cancer. Cancer Chemother Pharmacol, 76:397-408, 2015

4. Iwasa S, Nagashima K, Yamaguchi T, Matsumoto H, Ichikawa Y, Goto A, Yasui H, Kato K, Okita NT, Shimada Y, Yamada Y. S-1 and irinotecan with or without bevacizumab versus 5-fluorouracil and leucovorin plus oxaliplatin with or without bevacizumab in metastatic colorectal cancer: a pooled analysis of four phase II studies. Cancer Chemother Pharmacol, 76:605-614, 2015

5. Iwasa S, Souda H, Yamazaki K, Takahari D, Miyamoto Y, Takii Y, Ikeda S, Hamaguchi T, Kanemitsu Y, Shimada Y. Safety and efficacy of adjuvant therapy with oxaliplatin, leucovorin and 5-fluorouracil after mesorectal excision with lateral pelvic lymph node dissection for stage iii lower rectal cancer. Anticancer Res, 35:1815-1819, 2015

6. Nagashima K, Iwasa S, Yanai T, Hashimoto H, Suzuki K, Ohyanagi F, Shimada Y, Yamamoto N. A double-blind randomized Phase II study of olanzapine 10 mg versus 5 mg for emesis induced by highly emetogenic chemotherapy. Jpn J Clin Oncol, 45:229-231, 2015

7. Yoshino T, Komatsu Y, Yamada Y, Yamazaki K, Tsuji A, Ura T, Grothey A, Van Cutsem E, Wagner A, Cihon F, Hamada Y, Ohtsu A. Randomized phase III trial of regorafenib in metastatic colorectal cancer: analysis of the CORRECT Japanese and non-Japanese subpopulations. Invest New Drugs, 33:740-750, 2015

8. Shoji H, Yamada Y, Okita N, Takashima A, Honma Y, Iwasa S, Kato K, Hamaguchi T, Shimada Y. Amplification of FGFR2 Gene in Patients with Advanced Gastric Cancer Receiving Chemotherapy: Prevalence and Prognostic Significance. Anticancer Res, 35:5055-5061, 2015

9. Takahashi N, Yamada Y, Furuta K, Nagashima K, Kubo A, Sasaki Y, Shoji H, Honma Y, Iwasa S, Okita N, Takashima A, Kato K, Hamaguchi T, Shimada Y. Association between serum ligands and the skin toxicity of anti-epidermal growth factor receptor antibody in metastatic colorectal cancer. Cancer Sci, 106:604-610, 2015

10. Tanaka Y, Aoyagi K, Minashi K, Komatsuzaki R, Komatsu M, Chiwaki F, Tamaoki M, Nishimura T, Takahashi N, Oda I, Tachimori Y, Arao T, Nishio K, Kitano S, Narumi K, Aoki K, Fujii S, Ochiai A, Yoshida T, Muto M, Yamada Y, Sasaki H. Discovery of a Good Responder Subtype of Esophageal Squamous Cell Carcinoma with Cytotoxic T-Lymphocyte Signatures Activated by Chemoradiotherapy. PLoS One, 10:e0143804, 2015

11. Yamazaki K, Kuwano H, Ojima H, Otsuji T, Kato T, Shimada K, Hyodo I, Nishina T, Shirao K, Esaki T, Ohishi T, Denda T, Takeuchi M, Boku N. A randomized phase II study of combination therapy with S-1, oral leucovorin, and oxaliplatin (SOL) and mFOLFOX6 in patients with previously untreated metastatic colorectal cancer. Cancer Chemother Pharmacol, 75:569-577, 2015

12. Ioka T, Okusaka T, Ohkawa S, Boku N, Sawaki A, Fujii Y, Kamei Y, Takahashi S, Namazu K, Umeyama Y, Bycott P, Furuse J. Efficacy and safety of axitinib in combination with gemcitabine in advanced pancreatic cancer: subgroup analyses by region, including Japan, from the global randomized Phase III trial. Jpn J Clin Oncol, 45:439-448, 2015

13. Nozaki I, Kato K, Igaki H, Ito Y, Daiko H, Yano M, Udagawa H, Mizusawa J, Katayama H, Nakamura K, Kitagawa Y. Evaluation of safety profile of thoracoscopic esophagectomy for T1bN0M0 cancer using data from JCOG0502: a prospective multicenter study. Surg Endosc, 29:3519-3526, 2015

14. Fujiwara Y, Yonemori K, Shibata T, Okita N, Ushirozawa N. Japanese universal health care faces a crisis in cancer treatment. Lancet Oncol, 16:251-252, 2015

15. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishihara S, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Boku N, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K, Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol, 20:207-239, 2015

16. Yokota T, Ando N, Igaki H, Shinoda M, Kato K, Mizusawa J, Katayama H, Nakamura K, Fukuda H, Kitagawa Y. Prognostic Factors in Patients Receiving Neoadjuvant 5-Fluorouracil plus Cisplatin for Advanced Esophageal Cancer (JCOG9907). Oncology, 89:143-151, 2015

17. Shinoda M, Ando N, Kato K, Ishikura S, Kato H, Tsubosa Y, Minashi K, Okabe H, Kimura Y, Kawano T, Kosugi S, Toh Y, Nakamura K, Fukuda H, Japan Clinical Oncology Group. Randomized study of low-dose versus standard-dose chemoradiotherapy for unresectable esophageal squamous cell carcinoma (JCOG0303). Cancer Sci, 106:407-412, 2015

18. Kataoka K, Nakamura K, Mizusawa J, Fukuda H, Igaki H, Ozawa S, Hayashi K, Kato K, Kitagawa Y, Ando N. Variations in survival and perioperative complications between hospitals based on data from two phase III clinical trials for oesophageal cancer. Br J Surg, 102:1088-1096, 2015

19. Osawa M, Kudoh S, Sakai F, Endo M, Hamaguchi T, Ogino Y, Yoneoka M, Sakaguchi M, Nishimoto H, Gemma A. Clinical features and risk factors of panitumumab-induced interstitial lung disease: a postmarketing all-case surveillance study. Int J Clin Oncol, 20:1063-1071, 2015

20. Kataoka K, Tsushima T, Mizusawa J, Hironaka S, Tsubosa Y, Kii T, Shibuya Y, Chin K, Katayama H, Kato K, Fukuda H, Kitagawa Y, Japan Esophageal Oncology Group/Japan Clinical Oncology Group. A randomized controlled Phase III trial comparing 2-weekly docetaxel combined with cisplatin plus fluorouracil (2-weekly DCF) with cisplatin plus fluorouracil (CF) in patients with metastatic or recurrent esophageal cancer: rationale, design and methods of Japan Clinical Oncology Group study JCOG1314 (MIRACLE study). Jpn J Clin Oncol, 45:494-498, 2015

21. Mizukami T, Togashi Y, Sogabe S, Banno E, Terashima M, De Velasco MA, Sakai K, Fujita Y, Tomida S, Nakajima TE, Boku N, Nishio K. EGFR and HER2 signals play a salvage role in MEK1-mutated gastric cancer after MEK inhibition. Int J Oncol, 47:499-505, 2015

22. Horie Y, Yamazaki K, Funakoshi T, Hamauchi S, Taniguchi H, Tsushima T, Todaka A, Machida N, Taku K, Fukutomi A, Onozawa Y, Yasui H, Mizukami T, Izawa N, Hirakawa M, Tsuda T, Nakajima T, Boku N. Predictability of antitumor efficacy of cetuximab plus irinotecan based on skin rash severity according to observation period in patients with metastatic colorectal cancer following failure of fluorouracil, irinotecan and oxaliplatin. Mol Clin Oncol, 3:1029-1034, 2015

23. Feilchenfeldt J, Varga Z, Siano M, Grabsch HI, Held U, Schuknecht B, Trip A, Hamaguchi T, Gut P, Balague O, Khanfir K, Diebold J, Jochum W, Shoji H, Kushima R, Wagner D, Shimada Y, Cats A, Knuth A, Moch H, Aebi S, Hofer S. Brain metastases in gastro-oesophageal adenocarcinoma: insights into the role of the human epidermal growth factor receptor 2 (HER2). Br J Cancer, 113:716-721, 2015

24. Doi T, Yoshino T, Fuse N, Boku N, Yamazaki K, Koizumi W, Shimada K, Takinishi Y, Ohtsu A. Phase I study of TAS-102 and irinotecan combination therapy in Japanese patients with advanced colorectal cancer. Invest New Drugs, 33:1068-1077, 2015

Book

1. Kato K. Chemotherapy and Chemoradiotherapy. In: Ando N (ed), Esophageal Squamous Cell Carcinoma - Diagnosis and Treatment, Japan, Springer Japan, pp 197-225, 2015

25. Nishina T, Kato T, Yamazaki K, Yoshino T, Miyata Y, Esaki T, Moriwaki T, Boku N, Hyodo I. A phase II study of S-1, oxaliplatin, oral leucovorin, and bevacizumab combination therapy (SOLA) in patients with unresectable metastatic colorectal cancer. Cancer Chemother Pharmacol, 76:547-553, 2015

26. Ryu MH, Baba E, Lee KH, Park YI, Boku N, Hyodo I, Nam BH, Esaki T, Yoo C, Ryoo BY, Song EK, Cho SH, Kang WK, Yang SH, Zang DY, Shin DB, Park SR, Shinozaki K, Takano T, Kang YK, SOS study investigators. Comparison of two different S-1 plus cisplatin dosing schedules as first-line chemotherapy for metastatic and/or recurrent gastric cancer: a multicenter, randomized phase III trial (SOS). Ann Oncol, 26:2097-2101, 2015

27. Tahara M, Fuse N, Mizusawa J, Sato A, Nihei K, Kanato K, Kato K, Yamazaki K, Muro K, Takaishi H, Boku N, Ohtsu A. Phase I/II trial of chemoradiotherapy with concurrent S-1 and cisplatin for clinical stage II/III esophageal carcinoma (JCOG 0604). Cancer Sci, 106:1414-1420, 2015

28. Kataoka K, Tokunaga M, Mizusawa J, Machida N, Katayama H, Shitara K, Tomita T, Nakamura K, Boku N, Sano T, Terashima M, Sasako M, Stomach Cancer Study Group/Japan Clinical Oncology Group. A randomized Phase II trial of systemic chemotherapy with and without trastuzumab followed by surgery in HER2-positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1301 (Trigger Study). Jpn J Clin Oncol, 45:1082-1086, 2015

29. Ouchi K, Takahashi S, Yamada Y, Tsuji S, Tatsuno K, Takahashi H, Takahashi N, Takahashi M, Shimodaira H, Aburatani H, Ishioka C. DNA methylation status as a biomarker of anti-epidermal growth factor receptor treatment for metastatic colorectal cancer. Cancer Sci, 106:1722-1729, 2015

Department of Endoscopy, Gastrointestinal Endoscopy Division

Yutaka Saito, Takahisa Matsuda, Ichiro Oda, Yasuo Kakugawa, Takeshi Nakajima, Shigetaka Yoshinaga, Haruhisa Suzuki, Satoru Nonaka, Taku Sakamoto, Seiichiro Abe, Minori Matsumoto, Masayoshi Yamada, Masau Sekiguchi (Gastrointestinal Endoscopy, National Cancer Center Hospital)
Yuji Matsumoto, Takaaki Tsuchida, Takehiro Izumo (Bronchoscopy)

Introduction

Our Endoscopy Division moved to the New Endoscopy Center from 20th January 2014 and we believe this is currently the biggest Endoscopy Center in Japan (15 Endoscopy Rooms (251.112m^2) and 136.788m^2, and Recovery Rooms on two floors of 1,949.554m^2).

The total number of nursing staff increased to 15, and three endoscopy engineers are working with us.

The Gastrointestinal Endoscopy Division has 12 staff physicians in the National Cancer Center Hospital and in the Screening Technology and Development Division, 4 chief residents, 15 residents, 4 trainees and several rotating residents.

The Bronchoscopy Division has three staff members and one resident doctor, and the total number of bronchoscopies and therapeutic procedures has been dramatically increased.

Dramatic developments have recently changed the operational mechanism and design of endoscopes along with a variety of accessory devices and instruments, so clinical applications using the latest equipment are evolving on a continuous basis. In the Gastrointestinal Endoscopy Division, more advanced and technically difficult endoscopic treatments such as endoscopic submucosal dissection (ESD) are being used in place of conventional endoscopic mucosal resection (EMR) not only for early gastric cancer, but also for superficial esophageal and colorectal neoplasms. In addition, educational activities are an important part of our division's activities with many Japanese medical students, residents and staff physicians as well as approximately 100 overseas post-graduate physicians attending our training courses annually.

Routine activities in GI Endoscopy

Various diagnostic techniques including chromoendoscopy, magnifying endoscopy and endoscopic ultrasonography (EUS) are used to detect and evaluate early malignant lesions. Capsule endoscopy also has been accepted as being far less invasive. In our facility, small intestine capsule endoscopy has been performed since 2005. In order to obtain more accurate endoscopic diagnosis of gastrointestinal disease, we routinely use the recently developed narrow-band imaging (NBI) system. A total of 12,478, 4,450, 537, 97, 250, 83 and 120 screening and/or diagnostic procedures by gastroscopy, colonoscopy, EUS, EUS-fine needle aspiration (EUS-FNA), endoscopic retrograde cholangiopancreatography (ERCP), capsule endoscopy and double balloon endoscopies, respectively, were performed in 2015 (Table 1).

Due to the increasing number of patients with superficial gastrointestinal neoplasms, the number of therapeutic endoscopy procedures is also increasing in this field. In 2015, 2,667 endoscopic resections were carried out (pharynx 9, esophagus 159, stomach 370, duodenum 25 and colon 2,104). Among these, ESD, which was developed for large en-bloc resections with a low-risk of local recurrence, was performed for 91 superficial esophageal cancers, 370 early gastric cancers and 206 superficial colorectal neoplasms. For colorectal ESDs and some esophageal ESDs, the newly developed ball-tip bipolar needle knife (B-knife) and IT-knife nano were used together with CO_2 insufflation. Our colleagues originally developed these procedures and devices.

Table 1. Chronological Trend of Total Number of Diagnostic and Therapeutic Gastrointestinal Endoscopic Procedures

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015
Upper GI Endoscopy	10,910	10,909	10,174	10,644	10,810	11,193	11,314	11,481	12,478
Total Colonocopy	3.569	3,161	2,670	2,756	2,924	3,232	3,367	3,881	4,450
EUS	373	375	402	395	372	393	477	496	537
EUS-FNA	—	—	—	48	59	69	85	82	97
Therapeutic Endoscopy	1,854	1,848	1,849	1,756	1,984	2,077	2,146	2,164	3,039
Gastric EMR/ESD	24/410	19/397	36/375	23/334	23/343	361	375	340	370
Esophageal EMR/ESD	89/25	94/25	95/43	102/45	132/61	115/66	97/92	65/100	68/91
Colorectal EMR/ESD	1,212/97	1,216/97	1,177/123	1,132/120	1,210/125	1,402/133	1,398/184	1,465/194	1,898/206
Duodenal EMR	7	7	9	11	8	23	38	32	25
Pharyngeal EMR/ESD	18	7	8	9	20	24	34	23	9
Doble baloon endsocpy-Stenting. etc.						29	91	105	122
ERCP					49	104	140	175	250
Capusule endoscopy Small bowel/colon	25	30	25	22/ —	37/44	43/21	45/0	60/19	77/6
Screening canter								20,524	24,288

ESD achieves a higher en-bloc resection rate compared to the standard EMR technique and is less invasive than a surgical operation while EUS-FNA provides a less invasive procedure to improve diagnosis for patients with pancreatic tumors, lymph-node swelling, submucosal tumors of the GI tract, etc.

Image-reading conferences are held regularly and we attend all clinical conferences in the Surgery, Oncology, Radiology and Pathology Divisions to discuss and decide on treatment strategies.

Clinical activities in GI Endoscopy (Figure 1)

Our efforts have been focused on new diagnostic and therapeutic strategies. For more accurate

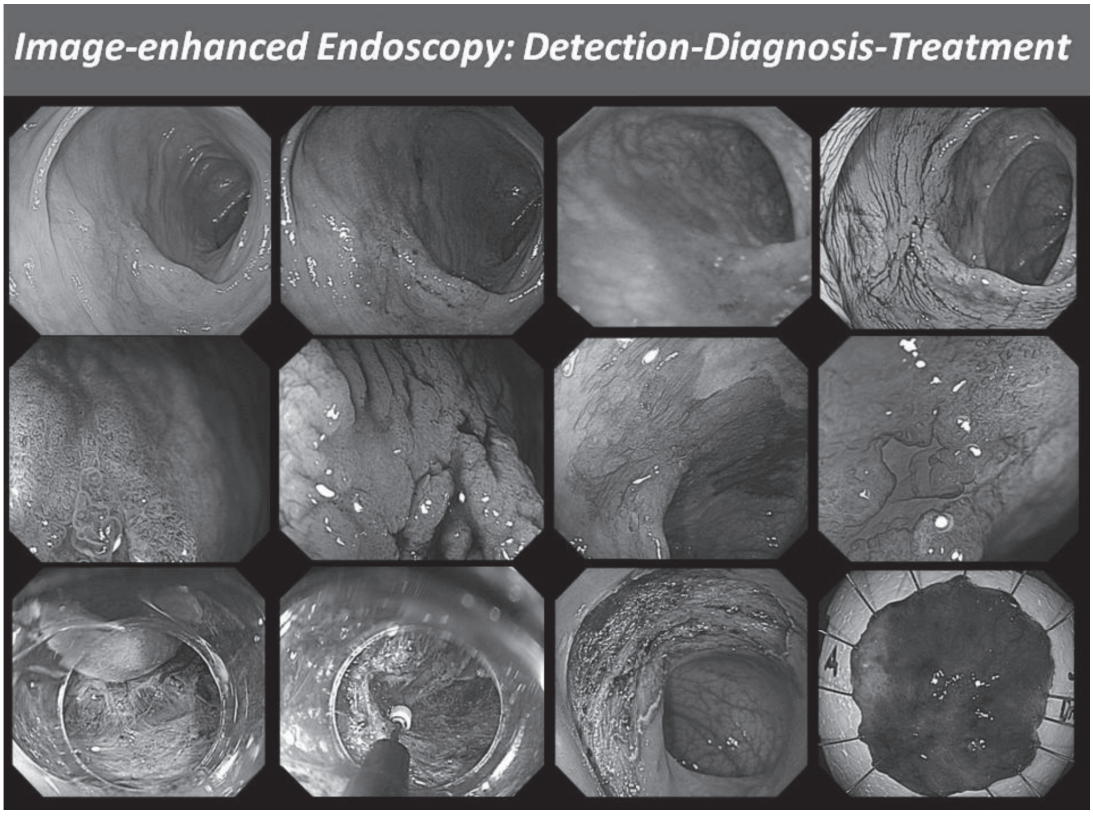


Figure 1. Endoscopic Diagnosis Using Image-enhanced Endoscopy (High-resolution Endoscopy, Narrow-band Imaging and Autofluorescence Imaging) and Endoscopic Submucosal Dissection (ESD) Procedure for Treating Early Colon Cancer

endoscopic diagnosis of gastrointestinal disease, we are utilizing the NBI system that enables us to narrow the spectral transmittance bandwidth of the optical filters used in the light source of electronic endoscope systems. In addition, we have conducted a trial study on an autofluorescence imaging (AFI) system. This system can identify lesions based on differences in tissue fluorescence properties and reveal gastrointestinal neoplasms that are not detectable with conventional endoscopy.

Clinical trials in GI Endoscopy

We have organized several multicenter study groups in order to evaluate the efficacy and clinical impact of newly developed endoscopies and medical devices prospectively.

Esophagus

A multicenter clinical trial is under way to identify the proper surveillance after EMR for superficial esophageal squamous cell carcinoma. Our Division has cooperated as a participating institution in a phase II study on the efficacy of EMR combined with chemo-radiotherapy for clinical stage I esophageal carcinoma (JCOG 0508). In addition, we are currently enrolling our patients in two multicenter randomized controlled trials. First, a phase II/III study has been introduced to compare endoscopic balloon dilatation combined with steroids to radial incision and cutting combined with steroids for refractory anastomotic stricture after esophagectomy (JCOG1207: RICS study). Second, a phase III study is ongoing to compare oral steroid administration to local steroid injection therapy for the prevention of esophageal stricture after endoscopic submucosal dissection (JCOG1217: Steroid EESD P3).

In collaboration with TWins (Tokyo Women's Medical University), we are going to conduct a clinical trial of cell sheet-based regenerative medicine, which could reduce complications such as severe stenosis and perforation related to intensive balloon dilations. This cell sheet-base regenerative medicine is one of innovation in the gastrointestinal field and we believe that cell-based regenerative medicine would be useful to improve the quality of life of patients after esophageal ESD.

Stomach

A nationwide cancer registry system has been developed for early gastric cancer treated with EMR/ESD. A five-year multicenter prospective cohort study has been ongoing using this cancer registry system since 2010 (J-WEB/EGC). Our division has also cooperated as a participating institution in phase II trials of endoscopic submucosal dissection to expand the indications for early gastric cancer (JCOG 0607) (JCOG1009/1010).

In a recent translational study, it was shown that *Helicobacter pylori* (*H. pylori*) infection induces methylation of CpG islands in non-cancerous mucosae and the methylation level in *H. pylori*-negative patients is closely associated with the risk of gastric cancer. A multicenter prospective observational study has confirmed the usefulness of the methylation level as a risk marker for metachronous gastric cancer after EMR/ESD followed by *H. pylori* eradication. Since 2015, a multicenter prospective observational study has been started to demonstrate the usefulness of the methylation level as a risk marker for gastric cancer developing after *H. pylori* eradication in healthy people. In addition, we are currently enrolling our patients in two multicenter randomized controlled trials. First, a CONNECT-G trial has been introduced to investigate the usefulness of endo-clip connecting dental floss (DFC) during gastric ESD that have a potential efficacy making a better view by traction with DFC. Second, a randomized controlled trial is ongoing to compare the second generation Narrow Band Imaging with White Light Imaging for detection of early gastric cancer (EGC Detection Trial).

Pancreas

We prospectively evaluated the efficacy and safety of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for pancreatic solid lesions in multicenters in Japan. This study was designed as a prospective cohort study conducted at the following five hospitals in Japan: National Cancer

Center Hospital, Tokyo Medical University, Aichi Cancer Center Hospital, Gifu University Hospital and Fukushima Medical University Aizu Medical Center. Two hundred and forty-nine patients were enrolled from November 2011 to June 2013. Diagnostic sensitivity of EUS-FNA in this study was 97.2%. Diagnostic specificity, accuracy, positive predictive value and negative predictive value were 88.0%, 96.2%, 100%, 81.4%, respectively. Complication after seven days was 1.6%. We could confirm the efficacy, and the safety of EUS-FNA for pancreatic solid lesions is quite satisfied.

Colorectum

RCTs concerning colorectal neoplasms are also ongoing.

The Japan Polyp Study (JPS) was started in February 2003. The JPS is a multicenter RCT designed to evaluate colorectal cancer surveillance strategies in patients who have undergone complete colonoscopies on two occasions with the removal of all detected neoplasia including flat and depressed lesions using a high-resolution colonoscope. Finally, about 4,000 patients have been enrolled in this study. This multicenter RCT is completed and analysis of data will help to develop future recommendations for surveillance guidelines in Japan after the excision of polyps including flat and depressed lesions.

Little is known about the long-term outcomes of patients with submucosal invasive colorectal cancer who undergo endoscopic or surgical resection. We performed a retrospective analysis of long-term outcomes of patients treated for submucosal colon and rectal cancer. We collected data from 549 patients with submucosal colon cancer and 209 with submucosal rectal cancer who underwent endoscopic or surgical resection at 6 institutions, over a median follow-up period of 60.5 months. We assessed recurrence rates, five-year disease-free survival, and five-year overall survival. As a result, of patients treated with only endoscopic resection, the risk for local recurrence was significantly higher in high-risk patients with submucosal rectal cancer than patients with submucosal colon cancer. The addition of surgery is therefore recommended for patients with submucosal rectal cancer with pathology features indicating a high risk of tumor progression (Gastroenterology 2012). Considering this study result, we have just started a prospective cohort study for the possibility of chemo-radiotherapy for high-risk rectal submucosal cancer after endoscopic resections.

A nationwide cancer registry system has also been developed for early colorectal cancer treated with ESD. A five-year multicenter prospective cohort study has been ongoing using this cancer registry system since 2013. A total of 2,066 patients were enrolled to this multicenter cohort study and this should be the largest cohort study in colorectal ESD in the world.

Molecular and fluorescence Imaging and Database Study

Molecular imaging endoscopy is one of a new era for very early cancer diagnosis and detection of metastasis. We have just started a collaborative study between the Endoscopy Division, Colorectal and Gastric Surgery Division, Pathology Division, Research Institute, Tokyo University and Jikei University.

Probe-based confocal laser endomicroscopy (pCLE) allows real-time, in vivo high resolution imaging of the gastrointestinal epithelium at a cellular level. We are going to conduct a multicenter prospective study supported by the Japan Gastroenterological Endoscopy Society (JGES) to evaluate the diagnostic yield of pCLE for gastric neoplasms.

We have been collaborating with the Japan Gastroenterological Endoscopy Society (JGES) in order to build an All Japan Endoscopy Database (JED) of gastrointestinal endoscopies including not only therapeutic but also diagnostic procedures. This all Japan project is named JED and has the potential to construct the largest and most precise database of all endoscopic procedures. Japanese endoscopists are well known as most excellent endoscopists, and, therefore, from now, we can create a lot of evidence using this huge endoscopy

database.

Colon Capsule Endoscopy

We conducted a multicenter prospective study to clarify the sensitivity of colon capsule endoscopy in detecting significant lesions compared with traditional colonoscopy and to evaluate its safety and acceptability in six facilities in Japan. Our study revealed that colon capsule endoscopy with a reduced preparation regimen was safe, with a sensitivity of 94% for detecting significant lesions, including laterally spreading tumors (LSTs). Until now, there has been limited information on the accuracy of colon capsule endoscopy for flat lesions, in particular LSTs, which are contributors to the development of colorectal cancer. Therefore, we think our study is noteworthy to practice colon capsule endoscopy in the screening setting in Japan. Colon capsule endoscopy was also safe and had a high level of patient acceptability. Our study was published in 2015 in gastrointestinal endoscopy (Gastrointestinal Endoscopy 2015).

List of papers published in 2015

Journal

1. Sato C, Abe S, Saito Y, So Tsuruki E, Takamaru H, Makazu M, Sato Y, Sasaki H, Tanaka H, Ikezawa N, Yamada M, Sakamoto T, Nakajima T, Matsuda T, Kushima R, Kamiya M, Maeda S, Urano Y. A pilot study of fluorescent imaging of colorectal tumors using a γ-glutamyl-transpeptidase-activatable fluorescent probe. Digestion, 91:70-76, 2015

2. Toyoshima N, Sakamoto T, Makazu M, Nakajima T, Matsuda T, Kushima R, Shimoda T, Fujii T, Inoue H, Kudo SE, Saito Y. Prevalence of serrated polyposis syndrome and its association with synchronous advanced adenoma and lifestyle. Mol Clin Oncol, 3:69-72, 2015

3. Hotta K, Katsuki S, Ohata K, Abe T, Endo M, Shimatani M, Nagaya T, Kusaka T, Matsuda T, Uraoka T, Yamaguchi Y, Murakami Y, Saito Y. Efficacy and safety of endoscopic interventions using the short double-balloon endoscope in patients after incomplete colonoscopy. Dig Endosc, 27:95-98, 2015

4. Nakamura F, Saito Y, Sakamoto T, Otake Y, Nakajima T, Yamamoto S, Murakami Y, Ishikawa H, Matsuda T. Potential perioperative advantage of colorectal endoscopic submucosal dissection versus laparoscopy-assisted colectomy. Surg Endosc, 29:596-606, 2015

5. Nonaka S, Oda I, Tada K, Mori G, Sato Y, Abe S, Suzuki H, Yoshinaga S, Nakajima T, Matsuda T, Taniguchi H, Saito Y, Maetani I. Clinical outcome of endoscopic resection for nonampullary duodenal tumors. Endoscopy, 47:129-135, 2015

6. Arezzo A, Matsuda T, Rembacken B, Miles WF, Coccia G, Saito Y. Piecemeal mucosectomy, submucosal dissection or transanal microsurgery for large colorectal neoplasm. Colorectal Dis, 171:44-51, 2015

7. Yoshinaga S, Hilmi IN, Kwek BE, Hara K, Goda K. Current status of endoscopic ultrasound for the upper gastrointestinal tract in Asia. Dig Endosc, 271:2-10, 2015

8. Sekiguchi M, Kushima R, Oda I, Suzuki H, Taniguchi H, Sekine S, Fukagawa T, Katai H. Clinical significance of a papillary adenocarcinoma component in early gastric cancer: a single-center retrospective analysis of 628 surgically resected early gastric cancers. J Gastroenterol, 50:424-434, 2015

9. Morino M, Risio M, Bach S, Beets-Tan R, Bujko K, Panis Y, Quirke P, Rembacken B, Rullier E, Saito Y, Young-Fadok T, Allaix ME, European Association for Endoscopic Surgery, European Society of Coloproctology. Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference. Surg Endosc, 29:755-773, 2015

10. Ikehara H, Saito Y, Uraoka T, Matsuda T, Miwa H. Specimen retrieval method using a sliding overtube for large colorectal neoplasm following endoscopic submucosal dissection. Endoscopy, 471:E168-E169, 2015

11. Ikematsu H, Matsuda T, Osera S, Imajoh M, Kadota T, Morimoto H, Sakamoto T, Oono Y, Kaneko K, Saito Y. Usefulness of narrow-band imaging with dual-focus magnification for differential diagnosis of small colorectal polyps. Surg Endosc, 29:844-850, 2015

12. Tanaka S, Kashida H, Saito Y, Yahagi N, Yamano H, Saito S, Hisabe T, Yao T, Watanabe M, Yoshida M, Kudo SE, Tsuruta O, Sugihara K, Watanabe T, Saitoh Y, Igarashi M, Toyonaga T, Ajioka Y, Ichinose M, Matsui T, Sugita A, Sugano K, Fujimoto K, Tajiri H. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Dig Endosc, 27:417-434, 2015

13. Wada Y, Kudo SE, Tanaka S, Saito Y, Iishii H, Ikematsu H, Igarashi M, Saitoh Y, Inoue Y, Kobayashi K, Hisabe T, Tsuruta O, Kashida H, Ishikawa H, Sugihara K. Predictive factors for complications in endoscopic resection of large colorectal lesions: a multicenter prospective study. Surg Endosc, 29:1216-1222, 2015

14. Urabe Y, Tanaka S, Saito Y, Igarashi M, Watanabe T, Sugihara K. Impact of revisions of the JSCCR guidelines on the treatment of T1 colorectal carcinomas in Japan. Z Gastroenterol, 53:291-301, 2015

15. Uraoka T, Tanaka S, Oka S, Matsuda T, Saito Y, Moriyama T, Higashi R, Matsumoto T. Feasibility of a novel colonoscope with extra-wide angle of view: a clinical study. Endoscopy, 47:444-448, 2015

16. Abe S, Council L, Cui X, Saito Y, Mönkemüller K. Endoscopic resection and enucleation of gastric submucosal tumor facilitated by subsequent closure of incision using over-the-scope clip. Endoscopy, 471:E153-E154, 2015

17. Saito Y, Nakajima T, Sakamoto T, Yamada M, Matsuda T, Mönkemüller K. Clinical pathway to discharge three days after colorectal endoscopic submucosal dissection: For whom and for what purpose? Dig Endosc, 27:662-664, 2015

18. Oka S, Tanaka S, Saito Y, Iishi H, Kudo SE, Ikematsu H, Igarashi M, Saitoh Y, Inoue Y, Kobayashi K, Hisabe T, Tsuruta O, Sano Y, Yamano H, Shimizu S, Yahagi N, Watanabe T, Nakamura H, Fujii T, Ishikawa H, Sugihara K, Colorectal Endoscopic Resection Standardization Implementation Working Group of the Japanese Society for Cancer of the Colon and Rectum, Tokyo, Japan. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. Am J Gastroenterol, 110:697-707, 2015

19. Iacopini F, Saito Y, Yamada M, Grossi C, Rigato P, Costamagna G, Gotoda T, Matsuda T, Scozzarro A. Curative endoscopic submucosal dissection of large nonpolypoid superficial neoplasms in ulcerative colitis (with videos). Gastrointest Endosc, 82:734-738, 2015

20. Bhatt A, Abe S, Kumaravel A, Vargo J, Saito Y. Indications and Techniques for Endoscopic Submucosal Dissection. Am J Gastroenterol, 110:784-791, 2015

21. Saito Y, Saito S, Oka S, Kakugawa Y, Matsumoto M, Aihara H, Watari I, Aoyama T, Nouda S, Kuramoto T, Watanabe K, Ohmiya N, Higuchi K, Goto H, Arakawa T, Tanaka S, Tajiri H. Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesions of the colon: prospective, multicenter, open study. Gastrointest Endosc, 82:861-869, 2015

22. Abe S, Oda I, Mori G, Nonaka S, Suzuki H, Yoshianaga S, Saito Y. Complete endoscopic closure of a large gastric defect with endoloop and endoclips after complex endoscopic submucosal dissection. Endoscopy, 471:E374-E375, 2015

23. Nonaka S, Kawaguchi Y, Oda I, Nakamura J, Sato C, Kinjo Y, Abe S, Suzuki H, Yoshinaga S, Sato T, Saito Y. Safety and effectiveness of propofol-based monitored anesthesia care without intubation during endoscopic submucosal dissection for early gastric and esophageal cancers. Dig Endosc, 27:665-673, 2015

24. Mori G, Nonaka S, Oda I, Abe S, Suzuki H, Yoshinaga S, Nakajima T, Saito Y. Novel strategy of endoscopic submucosal dissection using an insulation-tipped knife for early gastric cancer: near-side approach method. Endosc Int Open, 3:E425-E431, 2015

25. Kinjo Y, Nonaka S, Oda I, Abe S, Suzuki H, Yoshinaga S, Maki D, Yoshimoto S, Taniguchi H, Saito Y. The short-term and long-term outcomes of the endoscopic resection for the superficial pharyngeal squamous cell carcinoma. Endosc Int Open, 3:E266-E273, 2015

26. Abe S, Oda I, Suzuki H, Nonaka S, Yoshinaga S, Nakajima T, Sekiguchi M, Mori G, Taniguchi H, Sekine S, Katai H, Saito Y. Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection. Endoscopy, 47:1113-1118, 2015

27. Kanesaka T, Uedo N, Yao K, Ezoe Y, Doyama H, Oda I, Kaneko K, Kawahara Y, Yokoi C, Sugiura Y, Ishikawa H, Kato M, Takeuchi Y, Muto M, Saito Y. A significant feature of microvessels in magnifying narrow-band imaging for diagnosis of early gastric cancer. Endosc Int Open, 3:E590-E596, 2015

28. Suzuki H, Oda I, Sekiguchi M, Abe S, Nonaka S, Yoshinaga S, Nakajima T, Saito Y. Management and associated factors of delayed perforation after gastric endoscopic submucosal dissection. World J Gastroenterol, 21:12635-12643, 2015

29. Matsuda T, Ono A, Kakugawa Y, Matsumoto M, Saito Y. Impact of screening colonoscopy on outcomes in colorectal cancer. Jpn J Clin Oncol, 45:900-905, 2015

30. Makazu M, Sakamoto T, So E, Otake Y, Nakajima T, Matsuda T, Kushima R, Saito Y. Relationship between indeterminate or positive lateral margin and local recurrence after endoscopic resection of colorectal polyps. Endosc Int Open, 3:E252-E257, 2015

31. Oda I, Nonaka S, Abe S, Suzuki H, Yoshinaga S, Saito Y. Is there a need to shield ulcers after endoscopic submucosal dissection in the gastrointestinal tract? Endosc Int Open, 3:E152-E153, 2015

32. Sakamoto T, Abe S, Nakajima T, Matsuda T, Nakamura F, Kowazaki H, Saito Y. Complete removal of a colonic neoplasm extending into a diverticulum with hybrid endoscopic submucosal dissection-mucosal resection and endoscopic band ligation. Endoscopy, 471:E295-E296, 2015

33. Yoshinaga S, Oda I, Abe S, Nonaka S, Suzuki H, Takisawa H, Taniguchi H, Saito Y. Evaluation of the margins of differentiated early gastric cancer by using conventional endoscopy. World J Gastrointest Endosc, 7:659-664, 2015

34. Emura F, Mejía J, Donneys A, Ricaurte O, Sabbagh L, Giraldo-Cadavid L, Oda I, Saito Y, Osorio C. Therapeutic outcomes of endoscopic submucosal dissection of differentiated early gastric cancer in a Western endoscopy setting (with video). Gastrointest Endosc, 82:804-811, 2015

35. Sekiguchi M, Sekine S, Sakamoto T, Otake Y, Nakajima T, Matsuda T, Taniguchi H, Kushima R, Ohe Y, Saito Y. Excellent prognosis following endoscopic resection of patients with rectal neuroendocrine tumors despite the frequent presence of lymphovascular invasion. J Gastroenterol, 50:1184-1189, 2015

36. Shirahige A, Suzuki H, Oda I, Sekiguchi M, Mori G, Abe S, Nonaka S, Yoshinaga S, Sekine S, Kushima R, Saito Y, Fukagawa T, Katai H. Fatal submucosal invasive gastric adenosquamous carcinoma detected at surveillance after gastric endoscopic submucosal dissection. World J Gastroenterol, 21:4385-4390, 2015

37. Yamada M, Sakamoto T, Otake Y, Nakajima T, Kuchiba A, Taniguchi H, Sekine S, Kushima R, Ramberan H, Parra-Blanco A, Fujii T, Matsuda T, Saito Y. Investigating endoscopic features of sessile serrated adenomas/polyps by using narrow-band imaging with optical magnification. Gastrointest Endosc, 82:108-117, 2015

38. Suzuki S, Gotoda T, Suzuki H, Kono S, Iwatsuka K, Kusano C, Oda I, Sekine S, Moriyasu F. Morphologic and Histologic Changes in Gastric Adenomas After Helicobacter pylori Eradication: A Long-Term Prospective Analysis. Helicobacter, 20:431-437, 2015

39. Mochizuki S, Uedo N, Oda I, Kaneko K, Yamamoto Y, Yamashina T, Suzuki H, Kodashima S, Yano T, Yamamichi N, Goto O, Shimamoto T, Fujishiro M, Koike K, SAFE Trial Study Group. Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. Gut, 64:397-405, 2015

40. Kiriyama S, Naitoh H, Fukuchi M, Yuasa K, Horiuchi K, Fukasawa T, Tabe Y, Yamauchi H, Suzuki M, Yoshida T, Saito Y, Kuwano H. Evaluation of abdominal circumference and salivary amylase activities after unsedated colonoscopy using carbon dioxide and air insufflations. J Dig Dis, 16:747-751, 2015

41. Abe S, Oda I, Nakajima T, Suzuki H, Nonaka S, Yoshinaga S, Sekine S, Taniguchi H, Kushima R, Iwasa S, Saito Y, Katai H. A case of local recurrence and distant metastasis following curative endoscopic submucosal dissection of early gastric cancer. Gastric Cancer, 18:188-192, 2015

42. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishihara S, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Boku N, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K, Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol, 20:207-239, 2015

Book

1. Saito Y. Indication for colorectal ESD. In: Fukami N (ed), Endoscopic Submucosal Dissection, USA, Springer-Verlag New York, pp 19-24, 2015

2. Higashi R, Uraoka T, Sakamoto T, Matsuda T, Fujii T, Horimatsu T, Saito Y, Aoki T, Wada Y, Kudo S, Sano W, Kotaka M, Iwatate M, Katagiri A, Ikematsu H, Ono Y, Watanabe K, Nishishita M, Yamagami H, Hattori S, Fujimori T, Machida H, Yamamoto Y, Nishisaki H, Sano Y. Atlas of neoplastic lesions. In: Muto M, Yao K, Sano Y (eds), Atlas of Endoscopy with Narrow Band Imaging, Japan, Springer Japan, pp 293-340, 2015

Department of Endoscopy, Respiratory Endoscopy Division

Takehiro Izumo, Takaaki Tsuchida, Yuji Matsumoto

Introduction

For respiratory diseases, we have focused on the accurate and less-invasive diagnosis of minute peripheral malignancies detected by CT, which can lead to earlier surgical treatment and less-invasive treatments including bronchoscopic therapies. This is facilitated by a multi-purpose bronchoscopy system consisting of a flat-panel fluoroscope, as well as with the patient's cooperation and appropriate support by medical personnel. Endobronchial malignancies are diagnosed with videobronchoscopy, together with an endobronchial ultrasound system, and a high-resolution flat-panel fluoroscope. In addition, imaging diagnosis, including that with high-resolution CT, is also a routine activity for bronchoscopy, which leads to more accurate and safer diagnoses and the earlier detection of tracheobronchial malignancies.

Routine activities

Endobronchial ultrasonography (EBUS) is used not only to evaluate mediastinal or hilar malignant lesions but also to evaluate whether the biopsy devices can be directed to the peripheral lung lesions. One-hundred seventy six cases of EBUS-TBNA (EBUS-trans bronchial needle aspiration) were performed as a less invasive procedure to improve the diagnosis for patients with mediastinal or hilar lymph node swelling. The EBUS-GS (guide sheath) method was performed in most of the peripheral pulmonary lesions.

Endobronchial stenosis patients were treated with airway stent placement, photodynamic therapy and endobronchial electrocautery ablation. Medical thoracoscopy under local anesthesia in the operation suite was performed with unknown pleural effusion or a pleural tumor.

A weekly conference with CT imaging analysis and confirmation of the pathology results was held. Furthermore, we attended all clinical conferences in the Department of Thoracic Surgery, Pathology and Clinical Laboratories and Radiation Oncology to discuss and decide upon treatment strategies.

Research activities

Endobronchial ultrasound elastography is a new technique for describing the stiffness of tissue during endobronchial ultrasound-guided transbronchial needle aspiration.

We tried to improve the accuracy of GGO (ground grass opacity), which had been impossible to visualize using a routine chest radiography or X-ray fluoroscopy. Radial endobronchial ultrasound (R-EBUS) is a useful tool for precise localization of peripheral pulmonary lesions, but there have been no detailed reports about the use of R-EBUS images for GGO. R-EBUS images of GGO were identified based on the internal structure of the lesion and classified into two groups. Blizzard showed an enlarged, diffuse hyperintense acoustic shadow. Mixed blizzard showed a combination of blizzard and some diffuse heterogeneity with several hyperechoic dots and vessels.

Clinical trials

We conducted a multicenter prospective study for evaluation of photodynamic therapy for peripheral lung cancer. A study with CT workstation is ongoing with the multicenter.

Education

A flexible bronchoscope was developed for the first time in the world in this hospital. There are many resident and overseas doctors wishing to train at our hospital. I was given the opportunity of writing papers and conference presentations for many residents. Overseas training doctors came from many countries.

Future prospects

A multicenter trial of bronchoscopic therapy for peripheral lung cancer and a new diagnostic procedure such as electromagnetic navigation bronchoscopy are expected to be carried out.

Table 1. Type of procedure and number of patients

Diagnostic bronchoscopy without X-ray	157
Diagnostic bronchoscopy under X-ray fluoroscopy	640
Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA)	185
Medical thoracoscopy	16
Therapeutic bronchoscopy	21
Total	1,019

List of papers published in 2015

Journal

1. Izumo T, Sasada S, Chavez C, Matsumoto Y, Tsuchida T. Radial endobronchial ultrasound images for ground-glass opacity pulmonary lesions. Eur Respir J, 45:1661-1668, 2015

2. Izumo T, Sasada S, Chavez C, Matsumoto Y, Hayama M, Tsuchida T. The diagnostic value of histology and cytology samples during endobronchial ultrasound with a guide sheath. Jpn J Clin Oncol, 45:362-366, 2015

3. Chavez C, Sasada S, Izumo T, Watanabe J, Katsurada M, Matsumoto Y, Tsuchida T. Endobronchial ultrasound with a guide sheath for small malignant pulmonary nodules: a retrospective comparison between central and peripheral locations. J Thorac Dis, 7:596-602, 2015

4. Hayama M, Izumo T, Matsumoto Y, Chavez C, Tsuchida T, Sasada S. Complications with Endobronchial Ultrasound with a Guide Sheath for the Diagnosis of Peripheral Pulmonary Lesions. Respiration, 90:129-135, 2015

5. Mimori T, Kobayashi S, Tanaka A, Sasada S, Yoshida A, Izumo T, Sasaki N, Tsuchida T, Tsuta K. Novel use for an EGFR mutation-specific antibody in discriminating lung adenocarcinoma from reactive pneumocyte hyperplasia. Histopathology, 66:816-823, 2015

Department of Hepatobiliary and Pancreatic Surgery

Kazuaki Shimada, Minoru Esaki, Satoshi Nara, Yoji Kishi, Yoichi Miyata

Introduction

The Department of Hepatobiliary and Pancreatic (HBP) Surgery deals with malignant neoplasms arising from the liver, biliary tract including the gallbladder and pancreas. We conduct aggressive surgical treatment and also multidisciplinary treatment in cooperation with the Department of Diagnostic Radiology, Department of Hepatobiliary and Pancreatic (HBP) Oncology and Division of Pathology.

Routine activities

The HBP Surgery Department consists of four staff surgeons and we perform around 300 surgeries each year, along with one chief resident and three or four residents. Occasionally, trainees from both Japan and overseas join our group.

Operation and perioperative care

Five to seven major operations for hepatobiliary and pancreatic malignancies are performed every week. One staff surgeon and one resident are in charge of each patient, and conduct the operation and provide postoperative care. The chief resident attends all the operations, supervises the residents and manages the care of all inpatients.

Conferences

We have several clinical or educational conferences on the treatment of HBP malignancies. At the "Ward Conference", the clinical conditions of the perioperative patients and surgical strategies for preoperative cases are discussed. At the "Cherry Conference," surgeons and radiologists discuss imaging studies of mainly the patients scheduled for surgery. An "HBP Case Conference" is held by surgeons and medical oncologists to discuss the clinical course of both surgical and medical patients as well as common issues among HBP malignancies. The "Micro Conference" is a pathological conference on postoperative cases, where surgeons, radiologists, and pathologists participate in the discussion. In the "Research conference", which is held every three months, the progress of academic studies including clinical research and paper writing are evaluated.

Surgical strategies for HBP malignancies

Hepatocellular carcinoma (HCC): Surgical treatment for HCC is always determined based on the balance between tumor condition and hepatic functional reserve. Surgical resection is usually indicated in patients with solitary or only a few tumors and with favorable hepatic function. A huge tumor or HCC with macroscopic vasculobiliary tumor thrombosis are also indicated for resection as long as sufficient hepatic function and remnant liver volume is expected. Alternative treatments other than hepatectomy are performed in cooperation with medical oncologists and radiologists.

Pancreatic cancer: The prognosis of patients with invasive ductal carcinoma is poor even with aggressive surgical resection. Multidisciplinary treatments with curative resection followed by adjuvant chemotherapy is the standard strategy for this potentially noncurative disease. Resection of borderline malignancies, such as pancreatic cystic neoplasms, neuroendocrine tumors (NETs) is performed aggressively, since a favorable prognosis can be expected with surgical resection.

Biliary cancer – cholangiocarcinoma and gall bladder cancer: Based on careful imaging evaluations of cancer extension, a wide variety of surgical resections can be applied to biliary cancer. Pancreatoduodenectomy is conducted for middle to distal bile duct cancer. Extended hemihepatectomy with extrahepatic bile duct resection is considered as the first-line procedure for perihilar cholangiocarcinoma. When necessary, portal vein and/or hepatic artery resection and reconstruction

is performed to achieve curative resection.

Laparoscopic surgery: For the liver tumors located in the peripheral site, laparoscopic lateral bisegmentectomy or partial resection is considered as a choice of treatment. Laparoscopic distal pancreatectomy is considered for slowly growing malignant tumors.

Research activities

Dr. Shimada et al. conducts one prospective randomized trial to evaluate the safety of drain tube free hepatectomy (the safety of liver surgery with No-Drain policy: a multicenter randomized controlled trial, ND-trial) and plans another multi-institutional trials to evaluate the efficacy of administrating digestive enzymes to prevent postoperative hepatic steatosis in the patients who underwent pancreaticoduodenectomy (comparison of Berizym and Pancrelipase for the effect to suppress onset of Hepatic Steatosis after Pancreaticoduodenectomy, ESOP Trial). Dr. Kishi attends an international collaboration project by EORTC (European Organisation for Research and Treatment of Cancer) and JCOG (Japan Clinical Oncology Group) as a Japanese side manager. The project is to evaluate the accuracy of Diffusion-weighted Magnetic Resonance Imaging for the assessment of diminishing colorectal liver metastases by chemotherapy, which is named "Diffusion-weighted Magnetic REsonance Imaging Assessment of Liver Metastasis, DREAM study". This trial is to be started in August 2016.

Each staff attend three to four domestic or international academic meetings per year. Residents and Chief residents also have opportunities to make a presentation with the assistance of staff surgeons.

Clinical trials

In addition to the abovementioned two RCTs (ND-trial and ESOP trial) and DREAM study, we attend a JCOG1202 phase III trial that evaluates the efficacy of adjuvant S-1 treatment in the patients who underwent curative surgical resection for biliary tract cancer (a phase III trial of S-1 vs. observation in patients with resected biliary tract cancer, ASCOT trial).

Education

During three to six months of the trainee period, every week, each resident attends one to two major HBP surgeries mainly as a first assistant. They also have the chance to be an operator depending on their skill. For each case, they learn how to decide the indication and type of procedure. In the operation room, the residents learn not only each step of HBP surgery, but also tips on how to help safely proceed with the surgery. The chief resident trains them in a two-year program. In the first year, they devote themselves to the management of all inpatients and attend basically every surgery. Depending on the development of their skills, they have the opportunity to be an operating surgeon for major HBP surgery. In the second year, the chief resident works on research studies and publishes several English papers. Motivated residents also have the opportunity to make presentations in academic meetings and write English papers.

Visitors from both domestic and foreign institutions are welcome anytime.

Future prospects

HBP malignancy often requires technically demanding surgical procedures, whereas the long-term prognosis so far is not satisfactory. Our most important mission is to establish more safe and feasible surgical techniques including perioperative patient management, and to promote survival outcomes by multidisciplinary approaches. Due to the recent advances of chemotherapy, we have experienced a few patients who achieved curative surgical resection for initially unresectable pancreatic cancer due to local advancement. So the feasibility of conversion therapy should be assessed prospectively. We continue making efforts to create new skills and treatment strategies.

Table 1. Type of diseases

Type of disease	n
Invasive pancreatic cancer	90
Other pancreatic neoplasm	35
Hepatocellular carcinoma	36
Colorectal liver metastases	42
Liver metastases of other than colorectal cancer	12
Intrahepatic cholangiocarcinoma	7
Other liver neoplasm	2
Perihilar bile duct cancer	18
Extrahepatic bile duct cancer	13
Gallbladder cancer	16
Benign gallbladder disease	6
Ampullary tumor	5
Duodenal tumor	11
Others	30
Total	323

Table 2. Type of procedures

Procedure	n
Hepatectomy without biliary resection (open laparotomy)	92
Hepatectomy without biliary resection (laparoscopic)	3
Hepatectomy with biliary resection	16
Hemihepatectomy and pancreaticoduodenectomy (HPD)	5
Substomach preserving pancreaticoduodenectomy (SSPPD) or Classical Whipple (PD)	26
Pylorus-preserving pancreaticoduodenectomy (PPPD)	60
Distal pancreatectomy	32
Appleby operation	1
Medial pancreatectomy	6
Total pancreatectomy*	6
Extended cholecystectomy	9
Partial resection of duodenum	6
Other resections	19
No resection**	42
Total	323

*includes total resection of remnant pancreas
**includes bypass procedure, emergency operation, or exploratory laparotomy, etc.

Table 3. Postoperative survival rates of patients with a) pancreatic invasive ductal cancer (IDC) and b) hepatocellular carcinoma (HCC)

a) IDC (2002-2011)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	16	68	68
II	21	85	64
III	135	67	56
IVa	260	41	24
IVb	141	28	18
Total	573	47	33

b) HCC (2003-2012)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	36	91	75
II	139	89	85
III	177	77	63
IV	69	58	42
Total	421	79	69

List of papers published in 2015

Journal

1. Oguro S, Esaki M, Kishi Y, Nara S, Shimada K, Ojima H, Kosuge T. Optimal indications for additional resection of the invasive cancer-positive proximal bile duct margin in cases of advanced perihilar cholangiocarcinoma. Ann Surg Oncol, 22:1915-1924, 2015

2. Kinoshita T, Kinoshita T, Saiura A, Esaki M, Sakamoto H, Yamanaka T. Multicentre analysis of long-term outcome after surgical resection for gastric cancer liver metastases. Br J Surg, 102 (1):102-107, 2015

3. Shirota T, Ojima H, Hiraoka N, Shimada K, Rokutan H, Arai Y, Kanai Y, Miyagawa S, Shibata T. Heat shock protein 90 is a potential therapeutic target in cholangiocarcinoma. Mol Cancer Ther, 14 (9):1985-1993, 2015

4. Nakamura M, Wakabayashi G, Miyasaka Y, Tanaka M, Morikawa T, Unno M, Tajima H, Kumamoto Y, Satoi S, Kwon M, Toyama H, Ku Y, Yoshitomi H, Nara S, Shimada K, Yokoyama T, Miyagawa S, Toyama Y, Yanaga K, Fujii T, Kodera Y, Study Group of JHBPS, JSEPS, Tomiyama Y, Miyata H, Takahara T, Beppu T, Yamaue H, Miyazaki M, Takada T. Multicenter comparative study of laparoscopic and open distal pancreatectomy using propensity score-matching. J Hepatobiliary Pancreat Sci, 22:731-736, 2015

5. Gotohda N, Yamanaka T, Saiura A, Uesaka K, Hashimoto M, Konishi M, Shimada K. What are the True Advantages of Devices for Hepatic Parenchymal Transection in Open Surgery? Reply. World J Surg, 39:3030-3031, 2015

6. Kishi Y, Shimada K, Nara S, Esaki M, Kosuge T. Administration of Pancrelipase as Effective Treatment for Hepatic Steatosis After Pancreatectomy. Pancreas, 44 (6):983-987, 2015

7. Hiraoka N, Ino Y, Yamazaki-Itoh R, Kanai Y, Kosuge T, Shimada K. Intratumoral tertiary lymphoid organ is a favourable prognosticator in patients with pancreatic cancer. Br J Cancer, 112 (11):1782-1790, 2015

8. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, Hama N, Hosoda F, Urushidate T, Ohashi S, Hiraoka N, Ojima H, Shimada K, Okusaka T, Kosuge T, Miyagawa S, Shibata T. Genomic spectra of biliary tract cancer. Nat Genet, 47 (9):1003-1010, 2015

9. Fukutake N, Ueno M, Hiraoka N, Shimada K, Shiraishi K, Saruki N, Ito T, Yamakado M, Ono N, Imaizumi A, Kikuchi S, Yamamoto H, Katayama K. A Novel Multivariate Index for Pancreatic Cancer Detection Based On the Plasma Free Amino Acid Profile. PLoS One (7), 10:e0132223, 2015

10. Gotohda N, Yamanaka T, Saiura A, Uesaka K, Hashimoto M, Konishi M, Shimada K. Impact of energy devices during liver parenchymal transection: a multicenter randomized controlled trial. World J Surg, 39:1543-1549, 2015

11. Miyazaki M, Yoshitomi H, Miyakawa S, Uesaka K, Unno M, Endo I, Ota T, Ohtsuka M, Kinoshita H, Shimada K, Shimizu H, Tabata M, Chijiiwa K, Nagino M, Hirano S, Wakai T, Wada K, Isayama H, Iasayama H, Okusaka T, Tsuyuguchi T, Fujita N, Furuse J, Yamao K, Murakami K, Yamazaki H, Kijima H, Nakanuma Y, Yoshida M, Takayashiki T, Takada T. Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. J Hepatobiliary Pancreat Sci, 22 (4):249-273, 2015

12. Utsumi H, Honma Y, Nagashima K, Iwasa S, Takashima A, Kato K, Hamaguchi T, Yamada Y, Shimada Y, Kishi Y, Nara S, Esaki M, Shimada K. Bevacizumab and postoperative wound complications in patients with liver metastases of colorectal cancer. Anticancer Res, 35:2255-2261, 2015

13. Morita S, Onaya H, Kishi Y, Hiraoka N, Arai Y. Multiple Intraglandular Metastases in a Patient with Invasive Ductal Carcinoma of the Pancreas. Intern Med, 54:1753-1756, 2015

Department of Hepatobiliary and Pancreatic Oncology

Takuji Okusaka, Hideki Ueno, Chigusa Morizane, Shunsuke Kondo, Yasunari Sakamoto, Mitsuhito Sasaki

Introduction

The Department of Hepatobiliary and Pancreatic Oncology treats tumors originating from the liver, biliary system or pancreas, which include hepatocellular carcinoma (HCC), biliary tract cancer and pancreatic cancer. As part of the multi-disciplinary care given at the National Cancer Center Hospital (NCCH), we work closely with surgeons and radiologists who have expertise in these areas. We also conduct research into the pathophysiology of hepatobiliary and pancreatic tumors and seek to develop new and more effective diagnostic methods and treatments.

Routine activities

The Department consists of five staff oncologists and three to four residents. In 1990, the Division began using percutaneous ethanol injection (PEI) to treat patients with small HCCs. In 1999, radiofrequency ablation therapy (RFA) was introduced clinically as an alternative to PEI. Based on long-term observations of PEI-treated patients, we have used percutaneous ablation therapy as a valuable alternative to surgery for most patients with three or fewer HCC nodules, all of which are smaller than 3 cm in diameter. We also perform transcatheter arterial chemoembolization (TACE), mainly in patients with multiple HCC nodules. Systemic or intra-arterial chemotherapeutic regimens are indicated in advanced HCC patients for whom locoregional intervention and surgery are unsuitable or unsuccessful. In patients with unresectable pancreatic cancer or biliary tract cancer, chemotherapy is performed in clinical practice or as a clinical trial to develop active treatment. Patients with locally advanced pancreatic cancer may receive chemoradiotherapy, which has shown some clinical benefits for symptom control and survival.

Case conferences are held weekly with surgeons and radiologists to determine treatment strategies for these patients. Rounds and conferences for patients admitted to the division are made by all staff oncologists and residents every morning and evening.

Research activities

We conducted a phase I study of c-Met inhibitor tivantinib in Japanese patients with advanced hepatocellular carcinoma (Okusaka, Cancer Sci; 106:611-7). In this study, patients with HCC in whom sorafenib treatment has failed were enrolled to evaluate the safety, tolerability and pharmacokinetics of oral tivantinib as a single agent. The dose was escalated separately in EM and PM, from 120 mg BID to 240 mg BID, in both capsule and tablet formulations. 120 mg BID of tivantinib is recommended among Japanese patients with HCC regardless of CYP2C19 phenotype.

A phase I trial of S-1 in combination with gemcitabine and cisplatin in patients with advanced biliary tract cancer was conducted (Shoji, Morizane, Jpn J Clin Oncol; 46:132-7. We recommend gemcitabine at 800 mg/m(2)/week, cisplatin at 25 mg/m(2)/week and S-1 at 40 mg/m(2)/day during a 21-day cycle. Dose-limiting toxicities included a Grade 3 maculopapular rash, Grade 4 thrombocytopenia and consecutive administration skips of gemcitabine and cisplatin on Day 8. Five partial responses among 17 patients were observed.

We conducted a retrospective review of 100 consecutive patients with pancreatic neuroendocrine neoplasms (NENs), which are rare tumors (Shiba, Morizane, Pancreatology; 16:99-105). The 5-year survival rates of patients with NET G1, NET G2, and NEC were 91%, 69%, and 10%, respectively. Good performance status (PS), lower stage, and histopathological grade were identified as independent favorable prognostic factors.

Clinical trials

Twenty-four clinical trials are ongoing and seven are planned, including sixteen phase I or I/II trials, eight phase II or II/III trials, and seven phase III trials such as adjuvant chemotherapy after resection versus resection alone for patients with resectable tumor, and chemotherapy with a new regimen versus standard therapy for patients with advanced tumors. Our studies are supported by the National Cancer Center Research and Development Fund (Grant No. 26-A-4), Health and Labour Sciences Research Grants (Project for Development of Innovative Research on Cancer Therapeutics -075, -080, -141) from the Japan Agency for Medical Research and Development.

Education

Our staff members are working closely with residents and chief residents to support their skill development and knowledge expansion in both clinical and research fields. We are conducting conferences daily for clinical practice and weekly for research development. The residents in our department published five papers as first authors in peer-reviewed journals in 2015, and are performing eight ongoing studies as leading researchers with assistance from staff members.

Future prospects

Our department continues providing the best and latest diagnosis, treatment and supportive care, and developing more effective methods and techniques for all patients with hepatobiliary and pancreatic cancer in this country and all over the world. Among them, conducting clinical trials with novel promising agents for this disease is considered one of the most important tasks, and establishment of cutting-edge medical treatments in this field is the most significant mission for us. To achieve our aim, we are ongoing screening for biliary cancer patients with gene-mutations in the Kanto area as the first step, and are going to expand it to a nationwide program for accrual to clinical trials for new molecular targeted agents.

Table 1. Primary tumor

	No. of pts
Pancreatic cancer	
Invasive ductal	193
Neuroendocrine	23
Others	34
Biliary tract cancer	
Extrahepatic bile duct	18
Gallbladder	22
Papilla of Vater	6
Liver cancer	
Hepatocellular	176
Intrahepatic cholangio	39

Table 2. Treatment

	No. of pts
Pancreatic cancer	
Systemic chemotherapy	242
Chemoradiotherapy	11
Adjuvant	30
Biliary tract cancer and Intrahepatic cholangio carcinoma	
Systemic chemotherapy	81
Adjuvant	3
Hepatocellular carcinoma	
Ethanol injection	8
Radiofrequency ablation	47
Transcatheter arterial (chemo)embolization	96
Intra-arterial chemotherapy	13
Systemic chemotherapy	25
Radiotherapy	19

List of papers published in 2015

Journal

1. Okusaka T, Ueno H, Ikeda M, Mitsunaga S, Ozaka M, Ishii H, Yokosuka O, Ooka Y, Yoshimoto R, Yanagihara Y, Okita K. A Phase 1 and pharmacological trial of OPB-31121, a STAT3 inhibitor, in patients with advanced hepatocellular carcinoma. Hepatol Res, 45:1283-1291, 2015

2. Honda K, Kobayashi M, Okusaka T, Rinaudo JA, Huang Y, Marsh T, Sanada M, Sasajima Y, Nakamori S, Shimahara M, Ueno T, Tsuchida A, Sata N, Ioka T, Yasunami Y, Kosuge T, Miura N, Kamita M, Sakamoto T, Shoji H, Jung G, Srivastava S, Yamada T. Plasma biomarker for detection of early stage pancreatic cancer and risk factors for pancreatic malignancy using antibodies for apolipoprotein-AII isoforms. Sci Rep, 5:15921, 2015

3. Takai E, Totoki Y, Nakamura H, Morizane C, Nara S, Hama N, Suzuki M, Furukawa E, Kato M, Hayashi H, Kohno T, Ueno H, Shimada K, Okusaka T, Nakagama H, Shibata T, Yachida S. Clinical utility of circulating tumor DNA for molecular assessment in pancreatic cancer. Sci Rep, 5:18425, 2015

4. Ito T, Igarashi H, Nakamura K, Sasano H, Okusaka T, Takano K, Komoto I, Tanaka M, Imamura M, Jensen RT, Takayanagi R, Shimatsu A. Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. J Gastroenterol, 50:58-64, 2015

5. Okita K, Izumi N, Matsui O, Tanaka K, Kaneko S, Moriwaki H, Ikeda K, Osaki Y, Numata K, Nakachi K, Kokudo N, Imanaka K, Nishiguchi S, Okusaka T, Nishigaki Y, Shiomi S, Kudo M, Ido K, Karino Y, Hayashi N, Ohashi Y, Makuuchi M, Kumada H, Peretinoin Study Group. Peretinoin after curative therapy of hepatitis C-related hepatocellular carcinoma: a randomized double-blind placebo-controlled study. J Gastroenterol, 50:191-202, 2015

6. Grenader T, Nash S, Plotkin Y, Furuse J, Mizuno N, Okusaka T, Wasan H, Valle J, Bridgewater J. Derived neutrophil lymphocyte ratio may predict benefit from cisplatin in the advanced biliary cancer: the ABC-02 and BT-22 studies. Ann Oncol, 26:1910-1916, 2015

7. Zhu AX, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, Blanc JF, Chung HC, Baron AD, Pfiffer TE, Okusaka T, Kubackova K, Trojan J, Sastre J, Chau I, Chang SC, Abada PB, Yang L, Schwartz JD, Kudo M, REACH Trial Investigators. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol, 16:859-870, 2015

8. Mori M, Shimizu C, Ogawa A, Okusaka T, Yoshida S, Morita T. A National Survey to Systematically Identify Factors Associated With Oncologists' Attitudes Toward End-of-Life Discussions: What Determines Timing of End-of-Life Discussions? Oncologist, 20:1304-1311, 2015

9. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, Hama N, Hosoda F, Urushidate T, Ohashi S, Hiraoka N, Ojima H, Shimada K, Okusaka T, Kosuge T, Miyagawa S, Shibata T. Genomic spectra of biliary tract cancer. Nat Genet, 47:1003-1010, 2015

10. Miyazaki M, Yoshitomi H, Miyakawa S, Uesaka K, Unno M, Endo I, Ota T, Ohtsuka M, Kinoshita H, Shimada K, Shimizu H, Tabata M, Chijiiwa K, Nagino M, Hirano S, Wakai T, Wada K, Isayama H, Iasayama H, Okusaka T, Tsuyuguchi T, Fujita N, Furuse J, Yamao K, Murakami K, Yamazaki H, Kijima H, Nakanuma Y, Yoshida M, Takayashiki T, Takada T. Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. J Hepatobiliary Pancreat Sci, 22:249-273, 2015

11. Ikeda M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Kondo S, Morizane C, Ueno H, Okusaka T. Chemotherapy for advanced poorly differentiated pancreatic neuroendocrine carcinoma. J Hepatobiliary Pancreat Sci, 22:623-627, 2015

12. Watanabe T, Ueno H, Watabe Y, Hiraoka N, Morizane C, Itami J, Okusaka T, Miura N, Kakizaki T, Kakuya T, Kamita M, Tsuchida A, Nagakawa Y, Wilber H, Yamada T, Honda K. ACTN4 copy number increase as a predictive biomarker for chemoradiotherapy of locally advanced pancreatic cancer. Br J Cancer, 112:704-713, 2015

13. Kondo S, Shiba S, Udagawa R, Ryushima Y, Yano M, Uehara T, Asanabe M, Tamura K, Hashimoto J. Assessment of adverse events via a telephone consultation service for cancer patients receiving ambulatory chemotherapy. BMC Res Notes, 8:315, 2015

14. Okusaka T, Ueno H, Morizane C, Kondo S, Sakamoto Y, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Ikeda M. Cytotoxic chemotherapy for pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci, 22:628-633, 2015

15. Takahashi H, Ikeda M, Kumada T, Osaki Y, Kondo S, Kusumoto S, Ohkawa K, Nadano S, Furuse J, Kudo M, Ito K, Yokoyama M, Okusaka T, Shimoyama M, Mizokami M. Multicenter cooperative case survey of hepatitis B virus reactivation by chemotherapeutic agents. Hepatol Res, 45:1220-1227, 2015

16. Okusaka T, Ikeda M, Fukutomi A, Ioka T, Furuse J, Ohkawa S, Isayama H, Boku N. Response to Y. Sasaki et al.: Is repeating FOLFIRINOX in the original dosage and treatment schedule tolerable in Japanese patients with pancreatic cancer? Cancer Sci, 106:1101-1102, 2015

17. Murakami H, Ikeda M, Okusaka T, Inaba Y, Iguchi H, Yagawa K, Yamamoto N. A Phase I study of MEDI-575, a PDGFRα monoclonal antibody, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:631-639, 2015

18. Fuchs CS, Azevedo S, Okusaka T, Van Laethem JL, Lipton LR, Riess H, Szczylik C, Moore MJ, Peeters M, Bodoky G, Ikeda M, Melichar B, Nemecek R, Ohkawa S, Świeboda-Sadlej A, Tjulandin SA, Van Cutsem E, Loberg R, Haddad V, Gansert JL, Bach BA, Carrato A. A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial. Ann Oncol, 26:921-927, 2015

19. Ohkawa S, Okusaka T, Isayama H, Fukutomi A, Yamaguchi K, Ikeda M, Funakoshi A, Nagase M, Hamamoto Y, Nakamori S, Tsuchiya Y, Baba H, Ishii H, Omuro Y, Sho M, Matsumoto S, Yamada N, Yanagimoto H, Unno M, Ichikawa Y, Takahashi S, Watanabe G, Wakabayashi G, Egawa N, Tsuda M, Hosotani R, Hamada C, Hyodo I. Randomised phase II trial of S-1 plus oxaliplatin vs S-1 in patients with gemcitabine-refractory pancreatic cancer. Br J Cancer, 112:1428-1434, 2015

20. Yamaue H, Tsunoda T, Tani M, Miyazawa M, Yamao K, Mizuno N, Okusaka T, Ueno H, Boku N, Fukutomi A, Ishii H, Ohkawa S, Furukawa M, Maguchi H, Ikeda M, Togashi Y, Nishio K, Ohashi Y. Randomized phase II/III clinical trial of elpamotide for patients with advanced pancreatic cancer: PEGASUS-PC Study. Cancer Sci, 106:883-890, 2015

21. Okusaka T, Aramaki T, Inaba Y, Nakamura S, Morimoto M, Moriguchi M, Sato T, Ikawa Y, Ikeda M, Furuse J. Phase I study of tivantinib in Japanese patients with advanced hepatocellular carcinoma: Distinctive pharmacokinetic profiles from other solid tumors. Cancer Sci, 106:611-617, 2015

22. Shinohara A, Ikeda M, Okuyama H, Kobayashi M, Funazaki H, Mitsunaga S, Shimizu S, Ohno I, Takahashi H, Ichida Y, Takahashi K, Okusaka T, Saitoh S. Efficacy of prophylactic minocycline treatment for skin toxicities induced by erlotinib plus gemcitabine in patients with advanced pancreatic cancer: a retrospective study. Am J Clin Dermatol, 16:221-229, 2015

23. Okusaka T, Ueno H, Ikeda M, Mitsunaga S, Ozaka M, Ishii H, Yokosuka O, Ooka Y, Yoshimoto R, Yanagihara Y, Okita K. Phase 1 and pharmacological trial of OPB-31121, a signal transducer and activator of transcription-3 inhibitor, in patients with advanced hepatocellular carcinoma. Hepatol Res, 45:1283-1291, 2015

24. Ioka T, Okusaka T, Ohkawa S, Boku N, Sawaki A, Fujii Y, Kamei Y, Takahashi S, Namazu K, Umeyama Y, Bycott P, Furuse J. Efficacy and safety of axitinib in combination with gemcitabine in advanced pancreatic cancer: subgroup analyses by region, including Japan, from the global randomized Phase III trial. Jpn J Clin Oncol, 45:439-448, 2015

25. Okita K, Izumi N, Ikeda K, Osaki Y, Numata K, Ikeda M, Kokudo N, Imanaka K, Nishiguchi S, Kondo S, Nishigaki Y, Shiomi S, Ueshima K, Isoda N, Karino Y, Kudo M, Tanaka K, Kaneko S, Moriwaki H, Makuuchi M, Okusaka T, Hayashi N, Ohashi Y, Kumada H, Peretinoin Study Group. Survey of survival among patients with hepatitis C virus-related hepatocellular carcinoma treated with peretinoin, an acyclic retinoid, after the completion of a randomized, placebo-controlled trial. J Gastroenterol, 50:667-674, 2015

26. Okuyama H, Ikeda M, Kuwahara A, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Senda S, Okusaka T. Prognostic factors in patients with hepatocellular carcinoma refractory or intolerant to sorafenib. Oncology, 88:241-246, 2015

27. Aoki T, Kokudo N, Komoto I, Takaori K, Kimura W, Sano K, Takamoto T, Hashimoto T, Okusaka T, Morizane C, Ito T, Imamura M. Streptozocin chemotherapy for advanced/metastatic well-differentiated neuroendocrine tumors: an analysis of a multi-center survey in Japan. J Gastroenterol, 50:769-775, 2015

Department of Urology

Hiroyuki Fujimoto, Motokiyo Komiyama, Tomohiko Hara, Yasuo Shinoda, Aiko Maejima

Introduction

In the Department of Urology, all urogenital malignant diseases, including kidney cancer, urothelial cancer, prostate cancer, testicular germ cell tumors and retroperitoneal tumors, are the subject of diagnosis and treatment with comprehensive approaches, including radical surgery, irradiation, and chemotherapy.

Routine activities

The urology team consists of four staff physicians and one chief-resident and two residents. In addition, with the participation of a radiation oncologist, multi-disciplinary treatments for advanced disease including renal cancer, urothelial cancer, hormone-refractory prostate cancer and metastatic germ cell tumors, are performed. Every morning clinical rounds are started at 7:30 a.m., and a weekly conference to discuss inpatient management is held on Monday evenings.

Major urological malignant diseases are treated according to the following strategies:

1) Renal cell carcinoma: M0, partial or radical nephrectomy; M1: chemotherapy with target drugs with TKI or mTOR with or without palliative nephrectomy.
2) Bladder cancer. Carcinoma in situ: BCG instillation therapy. Ta, T1, transurethral resection of bladder cancer (TURBT), often combined with preoperative or postoperative BCG instillation. T2-T4, radical cystectomy with neoadjuvant chemotherapy by an M-VAC/GC regimen. N+, systemic chemotherapy, radiation; sometimes urinary diversion alone. M+, chemotherapy with a M-VAC or GC regimen.
3) Prostate cancer. Organ-confined disease, active surveillance, robotic-assisted or open radical prostatectomy, irradiation, or endocrine therapy. Specimen-confined disease, extended radical prostatectomy without neoadjuvant endocrine therapy, radiation therapy with endocrine therapy, or endocrine therapy alone. M1 disease, endocrine therapy and palliative radiation if necessary. For castration refractory disease, DTX chemotherapy is indicated.
4) Testicular germ cell tumor (GCT): Stage I, careful observation regardless of a pathological element. Stage II or higher, EP (etoposide + CDDP) or BEP (BLM + etoposide + CDDP) chemotherapy as the 1st line. In nonseminomatous cases, a salvage operation is performed after induction chemotherapy. In seminoma cases, careful observation rather than surgery is selected.

Research activities

We are constantly seeking ways to improve the treatment for malignant urological tumors.

1) Urothelial cancer: The effectiveness of a phase III study to confirm the efficacy of BCG instillation for high grade T1 bladder cancer (JCOG1019) is ongoing. For metastatic disease, a weekly CBDCA + PTX regimen has been indicated.
2) Prostate cancer: A phase II study to evaluate the efficacy of robotic-assisted laparoscopic radical prostatectomy for T1c-T3a prostate cancer is ongoing. A new operative method to achieve a complete surgical margin (extended radical prostatectomy) has been developed, and its efficacy in patients with specimen-confined disease has been evaluated without neoadjuvant endocrine therapy. This method was introduced in robotic-assisted laparoscopic radical prostatectomy with extended lymph node dissection. To provide a more precise preoperative diagnosis, a new imaging strategy using 3.0 Tesla MRI has been developed. For DTX refractory prostate cancer, a study on a vaccine regime with IKT1 is ongoing.
3) Testicular germ cell tumors: Advanced and/

or refractory cases: A so-called "desperate operation", which was designed for patients whose tumor markers do not normalize after induction chemotherapy, has been shown to be both efficacious and of clinical significance. For CDDP-refractory germ cell tumors, a second line TIP/TIN regimen has completed enrollment.

Clinical trials

We are actively involved in the following mainly ongoing protocol studies:

1) A phase III study: BCG instillation for high-grade T1 bladder cancer (JCOG1019)
2) A phase III study: Anti PD-L1 antibody (ATEZOLIZUMAB) for muscle invasive bladder cancer
3) A phase II study: Robotic-assisted laparoscopic prostatectomy for low and intermediate risk prostate cancer
4) A phase II study: IKT1 for chemo-refractory prostate cancer

Table 1. Patients' statistics: Major treatment

	2011	2012	2013	2014	2015
Radical/partial nephrectomy	30	46	39	33	25
Nephroureterectomy	12	17	8	10	14
Total cystectomy	24	25	24	17	17
TURBT	140	130	117	142	127
M-VAC	50	62	45	46	76
GC	84	83	70	83	77
Radical prostatectomy	111	87 (RALP 2)	84 (RALP32)	56 (RALP 42)	67 (RALP 49)
Prostatic biopsy	175	151	128	144	138
High orchyectomy	8	6	6	5	7
Retroperitoneal lymphadenectomy	13	6	5	7	5
Chemotherapy for testicular cancer	30	35	7	3	6
Retroperitoneal tumor resection	10	18	13	32	31

List of papers published in 2015

Journal

1. Narukawa T, Hara T, Arai E, Komiyama M, Kawahara T, Kanai Y, Fujimoto H. Tumour multifocality and grade predict intravesical recurrence after nephroureterectomy in patients with upper urinary tract urothelial carcinoma without a history of bladder cancer. Jpn J Clin Oncol, 45:488-493, 2015

2. Kanayama HO, Fukumori T, Fujimoto H, Nakanishi H, Ohyama C, Suzuki K, Nishiyama H, Eto M, Miki T, Kamoi K, Kubota Y, Takahashi S, Homma Y, Naito S. Clinicopathological characteristics and oncological outcomes in patients with renal cell carcinoma registered in 2007: The first large-scale multicenter study from the Cancer Registration Committee of the Japanese Urological Association. Int J Urol, 22:S1-S7, 2015

3. Hara T, Fujimoto H, Sakura M, Inokuchi J, Nishiyama H, Miyazaki J, Ohyama C, Koie T, Kikuchi E, Hinotsu S, Cancer Registration Committee of the Japanese Urological Association. Prognostic factors of recurrent disease in upper urinary tract urothelial cancer after radical nephroureterectomy: Subanalysis of the multi-institutional national database of the Japanese Urological Association. Int J Urol, 22:1013-1020, 2015

4. Miyazaki J, Nishiyama H, Fujimoto H, Ohyama C, Koie T, Hinotsu S, Kikuchi E, Sakura M, Inokuchi J, Hara T, Cancer Registration Committee of the Japanese Urological Association. Impact of smoking on the age at diagnosis of upper tract urothelial carcinoma: Subanalysis of the Japanese Urological Association multi-institutional national database. Int J Urol, 22:1023-1027, 2015

Department of Gynecology

Tomoyasu Kato, Shunichi Ikeda, Mitsuya Ishikawa, Takashi Uehara

Introduction

The Department of Gynecology deals with tumors originating from the female genital and reproductive organs. Surgery is the main treatment modality for most gynecologic cancers, but multidisciplinary treatments consisting of radiotherapy and chemotherapy are routinely considered in close cooperation with therapeutic radiation oncologists and medical oncologists. The incidences of three common gynecologic cancers, that is, cervical, endometrial and ovarian cancer, are now on the rise in Japan.

Routine activities

1) The staff members of the Department of Gynecology comprise four gynecologic oncologists. A new staff member, Dr. Uehara, has been in our Department since October 2015. In addition, our Division includes six residents in training. Current topics in the diagnosis and treatment of gynecologic malignancies are periodically discussed after the Monday general meeting. All patients under treatment are the subjects of presentations and discussions at the weekly joint conference on Wednesdays. A clinicopathological conference is held on the fourth Tuesday of each month.
2) Treatment strategy for uterine cervical cancer: Either conization or simple total hysterectomy is the treatment of choice for persistent Cervical intraepithelial neoplasia (CIN) III, carcinoma in situ, or cervical cancer stage IA1. Patients with stages IA2 to IIB usually undergo radical hysterectomy and pelvic lymphadenectomy. Autonomic nerves during radical hysterectomy should be preserved as much as possible to prevent severe neurogenic bladder. Postoperative whole pelvic irradiation following radical hysterectomy is only considered for patients with metastasis to the pelvic nodes or parametrial tissue as confirmed by pathological examination. Furthermore, in 2011, intensity-modulated radiation therapy (IMRT) started to be employed for postoperative adjuvant radiotherapy. Thereafter, none had severe radiation enterocolitis. Radiotherapy alone or concurrent chemo-radiotherapy is given to patients at any stage. Chemotherapy is occasionally used for the treatment of distant metastasis.
3) Treatment strategy for endometrial cancer: The primary treatment choice is hysterectomy with bilateral salpingo-oophorectomy. Pelvic lymph node dissection is also performed for patients with a high risk of metastasis. Para-aortic node dissection is limited to those with biopsy-proven nodal metastasis. Postoperative adjuvant chemotherapy is performed for patients with extra-uterine disease under management of the Department of Medical Oncology.
4) Treatment strategy for ovarian cancer: A simple total hysterectomy, bilateral salpingo-oophorectomy and omentectomy with or without combined resection of the involved intestine are the standard procedures for the treatment of ovarian cancer. When an intraperitoneal tumor can be optimally debulked and node metastasis is confirmed by pathologic sampling during the operation, combined pelvic and para-aortic lymph node dissection is indicated. For patients with advanced-stage cancer, surgery is followed by combination chemotherapy containing Carboplatin and Paclitaxel (TC or dose dense TC). Patients with more advanced stage III and IV disease, who are unlikely to be optimally debulked, are treated with Neoadjuvant chemotherapy (NAC). After three of four courses of chemotherapy, an interval debulking surgery (IDS) is usually performed for three patients. Surgery alone

can offer the chance of a cure for patients with recurrence, but only when the disease is completely resectable. The type of patient number and surgical procedure are shown in Tables 1 and 2, respectively.

Research activities

1) The Japan Clinical Oncology Group (JCOG) 0806-A: This report describes a determination of indications for less invasive modified radical hysterectomy for patients with the International Federation of Gynecology and Obsterics (FIGO) stage IB1 cervical cancer. We expected that patients with <2-3% parametrial involvement and ≥95% five-year OS would be good candidates for less invasive surgery. The primary target population was patients with a tumor diameter ≤2 cm as preoperatively assessed by magnetic resonance (MR) imaging and/or cone biopsy. They had lower risk of parametrial involvement (1.9%) and more favorable five-year OS (95.8%). This population is considered a good candidate for less invasive surgery such as modified radical hysterectomy. This paper would shed new light on candidates of less invasive surgery for cervical cancer stage IB1.
2) Ascites cell block system: To investigate the diagnostic utility of the ascites cell block system (CB), 48 patients with diagnosed carcinomatous peritonitis were reviewed retrospectively between 2010 and 2014. Ascites CB sections were stained with hematoxylin and eosin (HE) and immunohistochemistry. Of the 48 patients, 32 had peritoneal cancer or ovarian cancer, three had endometrial cancers, four had breast cancers, six had digestive system malignancies, and three had peritoneal mesotheliomas. A total of seven patients (14.5%) were different between clinical diagnosis (symptom, image and tumor marker) and the diagnosis by CB. A specific immunochemistry panel was helpful for the estimation of primary lesion, especially in the diagnosis of digestive system origin.
3) Adjuvant radiotherapy for vulvar cancer stage IIIA: The groin nodes are the most important prognostic factors in squamous cell carcinoma of the vulva. Adjuvant radiotherapy is indicated for patients with node-positive disease. The most common complication is the development of lower extremity lymphedema. Lymph drainage from the vulva rarely bypasses the superficial groin nodes, and from these superficial groin nodes the disease spreads to the deep groin nodes. We regard the absence of deep groin node metastasis as a low risk for pelvic lymph node metastasis, so we have omitted adjuvant radiotherapy for patients with node metastasis limited to the superficial groin region. We showed that five patients with stage IIIA are alive without postoperative radiotherapy, even though two of the five are those with two or more positive nodes.

Clinical trials

1) A nonrandomized confirmatory trial of modified radical hysterectomy for patients with FIGO Stage Ib1 (< 2 cm) uterine cervical cancer (JCOG1101) is ongoing as planned.
2) A non-randomized verification study regarding selection of fertility-sparing surgery for patients with epithelial ovarian cancer (JCOG1203) is ongoing as planned.
3) A randomized phase II/III trial conventional paclitaxel and carboplatin versus dose-dense paclitaxel and carboplatin in stage IVB, recurrent, or persistent cervical carcinoma (JCOG 1311) has started.

Table 1. Number of patients

Primary site	number of patients
Cervix	83
Endometrium	69
Ovary/tube/peritoneum	59
Vagina	3
Vulva	8
Benign or others	38

Table 2. Type of procedure

Radical hysterectomy	33
Modified radical hysterectomy	2
TAH+/-BSO+/-omentectomy+Paraaortic lymphadenectomy	22
TAH+/-BSO+/-omentectomy+pelvic lymphadectomy	17
TAH+/-BSO+/-omentectomy+/-LAR	3
TAH+/-BSO+/- omentectomy+/-retroperitoneal lymph node biopsy	117
Total pelvic exenteration	1
Radical vulvectomy	2
Simple vulvectomy	6
Conization	20
Others	40
	263

List of papers published in 2015

Journal

1. Kato T, Takashima A, Kasamatsu T, Nakamura K, Mizusawa J, Nakanishi T, Takeshima N, Kamiura S, Onda T, Sumi T, Takano M, Nakai H, Saito T, Fujiwara K, Yokoyama M, Itamochi H, Takehara K, Yokota H, Mizunoe T, Takeda S, Sonoda K, Shiozawa T, Kawabata T, Honma S, Fukuda H, Yaegashi N, Yoshikawa H, Konishi I, Kamura T, Gynecologic Oncology Study Group of the Japan Clinical Oncology Group. Clinical tumor diameter and prognosis of patients with FIGO stage IB1 cervical cancer (JCOG0806-A). Gynecol Oncol, 137:34-39, 2015

2. Satoh T, Tsuda H, Kanato K, Nakamura K, Shibata T, Takano M, Baba T, Ishikawa M, Ushijima K, Yaegashi N, Yoshikawa H, Gynecologic Cancer Study Group of the Japan Clinical Oncology Group. A non-randomized confirmatory study regarding selection of fertility-sparing surgery for patients with epithelial ovarian cancer: Japan Clinical Oncology Group Study (JCOG1203). Jpn J Clin Oncol, 45:595-599, 2015

3. Ikeda S, Ishikawa M, Kato T. Spontaneous ureteral rupture during concurrent chemoradiotherapy in a woman with uterine cervical cancer. Gynecol Oncol Rep, 13:18-19, 2015

4. Togami S, Sasajima Y, Kasamatsu T, Oda-Otomo R, Okada S, Ishikawa M, Ikeda S, Kato T, Tsuda H. Immunophenotype and human papillomavirus status of serous adenocarcinoma of the uterine cervix. Pathol Oncol Res, 21:487-494, 2015

5. Arimoto T, Kawana K, Adachi K, Ikeda Y, Nagasaka K, Tsuruga T, Yamashita A, Oda K, Ishikawa M, Kasamatsu T, Onda T, Konishi I, Yoshikawa H, Yaegashi N, Gynecologic Cancer Study Group of the Japan Clinical Oncology Group. Minimization of curative surgery for treatment of early cervical cancer: a review. Jpn J Clin Oncol, 45:611-616, 2015

6. Yoshida A, Yoshida H, Yoshida M, Mori T, Kobayashi E, Tanzawa Y, Yasugi T, Kawana K, Ishikawa M, Sugiura H, Maeda D, Fukayama M, Kawai A, Hiraoka N, Motoi T. Myoepithelioma-like Tumors of the Vulvar Region: A Distinctive Group of SMARCB1-deficient Neoplasms. Am J Surg Pathol, 39:1102-1113, 2015

7. Shimizu C, Kato T, Tamura N, Bando H, Asada Y, Mizota Y, Yamamoto S, Fujiwara Y. Perception and needs of reproductive specialists with regard to fertility preservation of young breast cancer patients. Int J Clin Oncol, 20:82-89, 2015

Department of Musculoskeletal Oncology and Rehabilitation

Hirokazu Chuuman, Akira Kawai, Fumihiko Nakatani, Yoshikazu Tanzawa, Eisuke Kobayashi, Makoto Endo, Nokitaka Setsu, Kouki Shimizu, Tomoaki Mori, Yoshihiro Araki, Masazumi Sugawara

Introduction

Malignant tumors arising from connective tissue are extremely rare, estimated to account for only 0.01% of newly developed cancers. The rarity itself sometimes causes several problems in treating patients with bone and soft tissue tumors, including retardation of accurate diagnoses and a lack of understanding regarding standardized therapeutic approaches. Since 1962, the Musculoskeletal Oncology Division of the National Cancer Center Hospital (NCCH) has been accumulating a vast array of clinical knowledge regarding musculoskeletal tumors in collaboration with radiologists and pathologists specializing in sarcomas, which has enabled us to offer well-organized treatment strategies to patients with various types of bone and soft tissue tumors. We have also been conducting basic and clinical studies using accumulated clinical samples and information to establish novel diagnostic methods and therapeutic approaches for treating musculoskeletal tumors. In addition, we have given weight to clinical trials on three different but inseparable fields: surgery, chemotherapy and radiation therapy for bone and soft tissue tumors.

Routine activities

The Musculoskeletal Oncology Division of the NCCH consists of six staff doctors, four residents and four physiotherapists, one occupational therapist and one speech therapist. Occasionally, several fellows from Japan and overseas join our group. Outpatient consultations are held every weekday. A constant number of over 25 patients are hospitalized for operation, chemotherapy or radiation therapy. Six or 10 major operations are routinely performed every week. In 2015, 410 operations were performed, including palliative operations for pathological fractures or spinal cord compression from metastatic bone and soft tissue tumors. Sarcomas in the trunk, including the 13 in the thoracic wall, 46 in the retroperitoneal space and three head and neck lesions were excised in cooperation with thoracic, general, urological or head-neck surgeons, respectively. A total of 66 reconstructive operations were conducted in collaboration with plastic surgeons to achieve adequate soft tissue coverage after the resection of malignant tumors of the trunk or limb-salvage operations for sarcomas of the extremities. As a result, almost 90% of the operations were performed with a limb-sparing approach. With regard to the patients' postoperative course, we have been collaborating with a physical therapist to rehabilitate the musculoskeletal system in cancer-bearing patients.

As for chemotherapy, we have been conducting neo-adjuvant and adjuvant chemotherapy for high-grade bone and soft tissue tumors, palliative chemotherapy for metastatic bone and soft tissue sarcomas, where necessary in collaboration with medical oncologists. We have been collaborating with pediatric oncologists for chemotherapeutic treatment of children and adolescents with sarcomas.

Research activities

Since 2004, we have been collaborating with the NCC Research Institute to develop novel molecular target therapies or tailor-made treatments for sarcoma patients. With a genome-wide microarray system or a protein-wide two dimensional fluorescence difference gel electrophoresis system, we have been analyzing the complete expression levels of mRNA and protein in the tumor samples from patients with Ewing's family tumors, osteosarcomas and soft tissue

sarcomas. Combined with each patient's clinical information, we have been establishing novel biomarkers for prediction of patients' prognoses or effects of the chemotherapeutic agents. Using the same method, we also have been searching for new genes or proteins for the molecular-targeted treatment approach. Since 2009, we have also been focusing on the aberrant microRNA expressions in Ewing's sarcoma and osteosarcoma with the aim of developing novel molecular targeted therapies or biomarkers.

Clinical trials

We also have been focusing on the standardization of adjuvant and second-line chemotherapy regimens for bone and soft tissue sarcomas. Four multi-institutional clinical trials are active as follows:

1) A multi-institutional phase III clinical trial of multi-drugs adjuvant chemotherapy for osteosarcomas (The Japan Clinical Oncology Group (JCOG) 0905) since 2010.
2) A multi-institutional phase 2 study of trabectedin for advanced soft tissue sarcoma since 2012.
3) A multi-institutional phase III clinical trial of multidrugs adjuvant chemotherapy for osteosarcomas (JCOG 1306) since 2014.
4) Phase Ⅱ clinical study of DXR vs. DXR + olaratumab (PDGFR α monoclonal antibody)

Education

Each resident performs 60-70 operations supervised by staff members every year, joins many domestic and international conferences and publishes several medical articles or reports during training courses. All staff members teach all clinical procedures and information related to oncological skills for bone and soft part sarcomas.

Future prospects

Our clinical divisions and translational study groups do many clinical trials of novel therapeutic innovations and promote clinical trials of novel drugs or targeted compounds for sarcomas and will continue to make focused efforts in the future.

Table 1. Number of patients (2015)

Soft tissue sarcomas	233
Bone sarcomas	38
Soft tissue tumors	216
Bone tumors	88
Metastasis consultation	159
Spinal cord tumors	6

Table 2. Type of procedure (2015)

Malignant soft tissue tumor surgery	123
Malignant bone tumor surgery	48
Soft tissue tumor excision or biopsy	114
Bone tumor excision or biopsy	59
Amputation	19
Others	26
Retroperitoneal sarcoma and tumor	46
Plastic surgery combined	66
Reconstruction with prosthesis	18
Spine surgery	4

List of papers published in 2015

Journal

1. Asano N, Yoshida A, Ogura K, Kobayashi E, Susa M, Morioka H, Iwata S, Ishii T, Hiruma T, Chuman H, Kawai A. Prognostic Value of Relevant Clinicopathologic Variables in Epithelioid Sarcoma: A Multi-Institutional Retrospective Study of 44 Patients. Ann Surg Oncol, 22:2624-2632, 2015

2. Miyamoto S, Fukunaga Y, Fujiki M, Nakatni F, Tanzawa Y, Sakuraba M. Accompanying artery of sciatic nerve as recipient vessel for free-flap transfer: a computed tomographic angiography study and case reports. Microsurgery, 35:284-289, 2015

3. Kikuta K, Kubota D, Yoshida A, Morioka H, Toyama Y, Chuuman H, Kawai A. An analysis of factors related to the tail-like pattern of myxofibrosarcoma seen on MRI. Skeletal Radiol, 44:55-62, 2015

4. Yoshida A, Asano N, Kawai A, Kawamoto H, Nakazawa A, Kishimoto H, Kushima R. Differential SALL4 immunoexpression in malignant rhabdoid tumours and epithelioid sarcomas. Histopathology, 66:252-261, 2015

5. Ogura K, Uehara K, Akiyama T, Iwata S, Shinoda Y, Kobayashi E, Saita K, Yonemoto T, Kawano H, Chuman H, Davis AM, Kawai A. Cross-cultural adaptation and validation of the Japanese version of the Toronto Extremity Salvage Score (TESS) for patients with malignant musculoskeletal tumors in the lower extremities. J Orthop Sci, 20:1098-1105, 2015

6. Ogura K, Fujiwara T, Yasunaga H, Matsui H, Jeon DG, Cho WH, Hiraga H, Ishii T, Yonemoto T, Kamoda H, Ozaki T, Kozawa E, Nishida Y, Morioka H, Hiruma T, Kakunaga S, Ueda T, Tsuda Y, Kawano H, Kawai A. Development and external validation of nomograms predicting distant metastases and overall survival after neoadjuvant chemotherapy and surgery for patients with nonmetastatic osteosarcoma: A multi-institutional study. Cancer, 121:3844-3852, 2015

7. Kimura H, Yamamoto N, Shirai T, Nishida H, Hayashi K, Tanzawa Y, Takeuchi A, Igarashi K, Inatani H, Shimozaki S, Kato T, Aoki Y, Higuchi T, Tsuchiya H. Efficacy of triplet regimen antiemetic therapy for chemotherapy-induced nausea and vomiting (CINV) in bone and soft tissue sarcoma patients receiving highly emetogenic chemotherapy, and an efficacy comparison of single-shot palonosetron and consecutive-day granisetron for CINV in a randomized, single-blinded crossover study. Cancer Med, 4:333-341, 2015

8. Ogura K, Miyamoto S, Sakuraba M, Fujiwara T, Chuman H, Kawai A. Intercalary reconstruction after wide resection of malignant bone tumors of the lower extremity using a composite graft with a devitalized autograft and a vascularized fibula. Sarcoma, 2015:861575, 2015

9. Joo MW, Shin SH, Kang YK, Kawai A, Kim HS, Asavamongkolkul A, Jeon DG, Kim JD, Niu X, Tsuchiya H, Puri A, Wang EH, Chung SH, Chung YG. Osteosarcoma in Asian Populations Over the Age of 40 Years: A Multicenter Study. Ann Surg Oncol, 22:3557-3564, 2015

10. Ogura K, Sakuraba M, Miyamoto S, Fujiwara T, Chuman H, Kawai A. Pelvic ring reconstruction with a double-barreled free vascularized fibula graft after resection of malignant pelvic bone tumor. Arch Orthop Trauma Surg, 135:619-625, 2015

11. Zhang L, Lyer AK, Yang X, Kobayashi E, Guo Y, Mankin H, Hornicek FJ, Amiji MM, Duan Z. Polymeric nanoparticle-based delivery of microRNA-199a-3p inhibits proliferation and growth of osteosarcoma cells. Int J Nanomedicine, 10:2913-2924, 2015

12. Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, Morioka H, Hiraga H, Hiruma T, Kunisada T, Matsumine A, Tanase T, Hasegawa T, Takahashi S. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol, 16:406-416, 2015

13. Yoshida A, Yoshida H, Yoshida M, Mori T, Kobayashi E, Tanzawa Y, Yasugi T, Kawana K, Ishikawa M, Sugiura H, Maeda D, Fukayama M, Kawai A, Hiraoka N, Motoi T. Myoepithelioma-like Tumors of the Vulvar Region: A Distinctive Group of SMARCB1-deficient Neoplasms. Am J Surg Pathol, 39:1102-1113, 2015

14. Fujiwara T, Fujiwara M, Numoto K, Ogura K, Yoshida A, Yonemoto T, Suzuki S, Kawai A. Second primary osteosarcomas in patients with retinoblastoma. Jpn J Clin Oncol, 45:1139-1145, 2015

15. Kikuta K, Morioka H, Kawai A, Kondo T. Global protein-expression profiling for reclassification of malignant fibrous histiocytoma. Biochim Biophys Acta, 1854:696-701, 2015

16. Yonemoto T, Hosono A, Iwata S, Kamoda H, Hagiwara Y, Fujiwara T, Kawai A, Ishii T. The prognosis of osteosarcoma occurring as second malignancy of childhood cancers may be favorable: experience of two cancer centers in Japan. Int J Clin Oncol, 20:613-616, 2015

17. Ichikawa H, Yoshida A, Kanda T, Kosugi S, Ishikawa T, Hanyu T, Taguchi T, Sakumoto M, Katai H, Kawai A, Wakai T, Kondo T. Prognostic significance of promyelocytic leukemia expression in gastrointestinal stromal tumor; integrated proteomic and transcriptomic analysis. Cancer Sci, 106:115-124, 2015

18. Kobayashi E, Setsu N. Osteosclerosis induced by denosumab. Lancet, 385:539, 2015

19. Yamaga K, Kobayashi E, Kubota D, Setsu N, Tanaka Y, Minami Y, Tanzawa Y, Nakatani F, Kawai A, Chuman H. Pediatric myositis ossificans mimicking osteosarcoma. Pediatr Int, 57:996-999, 2015

20. Fujiwara T, Ogura K, Kobayashi E, Tanzawa Y, Nakatani F, Chuman H, Kawai A. Clinical Outcomes of Surgical Treatments for Primary Malignant Bone Tumors Arising in the Acetabulum. Sarcoma, 2015:430576, 2015

21. Fujiki M, Miyamoto S, Nakatani F, Kawai A, Sakuraba M. Rotationplasty with vascular reconstruction for prosthetic knee joint infection. Case Rep Orthop, 2015:241405, 2015

22. Miyamoto S, Fujiki M, Nakatani F, Sakisaka M, Sakuraba M. Free flow-through anterolateral thigh flap for complex knee defect including the popliteal artery. Microsurgery, 35:485-488, 2015

Department of Dermatologic Oncology

Naoya Yamazaki, Arata Tsutsumida, Akira Takahashi, Kenjiro Namikawa, Wataru Omata

Introduction

The Department of Dermatologic Oncology has consistently served as the core hospital to establish treatment strategies for malignant skin tumors since the National Cancer Center opened in 1962, with over 2000 cases of malignant melanoma treated to date; an impressive number for a hospital or research institution in Japan. Today, patients are referred here from all over Japan. Particularly noteworthy is the total of 181 patients with malignant melanoma, approximately double the number of five years ago. Most of the patients are examined and treated for skin cancer, including malignant melanoma. Surgery is the main treatment modality for skin cancer, while multi-disciplinary treatments, comprising chemotherapy, immunotherapy and radiotherapy, are also routinely carried out. This Department is also actively involved in multicenter trials for new skin cancer agents all over Japan.

Routine activities

The Department has four staff dermatologic oncologists, one chief resident and three residents. We also engage in routine outpatient activities on Wednesdays and Thursdays in the National Cancer Center East.

Our Department has a high throughput, with an average of more than 200 patients with malignant melanoma seen annually for the past four years. This follows the establishment of a national network to develop treatment for malignant skin tumors, thanks to which nivolumab, an anti-PD-1 antibody, was approved as a therapeutic agent for malignant melanoma in Japan as a world first and reflecting vigorous new drug development.

An expanded access program featuring a BRAF inhibitor, vemurafenib, was also conducted through an investigator-initiated clinical trial.

About 20 patients are hospitalized to undergo surgery, chemotherapy, or radiation therapy. In 2013, 250 operations were performed, including 118 under general anesthesia. Rounds are made and case presentations are held every morning. A Division conference is also held every Monday to discuss the therapeutic principles for outpatients and inpatients. A clinicopathological conference focusing on surgically removed skin specimens is held with pathologists once a month.

We have also treated patients with advanced cases of mucosal melanoma in the nasal cavity, genital lesions, perianal lesions and uveal melanoma, despite our original "dermatologic" specialty.

Research activities

Malignant skin tumors are mainly treated by surgery (appended table). However, in recent years, several new drugs have been rapidly developed overseas to treat malignant melanoma and our Department has been conducting numerous clinical studies and trials, with the most important listed as follows:

- A multicenter study to establish standard therapy for refractory malignancies
- A study on the establishment of an early clinical development system of drugs for rare cancers and support for research.
- Development of a system for boron neutron capture therapy (BNCT) using an accelerator installed at the hospital
- A study for developing guidelines to support the physical appearance of cancer patients
- A study on methods for assessing skin changes associated with cancer treatment and establishment of standard care
- A study on the quantitative assessment of skin disorders associated with chemotherapy using

molecular-targeted agents and skin care
- A retrospective study to clarify the outcomes of conventional treatment for cutaneous angiosarcoma of the head and neck
- A retrospective study on the outcomes of TACE therapy using cisplatin for liver metastasis from primary ocular malignant melanoma
- A phase I/II trial of combined dabrafenib and trametinib in patients with BRAF V600E or V600K mutation-positive advanced solid cancer (for phase I trials) or cutaneous malignant melanoma (for phase II trials)
- A randomized double-blind Phase III study comparing placebo and combination therapy with dabrafenib (GSK2118436) and trametinib (GSK1120212), given as postoperative adjuvant therapy for BRAF V600 mutation-positive malignant melanoma (a group at high risk of recurrence)
- A phase II, open-label, multicenter study to evaluate the efficacy and safety of avelumab (MSB0010718C) in patients with Merkel cell carcinoma
- A phase I study of repeated intratumor administration of TBI-1401 (HF10) in patients with solid tumors with superficial lesions
- A working group to prepare guidelines on "Anti-immune checkpoint therapy and combination therapy" or leaflets explaining the guidelines
- "Development of innovative cancer immunotherapy by identifying essential aspects of the tumor microenvironment associated with malignant melanoma"
- Clinical evaluation of a practical, non-invasive diagnostic tool for superficial skin tumors (hyperspectral imager)
- Practical development of therapeutic agents for refractory skin cancer using innovative molecular-targeted agents inducing cancer-specific apoptosis through an investigator-initiated clinical trial

Clinical trials

Table 2 shows our clinical trials.

Education

Currently, three resident physicians and one oncology trainee are engaged in ongoing training in routine clinical practice under skilled guidance. Conferences with the Departments of Oncology, Radiotherapy and Pathology are also regularly held. The resident physicians and the oncology trainee made a total of ten presentations at domestic academic conferences and one presentation at an international academic conference as well as publishing two papers.

Future prospects

We have devised certain measures to resolve the drug lag between Japan and Western countries in the treatment of malignant melanomas and will further promote efforts to develop effective and safe treatment strategies.

Our Department is a high-volume center in Japan for malignant melanomas and other malignant skin tumors. With the advantageous data collection associated with such a large patient base, we will reinforce our research collaboration system even more than at present, leveraging a translational research platform with the National Cancer Center Research Institute.

Table 1. Number of New Patients

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Malignant melanoma	67	68	74	97	94	79	92	75	94	88	132	228	191	206	181
Squamous cell carcinoma	27	19	24	31	36	25	25	28	36	52	27	34	40	45	42
Basal cell carcinoma	40	29	31	47	33	23	25	33	31	28	28	33	38	37	42
Sweat gland carcinoma	3	10	7	8	10	17	6	10	10	9	9	8	7	16	16
Trichilemmal carcinoma	0	1	2	0	0	1	7	0	1	0	0	1	0	1	2
Paget's disease	10	16	13	12	18	16	19	20	21	19	22	18	16	22	22
Bowen's disease	16	8	7	12	9	8	4	2	10	3	9	5	14	11	8
Dermatofibrosarcoma protuberans	2	2	3	5	3	7	3	5	10	10	10	7	13	10	2
Angiosarcoma	7	5	3	3	5	9	6	12	9	9	9	6	10	11	5
Malignant fibrous histiocytoma	0	0	1	1	1	0	1	1	3	3	1	0	1	0	2
Epithelioid sarcoma	1	1	0	0	2	1	0	1	0	0	0	0	0	0	0
Malignant lymphoma	3	10	12	12	15	7	6	15	13	16	16	15	6	11	7
Merkel cell carcinoma	-	-	-	-	2	3	2	4	3	3	8	1	1	3	7
Others	2	5	5	4	5	12	11	8	7	17	19	19	14	8	19
Total	178	175	182	232	233	208	207	204	248	257	290	375	327	381	355

Table 2. Operative Procedures (total number) in 2015

Wide local excision	156
Local excision	47
Sentinel node biopsy	45
Lymph node biopsy	9
Lymph node dissection	35
(neck)	5
(axilla)	8
(inguinal)	7
(groin)	15
(popliteal)	0
(epitrochlear)	0
Skin graft	43
Local flap	8
Free flap	2
Amputation	10
others (biopsy/debridement)	3

Table 3. New Agent Studies in 2015

Agent	Eligible Cancer Type	Trial Phase
Dabrafenib / Trametinib	Melanoma	I/II
MSB0010718C	Solid Tumors	I
ONO-4538	Melanoma	II
MEK162 / LGX818	Melanoma	III
Ipilimumab (3mg/kg)	Melanoma	II
Dabrafenib/Trametinib (COMBI-AD)	Melanoma	III
MK-3475	Melanoma	I
HVJ-E	Melanoma	I
Ipilimumab + Nivolumab	Melanoma	II
HF10	Skin Tumors	I
Avelumab	Merkel Cell Carcinoma	II

List of papers published in 2015

Journal

1. Yamazaki N, Kiyohara Y, Sugaya N, Uhara H. Phase I/II study of vemurafenib in patients with unresectable or recurrent melanoma with BRAF(V) (600) mutations. J Dermatol, 42:661-666, 2015

2. Yamazaki N, Tanaka R, Tsutsumida A, Namikawa K, Eguchi H, Omata W, Oashi K, Ogawa T, Hayashi A, Nakamura N, Tsuta K. BRAF V600 mutations and pathological features in Japanese melanoma patients. Melanoma Res, 25:9-14, 2015

3. Yamazaki N, Kiyohara Y, Uhara H, Fukushima S, Uchi H, Shibagaki N, Tsutsumida A, Yoshikawa S, Okuyama R, Ito Y, Tokudome T. Phase II study of ipilimumab monotherapy in Japanese patients with advanced melanoma. Cancer Chemother Pharmacol, 76:997-1004, 2015

4. Yamazaki N, Uhara H, Fukushima S, Uchi H, Shibagaki N, Kiyohara Y, Tsutsumida A, Namikawa K, Okuyama R, Otsuka Y, Tokudome T. Phase II study of the immune-checkpoint inhibitor ipilimumab plus dacarbazine in Japanese patients with previously untreated, unresectable or metastatic melanoma. Cancer Chemother Pharmacol, 76:969-975, 2015

5. Sakaizawa K, Ashida A, Uchiyama A, Ito T, Fujisawa Y, Ogata D, Matsushita S, Fujii K, Fukushima S, Shibayama Y, Hatta N, Takenouchi T, Uehara J, Okuyama R, Yamazaki N, Uhara H. Clinical characteristics associated with BRAF, NRAS and KIT mutations in Japanese melanoma patients. J Dermatol Sci, 80:33-37, 2015

6. Nakamura Y, Ohara K, Kishi A, Teramoto Y, Sato S, Fujisawa Y, Fujimoto M, Otsuka F, Hayashi N, Yamazaki N, Yamamoto A. Effects of non-amputative wide local excision on the local control and prognosis of in situ and invasive subungual melanoma. J Dermatol, 42:861-866, 2015

7. Sato S, Nakamura Y, Shimizu M, Yamada K, Teramoto Y, Yamazaki N, Yamamoto A. Giant pedunculated pilomatrix carcinoma on the upper limb: A rare clinical appearance. Eur J Dermatol, 25:91-92, 2015

8. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Fujiwara Y, Tamura Y, Wakui H, Honda K, Mizugaki H, Kitazono S, Tanabe Y, Asahina H, Yamazaki N, Suzuki S, Matsuoka M, Ogita Y, Tamura T. Phase I and pharmacokinetics/pharmacodynamics study of the MEK inhibitor RO4987655 in Japanese patients with advanced solid tumors. Invest New Drugs, 33:641-651, 2015

Department of Hematology

Kensei Tobinai, Yukio Kobayashi, Dai Maruyama, Tatsuya Suzuki, Wataru Munakata, Suguru Fukuhara, Shinichi Makita, Nobuhiko Yamauchi, Kousuke Toyoda

Introduction

We are focusing on the diagnosis and treatment of hematological malignancies. In the past, our Department introduced several novel disease entities, including adult T-cell leukemia-lymphoma (ATL) (J Clin Oncol 2009; 27:453-9) and angioimmunoblastic T-cell lymphoma (Blood 1988; 72:1000-6). Our department is one of the leading hematology-oncology centers in the world, especially for lymphoid malignancies.

Routine activities

The number of patients with newly diagnosed hematological malignancies in the Division increased annually from 1997 to 2004, and then stabilized (Table 1). The diseases we treat are leukemia, MDS, lymphoma, and multiple myeloma. These diseases in a certain status require hematopoietic stem cell transplantation (HSCT), therefore, our Department is united with the Department of HSCT, and when necessary, HSCTs are provided by the HSCT Department. Such occasions include allogeneic HSCT against high risk AML, salvage autologous HSCT against lymphoma, and consolidative autologous HSCT against untreated multiple myeloma.

We hold a weekly case conference, where a summary of each hospitalized- or out-patient is presented. An educational cytology conference is held weekly for young doctors. Newly diagnosed lymphoma cases are presented at a weekly lymphoma case conference, where oncologists, pathologists, radiologists, and radiation oncologists discuss diagnosis and treatment plans. We also participate in weekly HSCT conferences, which deal with all HSCT cases.

In addition to patient care in the ward, our daily activities include management of hematology clinics and a diagnostic laboratory to perform bone marrow and peripheral blood microscopic examination, and flow cytometric and molecular-genetic analyses. Five staff physicians, three chief residents, and two to five rotating residents are involved in these routine activities.

Research activities

In addition to immunophenotypic analyses, molecular diagnosis is routinely performed, using polymerase chain reaction (PCR) and fluorescence in-situ hybridization (FISH) techniques for the detection of t(8;14), t(14;18), t(11;18), t(9;22), t(8;21), t(15;17), Flt3-ITD and so on. Our recent research has focused on indolent B-cell non-Hodgkin lymphoma (B-NHL). Clinical as well as molecular and cytogenetic analyses of ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma cases led to the discovery of a new tumor suppressor gene deleted at 6q23; we identified the A20 gene as a tumor suppressor gene in various B-cell malignancies (Nature 2009; 459:712-6). In 2015, we initiated quantitative PCR assay for detection of MyD88 gene. These genes are involved in NFκB signaling and we assume that these markers will serve as a sensitivity test when using BCR inhibitors in B-cell malignancies.

We have constructed a tumor sample banking system, collecting the rest of the samples taken as routine diagnostic procedures. The samples' DNA and RNAs are extracted and reserved for future use.

This year, we authored or coauthored 22 original articles related to hematological malignancies.

Clinical trials

In 2015, we conducted 41 new-agent studies, including 18 international ones (Table 2). The

number is still increasing including domestic studies. Almost all the new agents against hematological malignancies in Japan have been evaluated in our department, and a substantial number of them have been approved by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.

Various phase I and II trials are ongoing on T-cell malignancies. The agents include mogamulizumab, lenalidomide, romidepsin, pralatrexate, forodesine, darinaparsin, chidamide, and denileukin diftitox. Some of the agents are being evaluated in international studies. For indolent ATL, we are evaluating interferon-alfa and AZT, as a phase III study (JCOG1111).

With the completion of the phase I study of oligopeptide vaccine OCV-501 against WT1 protein in AML cells to keep cases in complete remission, a randomized phase II trial is ongoing to evaluate the efficacy. The agent was developed in Japan, and is the first study against hematological malignancies aiming for approval by the PMDA.

For treatment of B-cell malignancies, patient enrolment into a phase III trial for newly diagnosed, diffuse large B-cell lymphoma (DLBCL) (JCOG0601) was completed. In this trial, a dose-intense schedule of rituximab was compared with that of a standard 3-weekly regimen. We also completed patient enrolment into phase II studies of rituximab-incorporating dose-intensified chemotherapy regimens for high-risk, untreated DLBCL (JCOG0908), and untreated MCL (JCOG0406), using high-dose chemotherapy with autologous HSCT. For symptomatic multiple myeloma patients ineligible for HSCT, we are conducting a randomized phase II trial to find a more suitable combination regimen of bortezomib, melphalan and prednisolone (JCOG1105).

Education

We trained three chief residents and seven hematology residents following our residency program. We also trained five rotating medical oncology residents.

We are devoted to publication of guidelines for hematological malignancies, and act as lecturers or nominees in various hematology and oncology societies.

Future prospects

We have attracted and educated physicians in trainee programs. Many graduates from our program are actively engaged in hematology and oncology societies. We are steering JCOG and JALSG, which are major cooperative study groups for hematological malignancies in Japan. More involvement in international studies is necessary, and more cooperative studies with other departments such as the Department of Pathology and Clinical Laboratories in NCCH and Division of Hematological Malignancy in NCCRI. and Division of Hematological Malignancy in the National Cancer Center Research Institute.

Table 1. The number of patients with newly diagnosed hematologic malignancies who were managed in the Hematology Division

Disease / Year	2007	2008	2009	2010	2011	2012	2013	2014	2015
Acute myelocytic leukemia (AML)	10	6	10	8	13	12	7	9	4
Acute lymphocytic leukemia (ALL)	9	8	2	2	1	1	6	3	6
Chronic myelocytic leukemia (CML)	11	3	3	2	2	2	2	3	3
Myelodysplastic syndrome (MDS)	9	8	20	9	3	3	6	3	7
Hodgkin lymphoma (HL)	11	12	7	11	16	15	13	9	13
Non-Hodgkin lymphoma (NHL)	210	208	151	185	243	172	193	151	153
Adult T-cell leukemia-lymphoma (ATL)	4	5	5	3	6	6	4	10	2
Chronic lymphocytic leukemia (CLL)	5	6	4	2	1	4	1	1	6
Multiple myeloma (MM)	8	10	12	9	10	7	8	3	10
Waldenström macroglobulinemia (WM)	2	3	1	2	2	1	0	0	2
Total	279	269	215	233	297	223	240	192	206

Table 2. Clinical trials for new agent development

Disease	Agents	Phase	Enrolled patients in 2015	Enrolled Patients in Total (2015/12/31)
CML	Nilotinib	III	0	1
	Ponatinib	I/II	0	3
	Rogosertib	I	0	1
AML, MDS	WT1 (maintenance)	I	0	4
	WT1 vaccine	II	0	0
	Volasertib	III	0	2
	ASP2215	I	2	4
	SMO inhibitor (PF-04449913)	I	3	3
ALL	Inotuzumab ozogamicin	I	0	2
	Blinatumomab	I	1	1
MM	Carfilzomib (high-dose)	I	1	2
	Carfilzomib+dexametasone vs. Bortezomib+dexametazone	III	0	1
	Weekly vs biweekly Carfilzomib	III	0	0
	Afuresertib	I	0	0
	Pomalidomide	II	0	1
T-NHL	Forodesine	I/II	0	7
	KW-0761 (ATL)	II	0	0
	Romidepsin	I/II	2	12
	Pralatrexate	I	4	7
CD30 positive PTCL	SGN-35 + CHP vs. CHOP	III	1	4
CTCL	KW-0761 vs. Vorinostat	III	0	0
CLL, B-NHL	FCR	II	1	1
	Idelalisib	Ib	0	1
	ONO-4059 (BTK-inhibitor)	I	5	6
Indolent B- NHL	Ofatumumab vs. Rituximab	III	5	46
	Obinutuzumab (GALLIUM)	III	0	16
	BR (or R-CHOP) ± ibrutinib	III	0	8
	R-CHOP ± lenalidomide	III	0	2
	Rituximab ± lenalidomide	III	2	2
	Copanlisib	Ib	1	1
	BR (or R-CHOP) ± ibrutinib	III	4	4
MCL	VcR-CAP	III	0	2
	BR ± ibrutinib	III	0	1
	Ibrutinib	II	0	4
	Ofatumumab	III	0	3
	Everolimus	III	0	1
	R-CHOP ± ibrutinib	III	5	7
HL	SGN-35	III	2	2
	ONO-4538 (nivolumab)	II	5	5
NHL, MM, CLL	Venetoclax (bcl-2 inhibitor)	I	3	4

PTCL, peripheral T-cell lymphoma; FL, follicular lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; ML, malignant lymphoma; MP, melphalan, prednisolone; PSL, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, PSL; R, rituximab; VcR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, PSL

Table 3. Clinical studies of Cooperative Group

Disease / Protocol	Phase	Year	No. of pts (a)	% CR (b)	OS (b)
AML					
JALSG-AML 97	III	(98-01)	15	79%	47% (5-yr)
JALSG-AML 201	III	(02-06)	13	78%	57% (5-yr)
JALSG-APL 97	III	(98-02)	2	95%	86% (4-yr)
JALSG-APL 204	III	(04-11)	2	95%	89% (5-yr)
JALSG-AML209	IV	(11-)	9	NA	NA
JALSG-APL212G	II	(14-)	1	NA	NA
Therapy-related leukemia	II	(96-99)	16	75%	40% (3-yr)
ALL/Lymphoblastic lymphoma					
JCOG 9004	II	(91-94)	14	83%	31% (7-yr)
JCOG 9402	II	(94-99)	10	81%	29% (5-yr)
JALSG-ALL 97	II	(98-01)	8	74%	32% (5-yr)
JALSG-ALL 202	II	(03-10)	9	NA	NA
JALSG-ALL 2013	II	(14-)	4	NA	NA
JALSG Ph+ALL 2013	II	(14-)	1	NA	NA
CML					
JALSG-CML 207	III	(08-10)	1	NA	NA
JALSG-CML 212	III	(12-)	4	NA	NA
Hodgkin lymphoma					
JCOG 9305	II	(93-97)	7	79%	89% (5-yr)
JCOG 9705	II	(98-00)	6	70%	81% (5-yr)
Aggressive non-Hodgkin lymphoma / DLBCL					
JCOG 9505	II(c)	(95-98)	2	56%	42% (4-yr)
JCOG 9506	II	(95-97)	6	50%	49% (5-yr)
JCOG 9508	II	(96-99)	19	80%	68% (5-yr)
JCOG 9809	III	(99-02)	55	62%	56% (8-yr)
JCOG 0601	III	(08-14)	57	NA	NA
JCOG 0406	III	(08-12)	3	NA	NA
JCOG 0908	III	(08-15)	20	NA	NA
Indolent B-cell lymphoma					
JCOG 0203	II/III	(02-07)	52	77%	88% (6-yr)
Adult T-cell leukemia-lymphoma					
JCOG 9303	II	(94-97)	6	36%	31% (2-yr)
JCOG 9801	III	(98-03)	6	33%	19% (3-yr)
JCOG 0907	II	(11-)	3	NA	NA
JCOG 1111	III	(13-)	6	NA	NA
Nasal NK/T-lymphoma					
JCOG 0211-DI	I/II	(03-07)	8	77%	78% (2-yr)
Multiple myeloma					
JCOG 9301	III	(93-98)	10	50% (d)	50% (4-yr)
JCOG 0112	III	(02-05)	9	46% (d)	63% (2-yr)
JCOG 0904	II(c)	(09-)	7	NA	NA
JCOG 1105	III	(13-)	6	NA	NA

(a) The number of patients enrolled from our department; (b) As the number of enrolled patients in our department is relatively small, the % CR or OS for the entire number of enrolled patients in the JCOG or JALSG trials is shown here.
(c) Randomized phase II study
(d) CR + PR rate. Abbreviations: JCOG, Japan Clinical Oncology Group; JALSG, Japan Adult Leukemia Study Group; LSG, Lymphoma Study Group; OS, overall survival; NA, not available

List of papers published in 2015

Journal

1. Kamiyama Y, Kobayashi Y, Fukuhara S, Morikawa N, Munakata W, Miyagi Maeshima A, Maruyama D, Kim SW, Watanabe T, Terauchi T, Muramatsu Y, Tobinai K. Incidental detection of malignant lymphoma in subjects in a cancer surveillance programme. Br J Haematol, 169:138-142, 2015

2. Suzuki K, Ogura M, Abe Y, Suzuki T, Tobinai K, Ando K, Taniwaki M, Maruyama D, Kojima M, Kuroda J, Achira M, Iizuka K. Phase 1 study in Japan of siltuximab, an anti-IL-6 monoclonal antibody, in relapsed/refractory multiple myeloma. Int J Hematol, 101:286-294, 2015

3. Ishida T, Jo T, Takemoto S, Suzushima H, Uozumi K, Yamamoto K, Uike N, Saburi Y, Nosaka K, Utsunomiya A, Tobinai K, Fujiwara H, Ishitsuka K, Yoshida S, Taira N, Moriuchi Y, Imada K, Miyamoto T, Akinaga S, Tomonaga M, Ueda R. Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. Br J Haematol, 169:672-682, 2015

4. Tateishi U, Tatsumi M, Terauchi T, Ando K, Niitsu N, Kim WS, Suh C, Ogura M, Tobinai K. Prognostic significance of metabolic tumor burden by positron emission tomography/computed tomography in patients with relapsed/refractory diffuse large B-cell lymphoma. Cancer Sci, 106:186-193, 2015

5. Maeshima AM, Taniguchi H, Tanioka K, Kitahara H, Miyamoto K, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K, Kushima R. Clinicopathological characteristics of follicular lymphoma with peripheral blood involvement. Leuk Lymphoma, 56:2000-2004, 2015

6. Nakaseko C, Takahashi N, Ishizawa K, Kobayashi Y, Ohashi K, Nakagawa Y, Yamamoto K, Miyamura K, Taniwaki M, Okada M, Kawaguchi T, Shibata A, Fujii Y, Ono C, Ohnishi K. A phase 1/2 study of bosutinib in Japanese adults with Philadelphia chromosome-positive chronic myeloid leukemia. Int J Hematol, 101:154-164, 2015

7. Kataoka K, Nagata Y, Kitanaka A, Shiraishi Y, Shimamura T, Yasunaga J, Totoki Y, Chiba K, Sato-Otsubo A, Nagae G, Ishii R, Muto S, Kotani S, Watatani Y, Takeda J, Sanada M, Tanaka H, Suzuki H, Sato Y, Shiozawa Y, Yoshizato T, Yoshida K, Makishima H, Iwanaga M, Ma G, Nosaka K, Hishizawa M, Itonaga H, Imaizumi Y, Munakata W, Ogasawara H, Sato T, Sasai K, Muramoto K, Penova M, Kawaguchi T, Nakamura H, Hama N, Shide K, Kubuki Y, Hidaka T, Kameda T, Nakamaki T, Ishiyama K, Miyawaki S, Yoon SS, Tobinai K, Miyazaki Y, Takaori-Kondo A, Matsuda F, Takeuchi K, Nureki O, Aburatani H, Watanabe T, Shibata T, Matsuoka M, Miyano S, Shimoda K, Ogawa S. Integrated molecular analysis of adult T cell leukemia/lymphoma. Nat Genet, 47:1304-1315, 2015

8. Narita T, Inagaki A, Kobayashi T, Kuroda Y, Fukushima T, Nezu M, Fuchida S, Sakai H, Sekiguchi N, Sugiura I, Maeda Y, Takamatsu H, Tsukamoto N, Maruyama D, Kubota Y, Kojima M, Sunami K, Ono T, Ri M, Tobinai K, Iida S. t(14;16)-positive multiple myeloma shows negativity for CD56 expression and unfavorable outcome even in the era of novel drugs. Blood Cancer J, 5:e285, 2015

9. Ohmoto A, Maeshima AM, Taniguchi H, Tanioka K, Makita S, Kitahara H, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Histopathological analysis of B-cell non-Hodgkin lymphomas without light chain restriction by using flow cytometry. Leuk Lymphoma, 56:3301-3305, 2015

10. Maeshima AM, Taniguchi H, Nomoto J, Makita S, Kitahara H, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Clinicopathological features of classical Hodgkin lymphoma in patients ≥ 40 years old, with special reference to composite cases. Jpn J Clin Oncol, 45:921-928, 2015

11. Matsue K, Iwasaki H, Chou T, Tobinai K, Sunami K, Ogawa Y, Kurihara M, Midorikawa S, Zaki M, Doerr T, Iida S. Pomalidomide alone or in combination with dexamethasone in Japanese patients with refractory or relapsed and refractory multiple myeloma. Cancer Sci, 106:1561-1567, 2015

12. Miyagi Maeshima A, Taniguchi H, Makita S, Kitahara H, Miyamoto K, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Histopathological Characteristics of Lymphomas in the Upper Aerodigestive Tract. A Single-Institute Study in Japan. J Clin Exp Hematop, 55:7-11, 2015

13. Ogura M, Uchida T, Terui Y, Hayakawa F, Kobayashi Y, Taniwaki M, Takamatsu Y, Naoe T, Tobinai K, Munakata W, Yamauchi T, Kageyama A, Yuasa M, Motoyama M, Tsunoda T, Hatake K. Phase I study of OPB-51602, an oral inhibitor of signal transducer and activator of transcription 3, in patients with relapsed/refractory hematological malignancies. Cancer Sci, 106:896-901, 2015

14. Tanaka Y, Kobayashi Y, Maeshima AM, Oh SY, Nomoto J, Fukuhara S, Kitahara H, Munakata W, Suzuki T, Maruyama D, Tobinai K. Intravascular large B-cell lymphoma secondary to lymphoplasmacytic lymphoma: a case report and review of literature with clonality analysis. Int J Clin Exp Pathol, 8:3339-3343, 2015

15. Kusumoto S, Tanaka Y, Suzuki R, Watanabe T, Nakata M, Takasaki H, Fukushima N, Fukushima T, Moriuchi Y, Itoh K, Nosaka K, Choi I, Sawa M, Okamoto R, Tsujimura H, Uchida T, Suzuki S, Okamoto M, Takahashi T, Sugiura I, Onishi Y, Kohri M, Yoshida S, Sakai R, Kojima M, Takahashi H, Tomita A, Maruyama D, Atsuta Y, Tanaka E, Suzuki T, Kinoshita T, Ogura M, Mizokami M, Ueda R. Monitoring of Hepatitis B Virus (HBV) DNA and Risk of HBV Reactivation in B-Cell Lymphoma: A Prospective Observational Study. Clin Infect Dis, 61:719-729, 2015

16. Saito H, Maruyama D, Maeshima AM, Makita S, Kitahara H, Miyamoto K, Fukuhara S, Munakata W, Suzuki T, Kobayashi Y, Taniguchi H, Tobinai K. Prolonged lymphocytopenia after bendamustine therapy in patients with relapsed or refractory indolent B-cell and mantle cell lymphoma. Blood Cancer J, 5:e362, 2015

17. Kobayashi Y, Yamauchi T, Kiyoi H, Sakura T, Hata T, Ando K, Watabe A, Harada A, Taube T, Miyazaki Y, Naoe T. Phase I trial of volasertib, a Polo-like kinase inhibitor, in Japanese patients with acute myeloid leukemia. Cancer Sci, 106:1590-1595, 2015

18. Ito J, Yoshida A, Maeshima AM, Nakagawa K, Watanabe S, Kobayashi Y, Fukuhara S, Tsuta K. Concurrent thymoma, thymic carcinoma, and T lymphoblastic leukemia/lymphoma in an anterior mediastinal mass. Pathol Res Pract, 211:693-696, 2015

Department of Hematopoietic Stem Cell Transplantation

Takahiro Fukuda, Takuya Yamashita, Sung-Won Kim, Saiko Kurosawa, Shigeo Fuji, Yoshihiro Inamoto, Takashi Tanaka, Akio Ohnishi

Introduction

At the National Cancer Center Hospital, the Department of Hematopoietic Stem Cell Transplantation (HSCT) specializes in patients who undergo allogeneic or autologous HSCT. Twenty-six beds in ward 12B and an additional three beds on ward 11A, which are filtered by a central high-efficiency particulate air filtration system, are solely dedicated to our Transplant Unit.

Routine activities

Six staff physicians (Drs. Yamashita, Kim, Kurosawa, Fuji, Inamoto, and Fukuda) and two chief residents (Drs. Tanaka and Ohnishi) participate in the transplant program. Children who have undergone HSCT are managed in collaboration with Dr. Ogawa, the chief of the Department of Pediatric Oncology, and the transplant team. In 2015, a total of 106 transplantations were performed at the 12B and 12A transplant units. The numbers of each type of HCST between 2011 and 2015 are shown in Table 1, and the numbers of patients according to disease type are shown in Table 2.

At the weekly conference on Monday afternoons, in collaboration with doctors of the Dopartment of Hematology, about 30 hospitalized HSCT patients and those who have been referred for HSCT, are reviewed for clinical management and a decision regarding their eligibility for HSCT. The transplant unit is staffed by 24 nurses trained in oncology and specialized supportive care for HSCT patients. The nursing unit has been assuming leadership in an effort to facilitate improved care for skin and gut graft-versus-host disease (GVHD), and establishment of a Long-term Follow-up Unit (LTFU) for the education of patients and their family members. In 2015, 370 patients visited our LTFU clinic. At the weekly 12B ward meeting on Friday afternoons, all HSCT patients are reviewed in detail by all transplant team members including doctors, nurses, pharmacists, the nutritional support team, clinical research coordinators, and the transplant coordinator.

Research activities and clinical trials

Our transplant team has been focusing on the development of comprehensive cellular immunotherapy, including reduced-intensity stem cell transplants for elderly patients. A clinical trial of post-transplant consolidation with the WT1 vaccine has been completed. We have started nationwide studies focusing on HSCT for patients with adult T-cell leukemia. Our study suggested that the use of mogamulizumab, anti-CCR4 antibody, before allogeneic HSCT significantly worsened the clinical outcome, mainly due to an increased risk of acute GVHD. We have also published a large nationwide survey of quality of life (QOL) in 576 patients with acute leukemia. In 2015, we published 27 articles in peer-reviewed international journals.

Table 1. Number of each type of HSCT

Year		2011	2012	2013	2014	2015
Allogeneic		76	72	87	93	87
Unrelated	BMT	54	46	53	52	37
	PBSCT	0	3	5	6	7
	CBT	4	8	8	9	24
Related	BMT	2	0	1	2	0
	PBSCT	16	15	20	24	19
Autologous		25	25	23	10	19
Total		101	97	110	103	106

Table 2. Number of patients who underwent HSCT in 2015

Diagnosis	Allogeneic	Autologous
Acute myeloid leukemia	29	0
Myelodysplastic syndrome	6	0
Acute lymphocytic leukemia	13	0
Malignant lymphoma (including ATL)	36	9
Multiple myeloma	0	3
Solid tumors	0	7
Others	3	0
Total	87	19

List of papers published in 2015

Journal

1. Ueda R, Fuji S, Mori S, Hiramoto N, Hashimoto H, Tanaka T, Tada K, Kobayashi Y, Morikawa N, Shinohara A, Okinaka K, Maeshima AM, Kurosawa S, Kim SW, Yamashita T, Fukuda T. Characteristics and outcomes of patients diagnosed with norovirus gastroenteritis after allogeneic hematopoietic stem cell transplantation based on immunochromatography. Int J Hematol, 102:121-128, 2015

2. Kurosawa S, Yamaguchi T, Mori T, Kanamori H, Onishi Y, Emi N, Fujisawa S, Kohno A, Nakaseko C, Saito B, Kondo T, Hino M, Nawa Y, Kato S, Hashimoto A, Fukuda T. Patient-reported quality of life after allogeneic hematopoietic cell transplantation or chemotherapy for acute leukemia. Bone Marrow Transplant, 50:1241-1249, 2015

3. Fuji S, Yakushijin K, Kim SW, Yoshimura K, Kurosawa S, Fukuda T. Dynamic change of glycemic status during the early phase after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant, 50:1473-1475, 2015

4. Fuji S, Mori T, Khattry N, Cheng J, Do YR, Yakushijin K, Kohashi S, Fukuda T, Kim SW. Severe weight loss in 3 months after allogeneic hematopoietic SCT was associated with an increased risk of subsequent non-relapse mortality. Bone Marrow Transplant, 50:100-105, 2015

5. Fuji S, Kanda J, Kato S, Ikegame K, Morishima S, Miyamoto T, Hidaka M, Kubo K, Miyamura K, Tsudo M, Kobayashi H, Maesako Y, Eto T, Adachi S, Ichinohe T, Atsuta Y, Kanda Y, HLA Working Group of the Japan Society for Hematopoietic Cell Transplantation. A single high-resolution HLA mismatch has a similar adverse impact on the outcome of related hematopoietic stem cell transplantation as a single low-resolution HLA mismatch. Am J Hematol, 90:618-623, 2015

6. Fuji S. Haploidentical Related Peripheral Blood Stem Cell Transplantation as a Salvage Transplantation in Patients with Graft Failure. Intern Med, 54:2709-2710, 2015

7. Fuji S, Einsele H, Savani BN, Kapp M. Systematic Nutritional Support in Allogeneic Hematopoietic Stem Cell Transplant Recipients. Biol Blood Marrow Transplant, 21:1707-1713, 2015

8. Takano K, Fuji S, Uchida N, Ogawa H, Ohashi K, Eto T, Sakamaki H, Morishima Y, Kato K, Suzuki R, Fukuda T. Pre-transplant diabetes mellitus is a risk factor for non-relapse mortality, especially infection-related mortality, after allogeneic hematopoietic SCT. Bone Marrow Transplant, 50:553-558, 2015

9. Inamoto Y, Flowers ME, Wang T, Urbano-Ispizua A, Hemmer MT, Cutler CS, Couriel DR, Alousi AM, Antin JH, Gale RP, Gupta V, Hamilton BK, Kharfan-Dabaja MA, Marks DI, Ringdén OT, Socié G, Solh MM, Akpek G, Cairo MS, Chao NJ, Hayashi RJ, Nishihori T, Reshef R, Saad A, Shah A, Teshima T, Tallman MS, Wirk B, Spellman SR, Arora M, Martin PJ. Tacrolimus versus Cyclosporine after Hematopoietic Cell Transplantation for Acquired Aplastic Anemia. Biol Blood Marrow Transplant, 21:1776-1782, 2015

10. Inamoto Y, Sun YC, Flowers ME, Carpenter PA, Martin PJ, Li P, Wang R, Chai X, Storer BE, Shen TT, Lee SJ. Bandage Soft Contact Lenses for Ocular Graft-versus-Host Disease. Biol Blood Marrow Transplant, 21:2002-2007, 2015

11. Inamoto Y, Shah NN, Savani BN, Shaw BE, Abraham AA, Ahmed IA, Akpek G, Atsuta Y, Baker KS, Basak GW, Bitan M, DeFilipp Z, Gregory TK, Greinix HT, Hamadani M, Hamilton BK, Hayashi RJ, Jacobsohn DA, Kamble RT, Kasow KA, Khera N, Lazarus HM, Malone AK, Lupo-Stanghellini MT, Margossian SP, Muffly LS, Norkin M, Ramanathan M, Salooja N, Schoemans H, Wingard JR, Wirk B, Wood WA, Yong A, Duncan CN, Flowers ME, Majhail NS. Secondary solid cancer screening following hematopoietic cell transplantation. Bone Marrow Transplant, 50:1013-1023, 2015

12. Ogata M, Fukuda T, Teshima T. Human herpesvirus-6 encephalitis after allogeneic hematopoietic cell transplantation: what we do and do not know. Bone Marrow Transplant, 50:1030-1036, 2015

13. Takenaka K, Nishida T, Asano-Mori Y, Oshima K, Ohashi K, Mori T, Kanamori H, Miyamura K, Kato C, Kobayashi N, Uchida N, Nakamae H, Ichinohe T, Morishima Y, Suzuki R, Yamaguchi T, Fukuda T. Cytomegalovirus Reactivation after Allogeneic Hematopoietic Stem Cell Transplantation is Associated with a Reduced Risk of Relapse in Patients with Acute Myeloid Leukemia Who Survived to Day 100 after Transplantation: The Japan Society for Hematopoietic Cell Transplantation Transplantation-related Complication Working Group. Biol Blood Marrow Transplant, 21:2008-2016, 2015

14. Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M, Arat M, Bader P, Baron F, Bazarbachi A, Blaise D, Ciceri F, Corbacioglu S, Dalle JH, Duarte RF, Fukuda T, Huynh A, Masszi T, Michallet M, Nagler A, NiChonghaile M, Pagluica T, Peters C, Petersen FB, Richardson PG, Ruutu T, Savani BN, Wallhult E, Yakoub-Agha I, Carreras E. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant, 50:781-789, 2015

15. Nakasone H, Fukuda T, Kanda J, Mori T, Yano S, Kobayashi T, Miyamura K, Eto T, Kanamori H, Iwato K, Uchida N, Mori S, Nagamura-Inoue T, Ichinohe T, Atsuta Y, Teshima T, Murata M, GVHD working group of the Japan Society of Hematopoietic Cell Transplantation. Impact of conditioning intensity and TBI on acute GVHD after hematopoietic cell transplantation. Bone Marrow Transplant, 50:559-565, 2015

16. Nakane T, Fukuda T, Kanda J, Taniguchi S, Eto T, Ohashi K, Nakamae H, Kurokawa M, Mori T, Morishima Y, Nagamura-Inoue T, Sakamaki H, Atsuta Y, Murata M. Age influences post-graft-versus-host disease non-relapse mortality in adults with acute graft-versus-host disease of varying severity following allogeneic hematopoietic cell transplant. Leuk Lymphoma, 56:2392-2397, 2015

17. Arai Y, Aoki K, Takeda J, Kondo T, Eto T, Ota S, Hashimoto H, Fukuda T, Ozawa Y, Kanda Y, Kato C, Kurokawa M, Iwato K, Onizuka M, Ichinohe T, Atsuta Y, Takami A, AML and MDS Working Group of Japan Society for Hematopoietic Cell Transplantation. Clinical significance of high-dose cytarabine added to cyclophosphamide/total-body irradiation in bone marrow or peripheral blood stem cell transplantation for myeloid malignancy. J Hematol Oncol, 8:102, 2015

18. Nomoto H, Takami A, Espinoza JL, Matsuo K, Mizuno S, Onizuka M, Kashiwase K, Morishima Y, Fukuda T, Kodera Y, Doki N, Miyamura K, Mori T, Nakao S, Ohtake S, Morishita E. A donor thrombomodulin gene variation predicts graft-versus-host disease development and mortality after bone marrow transplantation. Int J Hematol, 102:460-470, 2015

19. Aoki T, Suzuki R, Kuwatsuka Y, Kako S, Fujimoto K, Taguchi J, Kondo T, Ohata K, Ito T, Kamoda Y, Fukuda T, Ichinohe T, Takeuchi K, Izutsu K, Suzumiya J. Long-term survival following autologous and allogeneic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm. Blood, 125:3559-3562, 2015

20. Tanaka M, Miyamura K, Terakura S, Imai K, Uchida N, Ago H, Sakura T, Eto T, Ohashi K, Fukuda T, Taniguchi S, Mori S, Nagamura-Inoue T, Atsuta Y, Okamoto S. Comparison of cord blood transplantation with unrelated bone marrow transplantation in patients older than fifty years. Biol Blood Marrow Transplant, 21:517-525, 2015

21. Kanda J, Ichinohe T, Fuji S, Maeda Y, Ohashi K, Fukuda T, Miyamura K, Iwato K, Eto T, Nakamae H, Kobayashi N, Mori T, Mori S, Morishima Y, Atsuta Y, Kanda Y, HLA Working Group of the Japan Society for Hematopoietic Cell Transplantation. Impact of HLA mismatch direction on the outcome of unrelated bone marrow transplantation: a retrospective analysis from the Japan Society for Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant, 21:305-311, 2015

22. Kako S, Izutsu K, Kato K, Kim SW, Mori T, Fukuda T, Kobayashi N, Taji H, Hashimoto H, Kondo T, Sakamaki H, Morishima Y, Kato K, Suzuki R, Suzumiya J, Adult Lymphoma Working Group of the Japanese Society for Hematopoietic Cell Transplantation. The role of hematopoietic stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Am J Hematol, 90:132-138, 2015

23. Aoki K, Ishikawa T, Ishiyama K, Aoki J, Itonaga H, Fukuda T, Kakihana K, Uchida N, Ueda Y, Eto T, Mori T, Kondo T, Iwato K, Morishima Y, Tanaka J, Atsuta Y, Miyazaki Y, Adult MyelodysplasticSyndromes Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT). Allogeneic haematopoietic cell transplantation with reduced-intensity conditioning for elderly patients with advanced myelodysplastic syndromes: a nationwide study. Br J Haematol, 168:463-466, 2015

24. Ishida H, Kato M, Kudo K, Taga T, Tomizawa D, Miyamura T, Goto H, Inagaki J, Koh K, Terui K, Ogawa A, Kawano Y, Inoue M, Sawada A, Kato K, Atsuta Y, Yamashita T, Adachi S. Comparison of Outcomes for Pediatric Patients With Acute Myeloid Leukemia in Remission and Undergoing Allogeneic Hematopoietic Cell Transplantation With Myeloablative Conditioning Regimens Based on Either Intravenous Busulfan or Total Body Irradiation: A Report From the Japanese Society for Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant, 21:2141-2147, 2015

25. Yano S, Mori S, Saito T, Yokoyama H, Machishima T, Shimada T, Yahagi Y, Sugiyama K, Ogasawara Y, Takahara S, Kasama K, Katsube A, Kamiyama Y, Suzuki K, Inui Y, Usui N, Aiba K, Yamashita T. Pharmacokinetics for once-daily modified release formulation of tacrolimus hydrate in unrelated hematopoietic stem cell transplantation. Ann Hematol, 94:491-496, 2015

26. Hashimoto H, Kitano S, Ueda R, Ito A, Tada K, Fuji S, Kim SW, Yamashita T, Tomura D, Nukaya I, Mineno J, Fukuda T, Mori S, Takaue Y, Heike Y. Infusion of donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene for recurrent hematologic malignancies after allogeneic hematopoietic stem cell transplantation. Int J Hematol, 102:101-110, 2015 (Erratum in : Int J Hematol. 102:506, 2015)

27. Hashimoto H, Kitano S, Yamagata S, Miyagi Maeshima A, Ueda R, Ito A, Tada K, Fuji S, Yamashita T, Tomura D, Nukaya I, Mineno J, Fukuda T, Mori S, Takaue Y, Heike Y. Donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene: detailed immunological function following add-back after haplo-identical transplantation. Cytotherapy, 17:1820-1830, 2015

Department of Blood Transfusion and Cellular Therapy

Ryuji Tanosaki

Introduction

The missions of the Department of Blood Transfusion and Cellular Therapy are management of in-hospital transfusion and support for the hematopoietic stem cell transplantation team in respect of providing safe and secure cellular products. In common with the Department of Clinical Laboratories, our blood transfusion examination laboratory received ISO 15189 accreditation, which certifies the quality and competence of a medical laboratory with regard to quality management and techniques, developed by the International Organization for Standardization Technical Committee 212 (ISO/TC 212). Our hospital is also accredited by the Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT). The chief doctor (R.T.) also supervises the phlebotomy section of the outpatient clinics.

Routine activities

Currently, our staff members consist of one JSTMCT-accredited medical doctor and six specifically engaged medical technologists (MT) (including two JSTMCT-accredited technologists) who come to us from the Department of Pathology and Clinical Laboratories. Most activities in our department are undertaken in collaboration with the Department of Pathology and Clinical Laboratories. The Transfusion Medicine Committee is held every month, an administrative meeting is held weekly, and an all-staff meeting is held weekly in our department and once a month in the Department of Clinical Laboratories.

As an in-hospital transfusion service section, we purchase blood products, which are required and ordered by clinicians, from the Red Cross, and examine and confirm the ABO blood type, and provide them for clinical use without any delay. In 2015, the total units of red blood cells (RBC), platelet concentrates (PC) and fresh frozen plasma (FFP), which were used in our hospital, were 9,871, 40,225 and 4,302, respectively, with wastage rates of RCC 0.5%, PC 0.04%, FFP 0.2%, respectively. Thanks to the Tokyo Red Cross and the convenient location of our hospital, blood products are available within one hour almost every time when they are needed in an emergency.

We employ the Type & Screen and computer cross-match system, but special attention is paid to blood typing, because about 100 cases of hematopoietic stem cell transplantation (SCT) are performed in our hospital every year including many ABO-mismatched donor-recipient pairs. All transfusion procedures are performed under a strict hemo-vigilant system that employs electronic medical records managed by the computer system at the blood transfusion service. Hematopoietic stem cells that are to be transplanted to the SCT patients, that is, grafts, are also subject to the same safety and bio-vigilant system as other blood products.

We also manage the processing, storage, and quality control of hematopoietic stem cells used for transplantation as a routine activity in collaboration with medical engineers and members of the Department of Hematopoietic Stem Cell Transplantation. We inform other SCT-team members of the optimal timing for peripheral blood stem cell harvest (PBSCH) by monitoring counts of chemotherapy/G-CSF-mobilized progenitor cells, for not only CD34-positive ($CD34^+$) cell count, but also HPC, a new enumeration marker developed in our department. The management meeting is held once a month, the members of which consist of staff from the Department of Hematopoietic Stem Cell Transplantation, Medical Engineering Section, the head of technologists, and the members of our department. The chief doctor is also involved in the management of transplant patients both as inpatients and in the outpatient

clinic as a staff member of the hematopoietic stem cell transplantation team, which facilitates and promotes inter-departmental collaboration, as mentioned above.

Since April 2015, we started a modified Cell-Free and Concentrated Ascites Reinfusion Therapy (KM-CART) for the management of patients with refractory ascites. Ascites from each patient were registered in our blood computer system with a minor modification, which could be processed in the same manner as a blood product. About 100 procedures were performed in the first year without any major problems, and almost no serious adverse events were observed in infusion to patients.

Research activities

One of the Department's research projects is to develop a new enumeration technique for hematopoietic stem cells using an automated hematology analyzer, which is designated as 'HPC', in collaboration with a medical diagnostic company. The multicenter study for evaluation of HPC with the support of JSTMCT demonstrated that there was a very strong correlation between HPC values and $CD34^+$ cell counts, and we concluded that HPC is very promising as a candidate of an alternative for $CD34^+$ cell.

Another project is to establish a nationwide infrastructure of processing and management of cellular products used for hematopoietic stem cell transplantation as a committee member of the corresponding academic societies with the support of the Ministry of Health, Labour and Welfare. In 2015, we conducted a nationwide external quality assessment of $CD34^+$ cell counts for the first time. We also published a Textbook of Cell Processing for Hematopoietic Stem Cell Transplantation. We also launched an accreditation system for Clinical Cell Therapy Specialists for the first time in Japan, and 431 medical experts were given accreditation in the first year.

Education

The chief doctor supervises the education program of the Department of Clinical Laboratories for all medical technologists. The education program consists of a monthly educational conference in which each medical technologist presents his or her research, doctors' lectures, and RCPC (twice a year) were performed. It also includes educational lectures concerning ISO 15189. We also support and facilitate academic presentations and publications by all the MT members.

List of papers published in 2015

Journal

1. Suehiro Y, Hasegawa A, Iino T, Sasada A, Watanabe N, Matsuoka M, Takamori A, Tanosaki R, Utsunomiya A, Choi I, Fukuda T, Miura O, Takaishi S, Teshima T, Akashi K, Kannagi M, Uike N, Okamura J. Clinical outcomes of a novel therapeutic vaccine with Tax peptide-pulsed dendritic cells for adult T cell leukaemia/lymphoma in a pilot study. Br J Haematol, 169:356-367, 2015

Department of Pediatric Oncology

Chitose Ogawa, Tadashi Kumamoto, Yuki Aoki, Ayumu Arakawa, Yasuhiro Fujiwara, Hiroshi Kawamoto, Ako Hosono, Naoko Yasui, Hide Kaneda

Introduction

Pediatric oncology includes a wide variety of malignancies in children and adolescents such as acute leukemia and malignant lymphoma, as well as solid tumors including osteosarcoma, soft tissue sarcoma, neuroblastoma, liver tumor and retinoblastoma. Many diseases are usually chemosensitive and curable with appropriate treatment. The common approach to these diseases is a "risk-adapted therapy" strategy considering long-term life expectancy. In the Department of Pediatric Oncology, patients with pediatric malignancies are managed by four pediatric oncologists and a pediatric surgeon. Although pediatric oncologists mainly treat and manage patients, a multidisciplinary team approach including radiation oncologists, orthopedic surgeons, ophthalmologic surgeons and others is incorporated for the treatment. To achieve treatment completion and optimal quality of hospital life for children, pediatric nurse specialists, teachers, child care staff, psychologists and psychiatrists also join our team. For young patients, educational opportunities ranging from elementary school to high school are available in the pediatric ward, where seven teachers work daily.

Routine activities

We deal with 50-80 new patients every year. Our daily activity in the pediatric outpatient clinic is to manage new patients, to treat patients with chemotherapy or blood transfusions and to provide follow-up care for patients who have completed intensive treatment. Patients receive multidisciplinary therapy, including surgical removal of tumors, radiation therapy, chemotherapy, and sometimes stem cell transplantation (SCT), as indicated.

A Pediatric Conference is held every morning, mainly to decide on individual treatment plans. The pediatric staff and trainees discuss various issues regarding pediatric inpatients on daily rounds. Inter-department conferences in cooperation with orthopedics, radiation oncology, and palliative care are individually scheduled every two weeks.

Research activities

1. For newly diagnosed patients, we participate in several multicenter studies in the Japan Children's Cancer Group (JCCG), including those by the Japan Ewing Sarcoma Study Group (JESS), the Japan Rhabdomyosarcoma Study Group (JRSG) and the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG). In addition, we also conduct our own clinical trials.
2. For relapsed patients, we are actively involved in the development of new drugs and treatments including off-label and unapproved medications.
3. For patients with veno-occlusive disease in stem cell transplantation and patients with delayed excretion of methotrexate, a phase II registration trial of defibrotide and glucarpidase are conducted.
4. For provision of a similar environment during the treatment to that of before patients' disease onset, we plan to construct a medical care system through the use of appropriate medical and social resources in their local communities.

Clinical trials

In 2015, we conducted 12 trials, including early phase trials, an international study and cooperative studies. The five trials (1, 4, 6, 7 and 12) are investigator-initiated registration-directed clinical trials conducted under the Pharmaceutical Affairs Law in Japan. Two international cooperative trials

are ongoing: in the No. 10 trial, we are collaborating with the International BFM group in Europe and in the No. 12 trial with the Children's Oncology Group in the USA.

1) A phase II trial of glucarpidase for patients who were treated with high-dose methotrexate resulting in delayed excretion.
2) A phase Ib study of 131I-metaiodobenzylguanidine (MIBG) therapy with valproic acid (VPA) for high risk or recurrent neuroblastoma
3) A phase Ib study of VPA and 13-cis-RA (isotretinoin) combination therapy for advanced and recurrent neuroblastoma.
4) A feasibility trial of ch14.18 combined with IL-2 and various colony-stimulating factors for recurrent neuroblastoma.
5) A phase I trial of immunotherapy using HLA-A2-and A24-restricted glypican-3 peptide vaccine for pediatric tumors.
6) Efficacy and safety study of defibrotide (DF) for the treatment of veno-occlusive disease (VOD).
7) Efficacy and safety study of defibrotide (DF) for the prophylaxis of veno-occlusive disease (VOD).
8) The Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) ALL-T11 and the Japan Adult Leukemia Study Group (JALSG) T-ALL-211-U ALL-T11: A Multi-Center Phase II Study in Children and Adolescents with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia
9) The Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) ALL-B12: A Multi-Center Phase II/III Study in Children with Newly Diagnosed B-cell Precursor Acute Lymphoblastic Leukemia
10) An International Study for Treatment of Standard Risk Childhood Relapsed ALL 2010 (IntReALL SR 2010): A randomized Phase III Study Conducted by the Resistant Disease Committee of the International BFM Study Group
11) A Multi-Center Seamless Phase II-III Randomized Trial of High-dose Cytarabine in Initial Induction with Evaluation of Flow-cytometry-based Minimal Residual Disease for Children with de Novo Acute Myeloid Leukemia (AML-12)
12) Treatment of Children with All Stages of Hepatoblastoma with Temsirolimus Added to High Risk Stratum Treatment: A Phase III Study

Education

We provide personnel training and education for the skills of diagnosis and management for pediatric hematological malignancies and solid tumors. Residents also learn the skills to treat not only newly diagnosed patients but also relapsed or refractory patients by global standard therapy. In addition, senior residents acquire the ability to plan studies for new agents or new therapies, which we regard as an important role of this center.

Future prospects

We promote the development of therapies for pediatric malignancies as a top priority. For this mission, we lead the planning of clinical or registration trials in cooperation with domestic and international centers as a core institution in Japan.

Our other mission is to provide individualized medicine for children with cancer. For this aim, we plan to expand the subjects in the comprehensive genetic testing project in our center to the pediatric age group. In addition, we promote clinical trials using molecular targeted agents for pediatric malignancies.

Table 1. Number of patients in 2015

Acute lymphoblastic leukemia	7
Acute myeloid leukemia	1
Non-Hodgkin lymphoma	1
Hodgkin lymphoma	1
Other hematologic malignancies	0
Neuroblastoma	7
Retinoblastoma*	7*
Osteosarcoma	8
Ewing sarcoma family tumor	10
Rhabdomyosarcoma	5
Other soft tissue tumors	7
Germ cell tumor	0
Other solid tumors	2
Total	56

* advanced cases only

Table 2. Type of procedure

Tumor resection	11	
Metastasis of Ewing sarcoma		4
Metastasis of osteosarcoma		4
Metastasis of rhabdomyosarcoma		1
Neuroblastoma		1
Other sarcoma		1
Lymph node dissection	2	
Central venous (CV) port / catheter removal	6	
Total	19	

List of papers published in 2015

Journal

1. Yoshida A, Asano N, Kawai A, Kawamoto H, Nakazawa A, Kishimoto H, Kushima R. Differential SALL4 immunoexpression in malignant rhabdoid tumours and epithelioid sarcomas. Histopathology, 66:252-261, 2015

2. Yasui N, Yoshida A, Kawamoto H, Yonemori K, Hosono A, Kawai A. Clinicopathologic analysis of spindle cell/sclerosing rhabdomyosarcoma. Pediatr Blood Cancer, 62:1011-1016, 2015

3. Ono R, Hasegawa D, Hirabayashi S, Kamiya T, Yoshida K, Yonekawa S, Ogawa C, Hosoya R, Toki T, Terui K, Ito E, Manabe A. Acute megakaryoblastic leukemia with acquired trisomy 21 and GATA1 mutations in phenotypically normal children. Eur J Pediatr, 174:525-531, 2015

4. Kato M, Manabe A, Saito AM, Koh K, Inukai T, Ogawa C, Goto H, Tsuchida M, Ohara A. Outcome of pediatric acute lymphoblastic leukemia with very late relapse: a retrospective analysis by the Tokyo Children's Cancer Study Group (TCCSG). Int J Hematol, 101:52-57, 2015

5. Mori M, Imaizumi M, Ishiwada N, Kaneko T, Goto H, Kato K, Hara J, Kosaka Y, Koike K, Kawamoto H, Maeda N, Yoshinari T, Kishino H, Takahashi K, Kawahara S, Kartsonis NA, Komada Y. Pharmacokinetics, efficacy, and safety of caspofungin in Japanese pediatric patients with invasive candidiasis and invasive aspergillosis. J Infect Chemother, 21:421-426, 2015

6. Kinuya S, Yoshinaga K, Higuchi T, Jinguji M, Kurihara H, Kawamoto H. Draft guidelines regarding appropriate use of (131)I-MIBG radiotherapy for neuroendocrine tumors : Guideline Drafting Committee for Radiotherapy with (131)I-MIBG, Committee for Nuclear Oncology and Immunology, The Japanese Society of Nuclear Medicine. Ann Nucl Med, 29:543-552, 2015

7. Yasui N, Kawamoto H, Fujiwara M, Aihara Y, Ogawa C, Hosono A, Suzuki S. High-dose chemotherapy for high-risk retinoblastoma: clinical course and outcome of 14 cases in the National Cancer Center, Japan. Bone Marrow Transplant, 50:221-224, 2015

Department of General Internal Medicine/Oncologic Emergencies

Ken Ohashi, Hisashi Baba, Keiichiro Osame, Masaaki Shoji, Takeshi Iwasa, Keiji Okinaka, Yukiko Okazaki

Introduction

The increasing number of cancer patients who visit the National Cancer Center Hospital have a wide range of non-cancer-related medical problems such as diabetes, hypertension, heart diseases, and kidney diseases. Cancer or its treatment can aggravate the pre-existing medical conditions and sometimes can cause these problems. These medical issues must be addressed and managed along with the cancer itself so that our patients can go through optimal cancer therapies and have a better outcome. The Department of General Internal Medicine was reorganized in October 2010 to better serve these diverse needs of cancer patients and provide more comprehensive, patient-centered care. Our staff have experience and expertise in their respective fields and provide comprehensive management of these issues.

Routine activities

We see cancer patients on both an inpatient and outpatient basis in consultation upon the request of NCCH cancer specialists. Reasons for consultation include preoperative assessment of surgical risks, assessment of ischemic heart disease, management of hyperglycemia, treatment of heart and renal failure, management of infections, and other medical disorders. When necessary, we also offer appropriate referral to other health care facilities for further evaluation or treatment. In addition, patients seen in consultation may be followed after discharge as outpatients for the duration of their care at the NCCH. Since April 2011, we have expanded diabetes consultation services into the NCC Hospital East, improving the quality of diabetes care there.

Cardiology:

Cardiologists take charge of ECG, echocardiography, in-hospital consultation, and the outpatient clinic. Consultations include preoperative assessment of surgical risks, assessment of ischemic heart disease, management of arrhythmia, management of heart failure, and management of other cardiological problems. The number of consultations is about 2,000 a year. When an emergency procedure is necessary, we consider transferring the patient to other facilities that have specialists. Recently, the number of clinical trials for cancer that require echocardiography assessment has been increasing, so we make every effort to practice tests more efficiently.

Diabetology:

We provided more than 600 diabetes consultations in 2015, which include perioperative management of diabetes and treatment of steroid-induced hyperglycemia during chemotherapy. In many cases, initiation of insulin is the treatment of choice. We also offer close follow-ups on an outpatient basis for those who have diabetes during their cancer treatment at the NCCH.

Infectious diseases:

Since August 2015, an Infectious Disease specialist has provided about 200 consultations including active interventions triggered by positive blood culture. An ID physician has been also responsible for control of healthcare-associated infections as the Chief of the Infection Control Team. Implementation of antimicrobials stewardship is the other main task of the ID physician in collaboration with pharmacists. Through these activities, we aim to provide safer and higher-quality cancer care in the NCCH.

Department of Dentistry

Takao Ueno, Wakako Yatsuoka, Kyoko Miyamoto, Hiromi Ishida, Yoko Suzuki, Chie Asano

Introduction

Oral complications are common in patients receiving chemotherapy or undergoing radiation therapy of the head and neck.

Oral complications during cancer treatment are directly linked to ingestion problems, and may even serve as a source of various infections such as aspiration pneumonia, thereby exacerbating systemic conditions, and sometimes preventing the completion of cancer treatment with negative effects on treatment prognoses.

The oral health status of patients with cancer is associated with the incidence rate and the degree of severity of oral complications. Effective oral hygiene management before initiating cancer treatment will contribute to the reduction of oral complications such as mouth sores, oral mucositis, or dental infections, and provide important support to facilitate smooth cancer treatment.

Routine activities

To prevent or reducing oral complications, we check complications during cancer treatment for oral conditions of the patients, identify the patients at risk, and start preventive measures before cancer therapy begins.

Our routine activities for cancer patients is below:

1) Management of oral complications of high-dose chemotherapy and/or stem cell transplant before treatment begins
2) Prevention and treatment of oral complications during chemotherapy and/or radiation therapy
3) Perioperative dental management for the prevention of postoperative pneumonia with oral, pharynx and esophageal surgery
4) Making prostheses for restoration of postoperative facial defects
5) Prevention and treatment of medication-related osteonecrosis of the jaw (MRONJ)
6) Cooperation business of a medical department and dentistry for the solution to dental problems of the cancer patient

Education

The lecture and the practice concerning oral health care were regularly held for nurses and residents.

Future prospects

Making a new system that strengthens collaboration with the nurse ~ An emphasis on preventive dental intervention, carried out screening of the oral cavity problem.

Contribute to medicine and dentistry collaboration in cancer care hospitals in the region.

Number of patients

The number of total patients：9,100
The number of new patients: 1,189

List of papers published in 2015

Book

1. Ueno T, Yurikusa T. 3. Oral health and lifestyle-related diseases, noncommunicable diseases (NCDs) 3) Cancer – Role of oral care in cancer treatment –. In: The current evidence of dental care and oral health for achieving healthy longevity in an aging society 2015, Japan, Japan Dental Assosiation, pp 86-108, 2015

2. Ueno T, Yurikusa T. 9. Effects of dental care 1) Effects of oral care on postoperative recovery period and state (including multidisciplinary cooperation) – Role of oral care in perioperative complications in surgery –. In: The current evidence of dental care and oral health for achieving healthy longevity in an aging society 2015, Japan, Japan Dental Assosiation, pp 236-244, 2015

Department of Anesthesia and Intensive Care

Tetsufumi Sato, Yoko Kinoshita, Minako Arai, Junya Matsumi, Nobuko Yokokawa, Seiji Shiraishi, Rie Suzuki, Mari Shibata, Yosuke Kawaguchi, Maria Ikegami, Ryota Tsukui, Miyako Nagaya, Kanae Tsutsumi, Fumiko Seto, Kazumasa Hiroi, Sayo Iwasaki, Kihoko Ichikawa, Yutaro Asagoe, Rutesara Kyuragi

Introduction

Our Department provides anesthesia and intensive care. Anesthetic services are provided for 15 main operating theatres and sessions in endoscopy. There are about 4,000 operations per year. The Intensive Care Unit has eight beds and provides care for all specialties including general medical and general surgical cases. There are over 500 admissions annually and the ICU is also responsible for resuscitation services within the hospital.

Routine activities

The Department of Anesthesia and Intensive Care at the National Cancer Research Center Central Hospital is comprised of seven staff anesthetists who are involved in critical care, education and research. Our Department provides perioperative care to the all patients who require general anesthesia and spinal analgesia. Our operation theater performs approximately 4,500 surgical procedures per year, which include neurosurgical, orthopedic, plastics, ophthalmologic, gynecologic, urologic, and general surgery (Table 1, 2). We also provide care to patients undergoing procedures in locations outside the main operating room such as sessions in endoscopy. In addition, many patients are seen in the Anesthesia Consulting Clinic, which runs every weekday. Many staff also have other clinical appointments including attending the ICU (the eight-bed Medical/Surgical Unit) and providing acute pain management. Some members of the department are actively involved in research at clinical levels and supervise post-doctorate, doctorate, postgraduate and undergraduate students.

Our ICU is certificated by the Japanese Society of Intensive Care Medicine. It provides care for all specialties including general medical, general surgical and neurosurgical cases. It is managed as a closed-system, supported by two certificated intensivists and a trainee. There are eight operational ICU beds and over 650 admissions annually (Table 3). The ICU is also responsible for resuscitation services within the hospital.

Clinical trials

One of the members is part of the faculty of the clinical trial group in the Japanese Society of Intensive Care Medicine. To understand the incidence and risk factors of severe adverse events in post-operative patients, epidemiological analysis was performed. To improve current care for perioperative patients, prospective studies are being conducted.

Table 1. Cases for anesthetic management

	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
Department of Neurosurgery and Neuro-Oncology	7	11	17	9	8	17	13	12	10	10	12	12
Department of Ophthalmic Oncology	26	24	30	20	26	24	32	26	28	32	28	32
Department of Head and Neck Oncology	17	23	22	21	17	21	27	22	24	23	26	22
Department of Plastic and Reconstructive Surgery	10	8	9	6	3	7	10	10	11	9	10	14
Department of Breast Surgery	43	41	53	46	41	57	58	48	44	50	48	42
Department of Breast and Medical Oncology	0	0	0	0	0	0	0	0	1	0	0	0
Department of Thoracic Surgery	53	52	55	51	43	64	68	53	46	50	57	56
Department of Esophageal Surgery	9	11	10	12	11	12	12	13	9	9	11	10
Department of Gastric Surgery	35	42	39	39	39	43	48	50	41	39	36	38
Department of Colorectal Surgery	43	44	44	41	33	46	49	48	54	44	39	41
Department of Gastrointestinal Medical Oncology	0	1	0	0	0	0	0	0	0	0	0	0
Department of Endoscopy, Gastrointestinal Endoscopy Division	7	6	10	7	6	5	4	6	8	4	5	7
Department of Hepatobiliary and Pancreatic Surgery	26	23	24	26	23	28	25	25	21	24	22	23
Department of Urology	22	25	29	26	27	30	35	31	28	27	29	30
Department of Gynecology	23	21	25	24	23	25	24	24	18	24	21	21
Department of Musculoskeletal Oncology and Rehabilitation	24	21	31	33	19	29	25	27	28	25	21	32
Department of Dermatologic Oncology	12	10	10	11	7	14	13	8	10	8	6	8
Department of Hematopoietic Stem Cell Transplantation	3	4	2	3	2	4	4	2	2	2	4	3
Department of Pediatric Oncology	2	0	1	2	0	2	1	2	0	0	0	0
Department of Anesthesia and Intensive Care	0	0	0	1	0	0	1	0	0	0	0	0
Department of Diagnostic Radiology	0	0	0	0	0	0	0	0	1	0	1	0
Department of Radiation Oncology	2	2	2	3	2	3	4	6	2	2	5	5
Total	364	369	413	381	330	431	453	413	386	382	381	396

Table 2. Type of procedures

	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
General Anesthesia	164	182	206	197	157	220	226	212	195	188	199	213
General Anesthesia + Epidural Anesthesia	193	179	165	171	161	171	169	159	143	157	147	141
Spinal Anesthesia + Epidural Anesthesia	0	0	0	0	0	0	0	0	0	0	0	0
Epidural Anesthesia	0	1	0	0	0	0	0	0	0	0	1	1
Spinal Anesthesia	1	2	42	6	6	40	57	41	47	37	32	41
Others	6	5	0	7	6	0	1	1	1	0	2	0
Total	364	369	413	381	330	431	453	413	386	382	381	396

Table 3. Number of cases, Deaths in ICU and ICU mortality

ICU Admission	No. of Cases	Deaths in ICU	ICU mortality
Department of Hepatobiliary and Pancreatic Surgery	160	2	1.30%
Department of Esophageal Surgery	120	1	0.80%
Department of Neurosurgery and Neuro-Oncology	114	0	0.00%
Department of Head and Neck Oncology	78	1	1.20%
Department of Gastric Surgery	41	0	0.00%
Department of Colorectal Surgery	39	0	0.00%
Department of Musculoskeletal Oncology and Rehabilitation	37	0	0.00%
Department of Hematopoietic Stem Cell Transplantation	24	4	16.70%
Department of Thoracic Surgery	18	1	5.60%
Department of Urology	11	0	0.00%
Department of Hematology	7	1	14.30%
Department of Breast and Medical Oncology	7	0	0.00%
Department of Endoscopy, Respiratory Endoscopy Division	6	2	33.30%
Department of Radiation Oncology	6	0	0.00%
Department of Gastrointestinal Medical Oncology	5	1	0.20%
Department of Hepatobiliary and Pancreatic Oncology	4	0	0.00%
Department of Dermatologic Oncology	4	0	0.00%
Department of Gynecology	3	0	0.00%
Department of Pediatric Oncology	1	0	0.00%
Total	685	13	

List of papers published in 2015

Journal

1. Nonaka S, Kawaguchi Y, Oda I, Nakamura J, Sato C, Kinjo Y, Abe S, Suzuki H, Yoshinaga S, Sato T, Saito Y. Safety and effectiveness of propofol-based monitored anesthesia care without intubation during endoscopic submucosal dissection for early gastric and esophageal cancers. Dig Endosc, 27:665-673, 2015

Department of Palliative Medicine

Eriko Satomi, Kaoru Nishijima, Daisuke Kiuchi

Introduction

The palliative care service started with a palliative care team of multidisciplinary professionals (palliative care specialists, psycho-oncologists, certified nurses, pharmacists, psychologists, Hospital Play Staff, an acupuncturist) in the National Cancer Center Hospital (NCCH) in 1999 and the Department of Palliative Care and Psychooncology was established in 2010 with the reorganization of the NCCH. In 2013, the Department of Palliative Medicine started. We provide palliative care to patients and families as members of the palliative care team with leading doctors, nurses and other professionals to create an individualized palliative care plan. Our goals are:

-Relieve pain and other physical symptoms
-Focus patients' emotional and spiritual concerns, and those of their caregivers
-Coordinate patients' care
-Improve the quality of life of patients with cancer
-Advanced care planning

Routine activities

Our missions are:

-Manage cancer-related pain and other symptoms
-Collaborate with other medical professionals and establish care plans
-Support patients' decision making and advanced care planning
-Teach basic skills in supportive and palliative medicine to resident doctors
-Research about new treatment for supportive and palliative medicine

1) For hospitalized patients

We work as a palliative care team and provide consulting and follow-up services to hospitalized patients throughout the NCCH. A consultation request is made by a physician (doctor in charge) or the medical staff. We provide support to the primary team. We follow up about 25 to 30 patients every day.

2) For outpatients

Our outpatient clinic for palliative medicine is open from Monday through Friday. It is possible for us to see patients on demand.

Research activities

We have just started the group J-SUPPORT (Japanese Supportive, Palliative and Psychosocial Oncology Group) for clinical trials in supportive and palliative care.

Clinical trials

JORTC-PAL08, PASQoL, PHASE-R (Olanzapine for nausea and vomiting: observational study), etc.

Education

We have two training courses for doctors who will be palliative care specialists and for residents to learn primary palliative care. All the surgical and medical oncologist residents in the NCCH need knowledge and skill about primary supportive and palliative care in oncology. They participate in our team for 4 weeks and undergo on-the-job training for palliative medicine. This includes an opportunity to attend home hospice rounds in cooperation with Chuo-ku medical association. A total of 20 residents finished the 4-week palliative medicine course in 2015. On the three-month course for palliative care specialists, two participants enrolled. They learned specialist palliative care in oncology including physical, psychosocial and spiritual supportive care during anti-cancer therapy, end-of-life care, support for decision making and advanced care planning.

Table 1. Number of patients

Cases	476	
Male/female	227	127
Age	53.9 (SD16.1)	

Table 2. Clinical stage

Ⅰ	9
Ⅱ	15
Ⅲ	20
Ⅳ	146
recurrence	224
others	26
unknown	36

Table 3. Primary site of cancer

brain, eyes	3
head and neck	8
esophagus	20
stomach	35
colorectal	58
hepatobiliary	5
pancreas	4
lung	20
breast	73
uterus, ovary	37
prostate	22
kidney, adrenal gland	2
thyroid	7
blood	3
bone	38
skin	3
soft tissue, methotelioma	49
unknown origin	46
others	13

Table 4. Symptoms

pain	402
breathlessness	108
nausea/vomiting	118
fatigue	65

List of papers published in 2015

Journal

1. Inoue I, Higashi T, Iwamoto M, Heiney SP, Tamaki T, Osawa K, Inoue M, Shiraishi K, Kojima R, Matoba M. A national profile of the impact of parental cancer on their children in Japan. Cancer Epidemiol, 39:838-841, 2015

Department of Psycho-Oncology

Ken Shimizu, Rika Nakahara, Yoshio Oshima, Masashi Kato, Saho Wada, Chikako Dotani, Hironobu Inoguchi, Saran Yoshida, Mariko Kobayashi, Chisato Kobayashi, Mae Endo

Introduction

The Department of Psycho-Oncology was reestablished in September 1995, together with the establishment of the Psycho-Oncology Division, the National Cancer Center Research Institute East (reorganized to the Division of Psycho-Oncology, Research Center for Innovative Oncology in 2005). One of the most important clinical activities of the department is the management of cancer patients' behavioral and social problems as well as their psychological distress. Furthermore, this Division's aim is to alleviate the distress of patients, patients' families and our staff. Research activity is focused on studying the psychosocial influence of cancer on the quality of life of patients, their families, and oncology staff.

Routine activities

The Department of Psycho-Oncology consists of four full-time staff psychiatrists, three full-time staff psychotherapists and three part-time psychotherapists. The Department provides two major services; a clinic for outpatients (five days a week) and consultation for referred inpatients. The purpose of the psychiatric consultation is to diagnose and treat the mental distress and cancer-related psychological problems of patients who have been referred by their attending physicians. Since 1999, the department has played an active role as a member of the palliative care team. There is a palliative care team meeting with other members of the team every Tuesday. Additionally, a multicenter joint clinical teleconference to discuss difficult cases is held biweekly on Thursday evenings with staff members from six cancer center hospitals and four university hospitals.

In 2015, a total of 1,032 patients were referred for psychiatric consultation (Table 1). The mean age was 52.3 years old and 21.8% percent of the referrals were outpatients. A total of 463 (44.9%) of all the referred patients were males (Table 1). The most common cancer referrals were patients with hematological and breast cancer (11.4%), followed by sarcoma (10.7%), colorectal cancer (10.2%), and lung cancer (9.4%). The most common psychiatric diagnosis that is based on the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) was adjustment disorders (25.5%), followed by delirium (20.9%), and major depressive disorder (11.1%), while 20.9% of the referrals had no psychiatric diagnosis. The three common mental disorders (delirium, adjustment disorders, and major depressive disorder) were responsible for half of the psychological problems.

Research activities

We are now developing the psychosocial intervention for allogenic hematopoietic stem cell transplant survivors, the purpose of which is to improve the quality of life. This year, we have planned an observational study to decide the intervention components.

We also explored the contents of "post-traumatic growth" in Japanese cancer patients. Post-traumatic growth is a positive dimension of patients' psychological change in the aftermath of trauma. Little is known about the process in Japanese cancer patients, and this result will provide precious information to develop interventions to support patients' psychological adaptation after cancer diagnosis.

Table 1. Psychiatric Consultation Data in 2015 (n=1,032)

	n	%
Age (years)	52.3	
Male	463	44.9
Inpatients	808	78.2
Top 5 cancers by site		
Hematological	118	11.4
Breast	118	11.4
Sarcoma	110	10.7
Colorectal	105	10.2
Lung	97	9.4
Psychiatric diagnoses		
Adjustment disorders	263	25.5
Delirium	216	20.9
Major depressive disorder	115	11.1
Others	222	21.5
No diagnosis	216	20.9

List of papers published in 2015

Journal

1. Wada S, Shimizu K, Inoguchi H, Shimoda H, Yoshiuchi K, Akechi T, Uchida M, Ogawa A, Fujisawa D, Inoue S, Uchitomi Y, Matsushima E. The Association Between Depressive Symptoms and Age in Cancer Patients: A Multicenter Cross-Sectional Study. J Pain Symptom Manage, 50:768-777, 2015

2. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Ogawa A, Fujisawa D, Sone T, Yoshiuchi K, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Personality traits and coping styles explain anxiety in lung cancer patients to a greater extent than other factors. Jpn J Clin Oncol, 45:456-463, 2015

Department of Diagnostic Radiology

Yasuaki Arai, Yasunori Mizuguchi, Gen Iinuma, Miyuki Sone, Hiroaki Kurihara, Nachiko Uchiyama, Hirokazu Watanabe, Minoru Machida, Mari Kikuchi, Tomoko Manabe, Mototaka Miyake, Syunsuke Sugawara, Hideaki Kobayashi, Koji Tomita

Introduction

The Department of Diagnostic Radiology provides a wide range of modalities, including interventional radiology (IR), general radiology, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, mammography and nuclear medicine. The Center for Interventional Radiology, launched in 2014, continues to provide various IR treatments for patients referred from other hospitals or clinics as well as patients at our hospital. We seek individuals with outstanding leadership capabilities, proven academic and administrative experience, the vision to build and sustain programs at the forefront of imaging research, and a commitment to clinical experience.

Table 1. Routine activities

Modality	Number of examinations
1 CT :	46,375
2 MRI :	8,665
3 IR :	5,591
4 RI :	4,597
5 Ultrasound :	16,062
6 Radiograph :	68,386
7 Gastrointestinal study :	1,972

Research activities

CT colonography (CTC) has been successfully introduced as an effective option for preoperative staging and colorectal screening in our center. Nearly 2,000 patients and/or candidates were examined with this modality in 2013. For the preparation of screening CTC, electronic cleansing with fecal barium tagging and automated CO_2 gas insufflation systems have been established in the formal National Cancer Center (NCC) collaboration studies with the associated companies. Furthermore, we are now developing computer-aided detection (CAD) for colorectal lesions, especially for flat lesions. The main purpose of our CTC research work is to conduct a multi-center trial to establish evidence regarding fully digitalized CTC for a colorectal screening system in Japan.

With use of one positron emission tomography (PET)/MRI scanner and three PET/CT scanners, molecular imaging of multi tracers consisting of [18F] FDG, [18F] FBPA, [11C] choline, [11C] methionine and [64Cu]-DOTA-antibody has been studied for cancer patients to improve the sensitivity and specificity of detecting tumor sites or tumor characteristics. [18F]-FDG dynamic PET sampling with Patrak-plot analysis allows us to calculate the glucose metabolic rate of the tumor site. [18F]-FBPA PET has been conducted in 22 cancer patients this year. [11C]-choline and [11C]-methionine PET examinations have been scheduled routinely for two days per week. As for [64Cu]-DOTA-antibody PET imaging, [64Cu]-DOTA-trastuzumab PET has been conducted in HER-2 positive breast cancer patients. Respiratory-gated PET was evaluated to reduce breathing-induced artifacts using a four-dimensional PET protocol. It provided better localization and quantification of tumors around the lower thorax to the upper abdomen. For cancer treatment, internal radiotherapy was carried out in 20 thyroid cancer patients with use of radioactive iodine (I-131) chloride.

In accordance with the achievement of collaborative research with the associated company since 2009, Digital breast tomosynthesis (DBT) has been introduced as an effective routine option for preoperative evaluation since March 2014. Up to December 2015, 1,067 patients were examined.

A multicenter study has started to establish the CT classification of lung adenocarcinomas corresponding to the new International Association for the Study of Lung Cancer, American Thoracic Society and European Respiratory Society (IASLC/ATS/ERS) pathological classification and to build

the database of small adenocarcinomas. Digital Imaging and Communications in Medicine (DICOM) data of resected lung cancers from each institute have been accumulated and evaluated in collaboration with the Japanese Society of Thoracic Radiology.

The Japan Response Evaluation Criteria in Solid Tumors (RECIST) working group has developed a tumor response evaluation computer system, which is capable of semiautomatic RECIST evaluation and is compliant with DICOM data.

Image guided preoperative Breast Marking using ultrasound alone or combined with mammography has been performed for partial mastectomy cases in which it is difficult to determine the spread of disease. This technique makes it possible to resect abnormal lesions more precisely and helps to prevent both re-operation and local recurrence. A total of 85 cases were handled from January 2015 to December 2015.

We investigate the correlation between the image findings and clinical course of ovarian clear cell carcinoma.

Clinical trials

A major departmental research theme is establishing evidence for interventional radiology procedures. We have led a multi-institutional cooperative study group of interventional radiology (JIVROSG: Japan Interventional Radiology in Oncology Study Group) since 2002 as a steering organization of 95 participating domestic institutions. In this study group, we are investigating the efficacy of palliative interventional radiology in randomized controlled trials (RCTs) to compare it with other therapies. These palliative RCTs include: a phase III study evaluating the efficacy of peritoneo-venous shunting (JIVROSG-0803); a phase III study evaluating the efficacy of percutaneous vertebroplasty for painful bone metastases (JIVROSG-0804); a phase III study evaluating the efficacy of percutaneous trans-esophageal gastric tubing (JIVROSG-0805); and a phase III study evaluating the efficacy of stenting for superior vena cava/inferior vena cava (SVC/IVC) syndrome (JIVROSG-0807). JIVROSG-0807 and JIVROSG-0805 completed patient enrollment in 2013 and 2014, respectively. A feasibility study of Epirubicin-eluting-bead Embolization for Hepatocellular Carcinoma (JIVROSG-1301) also completed patient enrollment in 2014. Other ongoing clinical trials are a phase II study evaluating the efficacy of arterial infusion chemotherapy and radiotherapy for unresectable maxillary carcinoma (JIVROSG-0808), a phase II trial of palliative intra-arterial epirubicin/5FU therapy for patients with chemotherapy-refractory locally advanced or metastatic breast cancer (JIVROSG-1107 RESAIC-II) and a phase II study evaluating the efficacy and safety of n-butyl-2-cyanoacrylate (NBCA) in embolization (JIVROSG-0802). A phase I/II study of radiofrequency ablation (RFA) for pelvic malignant tumors (JIVROSG-0204) was stopped in 2014 due to the insufficient number and speed of patient enrollment.

Education

The clinical education and training of young radiologists is an important part of our department's activities. During 2015, six residents and one short-term resident were trained by our department. Educational opportunities were also provided to six overseas physicians from Malaysia, Taiwan, and India. We have several clinical or educational conferences. A daily clinical interventional radiology (IVR) case conference, a weekly educational case conference on diagnostic radiology, and a monthly IVR research conference, are held.

Future prospects

The Department of Radiology strives for excellence in clinical care, education, and research. Our goal is to provide outstanding patient-centered radiology services and to establish evidence in this area. Future challenges include promoting the active role of the Center for Interventional Radiology and facilitating imaging as biomarkers for personalized cancer treatments such as molecular-targeted agents, immunoagents, and boron neutron capture therapy.

List of papers published in 2015

Journal

1. Kono Y, Shimizu Y, Wakatsuki Y, Yasui N, Aso T, Kawamoto H, Kurihara H. Letter to the editor. Radiat Prot Dosimetry, 163:533-534, 2015

2. Mori M, Tsunoda H, Takamoto Y, Murai M, Kikuchi M, Honda S, Suzuki K, Yamauchi H. MRI and ultrasound evaluation of invasive lobular carcinoma of the breast after primary systemic therapy. Breast Cancer, 22:356-365, 2015

3. Yang Y, Suzuki K, Abe E, Li C, Uno M, Akiyama F, Yamauchi H, Kikuchi M, Ohde S, Deshpande G, Shibahara Y, Nakamura Y, Sasano H. The significance of combined CK5/6 and p63 immunohistochemistry in predicting the risks of subsequent carcinoma development in intraductal papilloma of the breast. Pathol Int, 65:81-88, 2015

4. Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, Watanabe H, Wu YL, Zielinski M, Ball D, Rami-Porta R, International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Board Members, and Participating Institutions. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol, 10:1675-1684, 2015

5. Horikawa M, Miyayama S, Irie T, Kaji T, Arai Y. Development of Conventional Transarterial Chemoembolization for Hepatocellular Carcinomas in Japan: Historical, Strategic, and Technical Review. AJR Am J Roentgenol, 205:764-773, 2015

6. Hiraki T, Koizumi J, Arai Y, Sakurai Y, Kumada H, Nambu Y, Hori S. Transcatheter arterial embolization of hypervascular tumors with HepaSphere: prospective multicenter open label clinical trial of microspheres in Japan. Jpn J Radiol, 33:479-486, 2015

7. Sofue K, Arai Y, Takeuchi Y, Tsurusaki M, Sakamoto N, Sugimura K. Ultrasonography-guided central venous port placement with subclavian vein access in pediatric oncology patients. J Pediatr Surg, 50:1707-1710, 2015

8. Inaba Y, Yamaura H, Sato Y, Kato M, Kawada H, Murata S, Hasegawa T, Arai Y. Side-Hole Catheter Placement with Fixation and Embolization in Common Hepatic Artery for Hepatic Arterial Infusion Chemotherapy (Modified CHA-Coil Method) for Patients with Celiac Artery Stenosis or Occlusion. Cardiovasc Intervent Radiol, 38:1621-1626, 2015

9. Arai Y, Aoyama T, Inaba Y, Okabe H, Ihaya T, Kichikawa K, Ohashi Y, Sakamoto J, Oba K, Saji S. Phase II study on hepatic arterial infusion chemotherapy using percutaneous catheter placement techniques for liver metastases from colorectal cancer (JFMC28 study). Asia Pac J Clin Oncol, 11:41-48, 2015

10. Sone M, Nakajima Y, Woodhams R, Shioyama Y, Tsurusaki M, Hiraki T, Yoshimatsu M, Hyodoh H, Kubo T, Takeda S, Minakami H. Interventional radiology for critical hemorrhage in obstetrics: Japanese Society of Interventional Radiology (JSIR) procedural guidelines. Jpn J Radiol, 33:233-240, 2015

11. Yoshimoto M, Kurihara H, Fujii H. Theragnostic imaging using radiolabeled antibodies and tyrosine kinase inhibitors. ScientificWorldJournal, 2015:842101, 2015

12. Morita S, Onaya H, Kishi Y, Hiraoka N, Arai Y. Multiple Intraglandular Metastases in a Patient with Invasive Ductal Carcinoma of the Pancreas. Intern Med, 54:1753-1756, 2015

13. Kurihara H, Hamada A, Yoshida M, Shimma S, Hashimoto J, Yonemori K, Tani H, Miyakita Y, Kanayama Y, Wada Y, Kodaira M, Yunokawa M, Yamamoto H, Shimizu C, Takahashi K, Watanabe Y, Fujiwara Y, Tamura K. ^{64}Cu-DOTA-trastuzumab PET imaging and HER2 specificity of brain metastases in HER2-positive breast cancer patients. EJNMMI Res, 5:8, 2015

14. Kinuya S, Yoshinaga K, Higuchi T, Jinguji M, Kurihara H, Kawamoto H. Draft guidelines regarding appropriate use of (131)I-MIBG radiotherapy for neuroendocrine tumors : Guideline Drafting Committee for Radiotherapy with (131)I-MIBG, Committee for Nuclear Oncology and Immunology, The Japanese Society of Nuclear Medicine. Ann Nucl Med, 29:543-552, 2015

Book

1. Sone M, Arai Y. Section B. Coils and Plugs - 5. Gelfoam. In: Marcelo G, Riccardo L, Gary PS (eds), Embolization Therapy: Principles and Clinical Applications, Netherland, Wolters Kluwer, 2015

2. Arai Y. Section D. Liquid Agents - 9. Glue. In: Marcelo G, Riccardo L, Gary PS (eds), Embolization Therapy: Principles and Clinical Applications, Netherland, Wolters Kluwer, 2015

Department of Radiation Oncology

Jun Itami, Yoshinori Ito, Hiroshi Igaki, Naoya Murakami, Koichi Inaba, Kana Takahashi, Rei Umezawa, Shuhei Sekii, Mayuka Kitaguchi, Ken Harada, Hiroyuki Okamoto, Shie Nishioka, Akihisa Wakita, Satoshi Nakamura

Introduction

The role of the Department is to provide state-of-the-art radiation therapy to all relevant patients, to educate and develop the expertise of radiation oncologists, radiation technologists, and medical physicists, and to lead new developments in radiation oncology in Japan as well as worldwide. All departmental activities are dedicated to cancer patients. A linear accelerator for hospital-based boron neutron capture therapy (BNCT) was installed in the new facility and an epithermal neutron beam could be obtained in August 2015 and the neutron facility passed the governmental inspection for radiation leakage. The Department is now fully involved in the development of BNCT. Through the assistance of the management of the center, the number of medical physicists was increased to four.

Routine activities

The Department of Radiation Oncology of the National Cancer Center Hospital is one of the biggest radiation oncology departments in Japan. Five linear accelerators, CyberKnife, one X-ray simulator, three XCT-simulators, and 15 treatment planning computers are working together through on-line networks to provide state-of-the-art precision external beam radiation therapy. In addition to the conventional X-ray and electron therapies, stereotactic irradiations of brain and body tumors and intensity-modulated radiation therapy (IMRT) are performed routinely. Stereotactic brain irradiation is performed with CyberKnife in the treatment of metastatic as well as primary brain tumors. Stereotactic body tumor irradiation is performed in lung and liver tumors under respiratory gating in linear accelerators or CyberKnife. Four of the five linear accelerators have on-board kilovoltage CT imagers, which help to precisely align patient and tumor coordinates. These image-guided radiation therapy (IGRT) facilities enable the precise delivery of IMRT in head and neck cancers, brain tumors, prostate cancers, and postoperative cervical cancers. Gold marker fiducials have been implanted to improve geometric precision of radiation field reproducibility.

Brachytherapy is also intensively performed to improve local control and many patients are referred from all over Japan. For brachytherapy, the following modalities are being employed: an Ir-192 high dose rate (HDR) afterloading system including dedicated CT simulator and fluoroscopy, an I-125 seed implantation system, and other low dose rate (LDR) brachytherapy systems using Au grains, Ir-thin wires, and ruthenium eye plaques. The number of patients undergoing HDR brachytherapy continued to rise constantly. This Department is the only institution in Tokyo where HDR interstitial as well as intracavitary irradiations can be performed. HDR interstitial radiation is used mainly in gynecological, genitourinary, and head and neck tumors. Additionally, there are two beds in the shielded ward in Floor 13B. Ruthenium mold therapy is performed by ophthalmologists to treat retinoblastomas and choroidal melanomas. LDR interstitial implants are carried out by radiation oncologists using Au-198 grains and Ir-192 thin wires for the management of head and neck tumors and gynecological malignancies.

Research activities

Clinical research is an indispensable part of the daily activities of the Department. The primary interests of the research activities of the Department are 1) an optimal fractionation regimen for the pain palliation of bone metastasis; 2) the safety

and feasibility of shortened fractionation regimen for various malignancies, especially for breast cancer and vocal cord cancer; 3) image-guided HDR and LDR brachytherapy for genitourinary and gynecologic cancers; 4) hypofractionated stereotactic irradiation of brain and body tumors; 5) adaptive radiation therapy in accordance with the intratherapeutic tumor and normal tissue change; and 6) development of an accelerator-based BNCT system.

Clinical trials

Brain tumors: A multicenter phase II/III trial on interferon-beta and temozolomide combination therapy for newly diagnosed glioblastomas.

Metastatic brain tumor: Phase II trial of hippocampal sparing IMRT

Lung cancer: Phase II trial on high dose thorax irradiation excluding prophylactic mediastinal lymph node radiation concurrent with CDDP+VNL in unresectable stage III non-small-cell lung cancers (NSCLCs).

Lung cancer: Stereotactic radiation therapy for histologically non-verified lung tumors.

Pediatrics: Phase II clinical trial on multimodality therapy in localized Ewing sarcomas and related tumors (The Japan Ewing Sarcoma Study Group (JESS 04)).

Head and neck cancers: Various JCOG (The Japan Clinical Oncology Group) studies including IMRT for nasopharyngeal and oropharyngeal cancers

Breast cancer: Phase II trial of SAVI applicator HDR brachytherapy after partial mastectomy.

Liver cancer: Phase I trial on stereotactic hypofractionated radiation to hepatocellular carcinoma.

Cervical cancer: Phase I/II trial of hybrid brachytherapy of cervical cancer

F-BPA PET/CT: Feasibility study of F-BPA PET/CT in detecting malignancies with comparison to FDG PET/CT.

Development of an Adaptive Radiation Therapy System

Education

Five residents are trained in all fields of radiation oncology except particle beam therapy. Seminars about biology, physics, and clinical radiation oncology are regularly held in the evenings.

Future prospects

With the introduction of BNCT, new manpower will be required and research perspectives will be greatly widened. Additionally, installment of an MRI-Cobalt system is planned.

Table 1.

Year	No. of Patients 2014	2015
1) New patients referred to the Department	1,458	1,640
2) All patients undergoing radiation therapy	2,063	2,646
External Beam Radiation Therapy (EBRT)		
1) New patients undergoing EBRT	1,383	1,567
2) All patients undergoing EBRT	1,976	2,546
Brachytherapy (BT) and Radionuclide Therapy		
1) All patients undergoing intracavitary radiation	40	32
2) All patients undergoing interstitial radiation	78	101
3) All patients undergoing prostate permanent seed implantation	15	14
4) All patients undergoing I-131 therapy for thyroid cancer	22	6
5) All patients undergoing Sr-89 therapy for bone metastasis	2	4
Other Special Radiation Therapy		
1) All patients undergoing total body irradiation	68	56
2) All patients undergoing stereotactic brain radiation	247	426
3) All patients undergoing stereotactic body radiation	49	96
4) All patients undergoing intensity modulated radiation therapy	246	310
No. of New Patients according to the Primary Site		
1) CNS	48	56
2) Head and Neck	142	142
3) Esophagus	117	124
4) Intrathoracic	258	350
4)-a) Lung	136	305
5) Breast	296	332
6) Liver/Bile Duct/Pancreas	88	95
7) Digestive Tracts	252	277
8) GYN	80	74
9) GU	138	157
9)-a) Prostate	102	91
10) Hematopoietic/Lymphatic	88	95
11) Cutaneous/Bone/Soft Tissue	110	111
12) Other Malignancies	0	0
13) Benign	2	6
14) Children Less than 15 Years Old	19	24
Radiation Therapy of Brain or Bone Metastasis		
1) Brain metastasis	266	562
2) Bone metastasis	159	456

List of papers published in 2015

Journal

1. Murakami N, Yoshimoto S, Matsumoto F, Ueno T, Ito Y, Watanabe S, Kobayashi K, Harada K, Kitaguchi M, Sekii S, Takahashi K, Yoshio K, Inaba K, Morota M, Sumi M, Saito Y, Itami J. Severe gastrointestinal bleeding in patients with locally advanced head and neck squamous cell carcinoma treated by concurrent radiotherapy and Cetuximab. J Cancer Res Clin Oncol, 141:177-184, 2015

2. Satoh T, Dokiya T, Yamanaka H, Saito S, Ishiyama H, Itami J, Shibuya H, Nakano T, Shigematsu N, Aoki M, Egawa S, Hashimoto M, Nishimura T, Yorozu A. Postmortem radiation safety and issues pertaining to permanent prostate seed implantation in Japan. Brachytherapy, 14:136-141, 2015

3. Miyashita M, Kawakami S, Kato D, Yamashita H, Igaki H, Nakano K, Kuroda Y, Nakagawa K. The importance of good death components among cancer patients, the general population, oncologists, and oncology nurses in Japan: patients prefer ”fighting against cancer”. Support Care Cancer, 23:103-110, 2015

4. Murakami N, Kobayashi K, Nakamura S, Wakita A, Okamoto H, Tsuchida K, Kashihara T, Harada K, Yamada M, Sekii S, Takahashi K, Umezawa R, Inaba K, Ito Y, Igaki H, Itami J. A total EQD2 greater than 85 Gy for trachea and main bronchus D2cc being associated with severe late complications after definitive endobronchial brachytherapy. J Contemp Brachytherapy, 7:363-368, 2015

5. Murakami N, Okamoto H, Isohashi F, Murofushi K, Ohno T, Yoshida D, Saito M, Inaba K, Ito Y, Toita T, Itami J. A surveillance study of intensity-modulated radiation therapy for postoperative cervical cancer in Japan. J Radiat Res, 56:735-741, 2015

6. Kobayashi K, Murakami N, Wakita A, Nakamura S, Okamoto H, Umezawa R, Takahashi K, Inaba K, Igaki H, Ito Y, Shigematsu N, Itami J. Dosimetric variations due to interfraction organ deformation in cervical cancer brachytherapy. Radiother Oncol, 117:555-558, 2015

7. Murakami N, Kühnel A, Schmid TE, Ilicic K, Stangl S, Braun IS, Gehrmann M, Molls M, Itami J, Multhoff G. Role of membrane Hsp70 in radiation sensitivity of tumor cells. Radiat Oncol, 10:149, 2015

8. Otani Y, Nose T, Dokiya T, Saeki T, Kumazaki Y, Asahi S, Tsukiyama I, Fukuda I, Sekine H, Shikama N, Takahashi T, Yoshida K, Kotsuma T, Masuda N, Yoden E, Nakashima K, Matsumura T, Nakagawa S, Tachiiri S, Moriguchi Y, Itami J, Oguchi M. A Japanese prospective multi-institutional feasibility study on accelerated partial breast irradiation using interstitial brachytherapy: treatment planning and quality assurance. Radiat Oncol, 10:126, 2015

Department of Pathology and Clinical Laboratories

Atsushi Ochiai, Nobuyoshi Hiraoka, Koji Tsuta, Shigeki Sekine, Koh Furuta, Noriko Motoi, Akiko Maeshima, Taisuke Mori, Hirokazu Taniguchi, Reiko Watanabe, Masayuki Yoshida, Akihiko Yoshida, Hiroshi Yoshida, Aoi Sukeda, Kuniko Sunami, Yae Kanai, Eri Arai, Shintaro Fukushima, Yuko Sasajima, Junko Itoh, Taiki Hashimoto, Koko Mitsuma, Michiko Sugiyama

Introduction

In the Pathology Division, the practice, education and research of diagnostic and anatomic pathology are carried out. Diagnostic pathology practice comprises all issues on the processing of cell and tissue specimens obtained from patients, preparation of tissue blocks and pathology slides, and histological and cytopathological diagnoses of diseases. The practice of anatomic pathology consists of the autopsy, post-mortem systemic gross and microscopic examination of patients. Case conferences with each clinical division are held periodically. Residents and trainees are accepted for training of diagnostic pathology on a rotating basis. To provide more accurate and informative diagnosis in future, the staff members conduct basic, clinical, or translational research by themselves or in collaboration with other divisions or institutions.

The Clinical Laboratories Division provides an important service as an in-hospital diagnostic unit by examining laboratory specimens and screening for disorders. All laboratory data are provided for clinicians under strict internal and external quality control. The laboratories in this Division have acquired the accreditation of ISO 15189, which certifies the quality and competence of a medical laboratory with regard to quality management and techniques, developed by the International Organization for Standardization's Technical Committee 212 (ISO/TC 212). In order to start a genome medicine where gene mutation profiles occurring in cancer tissues can contribute to select treatment options, a new genetic analyzing laboratory was established for performing comprehensive gene mutation analysis to clinical cancer samples using new-generation-sequencers under accreditation of semi- Clinical Laboratory Improvement Amendments (CLIA). The staff of the Clinical Laboratories Division will continuously work to improve the quality and quantity of laboratory services.

Routine activities

Pathology Division: In 2015, a total of 17 board-certified pathologists, four residents and 13 medical technologists, including nine cytotechnologists, cooperatively performed routine histological and cytopathological diagnosis of specimens obtained from patients at the National Cancer Center Hospital (NCCH) and the Research Center for Cancer Prevention and Screening (RCCPS), and education of the residents. 16 pathologists working exclusively in the NCCH also shared management of the division. We provided a total of 23,720 histological diagnoses consisting of 23,720 biopsy specimens, including 2,102 intraoperative frozen sections, and 4,060 surgically resected specimens, a total of cytopathological diagnoses of 12,026 patients, including 446 for intraoperative diagnosis, and a total of 31 autopsies. We also provided a total of 222 pathological diagnoses for an outpatient clinic for pathology consultation (second opinion).

Clinical Laboratories Division: 52 full-time and nine part-time medical technologists, two photographers and five assistants provide services. These staff work in the sections of 1) general laboratory medicine and hematology, 2) biochemistry, 3) endocrinology, immunology, and tumor markers, 4) bacteriology, 5) genetic diagnostics, 6) transfusion, 7) phlebotomy, 8) physiological examination, and 9) pathology in the NCCH, and in the sections of phlebotomy and physiological examination in the RCCPS. The sections of 1) to 5) are to be supervised by Drs. Koh Furuta and Kuniko Sunami, 6) and 7) by

Dr. Ryuji Tanozaki (Transfusion Therapy), 8) by Dr. Yasunori Mizuguchi (Diagnostic Radiology), Drs. Masaaki Shoji and Takeshi Iwasa (General Internal Medicine), and Dr. Eriko Iwamoto (Breast Surgery), and 9) by doctors in the Pathology Division. The bacteriology staff are members of the Infection Control Team and participate in infection management activities. The actual number of laboratory tests performed in this division in 2015 is shown in Table 2.

Research activities

1. Hepato-biliary pancreatic pathology

Tumor-infiltrating $CD8^+$ T cells, lower ratios of BTLA/CD8 and Cbl-b/CD8 were unfavorable prognosticators in gallbladder cancer patients. It was suggested that upregulation of BTLA in cancer tissues is involved in inhibition of antitumor immunity. We identified a significant subgroup of HER2-positive gallbladder cancer cases (16.6 %), for whom a clinical trial with anti-HER2 therapy might be considered.

2. Gastrointestinal pathology

We demonstrated the frequent presence of activating *GNAS* and *KRAS* mutations in heterotopic gastric-type mucosa in the duodenum, suggesting that these lesions are precursors to adenocarcinomas with a gastric epithelial phenotype. The common presence of *APC* mutations in pyloric gland adenomas was revealed by a genetic analysis of familial adenomatous polyposis-associated cases. A detailed histological analysis revealed highly prevalent lymphovascular invasion even in minute rectal carcinoids; this observation raises a question regarding its significance as a risk factor for metastasis.

3. Hematopathology

We reported clinicopathological characteristics of follicular lymphoma with peripheral blood involvement, lymphomas in the upper aerodigestive tract, and classical Hodgkin lymphoma of the elderly. We also reported pitfalls of flow cytometry for B-cell non-Hodgkin lymphomas.

4. Thoracic pathology

Clinicopathological analysis was made on HER2-mutated non-small cell carcinomas. Adenocarcinomas with cavitary changes were characterized. Ciliated muconodular papillary tumors were studied in a series of 10 cases. Myocardial sleeve tissues incidentally identified in lung resection specimens were analyzed. The utility of AR and GATA3 immunostaining in diagnostic settings was validated. A case of concurrent thymoma, thymic carcinoma, and lymphoblastic lymphoma was reported.

5. Bone and soft tissue pathology

Unusual superficial SMARCB1-deficient ER-positive tumors were characterized in a series of nine cases and they were proposed to constitute a potentially new nosologic entity "myoepithelioma-like tumors of the vulvar region" (MELTVR). Spindle cell/sclerosing rhabdomyosarcomas were clinicopathologically analyzed in 16 cases. Prognostic factors of epithelioid sarcomas were identified in a multi-institutional series of 44 cases.

6. Breast pathology

The frequent presence of *MED12* mutations among the phyllodes tumors of the breast was found regardless of the tumor grade. We found also that *TERT* promoter mutations were frequent in phyllodes tumors but rare in fibroadenomas. We proposed that intraductal papillomas on core biopsy could be upgraded to carcinomas on subsequent excisional biopsy regardless of the presence of atypical features.

7. Gynecological pathology

Immune contexture and PD-L1 expression status of uterine cervical adenocarcinoma have been reported. We have made case reports of an unusual recurrence pattern of uterine carcinosarcoma and uterine metastasis from duodenal adenocarcinoma.

8. Head and Neck/Ophthalmic pathology

We reported that in persistent severe chronic graft versus host disease (cGvHD) that underwent bone marrow transplantation there was the risk of oral squamous cell carcinoma development in long-term follow-up cases. We published the first case on primary intraocular synovial sarcoma.

9. Clinical Laboratories

An in-hospital bio-bank has been maintained for use by various researchers, and more than 650,000 post-clinical-test blood samples have been stored at -20 °C as of the end of 2015. Three sections of hematology, biochemistry and endocrinology, immunology and tumor markers, participated in

the external quality control program endorsed by the Japanese Society of Laboratory Medicine. Some medical technologists made interesting findings in their routine practice and made presentations at several domestic medical assemblies. In the molecular diagnostic section, mutation analyses of *EGFR*, *KRAS*, *NRAS*, and *BRAF* were provided as routine tests. At the cytogenetics section, using the Metafer system (an automated image analysis-assisted fluorescence *in situ hybridization* [FISH] system), the technique to evaluate the FISH imaging of *HER2* gene amplification was established and maintained. These two sections provided data not only for clinical practices but also for research activities of doctors in the NCCH and/or the NCCRI.

Table 1. Numbers of histopathological and cytopathological specimens diagnosed and autopsies performed in the Pathology Division in 2015

Field	Histopathological Specimens	Cytopathological Specimens	Autopsies
Neurosurgery	290	48	2
Head and Neck	1,154	258	0
Breast	3,086	588	5
Respiratory organs	2,563	2,248	12
Gastrointestinal tracts	8,942	839	3
Hepatobiliary and Pancreas	805	638	3
Urology	858	2,795	0
Gynecology	1,397	3,886	0
Orthopedics	697	24	2
Dermatology	531	28	0
Hematology	1,639	366	3
Radiation Oncology	220	189	1
Others	305	117	0
Research Center for Cancer Prediction and Screening	1,233	2	0
Total	23,720	12,026	31

Table 2. Number of laboratory tests examined in the Clinical Laboratories Division in 2015

Section	Number
General laboratory medicine	544,154
Hematology	1,377,066
Biochemistry	3,264,652
Endocrinology, immunology, and tumor markers	409,377
Bacteriology	47,034
Physiology	102,574
Genetic diagnostics	35,470
Total	5,780,327

List of papers published in 2015

Journal

1. Abe S, Oda I, Suzuki H, Nonaka S, Yoshinaga S, Nakajima T, Sekiguchi M, Mori G, Taniguchi H, Sekine S, Katai H, Saito Y. Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection. Endoscopy, 47:1113-1118, 2015

2. Arita H, Narita Y, Matsushita Y, Fukushima S, Yoshida A, Takami H, Miyakita Y, Ohno M, Shibui S, Ichimura K. Development of a robust and sensitive pyrosequencing assay for the detection of *IDH1/2* mutations in gliomas. Brain Tumor Pathol, 32:22-30, 2015

3. Arita H, Narita Y, Yoshida A, Hashimoto N, Yoshimine T, Ichimura K. *IDH1/2* mutation detection in gliomas. Brain Tumor Pathol, 32:79-89, 2015

4. Asaga S, Kinoshita T, Hojo T, Jimbo K, Yoshida M. Predictive Factors for Non-Sentinel Lymph Node Metastasis in Patients With Clinically Node-Negative Ipsilateral Multiple Breast Cancer Treated With Total Mastectomy. Clin Breast Cancer, 15:362-369, 2015

5. Asano N, Yoshida A, Ogura K, Kobayashi E, Susa M, Morioka H, Iwata S, Ishii T, Hiruma T, Chuman H, Kawai A. Prognostic Value of Relevant Clinicopathologic Variables in Epithelioid Sarcoma: A Multi-Institutional Retrospective Study of 44 Patients. Ann Surg Oncol, 22:2624-2632, 2015

6. Fujita H, Yoshida A, Taniguchi H, Katai H, Sekine S. Adult-onset inflammatory myofibroblastic tumour of the stomach with a TFG-ROS1 fusion. Histopathology, 66:610-612, 2015

7. Fujiwara T, Fujiwara M, Numoto K, Ogura K, Yoshida A, Yonemoto T, Suzuki S, Kawai A. Second primary osteosarcomas in patients with retinoblastoma. Jpn J Clin Oncol, 45:1139-1145, 2015

8. Fujiwara Y, Nokihara H, Yamada Y, Yamamoto N, Sunami K, Utsumi H, Asou H, Takahashl O, Ogasawara K, Gueorguieva I, Tamura T. Phase 1 study of galunisertib, a TGF-beta receptor I kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1143-1152, 2015

9. Fukushima S, Yoshida A, Narita Y, Arita H, Ohno M, Miyakita Y, Ichimura K, Shibui S. Multinodular and vacuolating neuronal tumor of the cerebrum. Brain Tumor Pathol, 32:131-136, 2015

10. Fukutake N, Ueno M, Hiraoka N, Shimada K, Shiraishi K, Saruki N, Ito T, Yamakado M, Ono N, Imaizumi A, Kikuchi S, Yamamoto H, Katayama K. A Novel Multivariate Index for Pancreatic Cancer Detection Based On the Plasma Free Amino Acid Profile. PLoS One, 10:e0132223, 2015

11. Hashimoto T, Ogawa R, Matsubara A, Taniguchi H, Sugano K, Ushiama M, Yoshida T, Kanai Y, Sekine S. Familial adenomatous polyposis-associated and sporadic pyloric gland adenomas of the upper gastrointestinal tract share common genetic features. Histopathology, 67:689-698, 2015

12. Hattori Y, Yoshida A, Sasaki N, Shibuki Y, Tamura K, Tsuta K. Desmoplastic small round cell tumor with sphere-like clusters mimicking adenocarcinoma. Diagn Cytopathol, 43:214-217, 2015

13. Hattori Y, Yoshida A, Yoshida M, Takahashi M, Tsuta K. Evaluation of androgen receptor and GATA binding protein 3 as immunohistochemical markers in the diagnosis of metastatic breast carcinoma to the lung. Pathol Int, 65:286-292, 2015

14. Hiraoka N, Ino Y, Yamazaki-Itoh R, Kanai Y, Kosuge T, Shimada K. Intratumoral tertiary lymphoid organ is a favourable prognosticator in patients with pancreatic cancer. Br J Cancer, 112:1782-1790, 2015

15. Ichikawa H, Yoshida A, Kanda T, Kosugi S, Ishikawa T, Hanyu T, Taguchi T, Sakumoto M, Katai H, Kawai A, Wakai T, Kondo T. Prognostic significance of promyelocytic leukemia expression in gastrointestinal stromal tumor; integrated proteomic and transcriptomic analysis. Cancer Sci, 106:115-124, 2015

16. Ito J, Yoshida A, Maeshima AM, Nakagawa K, Watanabe S, Kobayashi Y, Fukuhara S, Tsuta K. Concurrent thymoma, thymic carcinoma, and T lymphoblastic leukemia/lymphoma in an anterior mediastinal mass. Pathol Res Pract, 211:693-696, 2015

17. Kakinuma R, Muramatsu Y, Kusumoto M, Tsuchida T, Tsuta K, Maeshima AM, Asamura H, Moriyama N. Solitary pure ground-glass nodules 5 mm or smaller: frequency of growth. Radiology, 276:873-882, 2015

18. Kamata T, Yoshida A, Kosuge T, Watanabe S, Asamura H, Tsuta K. Ciliated muconodular papillary tumors of the lung: a clinicopathologic analysis of 10 cases. Am J Surg Pathol, 39:753-760, 2015

19. Kamiyama Y, Kobayashi Y, Fukuhara S, Morikawa N, Munakata W, Miyagi Maeshima A, Maruyama D, Kim SW, Watanabe T, Terauchi T, Muramatsu Y, Tobinai K. Incidental detection of malignant lymphoma in subjects in a cancer surveillance programme. Br J Haematol, 169:138-142, 2015

20. Kato M, Uraoka T, Isobe Y, Abe K, Hirata T, Takada Y, Wada M, Takatori Y, Takabayashi K, Fujiyama Y, Sekiya K, Kawaguchi Y, Sukeda A, Shiraishi J. A case of gastric adenocarcinoma of fundic gland type resected by combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique (CLEAN-NET). Clin J Gastroenterol, 8:393-399, 2015

21. Katsuya Y, Fujiwara Y, Sunami K, Utsumi H, Goto Y, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Takashima Y, Osawa S, Ohe Y, Tamura T, Hamada A. Comparison of the pharmacokinetics of erlotinib administered in complete fasting and 2h after a meal in patients with lung cancer. Cancer Chemother Pharmacol, 76:125-132, 2015

22. Katsuya Y, Yoshida A, Watanabe S, Tsuta K. Tumour-to-tumour metastasis from papillary thyroid carcinoma with BRAF mutation to lung adenocarcinoma with EGFR mutation: the utility of mutation-specific antibodies. Histopathology, 67:262-266, 2015

23. Kihara K, Fujita S, Ohshiro T, Yamamoto S, Sekine S. Spontaneous regression of colon cancer. Jpn J Clin Oncol, 45:111-114, 2015

24. Kikuta K, Kubota D, Yoshida A, Morioka H, Toyama Y, Chuuman H, Kawai A. An analysis of factors related to the tail-like pattern of myxofibrosarcoma seen on MRI. Skeletal Radiol, 44:55-62, 2015

25. Kitazono S, Fujiwara Y, Tsuta K, Utsumi H, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Sasada S, Watanabe S, Asamura H, Tamura T, Ohe Y. Reliability of Small Biopsy Samples Compared With Resected Specimens for the Determination of Programmed Death-Ligand 1 Expression in Non--Small-Cell Lung Cancer. Clin Lung Cancer, 16:385-390, 2015

26. Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, Goto K. Beyond *ALK-RET, ROS1* and other oncogene fusions in lung cancer. Transl Lung Cancer Res, 4:156-164, 2015

27. Kojima H, Watanabe R, Isaka M, Shimizu R, Kayata H, Miyata N, Maniwa T, Takahashi S, Ito I, Kameya T, Funai K, Ohde Y, Nakajima T. High-Grade Neuroendocrine Carcinoma with Bronchial Intraepithelial Tumor Spread: Possibly a New Histologic Feature of Large-Cell Neuroendocrine Carcinoma. J Thorac Oncol, 10:1337-1340, 2015

28. Kurihara H, Hamada A, Yoshida M, Shimma S, Hashimoto J, Yonemori K, Tani H, Miyakita Y, Kanayama Y, Wada Y, Kodaira M, Yunokawa M, Yamamoto H, Shimizu C, Takahashi K, Watanabe Y, Fujiwara Y, Tamura K. ^{64}Cu-DOTA-trastuzumab PET imaging and HER2 specificity of brain metastases in HER2-positive breast cancer patients. EJNMMI Res, 5:8, 2015

29. Maeshima AM, Taniguchi H, Makita S, Kitahara H, Miyamoto K, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Histopathological Characteristics of Lymphomas in the Upper Aerodigestive Tract. A Single-Institute Study in Japan. J Clin Exp Hematop, 55:7-11, 2015

30. Maeshima AM, Taniguchi H, Nomoto J, Makita S, Kitahara H, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Clinicopathological features of classical Hodgkin lymphoma in patients ≥ 40 years old, with special reference to composite cases. Jpn J Clin Oncol, 45:921-928, 2015

31. Maeshima AM, Taniguchi H, Tanioka K, Kitahara H, Miyamoto K, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K, Kushima R. Clinicopathological characteristics of follicular lymphoma with peripheral blood involvement. Leuk Lymphoma, 56:2000-2004, 2015

32. Matsubara A, Ogawa R, Suzuki H, Oda I, Taniguchi H, Kanai Y, Kushima R, Sekine S. Activating GNAS and KRAS mutations in gastric foveolar metaplasia, gastric heterotopia, and adenocarcinoma of the duodenum. Br J Cancer, 112:1398-1404, 2015

33. Mimori T, Kobayashi S, Tanaka A, Sasada S, Yoshida A, Izumo T, Sasaki N, Tsuchida T, Tsuta K. Novel use for an EGFR mutation-specific antibody in discriminating lung adenocarcinoma from reactive pneumocyte hyperplasia. Histopathology, 66:816-823, 2015

34. Morita S, Onaya H, Kishi Y, Hiraoka N, Arai Y. Multiple Intraglandular Metastases in a Patient with Invasive Ductal Carcinoma of the Pancreas. Intern Med, 54:1753-1756, 2015

35. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, Hama N, Hosoda F, Urushidate T, Ohashi S, Hiraoka N, Ojima H, Shimada K, Okusaka T, Kosuge T, Miyagawa S, Shibata T. Genomic spectra of biliary tract cancer. Nat Genet, 47:1003-1010, 2015

36. Nakamura H, Tsuta K, Tsuda H, Katsuya Y, Naka G, Iizuka T, Igari T. NUT midline carcinoma of the mediastinum showing two types of poorly differentiated tumor cells: a case report and a literature review. Pathol Res Pract, 211:92-98, 2015

37. Oguro S, Ino Y, Shimada K, Hatanaka Y, Matsuno Y, Esaki M, Nara S, Kishi Y, Kosuge T, Hiraoka N. Clinical significance of tumor-infiltrating immune cells focusing on BTLA and Cbl-b in patients with gallbladder cancer. Cancer Sci, 106:1750-1760, 2015

38. Ohmoto A, Maeshima AM, Taniguchi H, Tanioka K, Makita S, Kitahara H, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Histopathological analysis of B-cell non-Hodgkin lymphomas without light chain restriction by using flow cytometry. Leuk Lymphoma, 56:3301-3305, 2015

39. Saito M, Shimada Y, Shiraishi K, Sakamoto H, Tsuta K, Totsuka H, Chiku S, Ichikawa H, Kato M, Watanabe S, Yoshida T, Yokota J, Kohno T. Development of lung adenocarcinomas with exclusive dependence on oncogene fusions. Cancer Res, 75:2264-2271, 2015

40. Sekiguchi M, Kushima R, Oda I, Suzuki H, Taniguchi H, Sekine S, Fukagawa T, Katai H. Clinical significance of a papillary adenocarcinoma component in early gastric cancer: a single-center retrospective analysis of 628 surgically resected early gastric cancers. J Gastroenterol, 50:424-434, 2015

41. Sekiguchi M, Sekine S, Sakamoto T, Otake Y, Nakajima T, Matsuda T, Taniguchi H, Kushima R, Ohe Y, Saito Y. Excellent prognosis following endoscopic resection of patients with rectal neuroendocrine tumors despite the frequent presence of lymphovascular invasion. J Gastroenterol, 50:1184-1189, 2015

42. Shiino S, Tsuda H, Yoshida M, Jimbo K, Asaga S, Hojo T, Kinoshita T. Intraductal papillomas on core biopsy can be upgraded to malignancy on subsequent excisional biopsy regardless of the presence of atypical features. Pathol Int, 65:293-300, 2015

43. Shirahige A, Suzuki H, Oda I, Sekiguchi M, Mori G, Abe S, Nonaka S, Yoshinaga S, Sekine S, Kushima R, Saito Y, Fukagawa T, Katai H. Fatal submucosal invasive gastric adenosquamous carcinoma detected at surveillance after gastric endoscopic submucosal dissection. World J Gastroenterol, 21:4385-4390, 2015

44. Shirota T, Ojima H, Hiraoka N, Shimada K, Rokutan H, Arai Y, Kanai Y, Miyagawa S, Shibata T. Heat shock protein 90 is a potential therapeutic target in cholangiocarcinoma. Mol Cancer Ther, 14:1985-1993, 2015

45. Springer S, Wang Y, Dal Molin M, Masica DL, Jiao Y, Kinde I, Blackford A, Raman SP, Wolfgang CL, Tomita T, Niknafs N, Douville C, Ptak J, Dobbyn L, Allen PJ, Klimstra DS, Schattner MA, Schmidt CM, Yip-Schneider M, Cummings OW, Brand RE, Zeh HJ, Singhi AD, Scarpa A, Salvia R, Malleo G, Zamboni G, Falconi M, Jang JY, Kim SW, Kwon W, Hong SM, Song KB, Kim SC, Swan N, Murphy J, Geoghegan J, Brugge W, Fernandez-Del Castillo C, Mino-Kenudson M, Schulick R, Edil BH, Adsay V, Paulino J, van Hooft J, Yachida S, Nara S, Hiraoka N, Yamao K, Hijioka S, van der Merwe S, Goggins M, Canto MI, Ahuja N, Hirose K, Makary M, Weiss MJ, Cameron J, Pittman M, Eshleman JR, Diaz LA, Papadopoulos N, Kinzler KW, Karchin R, Hruban RH, Vogelstein B, Lennon AM. A combination of molecular markers and clinical features improve the classification of pancreatic cysts. Gastroenterology, 149:1501-1510, 2015

46. Suzuki H, Aoki K, Chiba K, Sato Y, Shiozawa Y, Shiraishi Y, Shimamura T, Niida A, Motomura K, Ohka F, Yamamoto T, Tanahashi K, Ranjit M, Wakabayashi T, Yoshizato T, Kataoka K, Yoshida K, Nagata Y, Sato-Otsubo A, Tanaka H, Sanada M, Kondo Y, Nakamura H, Mizoguchi M, Abe T, Muragaki Y, Watanabe R, Ito I, Miyano S, Natsume A, Ogawa S. Mutational landscape and clonal architecture in grade II and III gliomas. Nat Genet, 47:458-468, 2015

47. Suzuki M, Shiraishi K, Yoshida A, Shimada Y, Suzuki K, Asamura H, Furuta K, Kohno T, Tsuta K. *HER2* gene mutations in non-small cell lung carcinomas: concurrence with Her2 gene amplification and her2 protein expression and phosphorylation. Lung Cancer, 87:14-22, 2015

48. Suzuki S, Gotoda T, Suzuki H, Kono S, Iwatsuka K, Kusano C, Oda I, Sekine S, Moriyasu F. Morphologic and Histologic Changes in Gastric Adenomas After Helicobacter pylori Eradication: A Long-Term Prospective Analysis. Helicobacter, 20:431-437, 2015

49. Takami H, Yoshida A, Fukushima S, Arita H, Matsushita Y, Nakamura T, Ohno M, Miyakita Y, Shibui S, Narita Y, Ichimura K. Revisiting TP53 Mutations and Immunohistochemistry--A Comparative Study in 157 Diffuse Gliomas. Brain Pathol, 25:256-265, 2015

50. Tanaka Y, Kobayashi Y, Maeshima AM, Oh SY, Nomoto J, Fukuhara S, Kitahara H, Munakata W, Suzuki T, Maruyama D, Tobinai K. Intravascular large B-cell lymphoma secondary to lymphoplasmacytic lymphoma: a case report and review of literature with clonality analysis. Int J Clin Exp Pathol, 8:3339-3343, 2015

51. Ueda R, Fuji S, Mori S, Hiramoto N, Hashimoto H, Tanaka T, Tada K, Kobayashi Y, Morikawa N, Shinohara A, Okinaka K, Maeshima AM, Kurosawa S, Kim SW, Yamashita T, Fukuda T. Characteristics and outcomes of patients diagnosed with norovirus gastroenteritis after allogeneic hematopoietic stem cell transplantation based on immunochromatography. Int J Hematol, 102:121-128, 2015

52. Watanabe S, Hirano S, Mine S, Yoshida A, Motoi T, Ishii S, Naka G, Takeda Y, Igari T, Sugiyama H, Kobayashi N. A case of endobronchial NUT midline carcinoma with intraluminal growth. Anticancer Res, 35:1607-1612, 2015

53. Watanabe T, Ueno H, Watabe Y, Hiraoka N, Morizane C, Itami J, Okusaka T, Miura N, Kakizaki T, Kakuya T, Kamita M, Tsuchida A, Nagakawa Y, Wilber H, Yamada T, Honda K. ACTN4 copy number increase as a predictive biomarker for chemoradiotherapy of locally advanced pancreatic cancer. Br J Cancer, 112:704-713, 2015

54. Watanabe Y, Kusumoto M, Yoshida A, Suzuki K, Asamura H, Tsuta K. Surgically resected solitary cavitary lung adenocarcinoma: association between clinical, pathologic, and radiologic findings and prognosis. Ann Thorac Surg, 99:968-974, 2015

55. Watanabe Y, Shiraishi K, Takahashi F, Yoshida A, Suzuki K, Asamura H, Takeuchi M, Furuta K, Tsuta K. Biomarker expression and druggable gene alterations for development of an appropriate therapeutic protocol for pulmonary adenosquamous carcinoma. Histopathology, 66:939-948, 2015

56. Yagishita S, Horinouchi H, Katsui Taniyama T, Nakamichi S, Kitazono S, Mizugaki H, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. Int J Radiat Oncol Biol Phys, 91:140-148, 2015

57. Yagishita S, Horinouchi H, Sunami KS, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T, Ohe Y. Impact of KRAS mutation on response and outcome of patients with stage III non-squamous non-small cell lung cancer. Cancer Sci, 106:1402-1407, 2015

58. Yamada M, Sakamoto T, Otake Y, Nakajima T, Kuchiba A, Taniguchi H, Sekine S, Kushima R, Ramberan H, Parra-Blanco A, Fujii T, Matsuda T, Saito Y. Investigating endoscopic features of sessile serrated adenomas/polyps by using narrow-band imaging with optical magnification. Gastrointest Endosc, 82:108-117, 2015

59. Yamanoi K, Sekine S, Higuchi K, Kushima R, Nakayama J. Decreased expression of gastric gland mucin-specific glycanα1,4-linked N-acetylglucosamine on its scaffold mucin 6 is associated with malignant potential of pyloric gland adenoma of the stomach. Histopathology, 67:898-904, 2015

60. Yamazaki N, Tanaka R, Tsutsumida A, Namikawa K, Eguchi H, Omata W, Oashi K, Ogawa T, Hayashi A, Nakamura N, Tsuta K. BRAF V600 mutations and pathological features in Japanese melanoma patients. Melanoma Res, 25:9-14, 2015

61. Yasui N, Yoshida A, Kawamoto H, Yonemori K, Hosono A, Kawai A. Clinicopathologic analysis of spindle cell/sclerosing rhabdomyosarcoma. Pediatr Blood Cancer, 62:1011-1016, 2015

62. Yazawa M, Mori T, Nakayama Y, Kishi K. Basic study of soft tissue augmentation by adipose-inductive biomaterial. J Biomed Mater Res B Appl Biomater, 103:92-96, 2015

63. Yoshida A, Asano N, Kawai A, Kawamoto H, Nakazawa A, Kishimoto H, Kushima R. Differential SALL4 immunoexpression in malignant rhabdoid tumours and epithelioid sarcomas. Histopathology, 66:252-261, 2015

64. Yoshida A, Kamata T, Iwasa T, Watanabe S, Tsuta K. Myocardial Sleeve Tissues in Surgical Lung Specimens. Am J Surg Pathol, 39:1427-1432, 2015

65. Yoshida A, Yoshida H, Yoshida M, Mori T, Kobayashi E, Tanzawa Y, Yasugi T, Kawana K, Ishikawa M, Sugiura H, Maeda D, Fukayama M, Kawai A, Hiraoka N, Motoi T. Myoepithelioma-like Tumors of the Vulvar Region: A Distinctive Group of SMARCB1-deficient Neoplasms. Am J Surg Pathol, 39:1102-1113, 2015

66. Yoshida M, Ogawa R, Yoshida H, Maeshima A, Kanai Y, Kinoshita T, Hiraoka N, Sekine S. TERT promoter mutations are frequent and show association with MED12 mutations in phyllodes tumors of the breast. Br J Cancer, 113:1244-1248, 2015

67. Yoshida M, Sekine S, Ogawa R, Yoshida H, Maeshima A, Kanai Y, Kinoshita T, Ochiai A. Frequent MED12 mutations in phyllodes tumours of the breast. Br J Cancer, 112:1703-1708, 2015

68. Yunokawa M, Tsuta K, Tanaka T, Nara E, Koizumi F, Ito J, Sekine S, Fujiwara Y, Tamura K. Back with a vengeance: microvascular tumor embolism. Am J Med, 128:834-836, 2015

Department of Experimental Therapeutics

Noboru Yamamoto, Kenji Tamura, Yutaka Fujiwara, Shunsuke Kondo, Satoru Iwasa, Shigehisa Kitano

Introduction

In April 2015, the affiliation of the Department of Experimental Therapeutics was changed from the National Cancer Center (NCC) - the Exploratory Oncology Research & Clinical Trial Center (EPOC) to the NCC-Hospital. The goal of our Department is to perform initial clinical evaluation of promising new anti-cancer compounds emerging from the laboratory in phase I trials. The staff of this Department consists of specialists from various oncology fields (that is, thoracic oncology, breast & medical oncology, gastro-intestinal oncology, hepato-biliary & pancreatic oncology, and immune-oncology).

Routine activities

This Department plays an important role in new anti-cancer drug development in Japan as well as in Asia. The top priority is to conduct First-In-Human (FIH) trials, and we also perform phase I trials for solid tumors (that is, all comers). Recently, we have joined the global phase I trial to accelerate new drug development in Japan. Web- or tele-conferences are held with the EU and US sites, and we discuss patient enrollment as well as further developmental strategy. Routine web-conferences are also held between NCC-Hospital (Tokyo) and NCC-East Hospital (Chiba) every Friday morning, and we share information about adverse events, patient enrollment and refer candidates to each other to accelerate enrollment.

Research activities

The elucidation of the proof of concept is essential in new anti-cancer drug development especially in early phases, so we conduct several translational research (TR) projects in collaboration with the adjoining research institute. Comprehensive genomic analyses, named TOP-GEAR-studies, are ongoing to facilitate patient enrollment for new molecular targeted drugs under investigation. Also, we conduct the TR with the pharmaceutical industry to discover new targets for anti-immune therapy using human tissue (tumor and normal tissue) samples.

Clinical trials

In 2015, 20 phase I trials including 8 FIH trials were conducted (Table 1).

Table 1. Number of patients

No.	Target of agents	FIH	Tumors	Enrollment in 2015	Status
1	PD-L1		Solid tumors	5	Ongoing
2	FGFR	○	Solid tumors	10	Ongoing
3	B7-H3	○	Solid tumors	5	Ongoing
4	FGFR	○	Solid tumors	2	Ongoing
5	MDM2		Solid tumors	5	Closed
6	PI3K		Solid tumors	6	Closed
7	Hedgehog		Solid tumors	3	Closed
8	PD-1		Solid tumors	1	Closed
9	FGFR		Solid tumors	1	Closed
10	PDGFR		Solid tumors	18	Closed
11	MDM2	○	Solid tumors	3	Ongoing
12	mTOR		Solid tumors	12	Ongoing
13	HSP90	○	Solid tumors	11	Ongoing
14	MET+VEGFR	○	Solid tumors	3	Ongoing
15	CTLA-4		Solid tumors	8	Ongoing
16	AKT		Solid tumors	4	Ongoing
17	HER2	○	Solid tumors	3	Ongoing
18	PD-1+CCR4	○	Solid tumors	13	Ongoing
19	PI3K & mTOR		Solid tumors	3	Ongoing
20	Chk-1		Solid tumors	4	Ongoing

FIH: first in human trial

List of papers published in 2015

Journal

1. Ono M, Tsuda H, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Kinoshita T, Fujiwara Y. Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers. Breast Cancer, 22:141-152, 2015

2. Yamamoto H, Ando M, Aogi K, Iwata H, Tamura K, Yonemori K, Shimizu C, Hara F, Takabatake D, Hattori M, Asakawa T, Fujiwara Y. Phase I and pharmacokinetic study of trastuzumab emtansine in Japanese patients with HER2-positive metastatic breast cancer. Jpn J Clin Oncol, 45:12-18, 2015

3. Yagishita S, Horinouchi H, Katsui Taniyama T, Nakamichi S, Kitazono S, Mizugaki H, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. Int J Radiat Oncol Biol Phys, 91:140-148, 2015

4. Utsumi H, Honma Y, Nagashima K, Iwasa S, Takashima A, Kato K, Hamaguchi T, Yamada Y, Shimada Y, Kishi Y, Nara S, Esaki M, Shimada K. Bevacizumab and postoperative wound complications in patients with liver metastases of colorectal cancer. Anticancer Res, 35:2255-2261, 2015

5. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Fujiwara Y, Tamura Y, Wakui H, Honda K, Mizugaki H, Kitazono S, Tanabe Y, Asahina H, Yamazaki N, Suzuki S, Matsuoka M, Ogita Y, Tamura T. Phase I and pharmacokinetics/pharmacodynamics study of the MEK inhibitor RO4987655 in Japanese patients with advanced solid tumors. Invest New Drugs, 33:641-651, 2015

6. Abe S, Oda I, Nakajima T, Suzuki H, Nonaka S, Yoshinaga S, Sekine S, Taniguchi H, Kushima R, Iwasa S, Saito Y, Katai H. A case of local recurrence and distant metastasis following curative endoscopic submucosal dissection of early gastric cancer. Gastric Cancer, 18:188-192, 2015

7. Asao T, Nokihara H, Yoh K, Niho S, Goto K, Ohmatsu H, Kubota K, Yamamoto N, Sekine I, Kunitoh H, Fujiwara Y, Ohe Y. Phase II study of amrubicin at a dose of 45 mg/m2 in patients with previously treated small-cell lung cancer. Jpn J Clin Oncol, 45:941-946, 2015

8. Chua C, Tan IB, Yamada Y, Rha SY, Yong WP, Ong WS, Tham CK, Ng M, Tai DW, Iwasa S, Lim HY, Choo SP. Phase II study of trastuzumab in combination with S-1 and cisplatin in the first-line treatment of human epidermal growth factor receptor HER2-positive advanced gastric cancer. Cancer Chemother Pharmacol, 76:397-408, 2015

9. Davies BR, Guan N, Logie A, Crafter C, Hanson L, Jacobs V, James N, Dudley P, Jacques K, Ladd B, D'Cruz CM, Zinda M, Lindemann J, Kodaira M, Tamura K, Jenkins EL. Tumors with AKT1E17K Mutations Are Rational Targets for Single Agent or Combination Therapy with AKT Inhibitors. Mol Cancer Ther, 14:2441-2451, 2015

10. Fujiwara Y, Kobayashi S, Nagano H, Kanai M, Hatano E, Toyoda M, Ajiki T, Takashima Y, Yoshimura K, Hamada A, Minami H, Ioka T. Pharmacokinetic Study of Adjuvant Gemcitabine Therapy for Biliary Tract Cancer following Major Hepatectomy (KHBO1101). PLoS One, 10:e0143072, 2015

11. Fujiwara Y, Nokihara H, Yamada Y, Yamamoto N, Sunami K, Utsumi H, Asou H, Takahashl O, Ogasawara K, Gueorguieva I, Tamura T. Phase 1 study of galunisertib, a TGF-beta receptor I kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1143-1152, 2015

12. Guidance Development Review Committee, Working Group for Clinical Studies of Cancer Immunotherapy, Working Group for Effector Cell Therapy, Working Group for CMC/Non-clinical Studies, Working Group for Cancer Vaccines and Adjuvants, Working Group for Anti-immune Checkpoint Therapy and Comprehensive Cancer Immunotherapy, Biostatistics Subcommittee. 2015 Guidance on cancer immunotherapy development in early-phase clinical studies. Cancer Sci, 106:1761-1771, 2015

13. Hashimoto H, Kitano S, Ueda R, Ito A, Tada K, Fuji S, Kim SW, Yamashita T, Tomura D, Nukaya I, Mineno J, Fukuda T, Mori S, Takaue Y, Heike Y. Erratum to: Infusion of donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene for recurrent hematologic malignancies after allogeneic hematopoietic stem cell transplantation. Int J Hematol, 102:506, 2015

14. Hashimoto H, Kitano S, Ueda R, Ito A, Tada K, Fuji S, Yamashita T, Tomura D, Nukaya I, Mineno J, Fukuda T, Mori S, Takaue Y, Heike Y. Infusion of donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene for recurrent hematologic malignancies after allogeneic hematopoietic stem cell transplantation. Int J Hematol, 102:101-110, 2015

15. Hashimoto H, Kitano S, Yamagata S, Miyagi Maeshima A, Ueda R, Ito A, Tada K, Fuji S, Yamashita T, Tomura D, Nukaya I, Mineno J, Fukuda T, Mori S, Takaue Y, Heike Y. Donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene: detailed immunological function following add-back after haplo-identical transplantation. Cytotherapy, 17:1820-1830, 2015

16. Hojo T, Masuda N, Mizutani T, Shibata T, Kinoshita T, Tamura K, Hara F, Fujisawa T, Inoue K, Saji S, Nakamura K, Fukuda H, Iwata H. Intensive vs. Standard Post-Operative Surveillance in High-Risk Breast Cancer Patients (INSPIRE): Japan Clinical Oncology Group Study JCOG1204. Jpn J Clin Oncol, 45:983-986, 2015

17. Horinouchi H, Yamamoto N, Fujiwara Y, Sekine I, Nokihara H, Kubota K, Kanda S, Yagishita S, Wakui H, Kitazono S, Mizugaki H, Tokudome T, Tamura T. Phase I study of ipilimumab in phased combination with paclitaxel and carboplatin in Japanese patients with non-small-cell lung cancer. Invest New Drugs, 33:881-889, 2015

18. Ikeda M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Kondo S, Morizane C, Ueno H, Okusaka T. Chemotherapy for advanced poorly differentiated pancreatic neuroendocrine carcinoma. J Hepatobiliary Pancreat Sci, 22:623-627, 2015

19. Ito A, Kondo S, Tada K, Kitano S. Clinical Development of Immune Checkpoint Inhibitors. Biomed Res Int, 2015:605478, 2015

20. Iwasa S, Nagashima K, Yamaguchi T, Matsumoto H, Ichikawa Y, Goto A, Yasui H, Kato K, Okita NT, Shimada Y, Yamada Y. S-1 and irinotecan with or without bevacizumab versus 5-fluorouracil and leucovorin plus oxaliplatin with or without bevacizumab in metastatic colorectal cancer: a pooled analysis of four phase II studies. Cancer Chemother Pharmacol, 76:605-614, 2015

21. Iwasa S, Souda H, Yamazaki K, Takahari D, Miyamoto Y, Takii Y, Ikeda S, Hamaguchi T, Kanemitsu Y, Shimada Y. Safety and efficacy of adjuvant therapy with oxaliplatin, leucovorin and 5-fluorouracil after mesorectal excision with lateral pelvic lymph node dissection for stage iii lower rectal cancer. Anticancer Res, 35:1815-1819, 2015

22. Kanai M, Hatano E, Kobayashi S, Fujiwara Y, Marubashi S, Miyamoto A, Shiomi H, Kubo S, Ikuta S, Yanagimoto H, Terajima H, Ikoma H, Sakai D, Kodama Y, Seo S, Morita S, Ajiki T, Nagano H, Ioka T. A multi-institution phase II study of gemcitabine/cisplatin/S-1 (GCS) combination chemotherapy for patients with advanced biliary tract cancer (KHBO 1002). Cancer Chemother Pharmacol, 75:293-300, 2015

23. Kanda S, Horinouchi H, Fujiwara Y, Nokihara H, Yamamoto N, Sekine I, Kunitoh H, Kubota K, Tamura T, Ohe Y. Cytotoxic chemotherapy may overcome the development of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) therapy. Lung Cancer, 89:287-293, 2015

24. Katsuya Y, Fujiwara Y, Sunami K, Utsumi H, Goto Y, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Takashima Y, Osawa S, Ohe Y, Tamura T, Hamada A. Comparison of the pharmacokinetics of erlotinib administered in complete fasting and 2 h after a meal in patients with lung cancer. Cancer Chemother Pharmacol, 76:125-132, 2015

25. Kitazono S, Fujiwara Y, Nakamichi S, Mizugaki H, Nokihara H, Yamamoto N, Yamada Y, Inukai E, Nakamura O, Tamura T. A phase I study of resminostat in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 75:1155-1161, 2015

26. Kitazono S, Fujiwara Y, Tsuta K, Utsumi H, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Sasada S, Watanabe S, Asamura H, Tamura T, Ohe Y. Reliability of Small Biopsy Samples Compared With Resected Specimens for the Determination of Programmed Death-Ligand 1 Expression in Non--Small-Cell Lung Cancer. Clin Lung Cancer, 16:385-390, 2015

27. Kondo S, Shiba S, Udagawa R, Ryushima Y, Yano M, Uehara T, Asanabe M, Tamura K, Hashimoto J. Assessment of adverse events via a telephone consultation service for cancer patients receiving ambulatory chemotherapy. BMC Res Notes, 8:315, 2015

28. Kurihara H, Hamada A, Yoshida M, Shimma S, Hashimoto J, Yonemori K, Tani H, Miyakita Y, Kanayama Y, Wada Y, Kodaira M, Yunokawa M, Yamamoto H, Shimizu C, Takahashi K, Watanabe Y, Fujiwara Y, Tamura K. ^{64}Cu-DOTA-trastuzumab PET imaging and HER2 specificity of brain metastases in HER2-positive breast cancer patients. EJNMMI Res, 5:8, 2015

29. Hattori Y, Yoshida A, Sasaki N, Shibuki Y, Tamura K, Tsuta K. Desmoplastic small round cell tumor with sphere-like clusters mimicking adenocarcinoma. Diagn Cytopathol, 43:214-217, 2015

30. Mizugaki H, Yamamoto N, Fujiwara Y, Nokihara H, Yamada Y, Tamura T. Current Status of Single-Agent Phase I Trials in Japan: Toward Globalization. J Clin Oncol, 33:2051-2061, 2015

31. Mizugaki H, Yamamoto N, Nokihara H, Fujiwara Y, Horinouchi H, Kanda S, Kitazono S, Yagishita S, Xiong H, Qian J, Hashiba H, Shepherd SP, Giranda V, Tamura T. A phase 1 study evaluating the pharmacokinetics and preliminary efficacy of veliparib (ABT-888) in combination with carboplatin/paclitaxel in Japanese subjects with non-small cell lung cancer (NSCLC). Cancer Chemother Pharmacol, 76:1063-1072, 2015

32. Motonaga M, Yamamoto N, Makino Y, Ando-Makihara R, Ohe Y, Takano M, Hayashi Y. Phase I dose-finding and pharmacokinetic study of docetaxel and gefitinib in patients with advanced or metastatic non-small-cell lung cancer: evaluation of drug-drug interaction. Cancer Chemother Pharmacol, 76:713-721, 2015

33. Nagashima K, Iwasa S, Yanai T, Hashimoto H, Suzuki K, Ohyanagi F, Shimada Y, Yamamoto N. A double-blind randomized Phase II study of olanzapine 10 mg versus 5 mg for emesis induced by highly emetogenic chemotherapy. Jpn J Clin Oncol, 45:229-231, 2015

34. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Honda K, Tamura Y, Wakui H, Sasaki T, Yusa W, Fujino K, Tamura T. A phase 1 study of lenvatinib, multiple receptor tyrosine kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1153-1161, 2015

35. Nishio M, Horiike A, Murakami H, Yamamoto N, Kaneda H, Nakagawa K, Horinouchi H, Nagashima M, Sekiguchi M, Tamura T. Phase I study of the HER3-targeted antibody patritumab (U3-1287) combined with erlotinib in Japanese patients with non-small cell lung cancer. Lung Cancer, 88:275-281, 2015

36. Nishio M, Horiike A, Nokihara H, Horinouchi H, Nakamichi S, Wakui H, Ohyanagi F, Kudo K, Yanagitani N, Takahashi S, Kuboki Y, Yamamoto N, Yamada Y, Abe M, Tahata T, Tamura T. Phase I study of the anti-MET antibody onartuzumab in patients with solid tumors and MET-positive lung cancer. Invest New Drugs, 33:632-640, 2015

37. Okusaka T, Ueno H, Morizane C, Kondo S, Sakamoto Y, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Ikeda M. Cytotoxic chemotherapy for pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci, 22:628-633, 2015

38. Shiba S, Morizane C, Hiraoka N, Sasaki M, Koga F, Sakamoto Y, Kondo S, Ueno H, Ikeda M, Yamada T, Shimada K, Kosuge T, Okusaka T. Pancreatic neuroendocrine tumors: A single-center 20-year experience with 100 patients. Pancreatology, 16:99-105, 2015

39. Shoji H, Yamada Y, Okita N, Takashima A, Honma Y, Iwasa S, Kato K, Hamaguchi T, Shimada Y. Amplification of FGFR2 Gene in Patients with Advanced Gastric Cancer Receiving Chemotherapy: Prevalence and Prognostic Significance. Anticancer Res, 35:5055-5061, 2015

40. Takahashi H, Ikeda M, Kumada T, Osaki Y, Kondo S, Kusumoto S, Ohkawa K, Nadano S, Furuse J, Kudo M, Ito K, Yokoyama M, Okusaka T, Shimoyama M, Mizokami M. Multicenter cooperative case survey of hepatitis B virus reactivation by chemotherapeutic agents. Hepatol Res, 45:1220-1227, 2015

41. Takahashi N, Yamada Y, Furuta K, Nagashima K, Kubo A, Sasaki Y, Shoji H, Honma Y, Iwasa S, Okita N, Takashima A, Kato K, Hamaguchi T, Shimada Y. Association between serum ligands and the skin toxicity of anti-epidermal growth factor receptor antibody in metastatic colorectal cancer. Cancer Sci, 106:604-610, 2015

42. Eba J, Shimokawa T, Nakamura K, Shibata T, Misumi Y, Okamoto H, Yamamoto N, Ohe Y, Lung Cancer Study Group of the Japan Clinical Oncology Group. A Phase II/III study comparing carboplatin and irinotecan with carboplatin and etoposide for the treatment of elderly patients with extensive-disease small-cell lung cancer (JCOG1201). Jpn J Clin Oncol, 45:115-118, 2015

43. Tamura Y, Fujiwara Y, Yamamoto N, Nokihara H, Horinouchi H, Kanda S, Goto Y, Kubo E, Kitahara S, Tsuruoka K, Tsuta K, Ohe Y. Retrospective analysis of the efficacy of chemotherapy and molecular targeted therapy for advanced pulmonary pleomorphic carcinoma. BMC Res Notes, 8:800, 2015

44. Tanaka Y, Aoyagi K, Minashi K, Komatsuzaki R, Komatsu M, Chiwaki F, Tamaoki M, Nishimura T, Takahashi N, Oda I, Tachimori Y, Arao T, Nishio K, Kitano S, Narumi K, Aoki K, Fujii S, Ochiai A, Yoshida T, Muto M, Yamada Y, Sasaki H. Discovery of a Good Responder Subtype of Esophageal Squamous Cell Carcinoma with Cytotoxic T-Lymphocyte Signatures Activated by Chemoradiotherapy. PLoS One, 10:e0143804, 2015

45. Yagishita S, Horinouchi H, Sunami KS, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T, Ohe Y. Impact of KRAS mutation on response and outcome of patients with stage III non-squamous non-small cell lung cancer. Cancer Sci, 106:1402-1407, 2015

46. Yunokawa M, Tsuta K, Tanaka T, Nara E, Koizumi F, Ito J, Sekine S, Fujiwara Y, Tamura K. Back with a vengeance: microvascular tumor embolism. Am J Med, 128:834-836, 2015

47. Takahashi RU, Miyazaki H, Takeshita F, Yamamoto Y, Minoura K, Ono M, Kodaira M, Tamura K, Mori M, Ochiya T. Loss of microRNA-27b contributes to breast cancer stem cell generation by activating ENPP1. Nat Commun, 6:7318, 2015

48. Ono M, Tsuda H, Kobayashi T, Takeshita F, Takahashi RU, Tamura K, Akashi-Tanaka S, Moriya T, Yamasaki T, Kinoshita T, Yamamoto J, Fujiwara Y, Ochiya T. The expression and clinical significance of ribophorin II (RPN2) in human breast cancer. Pathol Int, 65:301-308, 2015

49. Okita K, Izumi N, Ikeda K, Osaki Y, Numata K, Ikeda M, Kokudo N, Imanaka K, Nishiguchi S, Kondo S, Nishigaki Y, Shiomi S, Ueshima K, Isoda N, Karino Y, Kudo M, Tanaka K, Kaneko S, Moriwaki H, Makuuchi M, Okusaka T, Hayashi N, Ohashi Y, Kumada H, Peretinoin Study Group. Survey of survival among patients with hepatitis C virus-related hepatocellular carcinoma treated with peretinoin, an acyclic retinoid, after the completion of a randomized, placebo-controlled trial. J Gastroenterol, 50:667-674, 2015

50. Okuyama H, Ikeda M, Kuwahara A, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Senda S, Okusaka T. Prognostic factors in patients with hepatocellular carcinoma refractory or intolerant to sorafenib. Oncology, 88:241-246, 2015

Office of Infection Control and Prevention

Hisashi Baba, Noriko Wada, Keiichi Koido, Michi Shouji, Midori Ohkubo

Introduction

The mission of the Office of Infection Control and Prevention is to control healthcare-associated infections during a variety of cancer care including highly advanced cancer treatments. The Office consists of an Infectious Disease specialist (physician), a Certified Nurse in Infection Control, a Board-certified Pharmacist in Infection Control, an Infection Control Microbiological Technologist, and an office clerk. We execute our tasks in collaboration with the Infection Control Team, which consists of cross-sectional members from various areas throughout our hospital. We also collaborate with "link nurses" to facilitate appropriate infection control practice in each ward.

Routine activities

- Advice about the control and prevention of healthcare-associated infections, problematic pathogens including multidrug-resistant bacteria, and occupational infections.
- Supporting for physicians on appropriate diagnosis and treatments of infectious disease.
- Implementation of antimicrobials stewardship based on data from our hospital and clinical evidence.
- Monitoring of environmental maintenance and compliance with the manual of infection control practice in weekly ward rounds.
- Surveillance of healthcare-associated infections and drug-resistant bacteria.
- Staff education on various infection control practices including up-to-date evidence.
- Checking for immunization status of staff and vaccination for staff with insufficient protective immunity.
- Advice on building and refurbishment projects in terms of infection control aspect.
- Planning conferences among regional small and medium-sized hospitals to promote improvement of infection control in each hospital.

Research activities

- Effective education of infection control practice, especially medical device management.
- Appropriate dosing of antimicrobial drugs in cancer patients.
- Ideal system of infection control for cancer centers in Japanese medical care system.
- Virulence factors of *Bacillus cereus* isolated from an outbreak of bacteremia.

Future prospects

Our final goal is to establish an ideal and feasible model of an infection control system for cancer centers in Japan.

Outpatient Treatment Center

Kenji Tamura, Hiroshi Nokihara, Hidehito Horinouchi, Shunsuke Kondo, Satoru Iwasa, Chitose Ogawa, Yasuji Miyakita, Natsuko Okita, Atsuko Kitano, Mayumi Tsukagoshi, Mihoko Asanabe, Hiroe Ohara, Akiko Takeda, Tomonobu Otsuka, Hironobu Hashimoto, Toru Akagi, Satoshi Nakajima

Introduction

The Outpatient Treatment Center deals with all kinds of cancer patients who have received chemotherapies. Our mission is to provide safe, comfortable and high-quality chemotherapies. Several groups collaborate to ensure the best chemotherapies, consisting of medical oncologists, nurses, pharmacists, medical social workers (MSW) and clinical research coordinators (CRCs). Our visions are 1) To provide evidence-based medicine (EBM), and development of novel anti-cancer drugs. 2) To provide safe and efficient treatments, and management of adverse events. 3) To create a comfortable environment, and to maintain the quality of life of the patients.

Routine activities

1) Setup

Our Division consists of one director (doctor), another 11 medical doctors, one nurse manager, two deputy nurse managers, one deputy drug director, one chief pharmacist, one dispensing chief, one chief engineer, Dept. Clinical Laboratory, 15 nurses, three pharmacists, and two to three reception staff.

2) Performance

We established a second Outpatient Treatment Center in the beginning of 2015. There are 30 beds in the first Outpatient Treatment Center and 26 in the second Outpatient Treatment Center (a total of 56). We also have six beds for general infusions or blood transfusions.

In 2015, the Outpatient Treatment Center supported 31,861 patients who received anticancer drugs (Table 1). The breakdown by department was Breast and Medical Oncology (n=11,997), Gastrointestinal Medical Oncology (n=6,928), Hepatobiliary and Pancreatic Oncology (n=3,642), Hematology (n=2,912), Thoracic Oncology (n=2,870), and other departments (n=3,733). Clinical trials for unapproved drugs increased to around 240 cases per month. General infusions, general intramuscular or subcutaneous injections, blood transfusions, bone marrow puncture, lumbar puncture, intraperitoneal or chest drainage, and blood gas analyses were conducted in the center.

3) Staff meeting

The monthly staff meeting is held on the second Tuesday, 16:30-17:30, every month with the participation of physicians and nurses who are main members of the center. The steering committee is held on the third Thursday of every month.

4) Hot line and conference

We have a telephone consultation service (Hot line) for outpatients who have received chemotherapies. A case conference dedicated to the Hot line is held monthly on a Tuesday with the participation of multidisciplinary specialists, including medical oncologists, nurses, and pharmacists.

5) Research activities

- Treatment of platinum-containing regime in outpatient style.
- Efficacy of frozen globe against nail toxicities by docetaxel.
- Protection of allergic reaction by Oxaliplatin in outpatients.
- Management of skin toxicities as an adverse event of molecular-targeted drugs.
- Cosmetic support for female cancer patients
- Support for continuing working for outpatients.
- Telephone hot line for emergencies for outpatients who receive chemotherapy.

・Monitoring adverse events of immuno checkpoint inhibitors.

6) Publication

1) Kondo S, Shiba S, Udagawa R, Ryushima Y, Yano M, Uehara T, Asanabe M, Tamura K, Hashimoto J. Assessment of adverse events via a telephone consultation service for cancer patients receiving ambulatory chemotherapy. BMC Res Notes. BMC Res Notes. 2015 Jul 26; 8:315. doi:

Education

We provide educational opportunities for multidisciplinary specialists, including medical oncologists, nurses, and pharmacists. We also provide an educational program directed outside the hospital for medical oncologists, nurses, pharmacists and MSW in specially designed hospitals for cancer treatment in each prefecture.

Future prospects

We are planning to undertake more activities in the second Outpatient Treatment Center, and continue to propose a model for more clinical trials in an outpatient style. We aim to shorten waiting times, undertake the smooth administration of novel molecular targeted drugs for outpatients, put into practice multidisciplinary care, and create a comfortable environment for cancer patients who received chemotherapy in the Outpatient Treatment Center.

Table 1. Cumulative total number of patients who received anticancer drugs by intravenous administration

Department	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Total
Breast and Medical Oncology	937	951	991	979	918	999	1,074	939	998	1,052	1,027	1,132	11,997
Gastrointestinal Medical Oncology	600	549	565	612	569	550	624	547	544	537	543	688	6,928
Hepatobiliary and Pancreatic Oncology	292	283	282	315	289	277	342	304	304	298	327	329	3,642
Hematology	202	174	228	233	217	232	231	238	237	248	218	233	2,691
Thoracic Oncology	179	161	205	214	219	226	273	271	238	248	306	330	2,870
Others	322	213	319	325	346	316	321	314	325	298	316	318	3,733
Total	2,532	2,331	2,590	2,678	2,558	2,600	2,865	2,613	2,646	2,681	2,737	3,030	31,861

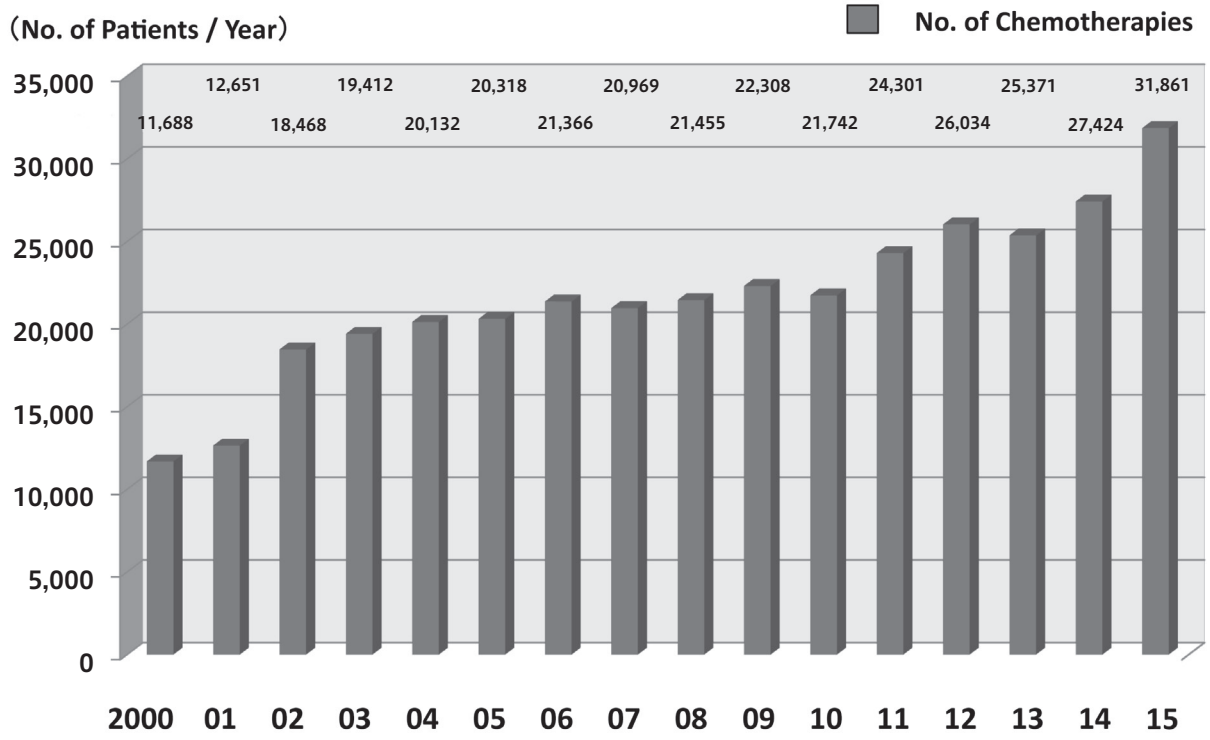


Figure 1. Total number of patients who received chemotherapy in Outpatients Treatment Center

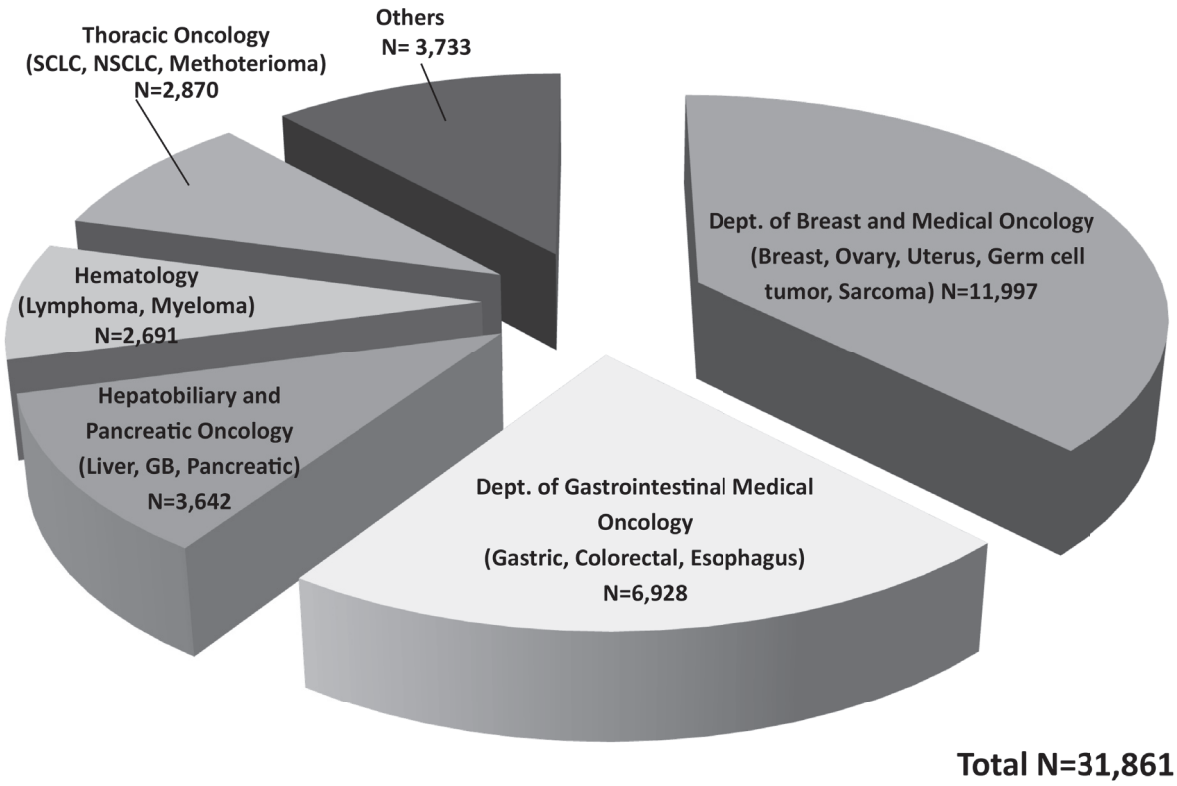


Figure 2. Proportion of cancer types in patients who received chemotherapy in Outpatients Treatment Center

List of papers published in 2015

Journal

1. Kondo S, Shiba S, Udagawa R, Ryushima Y, Yano M, Uehara T, Asanabe M, Tamura K, Hashimoto J. Assessment of adverse events via a telephone consultation service for cancer patients receiving ambulatory chemotherapy. BMC Res Notes, 8:315, 2015

Consultation, Counseling and Support Service Center

Masaki Kato, Kayoko Miyata, Natsuko Moroi, Rieko Shimizu, Naoko Goto, Mariko Tsuchiya, Miho Koitabashi, Megumi Ohsuga, Mariko Shimizu, Yumiko Fujimaki, Tomoko Asayama, Hyeon Ok Kim, Emi Takeuchi

Introduction

The Consultation, Counseling and Support Service Center provides psychosocial support services for people with cancer and their families. Staff, referred to as "Cancer Counseling and Support Specialists," were qualified as medical social workers, nurses and clinical psychologists. We make extensive efforts to solve patients' problems.

Routine activities

1) Consultation, Counseling and Support Services
   (1) Face-to-face counseling
   (2) Telephone counseling

Both face-to-face and telephone counseling are available for not only cancer patients but also their families and any people concerned with cancer. Any inquiries related to cancer such as cancer treatment and financial, social and psychological issues are accepted. We also make efforts to support special cases such as job seeking and infertility issues. Although we have tackled work-related issues so far, they are one of the major issues facing patients. Since 2013, we have cooperated with a "Hello Work Navigator," a job-finding advisor, and Social Insurance Labor Consultants to help cancer patients find new jobs and provide professional advice regarding managing cancer treatment and work. Moreover, we have prepared for the launch of a service for young adult patients who are concerned with impact of cancer treatment on fertility.

2) Activities accompanying Consultation, Counseling and Support Services
   (1) Holding group programs for patients and their families
   (2) Working on an interdisciplinary team with other medical staff
   (3) Coordinating care and patient pathways

We hold the following support groups and programs for the patients and their families

- The class for pancreatic cancer and biliary tract cancer
- The class for women before undergoing breast cancer surgery
- The support class for job seekers

We work with an interdisciplinary team with physicians, nurses and medical staff to improve or sustain patient's quality of life as much as possible. Also, in order to coordinate patient care and patient pathways, we arrange social resources and contact with other hospitals and institutions.

3) Cooperation activities with other regional hospitals and institutions
   (1) Information sharing with regional hospitals and institutions
   (2) Managing the medical institution database

4) Activities related to volunteers of the NCCH
5) Activities related to NCCH committees
6) Activities related to the education of NCCH staff
7) Administration of the patient library

Research activities

Research into young adult patients' concerns related to infertility has been conducted.

Education

We lecture and act as facilitators in seminars for education of Cancer Counseling and Support Specialists.

Future prospects

We practice high-quality cancer counseling and support, develop models and disseminate the results for the whole county.

Table 1. Number of cases (January 2015-December 2015)

1 Total	13,519
2 New cases	7,335
New cases from NCCH	3,608
New cases from other hospitals	3,727

Appearance Support Center

Keiko Nozawa, Naoya Yamazaki (Joint appointment in the Department of Onco-Dermatology), Chikako Shimizu (Joint appointment in the Department of Breast and Medical Oncology), Masahide Fujiki (Joint appointment in the Department of Plastic Surgery), Shoko Toma, Kazuko Aoki, Atsuko Ito, Eriko Takahashi

Introduction

The Appearance Support Center aims to support patients to be able to 'live in society' and to 'live as a human' through clinical research and educational practices regarding patients' physical appearance.

Clinical activities

Our team consists of two clinical psychologists (one full-time and one part-time) specialized in cosmetics, and they consult both in- and out-patients as well as their families for questions and concerns regarding physical appearance. Examples of issues are side effects of chemotherapy and radiotherapy on skin, nails, and hair, scarring and epithesis from surgeries, and breast surgery. In order to expand our practice beyond solely consultation, we are currently developing a new team in collaboration with a dermatologist, plastic surgeon, medical oncologist, pharmacist, and nurses.

The outpatient space is open to the public from Monday to Thursday between 12 am and 1 pm during which patients can try on different products and consult staff. Despite limited hours for security reasons, we had 894 users from January to December. Additionally, we conduct a patient support program titled "Cosmetic Information" every Tuesday and Thursday from 2 pm. Its main aim is to provide information to patients through group sessions. We had 99 sessions in which 438 patients participated. 40 men participated in "Men's Consultation Day" held on the fourth Wednesday of every month from 1 to 3 pm. In addition, we offered long-term inpatients a special program at the transplantation ward four times this year, and a total of 17 men and women participated.

As for individual consultations for new patients, there were a total of 1,696 consultations offered to 250 in- and out- patients. Patients' main concerns were coping strategies with specific symptoms. Following last year, consultations including seeking stress relief increased as patients with pediatric cancer increased. There were also consultations of concerns over significant life events such as the coming-of-age ceremony, weddings, and questions regarding mortuary makeup.

Research activities

Our center conducts research actively due to the lack of evidence regarding physical appearance. Current research projects are: the establishment of guidelines for support of cancer patients' appearance problems, the development of assessments and care methods for dermatological changes due to cancer treatment, the examination of distress by changes in physical appearance in male cancer patients and support by information provision, and the development of a program for an educational workshop on appearance care of cancer patients for cosmeticians.

Research outcomes

We instructed patients for treatments and care of side effects on physical appearance and developed a guideline that should guide medical staff (provisional). We also found that it was possible to evaluate skin symptoms by a device prior to grading by eyes. In addition, we investigated the effects of an appearance-related group program, and reported at the Annual Meeting of Japan Society of Clinical Oncology.

Education

In order to support medical staff to practice appearance care, "The Educational Workshop Regarding Appearance Care for Cancer Patients" was held three times in a year (237 participants) for medical staff working at designated regional cancer centers and hospitals. Additionally, we welcomed visitors of our hospital and held a special educational workshop to offer the same program conducted at Kobe University Hospital. We also held "The Educational Workshop on Appearance Care of Cancer Patients for Cosmeticians" once a year (30 participants).

Future prospects

We anticipate the emergence of patient needs of support for physical appearance as the variety of treatment drugs increases, longer-survival rates increase, and so on. Although responding to all patient needs is difficult as fulltime workers are scarce, we hope to expand human resources and develop this emerging field based on research.

Conferences

Sponsor: The Appearance Support Center (Center Hospital)
Conference title: The Educational Workshop on Appearance Care of Cancer Patients for Medical Staff: Basic course
Date: November 8th - December 20th, 2015
Location (prefecture): Tokyo

Sponsor: The Appearance Support Center (Center Hospital)
Conference title: The Educational Workshop on Appearance Care of Cancer Patients for Medical Staff: Advanced course
Date: October 11th, 2015
Location (prefecture): Tokyo

Sponsor: The Appearance Support Center (Center Hospital)
Conference title: The Educational Workshop on Appearance Care of Cancer Patients for Cosmeticians
Date: January 31st, 2016
Location (prefecture): Tokyo

List of papers published in 2015

Journal

1. Nozawa K, Ichimura M, Oshima A, Tokunaga E, Masuda N, Kitano A, Fukuuchi A, Shinji O. The present state and perception of young women with breast cancer towards breast reconstructive surgery. Int J Clin Oncol, 20:324-331, 2015

Rare Cancer Center

(NCCH) Akira Kawai, Yoshitaka Narita, Shigenobu Suzuki, Seiichi Yoshimoto, Kan Yonemori, Mayu Yunokawa, Makoto Kodaira, Tatsunori Shimoi, Yasushi Goto, Yoshitaka Honma, Chigusa Morizane, Motokiyo Komiyama, Tomoyasu Kato, Hirokazu Chuuman, Yoshikazu Tanzawa, Eisuke Kobayashi, Makoto Endo, Naoya Yamazaki, Arata Tsutsumida, Akira Takahashi, Kenjiro Namikawa, Wataru Munakata, Chitose Ogawa, Ayumu Arakawa, Miyuki Sone, Shunsuke Sugawara, Hiroshi Igaki, Kana Takahashi, Akihiko Yoshida, Noboru Yamamoto, Shunsuke Kondo, Koichi Ichimura, Tadashi Kondo, Takahiro Higashi, Takuro Sakurai, Makiko Murase, Yoko Katoh, Natumi Takeuchi,
(NCCHE) Naoto Gotohda, Tetsuo Akimoto, Fumihiko Nakatani, Ako Hosono, Toshihiko Doi, Yoichi Naito, Junya Ueno

Introduction

The Rare Cancer Center was launched in December 2013 and officially opened in June 2014 as a multidisciplinary team to take measures against the innate problems associated with rare cancers. Based on discussions, rare cancers are defined as those with an incidence < 6/100,000/year. Although each rare cancer is rare by itself, when the numbers of each rare cancer are combined, they correspond to up to 15% of all new cancer diagnoses. Information on rare cancers is scarce. Rare cancers are often inadequately diagnosed and treated in relation both to lack of knowledge and clinical expertise. Patients with rare cancers face great difficulty in having their diseases treated adequately.

Activities

The Rare Cancer Center plays a central role in the treating and managing of rare cancers in the National Cancer Center (NCC).

The mission statements of the Rare Cancer Center are as follows:

I) Establishing a vital network of diagnosis and treatment for rare cancers in the NCC Hospital and Hospital East.
II) Reviewing the problems associated with rare cancers in Japan and making proposals and taking up the issues as medical professionals.

To enable the Center to play its role, a total of 45 doctors, nurses and researchers dealing with rare cancers have joined as members of the Center. Each staff member of the Rare Cancer Center provides specialized, high-quality medical care to patients with rare cancers in cooperation with his/her Department staff.

The Rare Cancer Center provides consultation to the patients and relatives with rare cancers on the telephone (Rare Cancer Hotline). The number of telephone call was 3,006 cases in 2015. (Figure 1) The Center also provides comprehensive, scientifically based, up-to-date unbiased information about rare cancers to all patients, families and health professionals fighting against rare cancers via its website (Rare Cancer Center Homepage). The Rare Cancer Center organized the 1st International Cancer Research Symposium "Rare Cancers: Seeking Ideal Medical Care" on February 12 to 13, 2015. Also, staff of the Rare Cancer Center served as members of the committee on rare cancers (March to August, 2015) set up by Ministry of Health, Labour and Welfare.

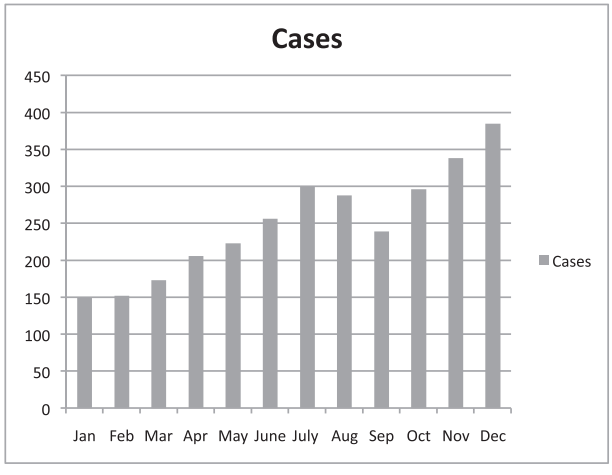


Figure 1. The Number of telephone calls to the Rare Cancer Hotline in 2015

List of papers published in 2015

Journal

1. Tahara M, Kiyota N, Mizusawa J, Nakamura K, Hayashi R, Akimoto T, Hasegawa Y, Iwae S, Monden N, Matsuura K, Fujii H, Onozawa Y, Homma A, Kubota A, Fukuda H, Fujii M. Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). Cancer Sci, 106:726-733, 2015

2. Kato T, Takashima A, Kasamatsu T, Nakamura K, Mizusawa J, Nakanishi T, Takeshima N, Kamiura S, Onda T, Sumi T, Takano M, Nakai H, Saito T, Fujiwara K, Yokoyama M, Itamochi H, Takehara K, Yokota H, Mizunoe T, Takeda S, Sonoda K, Shiozawa T, Kawabata T, Honma S, Fukuda H, Yaegashi N, Yoshikawa H, Konishi I, Kamura T, Gynecologic Oncology Study Group of the Japan Clinical Oncology Group. Clinical tumor diameter and prognosis of patients with FIGO stage IB1 cervical cancer (JCOG0806-A). Gynecol Oncol, 137:34-39, 2015

3. Hayashi N, Niikura N, Masuda N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M, Kondo N, Naito Y, Honda Y, Matsui A, Fujisawa T, Oshitanai R, Yasojima H, Yamauchi H, Saji S, Iwata H. Prognostic factors of HER2-positive breast cancer patients who develop brain metastasis: a multicenter retrospective analysis. Breast Cancer Res Treat, 149:277-284, 2015

4. Mukai H, Saeki T, Shimada K, Naito Y, Matsubara N, Nakanishi T, Obaishi H, Namiki M, Sasaki Y. Phase 1 combination study of eribulin mesylate with trastuzumab for advanced or recurrent human epidermal growth factor receptor 2 positive breast cancer. Invest New Drugs, 33:119-127, 2015

5. Yamazaki N, Kiyohara Y, Sugaya N, Uhara H. Phase I/II study of vemurafenib in patients with unresectable or recurrent melanoma with BRAF(V) (600) mutations. J Dermatol, 42:661-666, 2015

6. Yamazaki N, Tanaka R, Tsutsumida A, Namikawa K, Eguchi H, Omata W, Oashi K, Ogawa T, Hayashi A, Nakamura N, Tsuta K. BRAF V600 mutations and pathological features in Japanese melanoma patients. Melanoma Res, 25:9-14, 2015

7. Yamazaki N, Kiyohara Y, Uhara H, Fukushima S, Uchi H, Shibagaki N, Tsutsumida A, Yoshikawa S, Okuyama R, Ito Y, Tokudome T. Phase II study of ipilimumab monotherapy in Japanese patients with advanced melanoma. Cancer Chemother Pharmacol, 76:997-1004, 2015

8. Yamazaki N, Uhara H, Fukushima S, Uchi H, Shibagaki N, Kiyohara Y, Tsutsumida A, Namikawa K, Okuyama R, Otsuka Y, Tokudome T. Phase II study of the immune-checkpoint inhibitor ipilimumab plus dacarbazine in Japanese patients with previously untreated, unresectable or metastatic melanoma. Cancer Chemother Pharmacol, 76:969-975, 2015

9. Sakaizawa K, Ashida A, Uchiyama A, Ito T, Fujisawa Y, Ogata D, Matsushita S, Fujii K, Fukushima S, Shibayama Y, Hatta N, Takenouchi T, Uehara J, Okuyama R, Yamazaki N, Uhara H. Clinical characteristics associated with BRAF, NRAS and KIT mutations in Japanese melanoma patients. J Dermatol Sci, 80:33-37, 2015

10. Nakamura Y, Ohara K, Kishi A, Teramoto Y, Sato S, Fujisawa Y, Fujimoto M, Otsuka F, Hayashi N, Yamazaki N, Yamamoto A. Effects of non-amputative wide local excision on the local control and prognosis of in situ and invasive subungual melanoma. J Dermatol, 42:861-866, 2015

11. Sato S, Nakamura Y, Shimizu M, Yamada K, Teramoto Y, Yamazaki N, Yamamoto A. Giant pedunculated pilomatrix carcinoma on the upper limb: A rare clinical appearance. Eur J Dermatol, 25:91-92, 2015

12. Arita H, Narita Y, Matsushita Y, Fukushima S, Yoshida A, Takami H, Miyakita Y, Ohno M, Shibui S, Ichimura K. Development of a robust and sensitive pyrosequencing assay for the detection of IDH1/2 mutations in gliomas. Brain Tumor Pathol, 32:22-30, 2015

13. Takami H, Yoshida A, Fukushima S, Arita H, Matsushita Y, Nakamura T, Ohno M, Miyakita Y, Shibui S, Narita Y, Ichimura K. Revisiting TP53 Mutations and Immunohistochemistry-A Comparative Study in 157 Diffuse Gliomas. Brain Pathol, 25:256-265, 2015

14. Fukushima S, Yoshida A, Narita Y, Arita H, Ohno M, Miyakita Y, Ichimura K, Shibui S. Multinodular and vacuolating neuronal tumor of the cerebrum. Brain Tumor Pathol, 32:131-136, 2015

15. Murakami N, Yoshimoto S, Matsumoto F, Ueno T, Ito Y, Watanabe S, Kobayashi K, Harada K, Kitaguchi M, Sekii S, Takahashi K, Yoshio K, Inaba K, Morota M, Sumi M, Saito Y, Itami J. Severe gastrointestinal bleeding in patients with locally advanced head and neck squamous cell carcinoma treated by concurrent radiotherapy and Cetuximab. J Cancer Res Clin Oncol, 141:177-184, 2015

16. Ono M, Tsuda H, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Kinoshita T, Fujiwara Y. Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers. Breast Cancer, 22:141-152, 2015

17. Yamamoto H, Ando M, Aogi K, Iwata H, Tamura K, Yonemori K, Shimizu C, Hara F, Takabatake D, Hattori M, Asakawa T, Fujiwara Y. Phase I and pharmacokinetic study of trastuzumab emtansine in Japanese patients with HER2-positive metastatic breast cancer. Jpn J Clin Oncol, 45:12-18, 2015

18. Kinjo Y, Nonaka S, Oda I, Abe S, Suzuki H, Yoshinaga S, Maki D, Yoshimoto S, Taniguchi H, Saito Y. The short-term and long-term outcomes of the endoscopic resection for the superficial pharyngeal squamous cell carcinoma. Endosc Int Open, 3:E266-E273, 2015

19. Sone M, Nakajima Y, Woodhams R, Shioyama Y, Tsurusaki M, Hiraki T, Yoshimatsu M, Hyodoh H, Kubo T, Takeda S, Minakami H. Interventional radiology for critical hemorrhage in obstetrics: Japanese Society of Interventional Radiology (JSIR) procedural guidelines. Jpn J Radiol, 33:233-240, 2015

20. Asano N, Yoshida A, Ogura K, Kobayashi E, Susa M, Morioka H, Iwata S, Ishii T, Hiruma T, Chuman H, Kawai A. Prognostic Value of Relevant Clinicopathologic Variables in Epithelioid Sarcoma: A Multi-Institutional Retrospective Study of 44 Patients. Ann Surg Oncol, 22:2624-2632, 2015

21. Suzuki M, Shiraishi K, Yoshida A, Shimada Y, Suzuki K, Asamura H, Furuta K, Kohno T, Tsuta K. HER2 gene mutations in non-small cell lung carcinomas: concurrence with *Her2* gene amplification and her2 protein expression and phosphorylation. Lung Cancer, 87:14-22, 2015

22. Miyamoto S, Fukunaga Y, Fujiki M, Nakatni F, Tanzawa Y, Sakuraba M. Accompanying artery of sciatic nerve as recipient vessel for free-flap transfer: a computed tomographic angiography study and case reports. Microsurgery, 35:284-289, 2015

23. Kikuta K, Kubota D, Yoshida A, Morioka H, Toyama Y, Chuuman H, Kawai A. An analysis of factors related to the tail-like pattern of myxofibrosarcoma seen on MRI. Skeletal Radiol, 44:55-62, 2015

24. Yagishita S, Horinouchi H, Katsui Taniyama T, Nakamichi S, Kitazono S, Mizugaki H, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. Int J Radiat Oncol Biol Phys, 91:140-148, 2015

25. Yoshida A, Asano N, Kawai A, Kawamoto H, Nakazawa A, Kishimoto H, Kushima R. Differential SALL4 immunoexpression in malignant rhabdoid tumours and epithelioid sarcomas. Histopathology, 66:252-261, 2015

26. Ogura K, Uehara K, Akiyama T, Iwata S, Shinoda Y, Kobayashi E, Saita K, Yonemoto T, Kawano H, Chuman H, Davis AM, Kawai A. Cross-cultural adaptation and validation of the Japanese version of the Toronto Extremity Salvage Score (TESS) for patients with malignant musculoskeletal tumors in the lower extremities. J Orthop Sci, 20:1098-1105, 2015

27. Ogura K, Fujiwara T, Yasunaga H, Matsui H, Jeon DG, Cho WH, Hiraga H, Ishii T, Yonemoto T, Kamoda H, Ozaki T, Kozawa E, Nishida Y, Morioka H, Hiruma T, Kakunaga S, Ueda T, Tsuda Y, Kawano H, Kawai A. Development and external validation of nomograms predicting distant metastases and overall survival after neoadjuvant chemotherapy and surgery for patients with nonmetastatic osteosarcoma: A multi-institutional study. Cancer, 121:3844-3852, 2015

28. Kimura H, Yamamoto N, Shirai T, Nishida H, Hayashi K, Tanzawa Y, Takeuchi A, Igarashi K, Inatani H, Shimozaki S, Kato T, Aoki Y, Higuchi T, Tsuchiya H. Efficacy of triplet regimen antiemetic therapy for chemotherapy-induced nausea and vomiting (CINV) in bone and soft tissue sarcoma patients receiving highly emetogenic chemotherapy, and an efficacy comparison of single-shot palonosetron and consecutive-day granisetron for CINV in a randomized, single-blinded crossover study. Cancer Med, 4:333-341, 2015

29. Ogura K, Miyamoto S, Sakuraba M, Fujiwara T, Chuman H, Kawai A. Intercalary reconstruction after wide resection of malignant bone tumors of the lower extremity using a composite graft with a devitalized autograft and a vascularized fibula. Sarcoma, 2015:861575, 2015

30. Joo MW, Shin SH, Kang YK, Kawai A, Kim HS, Asavamongkolkul A, Jeon DG, Kim JD, Niu X, Tsuchiya H, Puri A, Wang EH, Chung SH, Chung YG. Osteosarcoma in Asian Populations Over the Age of 40 Years: A Multicenter Study. Ann Surg Oncol, 22:3557-3564, 2015

31. Ogura K, Sakuraba M, Miyamoto S, Fujiwara T, Chuman H, Kawai A. Pelvic ring reconstruction with a double-barreled free vascularized fibula graft after resection of malignant pelvic bone tumor. Arch Orthop Trauma Surg, 135:619-625, 2015

32. Zhang L, Lyer AK, Yang X, Kobayashi E, Guo Y, Mankin H, Hornicek FJ, Amiji MM, Duan Z. Polymeric nanoparticle-based delivery of microRNA-199a-3p inhibits proliferation and growth of osteosarcoma cells. Int J Nanomedicine, 10:2913-2924, 2015

33. Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, Morioka H, Hiraga H, Hiruma T, Kunisada T, Matsumine A, Tanase T, Hasegawa T, Takahashi S. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol, 16:406-416, 2015

34. Takai E, Totoki Y, Nakamura H, Morizane C, Nara S, Hama N, Suzuki M, Furukawa E, Kato M, Hayashi H, Kohno T, Ueno H, Shimada K, Okusaka T, Nakagama H, Shibata T, Yachida S. Clinical utility of circulating tumor DNA for molecular assessment in pancreatic cancer. Sci Rep, 5:18425, 2015

35. Kataoka K, Nagata Y, Kitanaka A, Shiraishi Y, Shimamura T, Yasunaga J, Totoki Y, Chiba K, Sato-Otsubo A, Nagae G, Ishii R, Muto S, Kotani S, Watatani Y, Takeda J, Sanada M, Tanaka H, Suzuki H, Sato Y, Shiozawa Y, Yoshizato T, Yoshida K, Makishima H, Iwanaga M, Ma G, Nosaka K, Hishizawa M, Itonaga H, Imaizumi Y, Munakata W, Ogasawara H, Sato T, Sasai K, Muramoto K, Penova M, Kawaguchi T, Nakamura H, Hama N, Shide K, Kubuki Y, Hidaka T, Kameda T, Nakamaki T, Ishiyama K, Miyawaki S, Yoon SS, Tobinai K, Miyazaki Y, Takaori-Kondo A, Matsuda F, Takeuchi K, Nureki O, Aburatani H, Watanabe T, Shibata T, Matsuoka M, Miyano S, Shimoda K, Ogawa S. Integrated molecular analysis of adult T cell leukemia/lymphoma. Nat Genet, 47:1304-1315, 2015

36. Narita Y, Shibui S, Committee of Brain Tumor Registry of Japan Supported by the Japan Neurosurgical Society. Trends and outcomes in the treatment of gliomas based on data during 2001-2004 from the Brain Tumor Registry of Japan. Neurol Med Chir (Tokyo), 55:286-295, 2015

37. Narita Y. Bevacizumab for glioblastoma. Ther Clin Risk Manag, 11:1759-1765, 2015

38. Okita Y, Narita Y, Miyahara R, Miyakita Y, Ohno M, Shibui S. Health-related quality of life in long-term survivors with Grade II gliomas: the contribution of disease recurrence and Karnofsky Performance Status. Jpn J Clin Oncol, 45:906-913, 2015

39. Yoshida A, Kamata T, Iwasa T, Watanabe S, Tsuta K. Myocardial Sleeve Tissues in Surgical Lung Specimens. Am J Surg Pathol, 39:1427-1432, 2015

40. Katsuya Y, Yoshida A, Watanabe S, Tsuta K. Tumour-to-tumour metastasis from papillary thyroid carcinoma with BRAF mutation to lung adenocarcinoma with EGFR mutation: the utility of mutation-specific antibodies. Histopathology, 67:262-266, 2015

41. Kamata T, Yoshida A, Kosuge T, Watanabe S, Asamura H, Tsuta K. Ciliated muconodular papillary tumors of the lung: a clinicopathologic analysis of 10 cases. Am J Surg Pathol, 39:753-760, 2015

42. Hattori Y, Yoshida A, Yoshida M, Takahashi M, Tsuta K. Evaluation of androgen receptor and GATA binding protein 3 as immunohistochemical markers in the diagnosis of metastatic breast carcinoma to the lung. Pathol Int, 65:286-292, 2015

43. Komatsu Y, Doi T, Sawaki A, Kanda T, Yamada Y, Kuss I, Demetri GD, Nishida T. Regorafenib for advanced gastrointestinal stromal tumors following imatinib and sunitinib treatment: a subgroup analysis evaluating Japanese patients in the phase III GRID trial. Int J Clin Oncol, 20:905-912, 2015

44. Takami H, Yoshida A, Fukushima S, Arita H, Matsushita Y, Nakamura T, Ohno M, Miyakita Y, Shibui S, Narita Y, Ichimura K. Revisiting TP53 Mutations and Immunohistochemistry--A Comparative Study in 157 Diffuse Gliomas. Brain Pathol, 25:256-265, 2015

45. Tajima T, Kito F, Ohta T, Kawai A, Kondo T. Interactome analysis reveals molecular mechanisms underlying the association between selenium binding protein 1 expression and the malignant features of tumor cells. J Electrophoresis, 59:1-6, 2015

46. Uemura N, Kondo T. Current advances in esophageal cancer proteomics. Biochim Biophys Acta, 1854:687-695, 2015

47. Watanabe S, Hirano S, Mine S, Yoshida A, Motoi T, Ishii S, Naka G, Takeda Y, Igari T, Sugiyama H, Kobayashi N. A case of endobronchial NUT midline carcinoma with intraluminal growth. Anticancer Res, 35:1607-1612, 2015

48. Watanabe Y, Shiraishi K, Takahashi F, Yoshida A, Suzuki K, Asamura H, Takeuchi M, Furuta K, Tsuta K. Biomarker expression and druggable gene alterations for development of an appropriate therapeutic protocol for pulmonary adenosquamous carcinoma. Histopathology, 66:939-948, 2015

49. Inoue I, Higashi T, Iwamoto M, Heiney SP, Tamaki T, Osawa K, Inoue M, Shiraishi K, Kojima R, Matoba M. A national profile of the impact of parental cancer on their children in Japan. Cancer Epidemiol, 39:838-841, 2015

50. Iwamoto M, Higashi T, Miura H, Kawaguchi T, Tanaka S, Yamashita I, Yoshimoto T, Yoshida S, Matoba M. Accuracy of using Diagnosis Procedure Combination administrative claims data for estimating the amount of opioid consumption among cancer patients in Japan. Jpn J Clin Oncol, 45:1036-1041, 2015

51. Tsukada Y, Nakamura F, Iwamoto M, Nishimoto H, Emori Y, Terahara A, Higashi T. Are hospitals in Japan with larger patient volume treating younger and earlier-stage cancer patients? An analysis of hospital-based cancer registry data in Japan. Jpn J Clin Oncol, 45:719-726, 2015

52. Ikeda S, Ishikawa M, Kato T. Spontaneous ureteral rupture during concurrent chemoradiotherapy in a woman with uterine cervical cancer. Gynecol Oncol Rep, 13:18-19, 2015

53. Togami S, Sasajima Y, Kasamatsu T, Oda-Otomo R, Okada S, Ishikawa M, Ikeda S, Kato T, Tsuda H. Immunophenotype and human papillomavirus status of serous adenocarcinoma of the uterine cervix. Pathol Oncol Res, 21:487-494, 2015

54. Yoshida A, Yoshida H, Yoshida M, Mori T, Kobayashi E, Tanzawa Y, Yasugi T, Kawana K, Ishikawa M, Sugiura H, Maeda D, Fukayama M, Kawai A, Hiraoka N, Motoi T. Myoepithelioma-like Tumors of the Vulvar Region: A Distinctive Group of SMARCB1-deficient Neoplasms. Am J Surg Pathol, 39:1102-1113, 2015

55. Wakisaka N, Hasegawa Y, Yoshimoto S, Miura K, Shiotani A, Yokoyama J, Sugasawa M, Moriyama-Kita M, Endo K, Yoshizaki T. Primary Tumor-Secreted Lymphangiogenic Factors Induce Pre-Metastatic Lymphvascular Niche Formation at Sentinel Lymph Nodes in Oral Squamous Cell Carcinoma. PLoS One, 10:e0144056, 2015

56. Utsumi H, Honma Y, Nagashima K, Iwasa S, Takashima A, Kato K, Hamaguchi T, Yamada Y, Shimada Y, Kishi Y, Nara S, Esaki M, Shimada K. Bevacizumab and postoperative wound complications in patients with liver metastases of colorectal cancer. Anticancer Res, 35:2255-2261, 2015

57. AJCC Ophthalmic Oncology Task Force. International Validation of the American Joint Committee on Cancer's 7th Edition Classification of Uveal Melanoma. JAMA Ophthalmol, 133:376-383, 2015

58. Suzuki S, Aihara Y, Fujiwara M, Sano S, Kaneko A. Intravitreal injection of melphalan for intraocular retinoblastoma. Jpn J Ophthalmol, 59:164-172, 2015

59. Fujiwara T, Fujiwara M, Numoto K, Ogura K, Yoshida A, Yonemoto T, Suzuki S, Kawai A. Second primary osteosarcomas in patients with retinoblastoma. Jpn J Clin Oncol, 45:1139-1145, 2015

60. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Fujiwara Y, Tamura Y, Wakui H, Honda K, Mizugaki H, Kitazono S, Tanabe Y, Asahina H, Yamazaki N, Suzuki S, Matsuoka M, Ogita Y, Tamura T. Phase I and pharmacokinetics/pharmacodynamics study of the MEK inhibitor RO4987655 in Japanese patients with advanced solid tumors. Invest New Drugs, 33:641-651, 2015

61. Mizowaki T, Aoki M, Nakamura K, Yorozu A, Kokubo M, Karasawa K, Kozuka T, Nakajima N, Sasai K, Akimoto T. Current status and outcomes of patients developing PSA recurrence after prostatectomy who were treated with salvage radiotherapy: a JROSG surveillance study. J Radiat Res, 56:750-756, 2015

62. Hashimoto Y, Akimoto T, Iizuka J, Tanabe K, Mitsuhashi N. Correlation between the changes in the EPIC QOL scores and the dose-volume histogram parameters in high-dose-rate brachytherapy combined with hypofractionated external beam radiation therapy for prostate cancer. Jpn J Clin Oncol, 45:81-87, 2015

63. Motegi A, Kawashima M, Arahira S, Zenda S, Toshima M, Onozawa M, Hayashi R, Akimoto T. Accelerated radiotherapy for T1 to T2 glottic cancer. Head Neck, 37:579-584, 2015

64. Doi T, Tamura K, Tanabe Y, Yonemori K, Yoshino T, Fuse N, Kodaira M, Bando H, Noguchi K, Shimamoto T, Ohtsu A. Phase 1 pharmacokinetic study of the oral pan-AKT inhibitor MK-2206 in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:409-416, 2015

65. Zenda S, Ishi S, Akimoto T, Arahira S, Motegi A, Tahara M, Hayashi R, Asanuma C. DeCoP, a Dermatitis Control Program using a moderately absorbent surgical pad for head and neck cancer patients receiving radiotherapy: a retrospective analysis. Jpn J Clin Oncol, 45:433-438, 2015

66. Asao T, Nokihara H, Yoh K, Niho S, Goto K, Ohmatsu H, Kubota K, Yamamoto N, Sekine I, Kunitoh H, Fujiwara Y, Ohe Y. Phase II study of amrubicin at a dose of 45 mg/m2 in patients with previously treated small-cell lung cancer. Jpn J Clin Oncol, 45:941-946, 2015

67. Doi T, Yoshino T, Shitara K, Matsubara N, Fuse N, Naito Y, Uenaka K, Nakamura T, Hynes SM, Lin AB. Phase I study of LY2603618, a CHK1 inhibitor, in combination with gemcitabine in Japanese patients with solid tumors. Anticancer Drugs, 26:1043-1053, 2015

68. Kawazoe A, Shitara K, Fukuoka S, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yamanaka T, Doi T, Ohtsu A, Yoshino T. A retrospective observational study of clinicopathological features of KRAS, NRAS, BRAF and PIK3CA mutations in Japanese patients with metastatic colorectal cancer. BMC Cancer, 15:258, 2015

69. Davies BR, Guan N, Logie A, Crafter C, Hanson L, Jacobs V, James N, Dudley P, Jacques K, Ladd B, D'Cruz CM, Zinda M, Lindemann J, Kodaira M, Tamura K, Jenkins EL. Tumors with AKT1E17K Mutations Are Rational Targets for Single Agent or Combination Therapy with AKT Inhibitors. Mol Cancer Ther, 14:2441-2451, 2015

70. Kawazoe A, Shitara K, Fukuoka S, Noguchi M, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yoshino T, Ohtsu A, Doi T. Clinical outcomes in 66 patients with advanced gastric cancer treated in phase I trials: the NCCHE experience. Invest New Drugs, 33:664-670, 2015

71. Fujiwara Y, Nokihara H, Yamada Y, Yamamoto N, Sunami K, Utsumi H, Asou H, Takahashl O, Ogasawara K, Gueorguieva I, Tamura T. Phase 1 study of galunisertib, a TGF-beta receptor I kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1143-1152, 2015

72. Oh DY, Doi T, Shirao K, Lee KW, Park SR, Chen Y, Yang L, Valota O, Bang YJ. Phase I Study of Axitinib in Combination with Cisplatin and Capecitabine in Patients with Previously Untreated Advanced Gastric Cancer. Cancer Res Treat, 47:687-696, 2015

73. Horinouchi H, Yamamoto N, Fujiwara Y, Sekine I, Nokihara H, Kubota K, Kanda S, Yagishita S, Wakui H, Kitazono S, Mizugaki H, Tokudome T, Tamura T. Phase I study of ipilimumab in phased combination with paclitaxel and carboplatin in Japanese patients with non-small-cell lung cancer. Invest New Drugs, 33:881-889, 2015

74. Ikeda M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Kondo S, Morizane C, Ueno H, Okusaka T. Chemotherapy for advanced poorly differentiated pancreatic neuroendocrine carcinoma. J Hepatobiliary Pancreat Sci, 22:623-627, 2015

75. Murakami N, Kobayashi K, Nakamura S, Wakita A, Okamoto H, Tsuchida K, Kashihara T, Harada K, Yamada M, Sekii S, Takahashi K, Umezawa R, Inaba K, Ito Y, Igaki H, Itami J. A total EQD2 greater than 85 Gy for trachea and main bronchus D2cc being associated with severe late complications after definitive endobronchial brachytherapy. J Contemp Brachytherapy, 7:363-368, 2015

76. Watanabe T, Ueno H, Watabe Y, Hiraoka N, Morizane C, Itami J, Okusaka T, Miura N, Kakizaki T, Kakuya T, Kamita M, Tsuchida A, Nagakawa Y, Wilber H, Yamada T, Honda K. ACTN4 copy number increase as a predictive biomarker for chemoradiotherapy of locally advanced pancreatic cancer. Br J Cancer, 112:704-713, 2015

77. Takahashi H, Kaniwa N, Saito Y, Sai K, Hamaguchi T, Shirao K, Shimada Y, Matsumura Y, Ohtsu A, Yoshino T, Doi T, Takahashi A, Odaka Y, Okuyama M, Sawada J, Sakamoto H, Yoshida T. Construction of possible integrated predictive index based on EGFR and ANXA3 polymorphisms for chemotherapy response in fluoropyrimidine-treated Japanese gastric cancer patients using a bioinformatic method. BMC Cancer, 15:718, 2015

78. Kobayashi K, Murakami N, Wakita A, Nakamura S, Okamoto H, Umezawa R, Takahashi K, Inaba K, Igaki H, Ito Y, Shigematsu N, Itami J. Dosimetric variations due to interfraction organ deformation in cervical cancer brachytherapy. Radiother Oncol, 117:555-558, 2015

79. Yasui N, Yoshida A, Kawamoto H, Yonemori K, Hosono A, Kawai A. Clinicopathologic analysis of spindle cell/sclerosing rhabdomyosarcoma. Pediatr Blood Cancer, 62:1011-1016, 2015

80. Kikuta K, Morioka H, Kawai A, Kondo T. Global protein-expression profiling for reclassification of malignant fibrous histiocytoma. Biochim Biophys Acta, 1854:696-701, 2015

81. Kanda S, Horinouchi H, Fujiwara Y, Nokihara H, Yamamoto N, Sekine I, Kunitoh H, Kubota K, Tamura T, Ohe Y. Cytotoxic chemotherapy may overcome the development of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) therapy. Lung Cancer, 89:287-293, 2015

82. Ueda S, Satoh T, Gotoh M, Gao L, Doi T. A phase ib study of safety and pharmacokinetics of ramucirumab in combination with paclitaxel in patients with advanced gastric adenocarcinomas. Oncologist, 20:493-494, 2015

83. Yonemoto T, Hosono A, Iwata S, Kamoda H, Hagiwara Y, Fujiwara T, Kawai A, Ishii T. The prognosis of osteosarcoma occurring as second malignancy of childhood cancers may be favorable: experience of two cancer centers in Japan. Int J Clin Oncol, 20:613-616, 2015

84. Katsuya Y, Fujiwara Y, Sunami K, Utsumi H, Goto Y, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Takashima Y, Osawa S, Ohe Y, Tamura T, Hamada A. Comparison of the pharmacokinetics of erlotinib administered in complete fasting and 2 h after a meal in patients with lung cancer. Cancer Chemother Pharmacol, 76:125-132, 2015

85. Kurose K, Ohue Y, Wada H, Iida S, Ishida T, Kojima T, Doi T, Suzuki S, Isobe M, Funakoshi T, Kakimi K, Nishikawa H, Udono H, Oka M, Ueda R, Nakayama E. Phase Ia Study of FoxP3+ CD4 Treg Depletion by Infusion of a Humanized Anti-CCR4 Antibody, KW-0761, in Cancer Patients. Clin Cancer Res, 21:4327-4336, 2015

86. Ichikawa H, Yoshida A, Kanda T, Kosugi S, Ishikawa T, Hanyu T, Taguchi T, Sakumoto M, Katai H, Kawai A, Wakai T, Kondo T. Prognostic significance of promyelocytic leukemia expression in gastrointestinal stromal tumor; integrated proteomic and transcriptomic analysis. Cancer Sci, 106:115-124, 2015

87. Kitazono S, Fujiwara Y, Nakamichi S, Mizugaki H, Nokihara H, Yamamoto N, Yamada Y, Inukai E, Nakamura O, Tamura T. A phase I study of resminostat in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 75:1155-1161, 2015

88. Arita H, Narita Y, Yoshida A, Hashimoto N, Yoshimine T, Ichimura K. *IDH1/2* mutation detection in gliomas. Brain Tumor Pathol, 32:79-89, 2015

89. Kitazono S, Fujiwara Y, Tsuta K, Utsumi H, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Sasada S, Watanabe S, Asamura H, Tamura T, Ohe Y. Reliability of Small Biopsy Samples Compared With Resected Specimens for the Determination of Programmed Death-Ligand 1 Expression in Non--Small-Cell Lung Cancer. Clin Lung Cancer, 16:385-390, 2015

90. Kurihara H, Hamada A, Yoshida M, Shimma S, Hashimoto J, Yonemori K, Tani H, Miyakita Y, Kanayama Y, Wada Y, Kodaira M, Yunokawa M, Yamamoto H, Shimizu C, Takahashi K, Watanabe Y, Fujiwara Y, Tamura K. ^{64}Cu-DOTA-trastuzumab PET imaging and HER2 specificity of brain metastases in HER2-positive breast cancer patients. EJNMMI Res, 5:8, 2015

91. Hattori Y, Yoshida A, Sasaki N, Shibuki Y, Tamura K, Tsuta K. Desmoplastic small round cell tumor with sphere-like clusters mimicking adenocarcinoma. Diagn Cytopathol, 43:214-217, 2015

92. Fujita H, Yoshida A, Taniguchi H, Katai H, Sekine S. Adult-onset inflammatory myofibroblastic tumour of the stomach with a TFG-ROS1 fusion. Histopathology, 66:610-612, 2015

93. Mizugaki H, Yamamoto N, Fujiwara Y, Nokihara H, Yamada Y, Tamura T. Current Status of Single-Agent Phase I Trials in Japan: Toward Globalization. J Clin Oncol, 33:2051-2061, 2015

94. Mizugaki H, Yamamoto N, Nokihara H, Fujiwara Y, Horinouchi H, Kanda S, Kitazono S, Yagishita S, Xiong H, Qian J, Hashiba H, Shepherd SP, Giranda V, Tamura T. A phase 1 study evaluating the pharmacokinetics and preliminary efficacy of veliparib (ABT-888) in combination with carboplatin/paclitaxel in Japanese subjects with non-small cell lung cancer (NSCLC). Cancer Chemother Pharmacol, 76:1063-1072, 2015

95. Kobayashi E, Setsu N. Osteosclerosis induced by denosumab. Lancet, 385:539, 2015

96. Motonaga M, Yamamoto N, Makino Y, Ando-Makihara R, Ohe Y, Takano M, Hayashi Y. Phase I dose-finding and pharmacokinetic study of docetaxel and gefitinib in patients with advanced or metastatic non-small-cell lung cancer: evaluation of drug-drug interaction. Cancer Chemother Pharmacol, 76:713-721, 2015

97. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Honda K, Tamura Y, Wakui H, Sasaki T, Yusa W, Fujino K, Tamura T. A phase 1 study of lenvatinib, multiple receptor tyrosine kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1153-1161, 2015

98. Nishio M, Horiike A, Murakami H, Yamamoto N, Kaneda H, Nakagawa K, Horinouchi H, Nagashima M, Sekiguchi M, Tamura T. Phase I study of the HER3-targeted antibody patritumab (U3-1287) combined with erlotinib in Japanese patients with non-small cell lung cancer. Lung Cancer, 88:275-281, 2015

99. Nishio M, Horiike A, Nokihara H, Horinouchi H, Nakamichi S, Wakui H, Ohyanagi F, Kudo K, Yanagitani N, Takahashi S, Kuboki Y, Yamamoto N, Yamada Y, Abe M, Tahata T, Tamura T. Phase I study of the anti-MET antibody onartuzumab in patients with solid tumors and MET-positive lung cancer. Invest New Drugs, 33:632-640, 2015

100. Yamaga K, Kobayashi E, Kubota D, Setsu N, Tanaka Y, Minami Y, Tanzawa Y, Nakatani F, Kawai A, Chuman H. Pediatric myositis ossificans mimicking osteosarcoma. Pediatr Int, 57:996-999, 2015

101. Guo J, Yonemori K, Le Marchand L, Turesky RJ. Method to Biomonitor the Cooked Meat Carcinogen 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine in Dyed Hair by Ultra-Performance Liquid Chromatography-Orbitrap High Resolution Multistage Mass Spectrometry. Anal Chem, 87:5872-5877, 2015

102. Okusaka T, Ueno H, Morizane C, Kondo S, Sakamoto Y, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Ikeda M. Cytotoxic chemotherapy for pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci, 22:628-633, 2015

103. Fujiwara T, Ogura K, Kobayashi E, Tanzawa Y, Nakatani F, Chuman H, Kawai A. Clinical Outcomes of Surgical Treatments for Primary Malignant Bone Tumors Arising in the Acetabulum. Sarcoma, 2015:430576, 2015

104. Hara M, Nakashima T, Harashima H, Ryushima Y, Shimizu C, Kodaira M, Yunokawa M, Yamamoto H, Hashimoto J, Tanabe Y, Bun S, Makino Y, Iwase H, Fujiwara Y, Tamura K, Hayashi Y. Efficacy and safety of aprepitant and dexamethasone in the prevention of nausea and vomiting from neoadjuvant or adjuvant anthracyclines and cyclophosphamide combination therapy in patients with breast cancer. J Pharm Health Care Sci, 41:603-611, 2015

105. Fujiki M, Miyamoto S, Nakatani F, Kawai A, Sakuraba M. Rotationplasty with vascular reconstruction for prosthetic knee joint infection. Case Rep Orthop, 2015:241405, 2015

106. Miyamoto S, Fujiki M, Nakatani F, Sakisaka M, Sakuraba M. Free flow-through anterolateral thigh flap for complex knee defect including the popliteal artery. Microsurgery, 35:485-488, 2015

107. Blake EA, Kodama M, Yunokawa M, Ross MS, Ueda Y, Grubbs BH, Matsuo K. Feto-maternal outcomes of pregnancy complicated by epithelial ovarian cancer: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol, 186:97-105, 2015

108. Shoji H, Yamada Y, Okita N, Takashima A, Honma Y, Iwasa S, Kato K, Hamaguchi T, Shimada Y. Amplification of FGFR2 Gene in Patients with Advanced Gastric Cancer Receiving Chemotherapy: Prevalence and Prognostic Significance. Anticancer Res, 35:5055-5061, 2015

109. Igaki H, Magome T, Sakuramachi M, Nomoto A, Sakumi A, Kitaguchi M, Haga A, Itami J, Nakagawa K. Patterns of recurrence in malignant glioma patients: association with subventricular zone and radiotherapy dose. Jacobs J Radiat Oncol, 2:020, 2015

110. Hanakita S, Koga T, Shin M, Igaki H, Saito N. The long-term outcomes of radiosurgery for arteriovenous malformations in pediatric and adolescent populations. J Neurosurg Pediatr, 16:222-231, 2015

111. Takahashi N, Yamada Y, Furuta K, Nagashima K, Kubo A, Sasaki Y, Shoji H, Honma Y, Iwasa S, Okita N, Takashima A, Kato K, Hamaguchi T, Shimada Y. Association between serum ligands and the skin toxicity of anti-epidermal growth factor receptor antibody in metastatic colorectal cancer. Cancer Sci, 106:604-610, 2015

112. Kokudo N, Hasegawa K, Akahane M, Igaki H, Izumi N, Ichida T, Uemoto S, Kaneko S, Kawasaki S, Ku Y, Kudo M, Kubo S, Takayama T, Tateishi R, Fukuda T, Matsui O, Matsuyama Y, Murakami T, Arii S, Okazaki M, Makuuchi M. Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). Hepatol Res, 45:2015

113. Eba J, Shimokawa T, Nakamura K, Shibata T, Misumi Y, Okamoto H, Yamamoto N, Ohe Y, Lung Cancer Study Group of the Japan Clinical Oncology Group. A Phase II/III study comparing carboplatin and irinotecan with carboplatin and etoposide for the treatment of elderly patients with extensive-disease small-cell lung cancer (JCOG1201). Jpn J Clin Oncol, 45:115-118, 2015

114. Tamura Y, Fujiwara Y, Yamamoto N, Nokihara H, Horinouchi H, Kanda S, Goto Y, Kubo E, Kitahara S, Tsuruoka K, Tsuta K, Ohe Y. Retrospective analysis of the efficacy of chemotherapy and molecular targeted therapy for advanced pulmonary pleomorphic carcinoma. BMC Res Notes, 8:800, 2015

115. Miyashita M, Kawakami S, Kato D, Yamashita H, Igaki H, Nakano K, Kuroda Y, Nakagawa K. The importance of good death components among cancer patients, the general population, oncologists, and oncology nurses in Japan: patients prefer "fighting against cancer". Support Care Cancer, 23:103-110, 2015

116. Matsumoto K, Katsumata N, Shibata T, Satoh T, Saitou M, Yunokawa M, Takano T, Nakamura K, Kamura T, Konishi I. Phase II trial of oral etoposide plus intravenous irinotecan in patients with platinum-resistant and taxane-pretreated ovarian cancer (JCOG0503). Gynecol Oncol, 136:218-223, 2015

117. Yagishita S, Horinouchi H, Sunami KS, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T, Ohe Y. Impact of KRAS mutation on response and outcome of patients with stage III non-squamous non-small cell lung cancer. Cancer Sci, 106:1402-1407, 2015

118. Yunokawa M, Tsuta K, Tanaka T, Nara E, Koizumi F, Ito J, Sekine S, Fujiwara Y, Tamura K. Back with a vengeance: microvascular tumor embolism. Am J Med, 128:834-836, 2015

119. Takami H, Fukushima S, Fukuoka K, Suzuki T, Yanagisawa T, Matsushita Y, Nakamura T, Arita H, Mukasa A, Saito N, Kanamori M, Kumabe T, Tominaga T, Kobayashi K, Nagane M, Iuchi T, Tamura K, Maehara T, Sugiyama K, Nakada M, Kanemura Y, Nonaka M, Yokogami K, Takeshima H, Narita Y, Shibui S, Nakazato Y, Nishikawa R, Ichimura K, Matsutani M. Human chorionic gonadotropin is expressed virtually in all intracranial germ cell tumors. J Neurooncol, 124:23-32, 2015

120. Ichimura K, Narita Y, Hawkins CE. Diffusely infiltrating astrocytomas: pathology, molecular mechanisms and markers. Acta Neuropathol, 129:789-808, 2015

121. Mimori T, Kobayashi S, Tanaka A, Sasada S, Yoshida A, Izumo T, Sasaki N, Tsuchida T, Tsuta K. Novel use for an EGFR mutation-specific antibody in discriminating lung adenocarcinoma from reactive pneumocyte hyperplasia. Histopathology, 66:816-823, 2015

122. Geisenberger C, Mock A, Warta R, Rapp C, Schwager C, Korshunov A, Nied AK, Capper D, Brors B, Jungk C, Jones D, Collins VP, Ichimura K, Backlund LM, Schnabel E, Mittelbron M, Lahrmann B, Zheng S, Verhaak RG, Grabe N, Pfister SM, Hartmann C, von Deimling A, Debus J, Unterberg A, Abdollahi A, Herold-Mende C. Molecular profiling of long-term survivors identifies a subgroup of glioblastoma characterized by chromosome 19/20 co-gain. Acta Neuropathol, 130:419-434, 2015

123. Takahashi RU, Miyazaki H, Takeshita F, Yamamoto Y, Minoura K, Ono M, Kodaira M, Tamura K, Mori M, Ochiya T. Loss of microRNA-27b contributes to breast cancer stem cell generation by activating ENPP1. Nat Commun, 6:7318, 2015

124. Watanabe Y, Kusumoto M, Yoshida A, Suzuki K, Asamura H, Tsuta K. Surgically resected solitary cavitary lung adenocarcinoma: association between clinical, pathologic, and radiologic findings and prognosis. Ann Thorac Surg, 99:968-974, 2015

125. Ono R, Hasegawa D, Hirabayashi S, Kamiya T, Yoshida K, Yonekawa S, Ogawa C, Hosoya R, Toki T, Terui K, Ito E, Manabe A. Acute megakaryoblastic leukemia with acquired trisomy 21 and GATA1 mutations in phenotypically normal children. Eur J Pediatr, 174:525-531, 2015

126. Iwakawa R, Kohno T, Totoki Y, Shibata T, Tsuchihara K, Mimaki S, Tsuta K, Narita Y, Nishikawa R, Noguchi M, Harris CC, Robles AI, Yamaguchi R, Imoto S, Miyano S, Totsuka H, Yoshida T, Yokota J. Expression and clinical significance of genes frequently mutated in small cell lung cancers defined by whole exome/RNA sequencing. Carcinogenesis, 36:616-621, 2015

127. Kato M, Manabe A, Saito AM, Koh K, Inukai T, Ogawa C, Goto H, Tsuchida M, Ohara A. Outcome of pediatric acute lymphoblastic leukemia with very late relapse: a retrospective analysis by the Tokyo Children's Cancer Study Group (TCCSG). Int J Hematol, 101:52-57, 2015

128. Yasui N, Kawamoto H, Fujiwara M, Aihara Y, Ogawa C, Hosono A, Suzuki S. High-dose chemotherapy for high-risk retinoblastoma: clinical course and outcome of 14 cases in the National Cancer Center, Japan. Bone Marrow Transplant, 50:221-224, 2015

129. Nagatsuma AK, Aizawa M, Kuwata T, Doi T, Ohtsu A, Fujii H, Ochiai A. Expression profiles of HER2, EGFR, MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma. Gastric Cancer, 18:227-238, 2015

130. Sasaki T, Fuse N, Kuwata T, Nomura S, Kaneko K, Doi T, Yoshino T, Asano H, Ochiai A, Komatsu Y, Sakamoto N, Ohtsu A. Serum HER2 levels and HER2 status in tumor cells in advanced gastric cancer patients. Jpn J Clin Oncol, 45:43-48, 2015

131. Fujiwara Y, Yonemori K, Shibata T, Okita N, Ushirozawa N. Japanese universal health care faces a crisis in cancer treatment. Lancet Oncol, 16:251-252, 2015

132. Ohmoto A, Maeshima AM, Taniguchi H, Tanioka K, Makita S, Kitahara H, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Histopathological analysis of B-cell non-Hodgkin lymphomas without light chain restriction by using flow cytometry. Leuk Lymphoma, 56:3301-3305, 2015

133. Maeshima AM, Taniguchi H, Nomoto J, Makita S, Kitahara H, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Clinicopathological features of classical Hodgkin lymphoma in patients ≥ 40 years old, with special reference to composite cases. Jpn J Clin Oncol, 45:921-928, 2015

134. Miyagi Maeshima A, Taniguchi H, Makita S, Kitahara H, Miyamoto K, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Histopathological Characteristics of Lymphomas in the Upper Aerodigestive Tract. A Single-Institute Study in Japan. J Clin Exp Hematop, 55:7-11, 2015

135. Ogura M, Uchida T, Terui Y, Hayakawa F, Kobayashi Y, Taniwaki M, Takamatsu Y, Naoe T, Tobinai K, Munakata W, Yamauchi T, Kageyama A, Yuasa M, Motoyama M, Tsunoda T, Hatake K. Phase I study of OPB-51602, an oral inhibitor of signal transducer and activator of transcription 3, in patients with relapsed/refractory hematological malignancies. Cancer Sci, 106:896-901, 2015

136. Aoki T, Kokudo N, Komoto I, Takaori K, Kimura W, Sano K, Takamoto T, Hashimoto T, Okusaka T, Morizane C, Ito T, Imamura M. Streptozocin chemotherapy for advanced/metastatic well-differentiated neuroendocrine tumors: an analysis of a multi-center survey in Japan. J Gastroenterol, 50:769-775, 2015

137. Doi T, Yoshino T, Fuse N, Boku N, Yamazaki K, Koizumi W, Shimada K, Takinishi Y, Ohtsu A. Phase I study of TAS-102 and irinotecan combination therapy in Japanese patients with advanced colorectal cancer. Invest New Drugs, 33:1068-1077, 2015

138. Tanaka Y, Kobayashi Y, Maeshima AM, Oh SY, Nomoto J, Fukuhara S, Kitahara H, Munakata W, Suzuki T, Maruyama D, Tobinai K. Intravascular large B-cell lymphoma secondary to lymphoplasmacytic lymphoma: a case report and review of literature with clonality analysis. Int J Clin Exp Pathol, 8:3339-3343, 2015

139. Ito J, Yoshida A, Maeshima AM, Nakagawa K, Watanabe S, Kobayashi Y, Fukuhara S, Tsuta K. Concurrent thymoma, thymic carcinoma, and T lymphoblastic leukemia/lymphoma in an anterior mediastinal mass. Pathol Res Pract, 211:693-696, 2015

Book

1. Sone M, Arai Y. Section B. Coils and Plugs - 5. Gelfoam. In: Marcelo G, Riccardo L, Gary PS (eds), Embolization Therapy: Principles and Clinical Applications, Netherland, Wolters Kluwer, 2015

Department of Radiation (Diagnosis)

Tomohiko Aso, Kanyu Ihara, Yuzuru Kouno, Takamasa Hirai, Noriko Nishikawa, Naoya Ikeno, Hirobumi Nagasawa, Jun Takita, Naotoshi Atoda, Chieko Nagashima, Akira Inagaki, Hideaki Kitamura, Mayumi Kitagawa, Akiko Nagoshi, Kiyoyuki Kodama, Masahiro Suzuki, Takeshi Murano, Junko Sonehara, Naoki Shimada, Toshimitsu Utsuno, Kenta Hiroi, Jun Torii, Eiko Taguchi, Midori Nagata, Mari Sakaguchi, Yusuke Miyamoto, Takumi Iwase, Yuji Jibiki, Yuya Kanai, Nao Ozaki, Gyoko To, Yuto Tanaka, Ryo Kawana, Yusuke Wakatsuki, Yuhei Shimizu, Aika Ozaki, Seiya Sato, Akira Yoshida, Syunichi Usui, Yuto Kakuta, Hiroyuki Saegusa, Tomomi Saito, Masae Fujisawa, Syuuji Teraoka, Syouta Kuribayashi

Introduction

The Department of Radiological Diagnosis has a wide range of radiological modalities, including interventional radiology (IR), general X-ray, computed tomography (CT), magnetic resonance imaging (MRI), mammography, ultrasound, and nuclear medicine (NM). This year we installed positron emission tomography (PET)-magnetic resonance imaging (MRI) to provide improved clinical information.

In order to meet increasing clinical needs, we put a considerable effort into education and training for the staff. Serving as a teaching hospital, we accept not only domestic but also oversees students, visitors, and trainees.

Routine activities

1) General X-ray

We have successfully reduced radiation exposure and installed real-time imaging by installing two wireless unlinked flat panel detector (FPD) systems. We provide qualified medical images, sharing patient information and the purpose of examination among the radiological technologists (RTs) before they take X-rays. The amount of mammography is also on the increase and inspection frames have been doubled, resulting in the patients' waiting time being reduced. RTs routinely take part in preoperative and pathological conferences. Ultrasonic mammography has been performed by RTs.

2) Computed Tomography (CT)

The number of examinations is on the increase.

We have performed a joint study with Toshiba medical systems. We gave many presentations and lectures on image quality assessment and clinical application of super high-definition CT both inside and outside Japan.

We gave some lectures to radiological technologists on the acquisition and reconstruction technique of CT for cancer patients at a skill improvement intensive seminar supported by the Ministry of Education, Culture, Sports, Science and Technology.

We have improved three dimensional (3D)-CT image displays that resulted in new stereography technology, which enables observers to see the object in three dimensions (3D) without any aids.

In the quality control (QC) activity scope, hand disinfection and glove procedures have been thoroughly installed as a measure against hospital acquired infection.

3) Magnetic Resonance Imaging (MRI)

The number of MRI cases amounted to over 8,500 this year. We have made a considerable effort to meet this increasing clinical demand. Since PET/MRI was installed and started working in October, we have offered technical support to the Nuclear Medicine section.

4) Interventional Radiology (IR)

We made some presentations on the education program for RTs and how we should be in this department at international conferences. We had discussions with nurses and RTs from Korea and Singapore. We made a survey on incomplete medical billing in cooperation with the accounting section and fed back the results. We started making bed-side explanations to the examinee before IR, resulting in improving their understanding and consent for such procedure.

5) Fluoroscopy

We perform various kinds of X-ray examinations including plain lung CT, CT colonography and conventional fluoroscopies. The number of plain lung CT and CT colonography (CTC) cases are on the increase. This trend owes to patient-friendly procedures especially in the case of CTC.

We accept RTs from other institutions for technical training on CTC, which contributes to disseminating and improving this technique.

6) Endoscopy

The number of endoscopies is on the increase according to the increasing clinical demand. We undertook joint research on improving 2D and 3D fluorography.

7) Nuclear Medicine

PET-MRI has been installed and the clinical significance of PET has been disseminated. New single photon emission computed tomography (SPECT) examination "somatostatin receptor scintigraphy" will be performed in 2016 for the first time in our institution.

The number of PET cases in 2015 was about 4,300 and that of SPECT was about 1,800.

Education

We train the staff and plan job rotation effectively using our own education and achievement program.

Our staff regularly attend various training sessions supported by the Ministry of Health, Labour and Welfare, the National Hospital Organization and so on.

The staff also attend clinical department conferences (for example, breast surgery and urology) sharing lots of information.

We accept not only domestic but also oversees students.

List of papers published in 2015

Journal

1. Kitamura H, Kono Y, Murano T, Hiroi K, Ihara K, Aso T, Inoue K, Fukushi M. Estimation of radioactivity in single-photon emission computed tomography for sentinel lymph node biopsy in a torso phantom study. Nucl Med Commun, 36:646-650, 2015

Book

1. Torii J, Nagai Y, Horita T, Matsumoto Y, Izumo T, Kitagawa M, Ihara K, Nakamura T, Mukoyoshi W, Tennmei K, Suzuki K, Hara A, Sasada S, Aso T. A study on quality improvement of x-ray imaging of the respiratory-system based on a new image processing technique. In: Hoeschen C, Kontos D (eds), Medical Imaging 2015: Physics of Medical Imaging (PROCEEDINGS OF SPIE VOLUME 9412), USA, SPIE Press, pp 941246, 2015

Department of Radiation (Oncology)

Yoshihisa Abe, Tooru Kato, Ako Aikawa, Masashi Ito, Minoru Hamada, Yosihiro Shibata, Yuya Suzuki, Tatsuya Mogaki, Emi Sakamoto, Toshiyoshi Katahira, Satoshi Nakajima, Yuuki Miura, Daisuke Fujiyama, Manabu Kimura, Kenta Hashimoto, Takuya Nakagawa, Rie Ishikawa, Shuuhei Kamikaji

Routine and research activities

1) Our Department installed a new Linear Accelerator (LINAC) and CyberKnife system last year and analyzed their operating efficiency. As a result, our Department effectively utilized those systems.
2) Our Department was able to perform on all the patients who needed Total Body Irradiation (TBI) treatment before bone marrow transplants.
3) Our Department performed the treatment with five LINACs, and also has seen stable operation with the new LINAC with various energy levels. Thus, high-precision treatment could be performed efficiently. No treatments were interrupted because they could be carried out among these LINACs.
4) Two years have passed since the installation of CyberKnife. Our Department had 20 new patients and an introduction rate of 20% per month on average. Stereotactic Radio Surgery (SRS) using real-time tracking capabilities has started.
5) A facility inspection by an administrative agency has been completed to allow the installation of a hospital-based accelerator Boron Neutron Capture Therapy (BNCT) system.

Research results

Our Department developed and assessed an automatic tumor identification system on CT imaging for BNCT.

Education

1) Our Department systematically rotated the staff and educated them effectively using our education program.
2) Our Department accepted many visitors and trainees from all around Japan.
3) Our Department accepted students from the Department of Radiological Science, Graduate School of International University of Health and Welfare.
4) Our Department accepted not only domestic but also overseas students studying radiological technology.

Future prospects

1) Our Department aims at the early start of BNCT by installing a LINAC system and its peripheral equipment specifically designed for this purpose.
2) Our Department contributes to immediate pharmaceutical approval of the BNCT system, and to disseminating the system worldwide.
3) Sixteen years have passed since installing the first LINAC system. Our Department plans to smoothly renew the LINAC system.

Clinical Laboratories

Satoshi Nakajima, Shigeyuki Hasuo, Masahiro Uchikawa, Susumu Wakai, Naoshi Sasaki, Motoi Miyakoshi, Koji Ono, Hiroshi Yamakawa, Ryuzaburo Ohtake, Akashi Koseki, Yoji Hashimoto, Yasuo Shibuki, Hiroki Kakishima, Tomohiro Nakatani, Michi Shoji, Tsutomu Watanabe, Rie Matsuo, Yukie Nakajima, Sachiko Kobayashi, Katsuhide Ikeda, Kazuya Tokita, Satoe Miyaki, Kumiko Nagasaki, Noriko Takahashi, Mizuho Fujima, Daisuke Asahina, Tomoe Ito, Midori Hashimoto, Kaori Ueki, Fumie Watanabe, Akino Chiba, Takako Takada, Kyoko Osanai, Yuko Adegawa, Ruriko Miyake, Asuka Matsunaga, Hiroshi Chigira, Go Sato, Sakiko Yoshimura, Yuu Aruga, Saori Kobayashi, Kaori Yamaguchi, Ryoko Uegaki, Kensyo Kashiwaya, Saori Nakabayashi, Shingo Nakajima, Hideya Matsubayashi, Saeko Shirahama, Akiko Takayanagi, Mei Fukuhara, Kumi Ohashi, Momoko Kitou, Moemi Kasane, Kazuki Ito, Haruki Sasaki, Asuka Takaku, Keiko Arai, Yuri Kurosawa, Megumi Masuda, Yoshiko Shibata, Naomi Fujiki, Ritsuko Tohyama, Chieko Nozawa, Kozaburo Endou, Keiko Mizukoshi, Kiyoaki Nomoto, Masahiko Ushigome, Minami Takahashi, Sachiko Katayama, Shigeru Tamura, Megumi Miura

Routine activities / Research activities

The services of the Clinical Laboratories are organized into five sections: in vitro diagnostics (routine tests, hematology, biochemistry, immunity and serology, bacteriology, and genetic diagnosis), transfusion and cell therapy testing, blood collection, physiological examination, and histopathology. The Clinical Laboratories have obtained accreditation under ISO 15189, the international standards for quality management and technical competence in medical laboratories, after successful completion of the second surveillance stage. The In Vitro Diagnosis Section has undertaken a complete renewal of hematology and coagulation test systems to improve its ability for timely provision of accurate test results. The Transfusion and Cell Therapy Testing Section is using KM-CART (novel cell-free and concentrated reinfusion therapy) for the management of patients with refractory ascites. It also has renewed the fully automated pre-transfusion testing system, achieving better safety in the management of blood products. The Histopathology Section has been reinforced with the introduction of an automatic thin section machine in response to the increase in the number of specimens, and is preparing it for full-scale operation. The Physiological Examination Section has been experiencing increases in electrocardiography and echocardiography in clinical trials and ultrasonography of lower extremities for the close assessment of deep vein thrombosis. In response, the Section has been refurbished with the renewal of the electrocardiography filing system and respiratory function test equipment, as well as the expansion of circulatory function tests. The Genetic Diagnosis Section has opened the Sysmex Cancer Innovation Laboratory (SCI-Lab), which performs exhaustive gene analysis using the next-generation sequencer (NGS) in collaboration with Sysmex. The total number of laboratory tests in 2015 was 5,780,327, recording a 7% increase from the previous year. In particular, genetic diagnosis tests and physiological examination increased by 9% and 10%, respectively (Tables 1 and 2). The Clinical Laboratories are also cooperating in the promotion of academy-industry-government joint research, clinical trials, and biobank projects.

Research achievement

The Clinical Laboratories are working actively toward the improvement of accuracy and standardization in genetic diagnosis.

Education

The Clinical Laboratories conducted a revision of their original system for accreditation in blood collection, which has been in place since the previous year. The system is being continued with the elongation of the period of training and enrichment of technical training, including

education in reception for blood collection, handling of specimens, response to mechanical problems, and dealing with patients. Young technologists are assigned to specialist sections after mastering the basics of laboratory work in the In Vitro Diagnostics Section. A workshop focusing on ISO 15189 was held to ensure the adherence to the quality management system under ISO. Because reinforcement of individual sections is essential to the improvement of the Clinical Laboratories as a whole, monthly study meetings were held and personnel were encouraged to participate in and give presentations at external seminars and academic conferences. As a new initiative, the Clinical Laboratories launched an internship program with universities, aiming to promote the appeal of medical laboratory work.

Future prospects

The Clinical Laboratories intend to construct a system in which medical laboratory technologists play a part in the services of SCI-Lab and participate in the development of advanced medical techniques. In the Microbiology Section, we intend to shorten the time to reporting of test results through the use of a mass spectrometer mainly in blood culture tests, where immediacy is demanded. In ultrasound tests, we intend to establish a system to evaluate the cardiotoxicity of anticancer agents. In response to the increasing number of patients, we strive to shorten waiting time with an emphasis on TAT (turnaround time) from blood collection to analysis and the reporting of results.

Table 1. Trends in the total number of laboratory tests

Item	Number in 2014	Number in 2015
Routine tests	507,051	544,154
Hematology	1,308,384	1,377,066
Biochemistry	2,999,388	3,264,652
Immunity and serology	368,436	409,377
Microbiology	49,126	47,034
Physiological function tests	93,522	102,574
Histopathology	34,352	35,470
Total	5,360,259	5,780,327
Tests for research purpose	192,563	190,551
Commissioned tests	23,355	28,713

Table 2. Trends in the number of genetic diagnosis tests

Item	Number in 2014	Number in 2015
Nucleic acid identification of hematopoietic neoplasm	330	352
HER2 gene (FISH)	180	242
Malignant soft tissue neoplasm (FISH)	41	35
EGFR	261	264
Total	812	893

Surgical Center

Hitoshi Katai

Introduction

The Surgical Center deals with all kinds of malignant neoplasm. Our mission is to provide safe surgical care to the patients (Safe Surgery Saves Lives). Several groups collaborate to ensure the best surgical care, consisting of anesthesiologists, surgeons from 18 surgical oncology groups, nurses, and medical-technical staff with support staff from Department of Pathology and Clinical Laboratories.

Routine activities

During 2015, the Surgical Center supported 5,294 surgical cases and 4,738 general anesthesia surgical cases, a 12.6% increase in the general anesthesia cases over 2014. Sentinel node navigation surgery in breast cancer, autonomic nerve preservation proximal gastrectomy with jejunal interposition in early gastric cancer, hepatectomy and pancreatectomy in patients with hepato-biliary and pancreas diseases, and placement of an artificial urinary sphincter for bladder incontinence after prostate cancer treatment are unique treatments in our institution, and are occasionally performed in the Surgical Center. Over the years, minimally invasive procedures have increased remarkably. Endobronchial brachytherapy under general anesthesia in lung cancer, endoscopic resection under general anesthesia in GI cancer are also unique treatments and are carried out in the Surgical Center.

The Da Vinci robotic surgical system has been introduced to provide less invasive surgery for the patients for not only prostate cancer but also rectal cancer.

The post-anesthesia care unit has been a part of the Surgical Center this year.

The multidisciplinary meeting started in 2014. The multidisciplinary team includes medical doctors, nurses, and ME, and meet to plan the best surgical pathways during operations.

The Surgical Center staff work as part of a multidisciplinary team active in planning the best utilization of operating rooms. Scheduling, equipment usage, and staffing in the 16 operating suites were evaluated to establish an optimal work flow, streamline room turnover, and improve start times.

A medical device nurse, who is engaged in equipment usage, has been assigned.

Education and training

All surgical oncology groups have their own training programs for their fellows with the support of the Surgical Center staff. Our Center also provides virtual reality simulators to allow fellows to develop the skills used in laparoscopic and thoracoscopic surgery. About 50 foreign doctors have visited our surgical center.

Table 1. Total number of operations

	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Anesthesia													
General	364	396	422	385	330	433	453	413	385	382	379	396	4,738
Others	31	48	39	57	33	46	44	43	48	48	53	66	556
Total	395	444	461	442	363	479	497	456	433	430	432	462	5,294

Table 2. Number of general anesthesia cases

	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Neurosurgery	7	11	19	8	8	17	13	12	10	10	11	12	138
Ophthalmology	26	24	30	23	26	24	32	26	28	32	28	32	331
Head and Neck Surgery	17	23	26	24	17	21	27	22	24	23	26	22	272
Breast Surgery	44	41	53	47	41	57	58	48	44	50	48	42	573
Thoracic Surgery	53	52	56	49	43	64	68	53	46	50	57	56	647
Esophageal Surgery	9	11	10	12	11	12	12	13	9	9	11	10	129
Gastric Surgery	35	42	39	41	39	43	48	50	41	39	36	38	491
Colorectal Surgery	43	44	44	42	33	46	49	48	54	44	39	41	527
Hepatobiliary and Pancreatic Surgery	26	23	24	28	23	28	25	25	21	24	22	23	292
Gynecology	23	21	25	23	23	25	24	24	18	24	22	21	273
Urology	22	25	30	28	27	32	35	31	28	27	28	30	343
Dermatology	12	10	11	10	7	14	13	8	10	8	6	8	117
Orthopedic Surgery	24	21	31	30	19	29	25	27	28	25	21	32	312
Plastic and Reconstructive Surgery	9	8	9	5	3	7	10	10	11	9	10	14	105
Endoscopy	7	7	10	7	6	5	4	6	8	4	4	7	75
Radiation Oncology	2	2	2	3	2	3	4	6	2	2	5	5	38
Transplantation	3	4	2	3	2	4	4	2	2	2	4	3	35
Pediatric Surgery	2	0	1	2	0	2	1	2	0	0	0	0	10
Total	364	369	422	385	330	433	452	413	384	382	378	396	4,708

Physician Referral Service Office

Hidehito Horinouchi, Makiko Murase, Maya Ozawa, Hisako Tanaka, Keiko Tsutsumi, Fumiko Onishi

Introduction

The physician referral service office was established as an independent section directly under the director of the hospital. The mission of this Office is to provide appropriate access to best cancer practice for more patients and their physicians. To help cancer patients with various needs to visit the National Cancer Center Hospital, the physician referral service office consists of a physician, a nurse, a medical social worker and one clerk. This office also corresponds with inquiries for patients' medical records from their physician. Another important activity is to record and analyze the information concerning patients' referral to the National Cancer Center Hospital.

Routine activities

1) Physician referral service
   Through strong collaboration with the reservation center, this office helps patients and their physicians promptly select the proper doctor.
2) Inquiry for patients' medical record
   We receive and correspond with inquiries for medical records from physicians who see patients from our hospital.
3) Relationship with affiliated hospitals and clinics
   We send reminders to patients' physicians at the time of patients' first visits to our hospital. To maintain our relationships, we hold regular meetings and invite physicians from affiliated hospitals and clinics.
4) Record and analysis of clinical information
   The information of all patients and their physicians is appropriately recorded in order to analyze and apply for next strategies for a better service.
5) Corporation with intramural departments and staff

To provide best practice, we make a considerable effort to collaborate with intramural departments, sections and staff.

Future prospects

The physician referral service office will continuously support patients, physicians and other medical staff for better cancer treatment and care.

Table 1. Routine activities of Physician Referral Service Office

	Referral reply letters	Medical record inquiries	FAX service	Reservation support
January	764	85	60	19
February	763	95	59	12
March	858	118	77	35
April	854	105	49	33
May	798	111	69	40
June	870	130	84	30
July	966	147	50	51
August	892	126	75	29
September	756	142	67	41
October	968	150	70	45
November	948	165	72	47
December	962	138	75	44
Total	10,399	1,512	807	426

Nutrition Management Office

Mayumi Miyauchi, Tomoko Suzuki, Hiroko Abe, Noriko Aoki, Saki Hoshino, Moe Nishio, Ayumi Makita, Maki Miura, Naomi Togashi

Introduction

In 2015, I placed emphasis on NST（Nutrition Support Team）activities. As for the number of interventions, the number increased 1.5 times. As a novel measure, I participated in the AYA (Adolescence and Young Adult) support team. The significance of the involvement of prandial activities to AYA was understood and the NST involvement number increased. In accordance with the amendment of the Overview of Dietary Reference Intake for Japanese (2015), I reexamined the patient's prandial standards. I participated in the creation of the guidelines as a committee member at the Japan Pancreas Society's pancreatic-carcinoma guideline meeting.

Routine activities

The therapeutic diet, which is provided as part of nutritional therapy, accounted for 441,164 meals. We also provided 1,432 dietary consultations. The NST accepted 931 patients, and consultations averaged 78 cases per month. It was 1.5 times greater than the number for the previous year. (Table 1)

Research activities

We created the assessment sheet corresponding to the prandial activities that we are performing through collaboration, and announced this to the Japan Society of Metabolism and Clinical Nutrition.

In addition, we are conducting research on nutrition and the diet management environment of cancer patients thanks to a cancer survivorship research grant from the Foundation for Promotion of Cancer Research.

I conducted the factual survey of the taste disorder in a stomach-cancer postoperative auxiliary treatment as a cancer research and development.

We participated in a seminar and symposium on cancer survivorship, holding such things as open classes, and performed the educational activities in the region.

The study meetings in 2015 were as follows:

1) The Nutritional Management Workshop for cancer patients marked its 34th anniversary, and "Nutrition past, present and future" was delivered as the President's lecture in Tokyo.
2) Cooperation to provide the meal courses for cancer prevention targeting the general public and cancer nutritional management courses held by the university (in Miyagi, Yamanashi and Tokyo)
3) Research initiatives

① Fact-finding for taste disorders
② Prospective observational study on the long-term follow-up system in a single facility after allogeneic hematopoietic stem cell transplantation
③ Cancer survivorship study

Education

In the field of human resources development, we have a strong commitment to education and training and conducted 10 university courses for registered dietitians within the university. By strengthening our cooperation with universities, our aim is to enhance future research activities through the development of human resources.

Future prospects

We aim to provide effective nutritional management and nutrition counseling services, to achieve improved treatment outcomes, as well as enhance vital prognosis and patient's QOL. In

addition, we try to cultivate human resources who are expected to become the core of the NST, which is involved in nutritional clinical research.

Table 1. Number of NST consultations in 2015

Clinical Departments	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sept	Oct	Nov	Dec	Total
Esophageal Surgery		1	1	2		4	4	2	4	2	3	6	29
Head and Neck Surgery	5	6	12	7	3	7	5	6	6	8	9	11	85
Gastrointestinal Medical Oncology	9	20	9	14	16	13	18	21	12	17	9	18	176
Hematopoietic Stem Cell Transplantation	11	10	8	13	11	10	13	8	11	13	14	7	129
Thoracic Oncology	5	16	10	16	10	11	18	13	17	9	15	15	155
Thoracic Surgery			1	4			1	3	1	1	1	1	13
Hepatobiliary and Pancreatic Oncology	11	5	8	5	7	5	3	4	3	8	3	7	69
Hepatobiliary and Pancreatic Surgery	9	6	3	7	8	8	7	8	6	18	18	17	115
Breast Oncology and Medical Oncology	3	2	3	3	3	1		3	3	5	9	11	46
Gynecology	1		2	2	3	1	1		2		4	3	19
Neurosurgery and Neuro-Oncology								1					1
Gastric Surgery	16	20	15	11	23	29	24	24	18	17	25	18	240
Colorectal Surgery	10	14	11	9	9	16	12	12	4	12	11	10	130
Urology	2	1	2	2	2	4	4	6	4	4	2	7	40
Pediatric Oncology		1			1			1		1			4
Musculoskeletal Oncology	1			2	1	4	5	3	6	9	4	4	39
Dermatologic Oncology		1		2	3	2	6	4	3	1		2	24
Hematology	5	4	2	5	1	5	2	3	4	7	5	3	46
Radiation Oncology	3	4	2	5	4	7	2	9	2	3	4	12	57
Diagnostic Radiology				1						1	1		3
Breast Surgery													0
Gastrointestinal Endoscopy						2		1	1	1			5
Respiratory Endoscopy													0
Plastic and Reconstructive Surgery			1										1
Experimental Therapeutics				1		1	1		1		1	1	6
Total	91	111	90	111	105	130	126	132	108	137	138	153	1,432
												mean	119

Health Information Management Office

Hiroshi Nishimoto, Mieko Furumoto, Shinobu Fukuoka, Yukiko Sekimizu, Masami Kakimoto, Marika Nozuki, Chie Ogura, Hisayo Nishizawa

Introduction

The Health Information Management Office was established in April 2011. We took over several duties from the Cancer Information Service and Surveillance Division. One of them was the medical record administration, and the others are the auditing activity for discharge summary and the National Cancer Center Hospital Cancer Registry (NCCH-CR), which is executed as a hospital-based cancer registry. Some statistical activities for the NCCH and prognostic investigation were taken over by the Medical Affairs Office, but since the main initiatives of the NCCH are activities against cancer, we will expand our role as the major statistics office of the NCCH.

Routine activities

1) Medical Record Administration

We perform the management of the patients' database based on their medical records. Their clinical data, such as examination, surgery, and outcomes are summarized and indexed.

2) Auditing Discharge Summary (quantitative inspection)

Data on discharge summaries should be entered by the attending physician. We inspected and checked about 16,000 summaries and where required, gave advice regarding correct input.

3) NCCH Cancer Registry (Hospital-based Cancer Registry)

The office has continuously managed the NCCH-CR since 2004, handling more than 5,000 records per year（Table 1）. We have provided our data to the Japanese Institutional Cancer Database that is handled by the Center for Cancer Control and Information Services of the NCC.

Future prospects

We have developed and tested software for medical record administration and cancer registry, "Hos-CanR", collaborating with the Surveillance Division of the NCC. We will effectively perform our duties using this integrated information system.

Table 1. Cancer Patients Data from the NCCH-CR

Year of Diagnosis	Number of New Cancer Cases
2010	5,440
2011	5,446
2012	5,543
2013	5,669

Department of Pharmacy

Hiroyuki Terakado

Introduction

The Department of Pharmacy stores and dispenses drugs, prepares injections (including aseptic mixtures), collects and disseminates drug information and provides patients with guidance regarding the proper use of drugs. Its services have improved toward the hospital's goal of envisaging the highest quality of medical care, practice and research. A state-of-the-art computerized system and other pharmacy-related equipment ensure quality control and inventory management, promote the proper use of drugs, and enhance the efficiency and quality of our services.

Routine activities

As part of the fundamental function of the hospital, the Department prepares and dispenses oral and topical medicines and injections for individual patients. All outpatients and inpatients are provided with aseptic mixtures of injectable chemotherapy agents prepared in the Department. As the importance of providing drug information for patients has been widely acknowledged, clinical pharmacists visit inpatients and give advice on taking medicine, focusing especially on pain control with opioids, and participate in the palliative-care support team, while the Pharmacy provides outpatients with guidance in the proper use of opioids and anti-cancer agents. The Department also places pharmacists in every hospital ward to provide a medication reconciliation service for inpatients, with a view to enhancing the quality of chemotherapy as well as to ease the burden of doctors and nurses.

Pharmacists collect, compile, and maintain a database of drug information and distribute pertinent information to the medical staff. Drug information is disseminated quickly throughout the hospital by paper distribution and/or on the in-hospital computer network. Pharmacists individualize dosage regimens for specified drugs such as tacrolimus, aminoglycosides, and vancomycin based on both measured blood concentrations and pharmacokinetic analysis to maximize their efficacy and minimize adverse events.

A physician places an order through the hospital's computerized electric medical record system. The prescription order is then redirected to the medicine-package-printing system that provides drug information. The medicine-package information, instructions and explanations, which are easy to understand for patients, for the proper use of drugs, such as those regarding efficacy and effectiveness, precautions, and guidance concerning symptoms at the early stage of adverse reactions, are automatically printed out for patients when a prescription is ordered.

The injection-order is directly linked to an automatic "picking system" device, and this linkage ensures that injections are made properly and efficiently. This injection-ordering system contains an additional function, a regimen-ordering system for anti-cancer drugs that makes it possible to check the dose as well as the interval of chemotherapy. The Department has a robot that prepares injection preparations without human assistance.

Research activities

Since an important mission of the Department is to contribute to the development of new drugs, inventory control and handling of new investigative drugs are performed in accordance with Good Clinical Practice regulations. Research on the safety management of chemotherapy is conducted including handling of chemotherapeutic drugs, reduction of incidents regarding drugs, and improvement of pain control for patients who need palliative care through the use of

guidance materials. A couple of studies on the pharmacokinetics and pharmacodynamics of cancer-related drugs have been performed and some of the results have been reported in international conferences and journals.

Information Services

The mission of the Pharmacy Information Services is to provide an evidence-based foundation for safe and effective drug therapy for cancer patients. The internal online pharmacy journal is published monthly. Current safety information, newly adopted drugs, questions-and-answers, and topic of approvals are available for medical staff on the in-hospital computer network. The Department also provides a variety of information on the Internet to the general public and medical experts outside the hospital.

Education and Training

The National Cancer Center Hospital offers three-year postgraduate pharmacist residency training in clinical oncology. In the first year, the program attaches the most importance to the technical aspects of cancer care. In the second year, through required rotations in a variety of focused hematology/oncology services, the resident will refine his/her clinical problem-solving skills in cancer management and patient education, as well as provide pharmaceutical care to ambulatory care patients and participate in an oncology-focused Drug Information Program. In the third year, residents participate in specialized pharmaco-clinical practice and research activities, which may be tailored to the resident's goals. The hospital also provides a two-year chief residency program in which post-residency trainees may develop their clinical research capabilities to a higher level. Moreover, there are opportunities for educational activities, such as a training course for visiting expert pharmacists and post-graduate students of pharmacy, and participation in a multi-institutional TV conference.

Table 1. Number of Prescriptions in 2015

1) Oral and topical preparations	
Prepared in the hospital pharmacy	149,234
Inpatients	137,476
Outpatients	11,758
Taken to outside pharmacies	104,190
(% of prescriptions filled outside)	89.9
2) Injections	
Inpatients	392,801
Outpatients	46,075

Table 2. Amounts of Drugs Consumed in 2015

	(including sales tax)	(%)
Total	6,397,942	100.0
Internal Medicines	549,116	8.6
External	48,465	0.8
Injection	4,876,590	76.2
Narcotics	132,865	2.1
Blood	435,756	6.8
X-ray Imaging	226,539	3.5
RI	71,852	1.1
Others	56,754	0.9

Unit: 1,000 yen

Table 3. Aseptic Preparation of Injectable Drugs in 2015

Anticancer Drugs	64,742
Others	43,391

Table 4. House Preparations in 2015

Sterilized	86
Non-sterilized	109

Table 5. Investigational Drugs

Newly Registered	79
Ongoing Study	179
Total	258

List of papers published in 2015

Journal

1. Motonaga M, Yamamoto N, Makino Y, Ando-Makihara R, Ohe Y, Takano M, Hayashi Y. Phase I dose-finding and pharmacokinetic study of docetaxel and gefitinib in patients with advanced or metastatic non-small-cell lung cancer: evaluation of drug-drug interaction. Cancer Chemother Pharmacol, 76:713-721, 2015

Department of Nursing

Kazuko Nasu

Introduction

The Department of Nursing bears responsibility for team healthcare at the National Cancer Center Hospital(NCCH), the core institution for national cancer treatment and control in Japan. The responsibility of the Nursing Department is to develop and improve the quality of cancer nursing as well as to contribute to the appropriate management of the hospital. The Department is also expected to foster nursing staff to achieve the best cancer nursing.

Routine activities

Based on the philosophy of the Nursing Department, which is to create and provide the best cancer nursing geared to the needs of patients, the Department is working to provide safe and reliable nursing in response to advances in medicine with the consciousness and responsibility of a nurse in the NCCH.

We adopted the two-shift nursing system in 13 units, comprising an 8-hour day shift and a 16-hour night shift. Inpatient unit nurses work together more closely than nurses in an outpatient clinic. Moreover, we have strengthened the support for the patient discharge process so that patients can return earlier to their own home or area.

We are accepting and meeting the challenge to provide numerous patient education programs produced by Certified Nurse Specialists and Certified Nurses. We have five patient education programs and consultation services, three outpatient clinics run by nurses, and a support program for patients and their families. Many patients and families have participated in the educational program for self-care and survivorship in their daily life.

Research activities

We presented 19 studies on nursing at annual conferences in 2015. We organized the Nursing Research Committee, the members of which must have a master's degree or a doctor's degree. They must also have sufficient experience regarding nursing research activities. They support nurses in their nursing research based on their clinical questions. We are making efforts to improve the quality of nursing research through support from some physicians and statisticians. We expect our nurses from the NCCH to move and develop cancer nursing to even higher levels of proficiency and expertise.

Education

1) Assist and support new nurses

We have worked to reduce the gap between the technical skill level of new nurses and the clinical nursing required for actual cancer care by carrying out practical nursing training. During the first month, we provide training courses on basic nursing skills for new nurses, who learn about clinical nursing practices by shadowing a senior nurse. We ensure that new nurses can work in a favorable, work-related, stress-free environment.

2) Development of knowledge and skills for cancer nursing

To develop the skills associated with cancer nursing, the Nursing Department is enhancing a system that can bring out individual expertise and an educational system to improve the careers of nurses. In particular, the interaction between large-group training and small-group training was increased to implement the knowledge and techniques acquired from years of continuing education, which resulted in improved patient care.

We have 11 specialized nurse training courses: Cancer chemotherapy nursing I and II; Palliative

care nursing I and II; Lymphedema care; Wound and skin care; Dysphagia nursing; Radiation therapy and IVR nursing; Support for discharge and home care coordination nursing; and nursing research. A total of 189 nurses have participated, all of whom have over four years' nursing experience. Many nurses want to participate in the courses. Through evaluation of the results of these courses this year, issues in the future are to improve the educational content for nurses to enable career development.

3) Certified Nurse Specialists and Certified Nurses

Currently, 11 certified nurse specialists and 32 certified nurses are working at the NCCH. They represent the role model for cancer nursing practice in both inpatient and outpatient settings. The number of consultations is increasing, which proves that the use of Certified Nurse Specialists and Certified Nurses is being accepted by the nurses in this hospital. The number of support meetings and consultations for patient's decision making by physician and CNS/CN was 1,162 cases, and the number of support meetings and consultations for psychosocial problems by CNS/CN was 1,758 cases in 2015.

As members of teams where different professionals work together in special areas, such as infection control, palliative care, nutritional support, and care of decubitus ulcers, and respiratory support, these Certified Nurses contribute to effective cooperation. The identification of problems and discussions from the point of view of multidisciplinary teams serve as a good model for other nurses and provide an important educational role in the clinical setting.

Certified Nurse Specialists contribute to education and coordination for ethical issues in a clinical setting. They support and empower not only patients and families, but also nursing staff.

Certified Nurse Specialists and Certified Nurses also engage in educational activities both within and outside the hospital, and contribute to the development of educational programs by giving lectures and practice training for the curricula of Certified Nurse Specialists or Certified Nurses.

Clinical Research Support office

Yasuhiro Fujiwara

- **Clinical Trial Coordination (& Support) Office:**
  Noboru Yamamoto, Hiroko Nakahama, Noriko Kobayashi, Miki Ito, Kikue Kamiyama, Harue Ui, Shino Ohsawa, Tamami Yamano, Suga Yamagami, Chie Miyano, Yuko Tagami, Yukari Nishiyama, Saki Yoshizawa, Ai Sekido, Akiko Saito, Asako Sakamoto, Kumiko Hirayama, Kiyoka Ishihama, Yukari Hoshina, Tomomi Tsuchiya, Katsuyuki Ikarashi, Mari Takahashi, Sho Murata, Yoshimi Yamaguchi, Keiko Wakakuwa, Yukiko Nishioka, Yumiko Ikuno, Mayumi Ikeda, Hiroko Minami, Kimiko Sega, Mai Koda, Haruka Sawamura, Harumi Mochizuki, Ami Hashimoto, Satomi Nakamori, Tsukina Soku
- **Clinical Trial Management Section:**
  Kenichi Nakamura, Hiroshi Katayama, Tamie Sukigara, Ritsuko Nagasaka, Tomomi Hata, Mamiko Kawasaki, Satoshi Kawashima, Miho Sakai, Junko Eba, Keisuke Kanato, Kenichi Miyamoto, Hideaki Kitahara, Taro Shibata, Aya Kuchiba, Junki Mizusawa, Kan Yonemori, Natsuko Okita, Hideki Ueno
- **Data Management Section:**
  Haruhiko Fukuda, Harumi Kaba, Yushi Nagai, Chika Asami, Nobuko Okamura, Ryuji Makiuchi, Futa Kikuhara, Miwa Kihara, Sakiko Fushimi, Kaoru Koike, Tamie Kawano
- **Office of Biobank and Translational Research:**
  Ken Kato, Teiko Yamane, Suga, Yamagami, Keiko Wakakuwa, Mayumi Ikeda, Harumi Mochizuki, Satomi Nakamori, Tokiko Konuma

Introduction

In 2015, the Research Coordination Division and the Research Promotion Division of the Center for Research Administration and Support (CRAS), the Clinical Trial Coordination (& Support) Office and Biobank and the Translational Research Support section of the National Cancer Center Hospital (NCCH) were reorganized into the Clinical Research Support Division of the NCCH. The Clinical Research Support Office supports clinical research conducted under the leadership of investigators in the Hospital. Supporting activities include protocol writing, central/local data management, statistical design and analysis, in-house/on-site monitoring, audits, patient recruitment, and other coordinating jobs.

Activities and future prospects of each section

・Clinical Trial Coordination (& Support) Office：

The Clinical Trial Coordination (& Support) Office supports a lot of the industry-sponsored registration trials as well as the physician-initiated registration-directed clinical trials. A total of 28 CRCs (clinical research coordinators) are supporting these trials. The number of industry-sponsored registration trials is increasing year by year, and we supported 270 registration-directed clinical trials including 20 physician-initiated registration-directed clinical trials in 2015 (Table 1). The number of supported clinical trials is increasing as previously described, and the supporting area covered by the CRCs will be expanded to include not only registration trials but also other investigator-initiated clinical trials. Therefore, the expansion of CRC staff members is highly anticipated. In view of the plan for the NCCH, all members of this Office will work together to contribute to reinforcing the clinical research capabilities of the NCCH and to making this Office a valuable unit for all members of our hospital.

Table 1. Supported Trials in Clinical Trial Coordination (& Support) Office in 2015

Phase	Ongoing	New (since 2015)	Total
I	56	30	86
I/II	15	3	18
II	31	17	48
II/III	1	0	1
III	64	20	84
POS	9	1	10
Medical device	2	1	3
In-vitro diagnostics	0	0	0
IITs	12	8	20
Total	190	80	270

POS: post marketing study
IITs: physician-initiated registration-directed clinical trials

・Clinical Trial Management Section

The Clinical Trial Management Section has five functions: i) Multi-institutional trial support, ii) Investigational new drug (IND) trial management, iii) Biostatistics, iv) Safety management, and v) Pharmaceutical affairs consultation. One of the strengths of the NCCH is implementing various types of clinical trials covering both early phase trials including first-in-human trials and late phase multi-institutional trials. The IND trial management function is responsible for comprehensive study coordination and site visit monitoring in early phase trials. The multi-institutional trial support function works as the JCOG Operations Office, which engages in protocol development, manuscript drafting, study coordination, etc., for late phase trials. The section is also responsible for coordination of the study planning consultation meeting and the concept review committee meeting. As a future direction, the section will reinforce the support function for various types of clinical trials including advanced medical care systems.

・Data Management Section

The section is responsible for central data management and in-house study monitoring in the investigator-initiated clinical trials for cancer therapeutic development. The Section consists of 3 teams: (1) Data managers in JCOG Data Center, (2) In-house research team, (3) Pediatric research team. The JCOG Data Center mostly supports late development multi-modality multi-institutional phase II or phase III trials for adult cancer. The in-house research team supports early phase adult cancer trials mainly for drug development including registration trials. The pediatric research team supports mainly registration trials for pediatric cancer.

The section is introducing a web-based electronic data capturing (EDC) system and is promoting standardization of all aspects of data management, such as data format, case report forms and monitoring reports for increasing data integrity and cost effectiveness of day-to-day work.

・Biobank and Translational Research Support Section

The Biobank and Translational Research Support Section has routinely obtained informed consent to participate as an NCCBB donor from patients who consult with the NCCH for the first time. Clinical research coordinators in this section coordinate translational research in several ways, such as assistance of registration for clinical trials, logistics of pathological specimens, data collection for case report forms and coordination between sections.

We explained the purpose of NCCBB to 5,991 patients from May 2015 to January 2016, and received consent for blood collection and research use of their surplus samples for research from 5,371 patients (89.7% consent rate). The patient load with our assistance in filling in the preliminary-diagnosis card and so on was 6,337.

We support 6 biomarker trials, and for registered patients (pts), 62 pts for BT-SCRUM, 74 pts for TOP-GEAR study, 14 pts for liver amino acid trial, 45 pts for GI-SCREEN_CRC, 42 pts for GI-SCREEN_nonCRC and 16 pts for DEF trial.

List of papers published in 2015

Journal

1. Kataoka K, Aoyama I, Mizusawa J, Eba J, Minashi K, Yano T, Tanaka M, Hanaoka N, Katayama H, Takizawa K, Fukuda H, Muto M, Gastrointestinal Endoscopy Study Group (GIESG) of the Japan Clinical Oncology Group. A randomized controlled Phase II/III study comparing endoscopic balloon dilation combined with steroid injection versus radial incision and cutting combined with steroid injection for refractory anastomotic stricture after esophagectomy: Japan Clinical Oncology Group Study JCOG1207. Jpn J Clin Oncol, 45:385-389, 2015
2. Kurokawa Y, Sasako M, Sano T, Yoshikawa T, Iwasaki Y, Nashimoto A, Ito S, Kurita A, Mizusawa J, Nakamura K, Japan Clinical Oncology Group (JCOG9502). Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia. Br J Surg, 102:341-348, 2015

3. Tahara M, Kiyota N, Mizusawa J, Nakamura K, Hayashi R, Akimoto T, Hasegawa Y, Iwae S, Monden N, Matsuura K, Fujii H, Onozawa Y, Homma A, Kubota A, Fukuda H, Fujii M. Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). Cancer Sci, 106:726-733, 2015

4. Kato T, Takashima A, Kasamatsu T, Nakamura K, Mizusawa J, Nakanishi T, Takeshima N, Kamiura S, Onda T, Sumi T, Takano M, Nakai H, Saito T, Fujiwara K, Yokoyama M, Itamochi H, Takehara K, Yokota H, Mizunoe T, Takeda S, Sonoda K, Shiozawa T, Kawabata T, Honma S, Fukuda H, Yaegashi N, Yoshikawa H, Konishi I, Kamura T, Gynecologic Oncology Study Group of the Japan Clinical Oncology Group. Clinical tumor diameter and prognosis of patients with FIGO stage IB1 cervical cancer (JCOG0806-A). Gynecol Oncol, 137:34-39, 2015

5. Satoh T, Tsuda H, Kanato K, Nakamura K, Shibata T, Takano M, Baba T, Ishikawa M, Ushijima K, Yaegashi N, Yoshikawa H, Gynecologic Cancer Study Group of the Japan Clinical Oncology Group. A non-randomized confirmatory study regarding selection of fertility-sparing surgery for patients with epithelial ovarian cancer: Japan Clinical Oncology Group Study (JCOG1203). Jpn J Clin Oncol, 45:595-599, 2015

6. Suzuki K, Watanabe S, Mizusawa J, Moriya Y, Yoshino I, Tsuboi M, Mizutani T, Nakamura K, Tada H, Asamura H, Japan Lung Cancer Surgical Study Group (JCOG LCSSG). Predictors of non-neoplastic lesions in lung tumours showing ground-glass opacity on thin-section computed tomography based on a multi-institutional prospective study†. Interact Cardiovasc Thorac Surg, 21:218-223, 2015

7. Etoh T, Inomata M, Watanabe M, Konishi F, Kawamura Y, Ueda Y, Toujigamori M, Shiroshita H, Katayama H, Kitano S. Success rate of informed consent acquisition and factors influencing participation in a multicenter randomized controlled trial of laparoscopic versus open surgery for stage II/III colon cancer in Japan (JCOG0404). Asian J Endosc Surg, 8:419-423, 2015

8. Hojo T, Masuda N, Mizutani T, Shibata T, Kinoshita T, Tamura K, Hara F, Fujisawa T, Inoue K, Saji S, Nakamura K, Fukuda H, Iwata H. Intensive vs. Standard Post-Operative Surveillance in High-Risk Breast Cancer Patients (INSPIRE): Japan Clinical Oncology Group Study JCOG1204. Jpn J Clin Oncol, 45:983-986, 2015

9. Homma A, Nakamura K, Matsuura K, Mizusawa J, Onimaru R, Fukuda H, Fujii M. Dose-finding and efficacy confirmation trial of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer (JCOG1212, RADPLAT-MSC). Jpn J Clin Oncol, 45:119-122, 2015

10. Eba J, Shimokawa T, Nakamura K, Shibata T, Misumi Y, Okamoto H, Yamamoto N, Ohe Y, Lung Cancer Study Group of the Japan Clinical Oncology Group. A Phase II/III study comparing carboplatin and irinotecan with carboplatin and etoposide for the treatment of elderly patients with extensive-disease small-cell lung cancer (JCOG1201). Jpn J Clin Oncol, 45:115-118, 2015

11. Matsumoto K, Katsumata N, Shibata T, Satoh T, Saitou M, Yunokawa M, Takano T, Nakamura K, Kamura T, Konishi I. Phase II trial of oral etoposide plus intravenous irinotecan in patients with platinum-resistant and taxane-pretreated ovarian cancer (JCOG0503). Gynecol Oncol, 136:218-223, 2015

12. Nozaki I, Kato K, Igaki H, Ito Y, Daiko H, Yano M, Udagawa H, Mizusawa J, Katayama H, Nakamura K, Kitagawa Y. Evaluation of safety profile of thoracoscopic esophagectomy for T1bN0M0 cancer using data from JCOG0502: a prospective multicenter study. Surg Endosc, 29:3519-3526, 2015

13. Yokota T, Ando N, Igaki H, Shinoda M, Kato K, Mizusawa J, Katayama H, Nakamura K, Fukuda H, Kitagawa Y. Prognostic Factors in Patients Receiving Neoadjuvant 5-Fluorouracil plus Cisplatin for Advanced Esophageal Cancer (JCOG9907). Oncology, 89:143-151, 2015

14. Shinoda M, Ando N, Kato K, Ishikura S, Kato H, Tsubosa Y, Minashi K, Okabe H, Kimura Y, Kawano T, Kosugi S, Toh Y, Nakamura K, Fukuda H, Japan Clinical Oncology Group. Randomized study of low-dose versus standard-dose chemoradiotherapy for unresectable esophageal squamous cell carcinoma (JCOG0303). Cancer Sci, 106:407-412, 2015

15. Kataoka K, Nakamura K, Mizusawa J, Fukuda H, Igaki H, Ozawa S, Hayashi K, Kato K, Kitagawa Y, Ando N. Variations in survival and perioperative complications between hospitals based on data from two phase III clinical trials for oesophageal cancer. Br J Surg, 102:1088-1096, 2015

16. Tahara M, Fuse N, Mizusawa J, Sato A, Nihei K, Kanato K, Kato K, Yamazaki K, Muro K, Takaishi H, Boku N, Ohtsu A. Phase I/II trial of chemoradiotherapy with concurrent S-1 and cisplatin for clinical stage II/III esophageal carcinoma (JCOG 0604). Cancer Sci, 106:1414-1420, 2015

17. Kataoka K, Tokunaga M, Mizusawa J, Machida N, Katayama H, Shitara K, Tomita T, Nakamura K, Boku N, Sano T, Terashima M, Sasako M, Stomach Cancer Study Group/Japan Clinical Oncology Group. A randomized Phase II trial of systemic chemotherapy with and without trastuzumab followed by surgery in HER2-positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1301 (Trigger Study). Jpn J Clin Oncol, 45:1082-1086, 2015

18. Nakamura K, Kuwata T, Shimoda T, Mizusawa J, Katayama H, Kushima R, Taniguchi H, Sano T, Sasako M, Fukuda H. Determination of the optimal cutoff percentage of residual tumors to define the pathological response rate for gastric cancer treated with preoperative therapy (JCOG1004-A). Gastric Cancer, 18:597-604, 2015

19. Mizutani T, Tanaka M, Eba J, Mizusawa J, Fukuda H, Hanaoka N, Takeuchi M, Aoyama I, Kojima T, Takizawa K, Ono H, Muto M, Gastrointestinal Endoscopy Study Group of the Japan Clinical Oncology Group (JCOG). A Phase III study of oral steroid administration versus local steroid injection therapy for the prevention of esophageal stricture after endoscopic submucosal dissection (JCOG1217, Steroid EESD P3). Jpn J Clin Oncol, 45:1087-1090, 2015

Genetic Medicine and Services

Teruhiko Yoshida, Narikazu Boku, Takayuki Kinoshita, Shimizu Chikako, Mitsuya Ishikawa, Takeshi Nakajima, Shigenobu Suzuki, Tadashi Kumamoto, Shigeki Sekine, Taisuke Mori, Nobuyoshi Hiraoka, Kuniko Sunami, Takahisa Matsuda, Hiromi Sakamoto, Hitoshi Zenbutsu, Mineko Ushiama, Takashi Kohno, Mamoru Kato, Hitoshi Ichikawa, Kokichi Sugano

Introduction

It has been estimated that roughly 5% of all cancer cases are caused by a highly penetrant monogenic mutation. Major causative genes for most hereditary cancer syndromes were identified in the 1990s, and since then, genetic diagnosis has been considered as a part of standard medical care in oncology clinics. The National Cancer Center Hospital (NCCH) launched the Outpatient Genetic Counseling Clinic in 1998 as a part of collaboration with the Research Institute, especially the Fundamental Innovative Oncology Core (FIOC). However, cancer medical genetics still has a number of issues to be addressed as shown in Figure 1, which is again shown this year with some modifications from the previous year, because it has been the basic set of the agenda of the Department of Genetic Medicine and Services (GeMS).

Routine activities

As shown on the National Cancer Center Hospital (NCCH) Web site the aim and mission of the clinical service of the Outpatient Genetic Counseling Clinic, which is the main routine clinical activity of the Department, are:

1) to provide consultation and appropriate medical and genetic information (that is, genetic counseling) to anyone who has a worry related to heredity cancer.
2) to provide genetic testing when appropriate.
3) to support early diagnosis and treatment based on family history and/or genetic test results.

In 2015, 173 patients and their relatives from 121 families visited the Clinic. In total, 1,414 clients from 955 families have visited the Clinic since its inception in 1998.

Research activities

Although at least one causative gene has been identified for each of the major hereditary cancer syndromes, overall sensitivity of the current genetic tests is far from 100% and may be around 70-80%, even for the cases that meet clinical and/or screening criteria for hereditary cancer syndromes. The false negative cases may include both inadequate technical sensitivity of the current genetic test methods on the established causative genes (allelic heterogeneity) and also yet-identified genes representing locus heterogeneity. There has been great expectation that the introduction of next generation sequencers (NGS) would change the situation. The staff of the Department of GeMS have established a new Common Protocol to perform NGS-based germline clinical sequencing for patients with negative test results by conventional genetic tests, who would represent a part of the Undiagnosed Disease Patients in the oncology field. The Common Protocol has been adopted by other hospitals and institutions in a long-standing multi-institute collaborative research group based on the National Cancer Center Research and Development Fund and its predecessor. In addition to whole exome sequencing (WES), a multi-gene panel has been developed based on Agilent SureSelect technology.

Clinical trials

The Outpatient Genetic Counseling Clinic has participated in a prospective clinical study to optimize BRCA1/2 genetic tests and a clinical trial of a PARP inhibitor for patients with ovarian or breast cancer, and both are directed by the departments of Breast and Medical Oncology and Breast Surgery.

Education

The Department has accepted attendees for outpatient genetic counseling, so that they could be eligible to take the examination for clinical geneticists and certified genetic counselors acknowledged by the Japanese Society of Human Genetics and the Japanese Society of Genetic Counseling. In 2015, eight doctors were registered as trainees for clinical geneticists in the education committee of clinical geneticists.

Future prospects

The Department of GeMS was launched in November 2015. Although this section reports on the routine clinical activity of the Department and clinical research associated directly with the Outpatient Genetic Counseling Clinic, the scope and mission of the Department extends beyond hereditary cancer syndromes and includes support of the genomic biomarker-driven personalized cancer treatments offered by other clinical departments (Figure 2). The core technology of the new discipline, also known as a precision medicine, is next-generation sequencers, which would bring massive amounts of genomic data to cancer diagnosis, treatment and prevention. The crux of this emerging opportunity is how to convert the sequence data to clinically valid and useful knowledge, which could include incidental or secondary findings. The Department of GeMS is expected to support other departments in the era of genomic medicine.

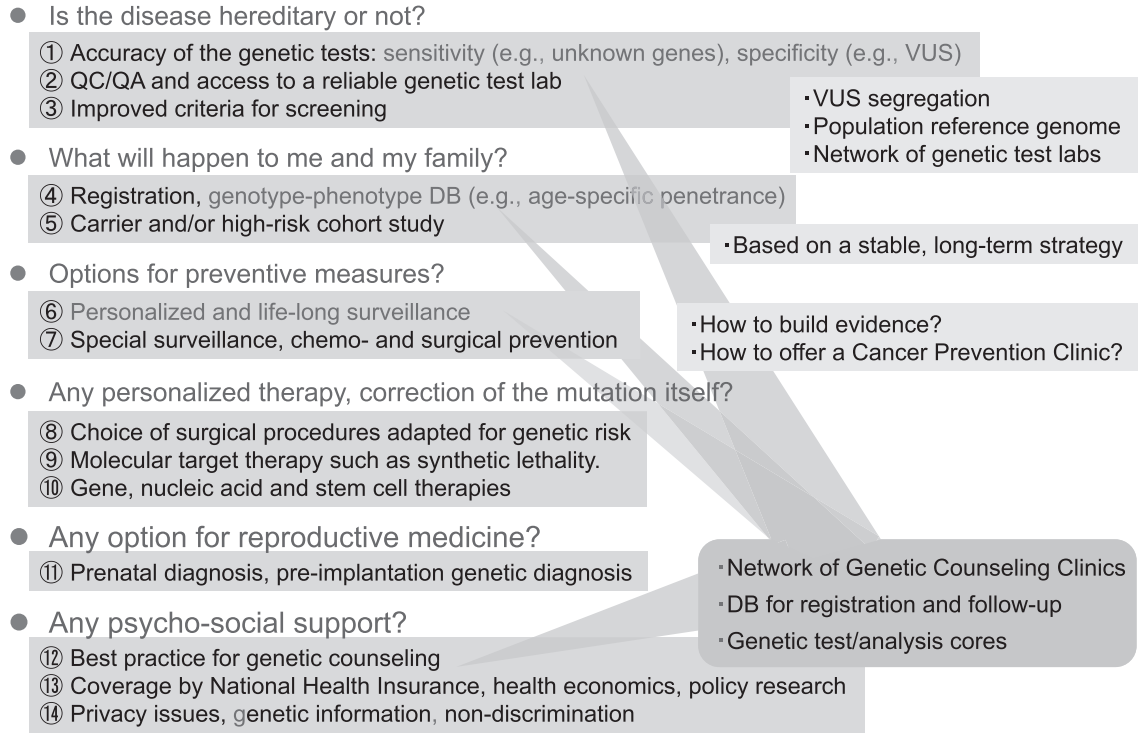


Figure 1. Major Questions of Patients and Families with Hereditary Cancer Syndromes

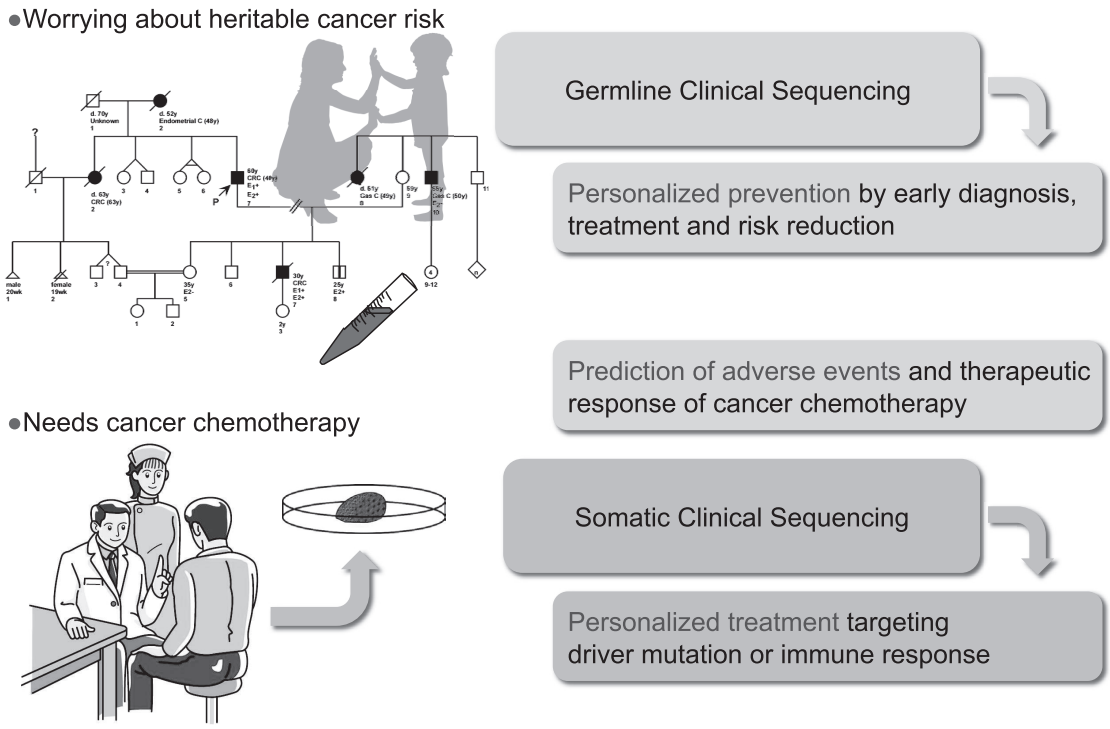


Figure 2. Patients and Families Faced With GeMS

Table 1. Number of patients

	Proband	Relative	Total
Lynch Syndrome (Hereditary Non-Polyposis Colon Cancer; HNPCC)	23	15	38
Familial Adenomatous Polyposis (FAP)	5	9	14
Retinoblastoma	15	11	26
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	66	9	75
Other diseases	7	8	15
Counseling only	5	0	5
Total	121	52	173

List of papers published in 2015

Journal

1. Hashimoto T, Ogawa R, Matsubara A, Taniguchi H, Sugano K, Ushiama M, Yoshida T, Kanai Y, Sekine S. Familial adenomatous polyposis-associated and sporadic pyloric gland adenomas of the upper gastrointestinal tract share common genetic features. Histopathology, 67:689-698, 2015

2. Tanakaya K, Furukawa Y, Nakamura Y, Hirata K, Tomita N, Tamura K, Sugano K, Ishioka C, Yoshida T, Ishida H, Watanabe T, Sugihara K, HNPCC registry and genetic testing project of the Japanese Society for Cancer of the Colon and Rectum, Yamaguchi T, Ishikawa H, Matsubara N, Arai M, Moriya Y. Relationship between smoking and multiple colorectal cancers in patients with Japanese Lynch syndrome: a cross-sectional study conducted by the Japanese Society for Cancer of the Colon and Rectum. Jpn J Clin Oncol, 45:307-310, 2015

3. Yamaguchi T, Furukawa Y, Nakamura Y, Matsubara N, Ishikawa H, Arai M, Tomita N, Tamura K, Sugano K, Ishioka C, Yoshida T, Moriya Y, Ishida H, Watanabe T, Sugihara K, HNPCC Registry and Genetic Testing Project of the Japanese Society for Cancer of the Colon and Rectum. Comparison of clinical features between suspected familial colorectal cancer type X and Lynch syndrome in Japanese patients with colorectal cancer: a cross-sectional study conducted by the Japanese Society for Cancer of the Colon and Rectum. Jpn J Clin Oncol, 45:153-159, 2015

4. Kumamoto K, Ishida H, Ohsawa T, Ishibashi K, Ushiama M, Yoshida T, Iwama T. Germline and somatic mutations of the APC gene in papillary thyroid carcinoma associated with familial adenomatous polyposis: Analysis of three cases and a review of the literature. Oncol Lett, 10:2239-2243, 2015

5. Saeki N, Ono H, Sakamoto H, Yoshida T. Down-regulation of Immune-related Genes by PSCA in Gallbladder Cancer Cells Implanted into Mice. Anticancer Res, 35:2619-2625, 2015

6. Nagashima K, Iwasa S, Yanai T, Hashimoto H, Suzuki K, Ohyanagi F, Shimada Y, Yamamoto N. A double-blind randomized Phase II study of olanzapine 10 mg versus 5 mg for emesis induced by highly emetogenic chemotherapy. Jpn J Clin Oncol, 45:229-231, 2015

7. Tanaka Y, Aoyagi K, Minashi K, Komatsuzaki R, Komatsu M, Chiwaki F, Tamaoki M, Nishimura T, Takahashi N, Oda I, Tachimori Y, Arao T, Nishio K, Kitano S, Narumi K, Aoki K, Fujii S, Ochiai A, Yoshida T, Muto M, Yamada Y, Sasaki H. Discovery of a Good Responder Subtype of Esophageal Squamous Cell Carcinoma with Cytotoxic T-Lymphocyte Signatures Activated by Chemoradiotherapy. PLoS One, 10:e0143804, 2015

8. Saeki N, Ono H, Yanagihara K, Aoyagi K, Sasaki H, Sakamoto H, Yoshida T. rs2294008T, a risk allele for gastric and gallbladder cancers, suppresses the PSCA promoter by recruiting the transcription factor YY1. Genes Cells, 20:382-391, 2015

9. Yamanoi K, Arai E, Tian Y, Takahashi Y, Miyata S, Sasaki H, Chiwaki F, Ichikawa H, Sakamoto H, Kushima R, Katai H, Yoshida T, Sakamoto M, Kanai Y. Epigenetic clustering of gastric carcinomas based on DNA methylation profiles at the precancerous stage: its correlation with tumor aggressiveness and patient outcome. Carcinogenesis, 36:509-520, 2015

10. Suzuki M, Chiwaki F, Sawada Y, Ashikawa M, Aoyagi K, Fujita T, Yanagihara K, Komatsu M, Narita M, Suzuki T, Nagase H, Kushima R, Sakamoto H, Fukagawa T, Katai H, Nakagama H, Yoshida T, Uezono Y, Sasaki H. Peripheral opioid antagonist enhances the effect of anti-tumor drug by blocking a cell growth-suppressive pathway *in vivo*. PLoS One, 10:e0123407, 2015

11. Budhathoki S, Iwasaki M, Yamaji T, Sasazuki S, Takachi R, Sakamoto H, Yoshida T, Tsugane S. Dietary heterocyclic amine intake, NAT2 genetic polymorphism, and colorectal adenoma risk: the colorectal adenoma study in Tokyo. Cancer Epidemiol Biomarkers Prev, 24:613-620, 2015

12. Fujita T, Chiwaki F, Takahashi RU, Aoyagi K, Yanagihara K, Nishimura T, Tamaoki M, Komatsu M, Komatsuzaki R, Matsusaki K, Ichikawa H, Sakamoto H, Yamada Y, Fukagawa T, Katai H, Konno H, Ochiya T, Yoshida T, Sasaki H. Identification and Characterization of CXCR4-Positive Gastric Cancer Stem Cells. PLoS One, 10:e0130808, 2015

13. Iwakawa R, Kohno T, Totoki Y, Shibata T, Tsuchihara K, Mimaki S, Tsuta K, Narita Y, Nishikawa R, Noguchi M, Harris CC, Robles AI, Yamaguchi R, Imoto S, Miyano S, Totsuka H, Yoshida T, Yokota J. Expression and clinical significance of genes frequently mutated in small cell lung cancers defined by whole exome/RNA sequencing. Carcinogenesis, 36:616-621, 2015

Hospital East

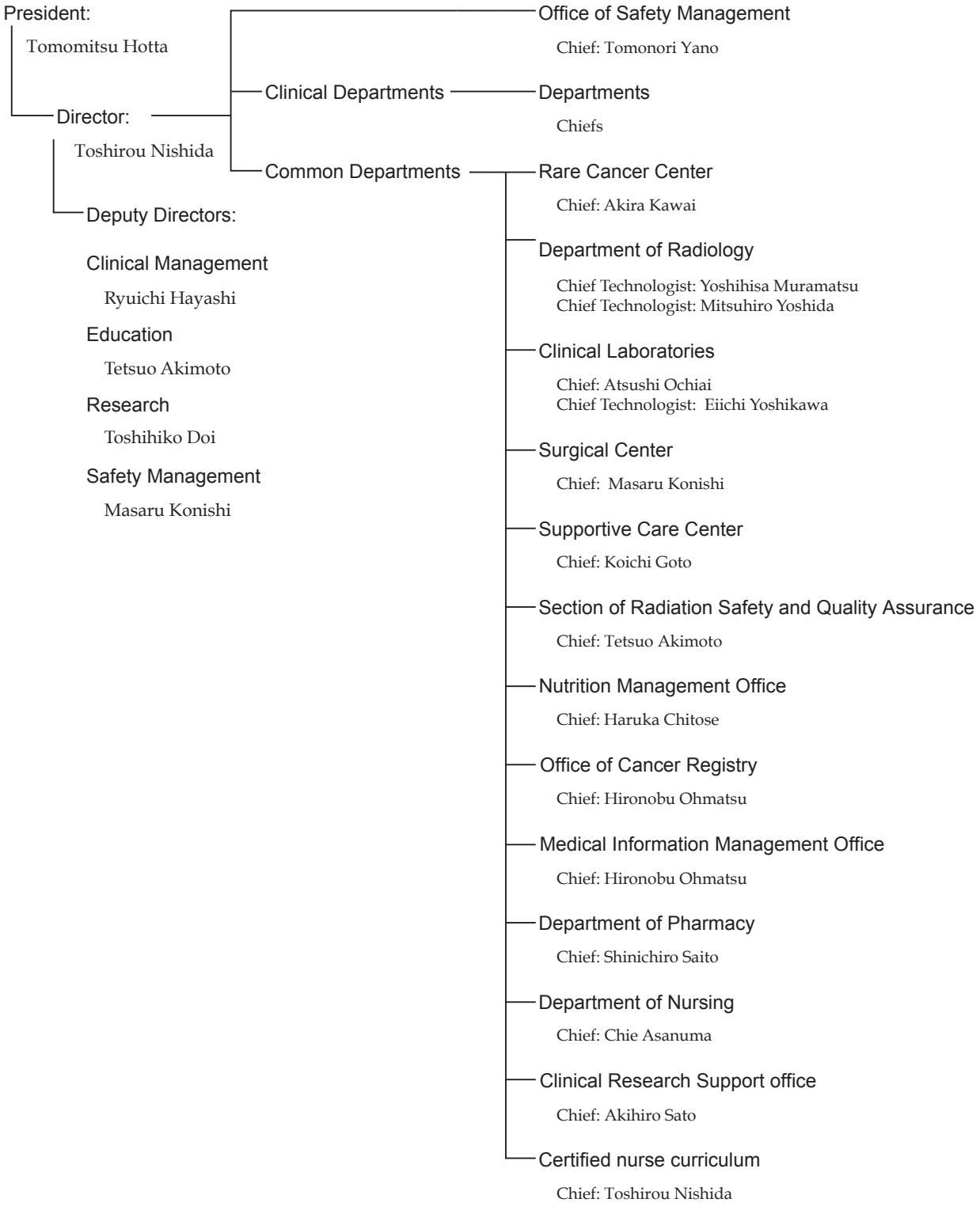
Preface

In 2015, the number of new cancer patients in the Hospital East increased constantly: the number of average patients in hospital stays was 388.9/day, with an occupied bed rate of 98.6%, and the number of outpatients was 1,071.2/day, respectively, which was the highest number in our hospital history. We opened a new outpatient ward in 2014, and expanded the Ambulance Treatment Center in response to the growing number of patients. In addition, the Center for Developing Next-generation Endoscopic-surgical Treatment (NEXT) will be completed in spring 2017, with plans for further expansion of the operating and endoscopy rooms. From a treatment perspective, our staff breaks down departmental barriers and works together laterally (under informed consent) to carry out the best treatment for patients. In addition, we provide patient support from multi-occupational teams consisting of physicians, nurses, pharmacists, nutritionists, social workers, certified social insurance labor consultants, and others. These teams give patients physical, emotional, and social aid through surgery and multiple hospital visits. As the Supportive Care Center, we have integrated multi-occupational teams since 2014, and have built a system by which we can provide patients with seamless support from the time of their first visit. We have also established a medical treatment concierge to treat patients from within Japan as well as from overseas. We have achieved top-level results in Japan in all the fields including the surgical field which performed high-difficulty minimally invasive surgery by specialists with a wealth of experience; the internal medicine field conducted the latest treatments with anticancer agents by experts in drug therapy; in radiation therapy, we implemented intensity-modulated radiation therapy (IMRT) under high-quality control in addition to taking the advantage of Japan's first proton radiation therapy facility; and the endoscopic field boasted skilled techniques and performed historic contributions to the development of endoscopic equipment.

From a research perspective, our hospital was selected as the "Core Hospital for Clinical Research" designated by the Ministry of Health, Labour, and Welfare in 2015. Together with the EPOC and Tsukiji campus, our hospital has realized numerous global achievements as a central hub for the development of cancer-related pharmaceutical products and medical devices in Japan. These facilities have realized top-class global achievements for promising new treatment drugs, from domestic and international FIH (first-in-human) studies to clinical development studies before approval, and have realized the best achievements in Japan for an investigator-initiated trial of an unapproved drug. In 2015, we launched a nationwide consortium for genomic cancer screening (SCRUM-Japan), in cooperation with more than 200 Japanese facilities and 15 pharmaceutical companies. Our institutes are the driving force behind construction of a system for precision medicine in cancer treatment in Japan, wherein the optimal treatment drug is selected according to the results of genetic analysis. In addition, current advances employ the latest equipment, even in remarkable immunotherapies; and research aimed at improved treatment outcomes and optimization for patients is progressing. In device development, our hospital was selected in recognition of activities to promote the practical use of innovative pharmaceutical products, medical devices, and regenerative therapy products (endoscopic field) in 2012, and has produced several recognized or approved devices in this field. In 2015, the "C-square", an academia-industry consortium for surgical devices development was started with the support of Chiba Prefecture Chamber of Commerce and Industry. Next year, the NEXT building, a high-level device developing center with a coordinating organization, will be launched.

Atsushi Ohtsu, M.D., Ph.D.
Director
National Cancer Center Hospital East

Organization



Clinical Departments

Director:
Toshirou Nishida

Deputy Directors:

Clinical Management
Ryuichi Hayashi

Education
Tetsuo Akimoto

Research
Toshihiko Doi

Safety Management
Masaru Konishi

- Department of Head and Neck Surgery
  Chief: Ryuichi Hayashi
- Department of Head and Neck Medical Oncology
  Chief: Makoto Tahara
- Department of Plastic and Reconstructive Surgery
  Chief: Minoru Sakuraba
- Department of Breast Surgery
  Chief: Vacant
- Department of Breast and Medical Oncology
  Chief: Tetsuo Akimoto
- Department of Thoracic Surgery
  Chief: Masahiro Tsuboi
- Department of Thoracic Oncology
  Chief: Koichi Goto
- Department of Esophageal Surgery
  Chief: Hiroyuki Daiko
- Department of Gastric Surgery
  Chief: Takahiro Kinoshita
- Department of Colorectal Surgery
  Chief: Masaaki Ito
- Department of Gastrointestinal Oncology
  Chief: Takayuki Yoshino
- Department of Endoscopy
  Chief: Kazuhiro Kaneko
- Department of Hepatobiliary and Pancreatic Surgery
  Chief: Masaru Konishi
- Department of Hepatobiliary and Pancreatic Oncology
  Chief: Masafumi Ikeda
- Department of Urology
  Chief: Masaaki Ito
- Department of Gynecology
  Chief: Ryuichi Hayashi
- Department of Musculoskeletal Oncology and Rehabilitation
  Chief: Ryuichi Hayashi
- Department of Hematology
  Chief: Kunihiro Tsukasaki
- Departments of General Internal Medicine, Dentistry, Cardiovascular Medicine, Pediatric Oncology
  Chief: Ryuichi Hayashi
- Department of Anesthesiology and Intensive Care Unit
  Chief: Hiroyuki Yamamoto
- Department of Palliative Medicine
  Chief: Hiroya Kinoshita
- Department of Psycho-Oncology Service
  Chief: Asao Ogawa
- Department of Diagnostic Radiology
  Chief: Masahiko Kusumoto
- Department of Radiation Oncology
  Chief: Tetsuo Akimoto
- Department of Pathology and Clinical Laboratories
  Chief: Atsushi Ochiai
- Department of Experimental Therapeutics
  Chief: Toshihiko Doi

Activities of the Departments

Department of Head and Neck Surgery

Ryuichi Hayashi, Masakazu Miyazaki, Takeshi Shinozaki, Toshifumi Tomioka, Takashi Maruo, Takashi Mukaigawa, Kazuki Hashimoto

Introduction

Surgical treatment of head and neck cancer must meet two contradictory requirements: (1) the resection volume must be sufficiently large to remove all cancer cells, and (2) the resection volume should be sufficiently small to preserve important functions such as swallowing, speech, vision, and cosmetic appearance. The Department of Head and Neck Surgery resolves these conflicting requirements mainly by two distinct approaches: (1) conservative surgery and (2) extensive resection with microsurgical reconstruction. We have been developing various larynx-preserving operations following the establishment of the National Cancer Center. These procedures include a partial laryngectomy which is indicated for T1/T2 recurrent glottis carcinoma after radiotherapy. Another example of conservative surgery is partial hypopharyngectomy with preservation of the larynx for hypopharyngeal carcinoma. Recently, trans-oral resection, such as ER or ELPS, for pharyngo-laryngeal cancer using an endoscope has been increasing after detection of superficial head and neck cancer. On the other hand, extensive resection with microsurgical reconstruction is designed to minimize loss of function following ablative surgery by employing the microsurgical transfer of various flaps.

Routine activities

The current treatment policy for head and neck cancer is multimodal therapy. To effectively implement available therapeutic modalities, four staff surgeons at the Department work closely with plastic surgeons, radiotherapists, medical oncologists, pathologists, dentists, psycho-oncologists, nurses, and other hospital staff. To facilitate regular communication among the members of this large team, several weekly conferences are conducted. The number of new cases who were treated in the hospital was 543 and the number of operations was 531. A total of 68 cases underwent ESD or ELPS and 97 cases underwent free flap reconstruction.

Research activities

1) Cystadenocarcinoma of the salivary glands with potential lymph node metastasis.

Cystadenocarcinoma is classified as a low-grade histological subtype of salivary gland tumors. Although the tumor has the potential to produce lymph node metastases, it is generally an indolent tumor with a good prognosis as compared with high-grade subtypes. Long-term follow-up paying close attention to lymph node metastases is necessary for cystadenocarcinoma.

2) Nine cases of carcinoma with neuroendocrine features in the head and neck: clinicopathological characteristics and clinical outcomes

As neuroendocrine carcinomas in the head and neck region are extremely rare, their clinicopathological characteristics remain largely unknown. Moreover, the 2005 World Health Organization classification criteria for head and neck carcinomas with neuroendocrine features have numerous limitations. Therefore, the clinicopathological features and patient outcomes of these tumors must be clarified. Carcinomas with neuroendocrine features were found to have an aggressive clinical course, which corresponded with the Ki-67 index and mitotic count. Owing to the difficulty in appropriately diagnosing head and neck carcinomas with neuroendocrine features using the current classification system, a new classification system should be developed for use in these cases.

Clinical trials

1) Multicenter study to establish the indication of neck dissection for head and neck squamous cell carcinoma. A prospective observation study is being conducted and over 300 cases have been enrolled to this study from nine hospitals. Neck dissection at Level IIb and V areas influence the rate of postoperative accessory nerve palsy but the necessity of dissection of these areas is still controversial because of the low prevalence rate of lymph node metastasis. A randomized clinical trial will be run after evaluating the results of this study.
2) Evaluation of swallowing function related to the treatment for head and neck cancer

This prospective observation study is conducted to evaluate the swallowing function after treatment for oropharyngeal cancer. This study is related to standardizing the assessment of the swallowing function.

Education

Two senior residents and two residents were recruited to our department in 2015. One head and neck surgeon from Hong Kong visited our department for training. Our Department was assigned as one of the observation centers of the International Federation of Head and Neck Oncologic Societies (IFHNOS) fellowship program from 2014.

Future prospects

Trans-oral resection by using an endoscope has become a standard surgical procedure for superficial pharyngeal cancer. We are going to get authorization for insurance about endoscopic resection and are planning to develop new surgical equipment for these operations.

Table 1. Number of new patients

Oral cavity	125
Pharynx	158
Larynx	73
Sino-nasal cavity	33
Thyroid gland	85
Major salivary glands	34
Others	35
Total	543

Table 2. Number of surgery patients

Oral cavity	149
Pharynx	165
Larynx	45
Sino-nasal cavity	10
Thyroid gland	66
Major salivary glands	25
Others	71
Total	531

List of papers published in 2015

Journal

1. Hamamoto T, Fujii S, Miyazaki M, Shinozaki T, Tomioka T, Hayashi R. Nine cases of carcinoma with neuroendocrine features in the head and neck: clinicopathological characteristics and clinical outcomes. Jpn J Clin Oncol, 45:328-335, 2015

Department of Head and Neck Medical Oncology

Makoto Tahara, Susumu Okano, Tomoko Yamazaki, Tomohiro Enokida, Tetsuro Wakasugi

Introduction

The Department of Head and Neck Medical Oncology is engaged in the clinical management of patients with head and neck cancer (HNC), and research into anticancer drugs for the treatment of HNC.

Our missions are to: 1) provide the best evidence-based treatment; 2) promote the importance of supportive care in the treatment of patients with HNC; 3) facilitate the timely approval of new drugs by active participation in global clinical trials to eliminate the drug lag; 4) develop cutting-edge treatments; and 5) train experts in head and neck medical oncology.

Routine activities

Our department consists of three physicians, one senior resident and one resident. We manage the treatment of HNC patients who receive anticancer drugs. An estimated 60% of HNC patients require a multidisciplinary approach, including surgery, radiotherapy, and chemotherapy. Furthermore, HNC patients are at risk of injury and impairment of vital organs both from the cancer itself and from the series of treatments provided to cure it. In treating patients, we therefore, carefully assess both the curability of the condition and possible subsequent complications, such as swallowing dysfunction and cosmetic changes. Given the increasing complexity of the management of HNC, the recommended treatment for patients who are referred to our institution is decided at weekly tumor board meetings attended by a multidisciplinary team.

A total of 276 patients were referred to our department from January 2015 to December 2015 (Table 1). The outpatient service of our department is available from Monday to Friday. We carefully follow patients during and after treatment and provide palliative chemotherapy as an outpatient service.

Research activities

Our research activity has focused on two areas: the development of new treatments in clinical trials for HNC and biomarker analysis in HNC.

1) Development of new treatments

Based on the results of our previously reported feasibility study (Kiyota N, Tahara M, et. al, The Japanese Journal of Clinical Oncology 2012), a multicenter phase II/III trial of postoperative concurrent chemoradiotherapy with weekly CDDP compared with postoperative concurrent chemoradiotherapy with 3-weekly CDDP for high risk squamous cell carcinoma of the head and neck (SCCHN) (The Japan Clinical Oncology Group (JCOG) 1008) is now ongoing. In phase II, the safety of both treatment arms has been confirmed.

After the approval of cetuximab for HNC in Japan, the following multicenter clinical trials that we planned as the primary investigator are ongoing: 1) CSPOR-HN01: The phase II study of docetaxel, cisplatin and cetuximab (TPE) followed by cetuximab with concurrent radiotherapy in patients with local advanced SCCHN, 2) CSPOR-HN02: Phase II trial of a combination with paclitaxel, carboplatin and cetuximab (PCE) as a first line treatment in patients with recurrent and/or metastatic SCCHN. Patient enrollments of both trials have been completed and the results will be open soon.

2) Biomarker analysis

An analysis of gene expression profiles in tongue squamous cell carcinoma (TSCC) is being carried out to determine the biomarker that can predict treatment outcomes. We then identified 27 genes with the most predictive value for recurrence, five genes highly expressed in the low-risk

group and 22 highly expressed in the high-risk group. Clustering into high- and low-risk groups based on this 27-gene expression in a validation study also showed a significant association with recurrence. Clinicopathological and biomarker analyses of early stage (T1/2) TSCC are also ongoing.

A prospective study to compare the miRNA expression patterns in head and neck cancer patients revealed that an extreme change of expression was observed in 6 miRNAs before and after completion of surgery and 20 miRNAs between healthy volunteers and head and neck cancer patients. These results suggest that these miRNAs will be good candidates for biomarkers to predict either incidence or recurrence for HNC.

Clinical trials

A feasibility study of a combination with docetaxel, cisplatin and 5-FU (TPF) as an induction chemotherapy (IC) for locally advanced SCCHN has been completed. A total of 48 patients were accrued. 41 patients (85.4%) received the full course of IC and 33 patients (82.5%) received the planned cardiac resynchronization therapy (CRT). To evaluate the feasibility of a combination with paclitaxel, carboplatin and cetuximab (PCE) as IC, a feasibility study for unresectable locally advanced SCCHN is now ongoing.

To facilitate the timely approval of new drugs and eliminate the drug lag, we have also participated in the global phase trials including immune-checkpoint inhibitors.

Education

We educate not only medical staff in our institute but also outside of our institute by conducting the following education program: 1) Seminar of Japan society of supportive care for patients with HNC and 2) Preceptorship in HNC. A number of Asian physicians participated in preceptorship in HNC this year. Furthermore, our department is accepting trainees all the time.

Future prospects

We hope that ongoing or planned clinical trials will change the standard of care for HNC and our biomarker analysis will lead to the development of new treatment strategies. Our education program will increase the number of medical oncologists who take charge of treatment for HNC, leading to improving patient's quality of life.

Table 1. Number of patients according to sites

Primary site	No. of patients (N=276)
Nasal cavity	33
Nasopharynx	17
Oropharynx	44
Hypopharynx	55
Oral cavity	57
Larynx	16
Salivary	14
Thyroid	28
Other	12

Table 2. Number of patients according to procedure

Type of procedure	No. of patients (N=263)
Induction chemotherapy followed by CRT	45
CRT	34
Palliative chemotherapy	47
Study drug	12
Others	136

List of papers published in 2015

Journal

1. Tahara M, Kiyota N, Mizusawa J, Nakamura K, Hayashi R, Akimoto T, Hasegawa Y, Iwae S, Monden N, Matsuura K, Fujii H, Onozawa Y, Homma A, Kubota A, Fukuda H, Fujii M. Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). Cancer Sci, 106:726-733, 2015

2. Zenda S, Ishi S, Akimoto T, Arahira S, Motegi A, Tahara M, Hayashi R, Asanuma C. DeCoP, a Dermatitis Control Program using a moderately absorbent surgical pad for head and neck cancer patients receiving radiotherapy: a retrospective analysis. Jpn J Clin Oncol, 45:433-438, 2015

3. Zenda S, Kawashima M, Arahira S, Kohno R, Nishio T, Tahara M, Hayashi R, Akimoto T. Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up. Int J Clin Oncol, 20:447-454, 2015

4. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med, 372:621-630, 2015

5. Kiyota N, Tahara M, Fujii M. Adjuvant treatment for post-operative head and neck squamous cell carcinoma. Jpn J Clin Oncol, 45:2-6, 2015

6. Machiels JP, Haddad RI, Fayette J, Licitra LF, Tahara M, Vermorken JB, Clement PM, Gauler T, Cupissol D, Grau JJ, Guigay J, Caponigro F, de Castro G, de Souza Viana L, Keilholz U, Del Campo JM, Cong XJ, Ehrnrooth E, Cohen EE, LUX-H&N 1 investigators. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. Lancet Oncol, 16:583-594, 2015

7. Schlumberger M, Tahara M, Wirth LJ. Lenvatinib in radioiodine-refractory thyroid cancer. N Engl J Med, 372:1868, 2015

8. Kiyota N, Schlumberger M, Muro K, Ando Y, Takahashi S, Kawai Y, Wirth L, Robinson B, Sherman S, Suzuki T, Fujino K, Gupta A, Hayato S, Tahara M. Subgroup analysis of Japanese patients in a phase 3 study of lenvatinib in radioiodine-refractory differentiated thyroid cancer. Cancer Sci, 106:1714-1721, 2015

9. Tahara M, Fuse N, Mizusawa J, Sato A, Nihei K, Kanato K, Kato K, Yamazaki K, Muro K, Takaishi H, Boku N, Ohtsu A. Phase I/II trial of chemoradiotherapy with concurrent S-1 and cisplatin for clinical stage II/III esophageal carcinoma (JCOG 0604). Cancer Sci, 106:1414-1420, 2015

Book

1. Tahara M. Systemic chemotherapy. In: Kirita T, Omura K (eds), Oral Cancer - Diagnosis and Therapy, Japan, Springer Japan, pp 307-318, 2015

Department of Plastic and Reconstructive Surgery

Minoru Sakuraba, Takuya Higashino, Azusa Oshima, Yaso Saito, Shuchi Azuma, Satsuki Tachibana

Introduction

The Department of Plastic and Reconstructive Surgery has mainly focused on surgical reconstruction following cancer ablation. In our institution, reconstructive procedures using free flap transfer with microvascular anastomosis are the most important operations (Figure 1). In addition, several methods such as tissue transfer with pedicled flaps, local flaps and skin grafts are used for reconstructive surgery. The objectives of reconstructive surgery are not only morphological reconstruction, but also the restoration of postoperative functions after ablative surgery. The quality of life (QOL) of the patients can be improved with functional and morphological reconstruction.

Routine activities

Five plastic surgeons cover reconstructive operations both in the National Cancer Center Hospital (NCCH) East in Kashiwa and the NCCH in Tokyo, and train the residents in the two hospitals. These reconstructive surgeries are performed in cooperation with the surgeons of other departments of the hospital, such as the Department of Head and Neck Surgery, Breast Surgery, Orthopedic Surgery, Esophageal Surgery, and Colorectal Surgery and Urology (Table 1). In the NCCH East, Head and Neck reconstruction is the most frequently performed operation accounting for about 60% of reconstructive surgery. In the Head and Neck region, a free jejunal transfer and anterolateral thigh flap transfer are the most frequently used procedures (Table 2). A weekly conference is held with doctors of the Department of Head and Neck surgery, Radiation Oncology and Head and Neck Oncology. Breast reconstruction using autologous tissue transfer was employed in 2005, since then, patients' needs for breast reconstruction is increasing. Also, lymphatico-venular anastomosis as a surgical treatment for lymphedema of the extremities was introduced in 2013.

Research activities and Clinical trials

Plastic and reconstructive surgery has focused on the following four aspects in the surgical treatment of cancer for the purpose of contributing to the improvement of the QOL of patients.

1) Obtaining good functional recovery
2) Reduction of postoperative complications
3) Achieving less donor site morbidity
4) Treatment of postoperative complications after cancer ablation.

With the objective of addressing these four aspects, establishing a standard for reconstructive surgery and developing new techniques of reconstructive surgery are the most important aims of our studies. Multi-institutional analysis of postoperative complication and swallowing function after total pharyngo-laryngo-esophagectomy and reconstruction with a free jejenal graft was performed continuously. This study was supported by a Grant-in-Aid for Cancer Research. The aim of the study is to clarify the relationship between surgical procedures and postoperative complication and function.

Another multi-institutional analysis of postoperative complication after microsurgical head and neck reconstruction was carried out to clarify the risk factor of postoperative vascular thrombosis. Data registration was closed and the data is now under evaluation.

In 2015, we also started to take an active part in a new multi-institutional analysis of risk factors for functional outcome after tongue reconstruction.

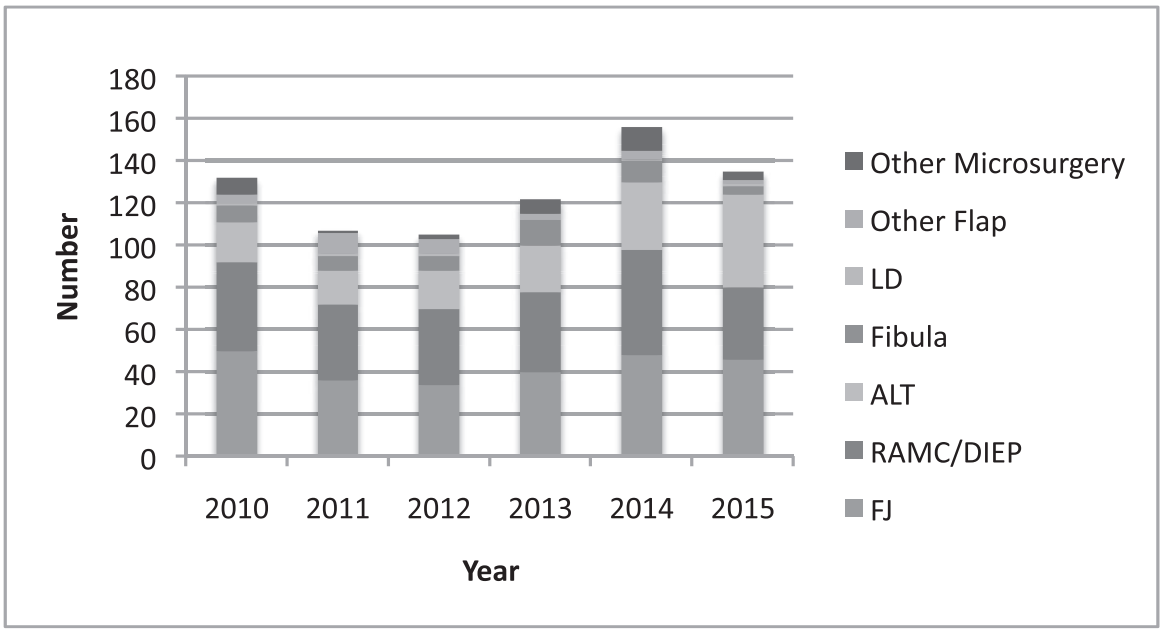


Figure 1. Number of Microsurgeries

Table 1. Number of patients

Cooperation with other divisions	
NCCH East	No. of patients
Head and neck surgery	130
Musculoskeletal oncology	7
Esophageal surgery	5
Breast surgery	66
Dermatologic oncology	—
Urology	0
Hepatobiliary and pancreatic surgery	2
Ophthalmic oncology	—
Colorectal surgery	4
Gastric surgery	1
Thoracic surgery	2
Gynecology	—
Plastic and reconstructive surgery	9
Others	2
Total	228

Table 2. Type of procedures

Operative procedures	
NCCH East	No. of flaps
Microvascular free flap	131
Jejunum	46
RAMC / DIEP	25 / 9
Anterolateral thigh	44
Fibula bone	4
Latissimus dorsi	1
Radial forearm	1
Other flaps	1
Other Microsurgery	4
Supe charge	0
Nerve graft	0
Limb salvage	0
Hepatic artery	1
Lymphatico-Venular anast	2
Others	1
Subtotal	135
Pedicled flaps	33
PMMC	9
Latissimus dorsi	5
RAMC	2
Other flaps	17
Breast reconstruction	43
Tissue expander	19
Silicone breast implant	11
(Autologous tissue	13)
Other procedures	32
Total	230

Department of Breast Surgery

Kimiyasu Yoneyama, Takashi Hojo, Chisako Yamauchi

Introduction

We treat patients with operable malignant mammary glands. Diagnosis of breast disease, surgical treatment and follow-up for breast cancer patients are mainly our professional practice. The Department consists of three staff surgeons and one resident, and is committed to providing the latest, most comprehensive breast treatments for our patients. The multidisciplinary approach to the diagnosis and treatment of cancer are carried out through cooperation between related specialists: surgeons, radiologists, plastic surgeons, pathologists, medical oncologists, specialized nurses, and technicians.

The Department mainly focuses on "minimally invasive surgery" and performs a thorough investigation for an oncologically safe approach, less morbidity and good cosmesis. For example, although sentinel lymph node (SLN) biopsy has already been established as the standard care for clinical node negative patients, omitting axillary lymph node dissection (ALND) for positive SLNs with micro- or macrometastasis has started in clinical practice as an expanded indication. On the other hand, preoperative systemic therapy provides the opportunity for a curative operation or breast-conserving surgery to avoid mastectomy. Moreover, we can provide breast reconstructive surgery in collaboration with the Plastic Surgery Division. These procedures will contribute to a better quality of life for patients with breast cancer.

Routine activities

For the regular activities of the Department, a daily morning routine round is scheduled for inpatients by all staff and residents. Moreover, our weekly preoperative diagnostic imaging conference on breast cancer is conducted on Monday evenings to discuss the surgical treatment planning for each patient. A clinical conference to decide on courses of treatment by multidisciplinary breast care team members is held twice a month. A monthly pathological conference on breast cancer is also conducted on the last Friday of each month. At those conferences, individual cases are presented to a team of highly trained cancer specialists, including radiologists, breast surgeons, pathologists, radiation oncologists, and medical oncologists. Indeed, our multidisciplinary team approach to breast cancer treatment sets the quality of care we provide for our patients well apart from the norm.

Changes in the annual number of patients with breast cancer who underwent surgery are shown in Table 1. A total of 313 patients with primary breast cancer and 46 patients with recurrence or other breast disease were operated on. 14 immediate breast reconstruction surgeries were included. Of the patients with primary breast cancer, 71 (23%) underwent primary systemic therapy. The types and number of operative procedures performed in 2015 are shown in Table 2. The rate of breast-conserving surgeries (including two radiofrequency ablation alone cases) was 60% (187/313). Sentinel node biopsy was performed in 255 patients, and 238 patients were spared from ALND.

Research activities

1) Evaluation of the potential role of Ki67 as a biomarker for breast cancer patients.

The Ki67 index is a marker for cell proliferation. A retrospective search of a prospectively maintained clinical breast cancer database was performed. It was concluded that the pre-therapy Ki67 index was a useful predictor for the therapeutic response to neoadjuvant chemotherapy and Ki67 post-therapy was shown to predict outcomes for patients with residual invasive disease.

2) Long-term results of patients treated with sentinel node biopsy (SNB) omitting ALND.

In an observational study, there was not a significant difference in the overall survival and relapse-free survival between SLN negative patients without ALND and those with ALND. We concluded that SLN biopsy without ALND is validated as a safe and effective method for regional node treatment of SLN negative breast cancer patients. We are planning to omit ALND even in SLN positive patients.

3) In vivo cancer detection with a newly designed fluorescent probe.

γ -glutamyl hydroxymethyl rhodamine green (gGlu-HMRG) is a small-molecule aminopeptidase probe which was enzymatically cleaved, revealing a bright fluorescent region of cancer cells which overexpress the enzyme γ -glutamyltranspeptidase (GGT). Visualized tiny cancerous nodules may allow us to delineate the border of tumors and confirm that there are no residual tumors.

Clinical trials

1) Radiofrequency ablation (RFA) using a Cool-tip electrode system (RAFAELO study).

A phase II study on RFA without resection was performed for T=<1.5 cm, N0 breast cancer patients with no extensive intraductal components using a Cool-tip electrode system. This study is certified as an advanced medical treatment by the Ministry of Health, Labour and Welfare.

2) Effectiveness of primary tumor resection for metastatic breast cancer (The Japan Clinical Oncology Group (JCOG) 1017).

In this multicenter clinical trial, the primary tumor resection plus systemic therapy arm is compared to the systemic therapy alone arm in metastatic breast cancer.

3) Intensive vs. standard post-operative surveillance in high-risk breast cancer patients (JCOG1204, INSPIRE Trial).

This is a multi-center randomized phase III trial which started in 2012. This clinical trial is to confirm the superiority of an intensive follow-up to standard follow-up in terms of overall survival in high-risk breast cancer patients.

4) Postoperative therapy with endocrine and TS-1 (POTENT study).

This multi-center randomized trial started in 2012 and is a randomized, controlled study to determine whether S-1 combined with standard postoperative endocrine therapy more effectively inhibits recurrence than standard postoperative endocrine therapy alone in patients with estrogen receptor (ER)-positive, HER2-negative primary breast cancer.

5) Observational study of axilla treatment for breast cancer patients with SLN positive.

This multi-center study is designed to evaluate the outcome of no ALND in sentinel node-positive breast cancer using the propensity score. Patients with 1 to 3 positive micrometastasis or macrometastasis in sentinel lymph nodes are eligible. The primary endpoint is the recurrence rate of regional lymph nodes in patients treated with SNB. Patients treated with SNB followed by ALND are also registered simultaneously to compare the prognosis.

Education

Our education targets are to raise knowledge about breast disease and to operative technical improvement.

Future prospects

We want to solve the appropriate postoperative follow-up that was a longtime problem in breast cancer medical care by clinical trial. And aim at operative development with more minimally invasive surgery.

Table 1. Number of primary breast cancer patients operated on during 2006-2015

Clinical stage	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Stage 0	34	27	23	38	39	43	28	25	29	17
Stage I	79	94	84	86	80	86	91	112	88	131
Stage II	103	87	87	122	137	112	128	138	123	136
Stage III	34	25	33	42	32	43	49	29	39	26
Stage IV	1	4	0	3	1	1	4	2	3	3
Total	251	237	227	291	289	285	300	306	282	313

Table 2. Type of operative procedures performed in 2015 for primary breast cancer

Type of operation	N
BT + SNB	76
BT + SNB→ALND	13
BT + ALND	37
BT alone	0
BP + SNB	149
BP + SNB→ALND	4
BP + ALND	13
BP alone	8
RFA + SNB	13
Total	313

Total mastectomy with immediate breast reconstruction was performed in 30 patients.
BP: partial mastectomy, BT: total mastectomy, SNB: sentinel node biopsy, ALND: axillary lymph node dissection, RFA: radio frequency ablation

List of papers published in 2015

Journal

1. Hojo T, Masuda N, Mizutani T, Shibata T, Kinoshita T, Tamura K, Hara F, Fujisawa T, Inoue K, Saji S, Nakamura K, Fukuda H, Iwata H. Intensive vs. Standard Post-Operative Surveillance in High-Risk Breast Cancer Patients (INSPIRE): Japan Clinical Oncology Group Study JCOG1204. Jpn J Clin Oncol, 45:983-986, 2015
2. Komoike Y, Inokuchi M, Itoh T, Kitamura K, Kutomi G, Sakai T, Jinno H, Wada N, Ohsumi S, Mukai H, Japanese Breast Cancer Society. Japan Breast Cancer Society clinical practice guideline for surgical treatment of breast cancer. Breast Cancer, 22:37-48, 2015

Department of Breast and Medical Oncology

Tetsuo Akimoto, Hirofumi Mukai, Nobuaki Matsubara, Yoichi Naito, Masaoki Sasaki, Ako Hosono, Mai Onomura, Yoko Yamada, Hiroaki Izumi, Tetsuya Urasaki, Yujiro Ueda, Takaaki Yokoyama

Introduction

Patients with different types of cancer, including those with breast and genitourinary tract cancers, are treated with standard chemotherapy and/or managed in clinical trials in daily medical practice at the Department of Breast/Medical Oncology. Gynecological malignancies and soft tissue sarcomas are also treated with chemotherapy. Another major target of the Department is cancer of unknown primary origin. The clinical and research activities of the Department primarily focus on the following fields: Standard chemotherapeutic treatment in medical practice, disease-oriented clinical trials, developmental therapeutics of new anticancer agents sponsored by pharmaceutical companies and development of combination chemotherapy involving newly developed drugs or new combinations of currently available drugs.

Routine activities

The major and specific target disease of the Department comprised breast cancer. Eligible patients were invited to participate in large phase II/III studies. The Department also treated cancers of the genitourinary tract, cancer of unknown primary origin, soft tissue sarcomas and gynecological cancers including uterine and ovarian cancers. For patients with diseases treated with established standard chemotherapeutic regimens, standard chemotherapy was administered in routine medical practice. Patients in whom standard chemotherapy had failed and those with cancers for which standard chemotherapy was unavailable were invited to participate in clinical studies on experimental drugs and regimens. In 2015, 624 patients with different types of cancer visited the Department for consultation. Approximately 400 patients per month received routine chemotherapy as an outpatient service by the Department. The overall inpatient care system of the held on every morning. A weekly educational meeting is conducted on Thursday morning. Moreover, a biweekly joint conference is held on Wednesday evenings and on Monday evenings with breast surgeons and with urologists, respectively. Morning journal clubs also meet on Mondays and Fridays at the Department in collaboration with the Division of hematology.

Research activities

Phase I studies of the following anticancer agents were conducted: K912 (epirubicin-incorporating micellar nanoparticle formulation) for patients with solid tumors for which standard chemotherapy was unavailable, and NK105 (paclitaxel-incorporating micellar nanoparticle formulation) for patients with advanced or metastatic cancer. Phase I/II studies of new anticancer agents for specific disease targets are conducted in collaboration with pharmaceutical companies.

In addition, many phase III studies are being conducted as follows: Randomized, optimal dose finding, Phase II Study of triweekly Abraxane in patients with metastatic breast cancer; Evaluation of Oral Care to Prevent Oral Mucositis in Estrogen Receptor Positive Metastatic Breast Cancer Patients Treated with Everolimus. (Oral Care-BC): Randomized Controlled Phase III Trial; A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer; Intensive vs. standard post-operative surveillance in high risk breast cancer patients; Adjuvant Chemotherapy Trial of S-1 for breast cancer with ER-positive and HER2-negative; a randomized double-blind placebo-controlled trial of neratinib (an erbB1/2/4

inhibitor) after trastuzumab in women with early-stage HER-2 overexpressed/amplified breast cancer; a randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer (APHINITY: Adjuvant Pertuzumab and Herceptin IN Initial Therapy); a randomized phase III study on NK105 versus paclitaxel in patients with recurrent or metastatic breast cancer; and a randomized phase III study on lapatinib, trastuzumab, and both lapatinib and trastuzumab, combined with aromatase inhibitor in patients with HER-2 overexpressed breast cancer who received neo-/adjuvant therapy with trastuzumab and endocrine therapy.

Table 1. Number of new patients

Breast cancer	278
Genitourinary cancers	191
Gynecological cancers	30
Cancer of unknown primary	58
Others	67
Total	624

List of papers published in 2015

Journal

1. Hayashi N, Niikura N, Masuda N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M, Kondo N, Naito Y, Honda Y, Matsui A, Fujisawa T, Oshitanai R, Yasojima H, Yamauchi H, Saji S, Iwata H. Prognostic factors of HER2-positive breast cancer patients who develop brain metastasis: a multicenter retrospective analysis. Breast Cancer Res Treat, 149:277-284, 2015

2. Mukai H, Saeki T, Shimada K, Naito Y, Matsubara N, Nakanishi T, Obaishi H, Namiki M, Sasaki Y. Phase 1 combination study of eribulin mesylate with trastuzumab for advanced or recurrent human epidermal growth factor receptor 2 positive breast cancer. Invest New Drugs, 33:119-127, 2015

3. Taira N, Arai M, Ikeda M, Iwasaki M, Okamura H, Takamatsu K, Yamamoto S, Ohsumi S, Mukai H, Japanese Breast Cancer Society. The Japanese Breast Cancer Society clinical practice guideline for epidemiology and prevention of breast cancer. Breast Cancer, 22:16-27, 2015

4. Mukai H, Masuda N, Ishiguro H, Mitsuma A, Shibata T, Yamamura J, Toi M, Watabe A, Sarashina A, Uttenreuther-Fischer M, Ando Y. Phase I trial of afatinib plus vinorelbine in Japanese patients with advanced solid tumors, including breast cancer. Cancer Chemother Pharmacol, 76:739-750, 2015

5. Nozawa M, Mukai H, Takahashi S, Uemura H, Kosaka T, Onozawa Y, Miyazaki J, Suzuki K, Okihara K, Arai Y, Kamba T, Kato M, Nakai Y, Furuse H, Kume H, Ide H, Kitamura H, Yokomizo A, Kimura T, Tomita Y, Ohno K, Kakehi Y. Japanese phase I study of cabazitaxel in metastatic castration-resistant prostate cancer. Int J Clin Oncol, 20:1026-1034, 2015

6. Gelmon KA, Boyle FM, Kaufman B, Huntsman DG, Manikhas A, Di Leo A, Martin M, Schwartzberg LS, Lemieux J, Aparicio S, Shepherd LE, Dent S, Ellard SL, Tonkin K, Pritchard KI, Whelan TJ, Nomikos D, Nusch A, Coleman RE, Mukai H, Tjulandin S, Khasanov R, Rizel S, Connor AP, Santillana SL, Chapman JA, Parulekar WR. Lapatinib or Trastuzumab Plus Taxane Therapy for Human Epidermal Growth Factor Receptor 2-Positive Advanced Breast Cancer: Final Results of NCIC CTG MA.31. J Clin Oncol, 33:1574-1583, 2015

7. Mukai H, Aihara T, Yamamoto Y, Takahashi M, Toyama T, Sagara Y, Yamaguchi H, Akabane H, Tsurutani J, Hara F, Fujisawa T, Yamamoto N, Ohsumi S, Japanese Breast Cancer Society. The Japanese Breast Cancer Society Clinical Practice Guideline for systemic treatment of breast cancer. Breast Cancer, 22:5-15, 2015

8. Tozaki M, Isomoto I, Kojima Y, Kubota K, Kuroki Y, Ohnuki K, Ohsumi S, Mukai H, Japanese Breast Cancer Society. The Japanese Breast Cancer Society Clinical Practice Guideline for screening and imaging diagnosis of breast cancer. Breast Cancer, 22:28-36, 2015

9. Mukai H, Noguchi S, Akiyama F, Inaji H, Iwase H, Horiguchi J, Kurebayashi J, Hirata K, Toi M, Kurosumi M, Kohno N, Nishimura R, Nakamura S, Imoto S, Iwase T, Endo T, Saeki T, Ogawa Y, Ito Y, Tokuda Y, Ikeda T. 2013 clinical practice guidelines (The Japanese Breast Cancer Society): history, policy and mission. Breast Cancer, 22:1-4, 2015

10. Horii R, Honma N, Ogiya A, Kozuka Y, Fukuda T, Yoshida M, Ohsumi S, Mukai H, Japanese Breast Cancer Society. The Japanese Breast Cancer Society Clinical Practice Guideline for pathological diagnosis of breast cancer. Breast Cancer, 22:59-65, 2015

11. Sekiguchi K, Ogawa Y, Sanuki N, Arahira S, Ogo E, Yoshimura M, Yamauchi C, Oguchi M, Ohsumi S, Mukai H, Japanese Breast Cancer Society. The Japanese Breast Cancer Society clinical practice guideline for radiotherapy of breast cancer. Breast Cancer, 22:49-58, 2015

12. Ueda Y, Matsubara N, Takizawa I, Nishiyama T, Tabata K, Satoh T, Kamiya N, Suzuki H, Kawahara T, Uemura H. A multicenter retrospective analysis of sequential treatment of abiraterone acetate followed by docetaxel in Japanese patients with metastatic castration-resistant prostate cancer. Jpn J Clin Oncol, 45:774-779, 2015

13. Komoike Y, Inokuchi M, Itoh T, Kitamura K, Kutomi G, Sakai T, Jinno H, Wada N, Ohsumi S, Mukai H, Japanese Breast Cancer Society. Japan Breast Cancer Society clinical practice guideline for surgical treatment of breast cancer. Breast Cancer, 22:37-48, 2015

14. Iwata H, Fujii H, Masuda N, Mukai H, Nishimura Y, Katsura K, Ellis CE, Gagnon RC, Nakamura S. Efficacy, safety, pharmacokinetics and biomarker findings in patients with HER2-positive advanced or metastatic breast cancer treated with lapatinib in combination with capecitabine: results from 51 Japanese patients treated in a clinical study. Breast Cancer, 22:192-200, 2015

15. Yamaguchi T, Mukai H, Yamashita S, Fujii S, Ushijima T. Comprehensive DNA methylation and extensive mutation analyses of HER2-positive breast cancer. Oncology, 88:377-384, 2015

Department of Thoracic Surgery

Masahiro Tsuboi, Junji Yoshida, Tomoyuki Hishida, Keiju Aokage, Masahito Naito, Tomohiro Miyoshi

Introduction

The Department of Thoracic Oncology has three missions: surgical treatment, surgical resident training, and clinical research. Thoracic surgeries involve the treatment of thoracic neoplasms, primary and metastatic lung tumors, as well as mediastinal, pleural, and chest wall tumors. The Department specializes in the surgical treatment of pulmonary carcinomas. Routine surgical treatment modalities for carcinomas include limited resection (wedge or segmental resection) and simple resection (lobectomy or pneumonectomy) with or without systematic lymph node dissection. Thoracoscopic assistance is almost always used. Non-routine surgical procedures involve complex approaches such as broncho-/angio-plasty, combined resection with adjacent structures, and perioperative adjuvant treatment.

Since its establishment in 1992, the Department has been one of the most active leaders in the field of lung cancer in Japan. Moreover, it has been an active participant in international and national scientific venues. This year, in addition to 13 scientific papers published in English, the Department made 31 presentations: 4 international, 23 national, and 4 regional.

Routine Activities

The Department is presently composed of four consultant surgeons and five or six residents.

The Department has adopted a team approach in patient treatment and resident training. Potential surgical intervention candidate cases are presented every Tuesday evening at a multidisciplinary team conference of thoracic surgeons, oncology physicians, radiologists and residents. Each case is thoroughly and vigorously reviewed and discussed. To improve the English fluency of staff members and residents in preparation for international presentations, and to better involve visiting physicians from other countries, treatment modality discussions are conducted in English. Moreover, selected patients' records are radiologically and cytopathologically reviewed every Friday morning. These reviews aim to improve the interpretation of radiologic indications to pathology findings, accurately evaluate surgical indications, and upgrade knowledge on rare histologies. The Department believes that these activities improve the knowledge base, treatment indications, and surgical treatment.

For non-small cell histology, primary pulmonary carcinomas in clinical stages I/II and IIIA without bulky or multistation-involved mediastinal nodes, and primary pulmonary small cell carcinomas in clinical stage I, surgical resection is indicated for the cure. Optimum treatment modalities are being sought via clinical trials with the aim of improving the poor prognosis of patients with bulky or clinically and histologically proven multistation mediastinal lymph node metastases, with disease invading the neighboring vital structures, or with small cell cancers in clinical stage II and later.

Resection of metastatic lung tumor is attempted based on modified Thomfold's criteria after consultation with the patient. The majority of these cases are metastases from colorectal carcinomas, while most of the mediastinal tumors are thymic epithelial tumors.

The surgical procedures of the Department have generally remained similar for the past decade, but we have employed port-access thoracoscopic surgery more often for the last several years. Approximately 20% of the surgeries are completed via a 3-port access, and 70% of the surgeries are video-thoracoscopically assisted. To date, the average postoperative hospital stays of patients in the Department have improved and became shorter; three days being the shortest with a median

of seven days for cases of primary lung cancer. These shorter hospital stays are achieved with a slightly better complication rate than the normal rate. This year, 30-day operative mortality occurred in 2 patients undergoing surgery for primary lung cancer.

Research Activities

Research in the area of combined treatments, especially immunotherapy, has now advanced to clinical trials. It is a goal of researchers in the Department to acquire a basic understanding of the cellular and molecular mechanisms leading to the development and progression of lung cancer and apply these findings to further the development of immunotherapy-based prevention and treatment strategies

Clinical Trials

1) Surgical margin lavage cytology examination in limited resection for primary and metastatic lung cancer patients [observational].
2) Primary investigator and a member of an organized trial of TS-1 vs. UFT adjuvant chemotherapy for completely resected pathologic stage I (> 2 cm) non-small cell lung cancer [JCOG0707, phase III, patient accrual completed].
3) Primary investigator and a member of an organized trial of sublobar resection for peripheral GGO dominant cT1aN0M0 lung adenocarcinomas [JCOG0804, phase II, patient accrual completed].
4) Study coordinator and a member of an organized trial of segmental resection vs. lobectomy for peripheral T1aN0M0 non-small cell lung cancers [JCOG0802, phase III, patient accrual completed].
5) Study coordinator and a member of an organized trial of sublobar resection for peripheral GGO dominant cT1bN0M0 lung adenocarcinomas [JCOG1211, phase III, patient accrual completed]
6) Primary investigator and a member of an organized trial of Cisplatin/Pemetrexed vs. Cisplatin/Vinorelbine adjuvant chemotherapy for completely resected pathologic stage II-IIIA non-small cell lung cancer [JIPANG, phase III, patient accrual ongoing].
7) A member of an organized trial of Human Atrial Natriuretic Peptide during perioperative period for completed resectable non-small cell lung cancer [JANP, randomized phase II, patient accrual ongoing].
8) A member of an organized trial of postoperative maintenance adjuvant immunotherapy with S-588410 for completed resected stage II-IIIA non-small cell lung cancer [S-588410, phase II, patient accrual ongoing]

Education

Our educational program is to educate residents by expanding their knowledge and technical skills in the treatment of lung cancer, other thoracic malignancies and benign tumors, such as hamartoma and mediastinal cystic lesions. In addition, we seek to instill in the trainee a desire for continued introspection and self-education, open communication between all health care providers, while maintaining a respectful and professional demeanor.

Future prospects

Treatment advances in thoracic cancers including lung, mesothelioma, thymic malignancies and lung metastases have been slow to develop, even though these cancers are among the most common clinical problems. This clinical and laboratory research is vital to making progress.

Table 1. Number of patients

Lung cancer	411
Metastatic lung tumor	70
Mediastinal tumor	17
Others	65
Total	563

Table 2. Type of procedure-primary lung cancer

Pneumonectomy	15
Lobectomy	321
Segmentectomy	23
Wedge resection	35
(Combined resection)	(24)
Others	17
Total	411

Table 3. Overall survival

Diagnosis (primary lung cancer)	No. of pts	MST (mo)	5-yr survival (%)
Pathologic stage			
IA	1,334	NR	87.1
IB	540	127.0	71.7
IIA	315	73.5	56.4
IIB	226	47.8	46.1
IIIA	449	42.7	40.6

Data source from surgical records between 2002 and 2012;
Pathological stages according to the TNM Classification 7th edition;
NR: not reached.

List of papers published in 2015

Journal

1. Suzuki K, Watanabe S, Mizusawa J, Moriya Y, Yoshino I, Tsuboi M, Mizutani T, Nakamura K, Tada H, Asamura H, Japan Lung Cancer Surgical Study Group (JCOG LCSSG). Predictors of non-neoplastic lesions in lung tumours showing ground-glass opacity on thin-section computed tomography based on a multi-institutional prospective study†. Interact Cardiovasc Thorac Surg, 21:218-223, 2015

2. Sugiyama E, Umemura S, Nomura S, Kirita K, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Ohe Y, Goto K. Impact of single nucleotide polymorphisms on severe hepatotoxicity induced by EGFR tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring EGFR mutations. Lung Cancer, 90:307-313, 2015

3. Omori T, Tajiri M, Baba T, Ogura T, Iwasawa T, Okudela K, Takemura T, Oba MS, Maehara T, Nakayama H, Tsuboi M, Masuda M. Pulmonary Resection for Lung Cancer in Patients With Idiopathic Interstitial Pneumonia. Ann Thorac Surg, 100:954-960, 2015

4. Haruki T, Aokage K, Miyoshi T, Hishida T, Ishii G, Yoshida J, Tsuboi M, Nakamura H, Nagai K. Mediastinal nodal involvement in patients with clinical stage I non-small-cell lung cancer: possibility of rational lymph node dissection. J Thorac Oncol, 10:930-936, 2015

5. Mimae T, Suzuki K, Tsuboi M, Nagai K, Ikeda N, Mitsudomi T, Saji H, Okumura S, Okumura M, Yoshimura K, Okada M. Surgical Outcomes of Lung Cancer in Patients with Combined Pulmonary Fibrosis and Emphysema. Ann Surg Oncol, 223:1371-1379, 2015

6. Yoshida J, Ishii G, Hishida T, Aokage K, Tsuboi M, Ito H, Yokose T, Nakayama H, Yamada K, Nagai K. Limited resection trial for pulmonary ground-glass opacity nodules: case selection based on high-resolution computed tomography-interim results. Jpn J Clin Oncol, 45:677-681, 2015

7. Hamanaka R, Yokose T, Sakuma Y, Tsuboi M, Ito H, Nakayama H, Yamada K, Masuda R, Iwazaki M. Prognostic impact of vascular invasion and standardization of its evaluation in stage I non-small cell lung cancer. Diagn Pathol, 10:17, 2015

8. Hishida T, Tsuboi M, Shukuya T, Takamochi K, Sakurai H, Yoh K, Ohashi Y, Kunitoh H. Multicenter observational cohort study of post-operative treatment for completely resected non-small-cell lung cancer of pathological stage I (T1 >2 cm and T2 in TNM classification version 6). Jpn J Clin Oncol, 45:499-501, 2015

9. Noma D, Morohoshi T, Adachi H, Natsume I, Ookouchi M, Tsuura Y, Tsuboi M, Masuda M. A resected case of combined small cell lung carcinoma with carcinosarcoma. Pathol Int, 65:332-334, 2015

10. Udagawa H, Ishii G, Morise M, Umemura S, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A, Ohe Y. Comparison of the expression levels of molecular markers among the peripheral area and central area of primary tumor and metastatic lymph node tumor in patients with squamous cell carcinoma of the lung. J Cancer Res Clin Oncol, 141:1417-1425, 2015

11. Adachi H, Tsuboi M, Nishii T, Yamamoto T, Nagashima T, Ando K, Ishikawa Y, Woo T, Watanabe K, Kumakiri Y, Maehara T, Morohoshi T, Nakayama H, Masuda M. Influence of visceral pleural invasion on survival in completely resected non-small-cell lung cancer. Eur J Cardiothorac Surg, 48:691-7; discussion 697, 2015

12. Koriyama H, Ishii G, Yoh K, Neri S, Morise M, Umemura S, Matsumoto S, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A. Presence of podoplanin-positive cancer-associated fibroblasts in surgically resected primary lung adenocarcinoma predicts a shorter progression-free survival period in patients with recurrences who received platinum-based chemotherapy. J Cancer Res Clin Oncol, 141:1163-1170, 2015

13. Samejima J, Tajiri M, Ogura T, Baba T, Omori T, Tsuboi M, Masuda M. Thoracoscopic lung biopsy in 285 patients with diffuse pulmonary disease. Asian Cardiovasc Thorac Ann, 23:191-197, 2015

14. Arai H, Inui K, Watanabe K, Watanuki K, Okudela K, Tsuboi M, Masuda M. Lung abscess combined with chronic osteomyelitis of the mandible successfully treated with video-assisted thoracoscopic surgery. Clin Respir J, 9:253-256, 2015

15. Matsumura Y, Umemura S, Ishii G, Tsuta K, Matsumoto S, Aokage K, Hishida T, Yoshida J, Ohe Y, Suzuki H, Ochiai A, Goto K, Nagai K, Tsuchihara K. Expression profiling of receptor tyrosine kinases in high-grade neuroendocrine carcinoma of the lung: a comparative analysis with adenocarcinoma and squamous cell carcinoma. J Cancer Res Clin Oncol, 141:2159-2170, 2015

16. Morise M, Hishida T, Takahashi A, Yoshida J, Ohe Y, Nagai K, Ishii G. Clinicopathological significance of cancer stem-like cell markers in high-grade neuroendocrine carcinoma of the lung. J Cancer Res Clin Oncol, 141:2121-2130, 2015

17. Suzuki S, Ishii G, Matsuwaki R, Neri S, Hashimoto H, Yamauchi C, Aokage K, Hishida T, Yoshida J, Kohno M, Nagai K, Ochiai A. Ezrin-expressing lung adenocarcinoma cells and podoplanin-positive fibroblasts form a malignant microenvironment. J Cancer Res Clin Oncol, 141:475-484, 2015

18. Kinoshita T, Yoshida J, Ishii G, Hishida T, Wada M, Aokage K, Nagai K. The availability of pre- and intraoperative evaluation of a solitary pulmonary nodule in breast cancer patients. Ann Thorac Cardiovasc Surg, 21:31-36, 2015

19. Yano M, Yoshida J, Koike T, Kameyama K, Shimamoto A, Nishio W, Yoshimoto K, Utsumi T, Shiina T, Watanabe A, Yamato Y, Watanabe T, Takahashi Y, Sonobe M, Kuroda H, Oda M, Inoue M, Tanahashi M, Adachi H, Saito M, Hayashi M, Otsuka H, Mizobuchi T, Moriya Y, Takahashi M, Nishikawa S, Matsumura Y, Moriyama S, Nishiyama T, Fujii Y, Japanese Association for Chest Surgery. Survival of 1737 lobectomy-tolerable patients who underwent limited resection for cStage IA non-small-cell lung cancer. Eur J Cardiothorac Surg, 47:135-142, 2015

20. Tsubokawa N, Mimae T, Aokage K, Hattori A, Suzuki K, Nagai K, Tsuboi M, Okada M. Surgical outcomes of non-small-cell lung carcinoma in patients previously treated for gastric cancer. Eur J Cardiothorac Surg, 47:648-652, 2015

Department of Thoracic Oncology

Koichi Goto, Hironobu Ohmatsu, Seiji Niho, Kiyotaka Yoh, Shigeki Umemura, Shingo Matsumoto, Keisuke Kirita, Eri Sugiyama, Yoshitaka Zenke

Introduction

The Department of Thoracic Oncology provides care for patients with primary lung cancer, mediastinal tumors, and pleural tumors. The Department aims to provide the highest quality treatment and establish new effective treatments against lung cancer and other thoracic malignancies through innovative clinical and translational research. To provide assistance to our patients through multidisciplinary care, the staff members of the Department work closely with thoracic surgeons, radiation oncologists, pharmacists, clinical research coordinators, and psychiatrists who have expertise in these areas. Moreover, residents and trainees from other institutions have joined the Thoracic Oncology Program.

Routine activities

Our Outpatient Clinic, managed by the staff members and senior residents, is open from Monday to Friday for the examination of all new referred patients and the evaluation of returning patients. Returning patients also receive oral chemotherapy and/or intravenous chemotherapy in the Ambulatory Care Center. Bronchoscopy and EBUS for diagnosis is performed on Monday, Tuesday, and Thursday afternoon. Fluoroscopic-CT guided needle lung biopsies are carried out on Tuesday afternoon. For patient management, we use approximately 70 beds in 8F, 6A, 5A and 5B wards.

Case conferences on thoracic surgery and medical oncology are scheduled on Tuesday evenings and Wednesday evenings, respectively. The staff members and residents of the Department participate in a journal club on Monday and Wednesday mornings. At monthly meetings with physicians in private practice, the staff members and residents are teaching methods for reading chest X-ray and CT scan films.

Research activities

Our research activities are focused on four areas: 1) development of new and effective diagnosis and treatment modalities; 2) detection, diagnosis, and treatment of peripheral-type minute lung cancers that are not visible in plain chest X-rays; 3) collaborative studies with the Research Center for Innovative Oncology in the following areas: detection of driver mutation for small cell lung cancer; development of a new diagnostic method of rare driver gene alterations for lung cancer; correlation between gene abnormalities and clinical characteristics; correlation between sensitivity of EGFR-TKI and CAF (cancer-associated fibroblasts); and 4) translational research from bench to bed-side or from bed-side to bench for the development of innovative treatment strategies.

Especially, hole genome analysis of small cell cancer to detect new driver mutations and establishment of multiplex diagnosis methods for rare gene alteration of lung cancer such as ALK, RET and ROS1 fusion gene and BRAF mutation are under investigation as a collaboration with the Research Center for Innovative Oncology.

Clinical trials

The Department of Thoracic Oncology is currently conducting and participating in multi-institutional phase III studies to establish new standard treatments against lung cancer such as the Japan Clinical Oncology Group (JCOG) trials, West Japan Oncology Group (WJOG), Thoracic Oncology Research Group (TORG) and global trials conducted by pharmaceutical companies.

Recently, the usefulness of TS-1 and

pemetrexed combined with thoracic radiotherapy has been reported for locally advanced NSCLC. Therefore, a randomized phase II study of cisplatin plus TS-1 vs. cisplatin plus pemetrexed combined with thoracic radiotherapy for stage III non-squamous NSCLC is now ongoing.

Alectinib is a newly developing selective ALK inhibitor and very effective for ALK fusion positive NSCLC, although 4-5% of NSCLC are positive for ALK fusion protein. A phase I/II study of alectinib demonstrated durable response and higher than 90% response rate without severe toxicity. A phase III study of alectinib comparing with crizotinib for ALK positive lung cancer was conducted and the patient enrollment was completed. The study of AZD9291, 3rd generation EGFR-TKI, was conducted and a good response for T790M-resistant mutation positive lung cancer was observed with minimal toxicities.

In addition, many recent clinical trials indicated that PD-1/PD-L1 immune checkpoint inhibitors showed remarkable clinical response against advanced NSCLC including squamous cell lung cancer. Nivolumab, one of the PD-1 antibodies, was approved in December 2015, in Japan.

LC-SCRUM-Japan (Lung Cancer Genomic Screening Project for Individualized Medicine in Japan), a nationwide genomic screening project of lung cancer with rare driver oncogenes, such as ALK, RET and ROS1 fusion, and BRAF mutation was started in February 2013. As of December 2015, 2,301 patients were enrolled and 51 (3%) RET and 86 (4%) ROS1 fusion positive patients were detected. Many lung cancers with oncogenic alterations detected in LC-SCRUM-Japan had been entered into clinical trials of molecular targeting agents. In addition, from February 2015, to further develop genomic screening and to establish precision medicine in Japan, LC-SCRUM-Japan and genomic screening network for gastrointestinal cancer (GI-SCREEN), developed the collaborative genomic screening organization between academia and 14 pharmaceutical companies, named SCRUM-Japan.

Table 1. Number of patients in 2015

Lung Cancer		446
	Small cell lung cancer	68
	Adenocarcinoma	256
	Squamous cell carcinoma	74
	Large cell carcinoma	1
	NSCLC NOS	30
	Others	17
Thymic cancer		2
Thymoma		1
Malignant pleural mesothelioma		3
Other pleural tumor		5

Table 2. Initial treatment for lung cancer in 2015

Chemotherapy	274
Chemoradiotherapy	72
Surgery followed by chemotherapy	37
Radiotherapy	18
Palliative care	32
Others	13

List of papers published in 2015

Journal

1. Watanabe N, Umemura S, Niho S, Kirita K, Matsumoto S, Yoh K, Ohmatsu H, Goto K. Docetaxel for platinum-refractory advanced thymic carcinoma. Jpn J Clin Oncol, 45:665-669, 2015

2. Tsukada H, Yokoyama A, Goto K, Shinkai T, Harada M, Ando M, Shibata T, Ohe Y, Tamura T, Saijo N, Lung Cancer Study Group of the Japan Clinical Oncology Group (JCOG). Randomized controlled trial comparing docetaxel-cisplatin combination with weekly docetaxel alone in elderly patients with advanced non-small-cell lung cancer: Japan Clinical Oncology Group (JCOG) 0207†. Jpn J Clin Oncol, 45:88-95, 2015

3. Yoshida T, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Ohe Y, Goto K. RECIST progression patterns during EGFR tyrosine kinase inhibitor treatment of advanced non-small cell lung cancer patients harboring an EGFR mutation. Lung Cancer, 90:477-483, 2015

4. Daga H, Takeda K, Okada H, Miyazaki M, Ueda S, Kaneda H, Okamoto I, Yoh K, Goto K, Konishi K, Sarashina A, Tanaka T, Kaiser R, Nakagawa K. Phase I study of nintedanib in combination with pemetrexed as second-line treatment of Japanese patients with advanced non-small cell lung cancer. Cancer Chemother Pharmacol, 76:1225-1233, 2015

5. Yoshida T, Ishii G, Goto K, Neri S, Hashimoto H, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Iida S, Niimi A, Nagai K, Ohe Y, Ochiai A. Podoplanin-positive cancer-associated fibroblasts in the tumor microenvironment induce primary resistance to EGFR-TKIs in lung adenocarcinoma with EGFR mutation. Clin Cancer Res, 21:642-651, 2015

6. Sugiyama E, Umemura S, Nomura S, Kirita K, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Ohe Y, Goto K. Impact of single nucleotide polymorphisms on severe hepatotoxicity induced by EGFR tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring EGFR mutations. Lung Cancer, 90:307-313, 2015

7. Hishida T, Tsuboi M, Shukuya T, Takamochi K, Sakurai H, Yoh K, Ohashi Y, Kunitoh H. Multicenter observational cohort study of post-operative treatment for completely resected non-small-cell lung cancer of pathological stage I (T1 >2 cm and T2 in TNM classification version 6). Jpn J Clin Oncol, 45:499-501, 2015

8. Udagawa H, Ishii G, Morise M, Umemura S, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A, Ohe Y. Comparison of the expression levels of molecular markers among the peripheral area and central area of primary tumor and metastatic lymph node tumor in patients with squamous cell carcinoma of the lung. J Cancer Res Clin Oncol, 141:1417-1425, 2015

9. Koriyama H, Ishii G, Yoh K, Neri S, Morise M, Umemura S, Matsumoto S, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A. Presence of podoplanin-positive cancer-associated fibroblasts in surgically resected primary lung adenocarcinoma predicts a shorter progression-free survival period in patients with recurrences who received platinum-based chemotherapy. J Cancer Res Clin Oncol, 141:1163-1170, 2015

10. Matsumura Y, Umemura S, Ishii G, Tsuta K, Matsumoto S, Aokage K, Hishida T, Yoshida J, Ohe Y, Suzuki H, Ochiai A, Goto K, Nagai K, Tsuchihara K. Expression profiling of receptor tyrosine kinases in high-grade neuroendocrine carcinoma of the lung: a comparative analysis with adenocarcinoma and squamous cell carcinoma. J Cancer Res Clin Oncol, 141:2159-2170, 2015

11. Asao T, Nokihara H, Yoh K, Niho S, Goto K, Ohmatsu H, Kubota K, Yamamoto N, Sekine I, Kunitoh H, Fujiwara Y, Ohe Y. Phase II study of amrubicin at a dose of 45 mg/m2 in patients with previously treated small-cell lung cancer. Jpn J Clin Oncol, 45:941-946, 2015

12. Makinoshima H, Takita M, Saruwatari K, Umemura S, Obata Y, Ishii G, Matsumoto S, Sugiyama E, Ochiai A, Abe R, Goto K, Esumi H, Tsuchihara K. Signaling through the Phosphatidylinositol 3-Kinase (PI3K)/Mammalian Target of Rapamycin (mTOR) Axis Is Responsible for Aerobic Glycolysis mediated by Glucose Transporter in Epidermal Growth Factor Receptor (EGFR)-mutated Lung Adenocarcinoma. J Biol Chem, 290:17495-17504, 2015

13. Umemura S, Tsuchihara K, Goto K. Genomic profiling of small-cell lung cancer: the era of targeted therapies. Jpn J Clin Oncol, 45:513-519, 2015

14. Kubota K, Sakai H, Katakami N, Nishio M, Inoue A, Okamoto H, Isobe H, Kunitoh H, Takiguchi Y, Kobayashi K, Nakamura Y, Ohmatsu H, Sugawara S, Minato K, Fukuda M, Yokoyama A, Takeuchi M, Michimae H, Gemma A, Kudoh S, Tokyo Cooperative Oncology Group. A randomized phase III trial of oral S-1 plus cisplatin versus docetaxel plus cisplatin in Japanese patients with advanced non-small-cell lung cancer: TCOG0701 CATS trial. Ann Oncol, 26:1401-1408, 2015

15. Shukuya T, Yamanaka T, Seto T, Daga H, Goto K, Saka H, Sugawara S, Takahashi T, Yokota S, Kaneda H, Kawaguchi T, Nagase S, Oguri T, Iwamoto Y, Nishimura T, Hattori Y, Nakagawa K, Nakanishi Y, Yamamoto N, West Japan Oncology Group. Nedaplatin plus docetaxel versus cisplatin plus docetaxel for advanced or relapsed squamous cell carcinoma of the lung (WJOG5208L): a randomised, open-label, phase 3 trial. Lancet Oncol, 16:1630-1638, 2015

16. Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, Goto K. Beyond ALK-RET, ROS1 and other oncogene fusions in lung cancer. Transl Lung Cancer Res, 4:156-164, 2015

17. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Ogawa A, Fujisawa D, Sone T, Yoshiuchi K, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Personality traits and coping styles explain anxiety in lung cancer patients to a greater extent than other factors. Jpn J Clin Oncol, 45:456-463, 2015

18. Enomoto Y, Kenmotsu H, Watanabe N, Baba T, Murakami H, Yoh K, Ogura T, Takahashi T, Goto K, Kato T. Efficacy and Safety of Combined Carboplatin, Paclitaxel, and Bevacizumab for Patients with Advanced Non-squamous Non-small Cell Lung Cancer with Pre-existing Interstitial Lung Disease: A Retrospective Multi-institutional Study. Anticancer Res, 35:4259-4263, 2015

19. Soria JC, Wu YL, Nakagawa K, Kim SW, Yang JJ, Ahn MJ, Wang J, Yang JC, Lu Y, Atagi S, Ponce S, Lee DH, Liu Y, Yoh K, Zhou JY, Shi X, Webster A, Jiang H, Mok TS. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol, 16:990-998, 2015

20. Takahashi A, Ishii G, Neri S, Yoshida T, Hashimoto H, Suzuki S, Umemura S, Matsumoto S, Yoh K, Niho S, Goto K, Ohmatsu H, Nagai K, Gemma A, Ohe Y, Ochiai A. Podoplanin-expressing cancer-associated fibroblasts inhibit small cell lung cancer growth. Oncotarget, 6:9531-9541, 2015

21. Watanabe N, Niho S, Kirita K, Umemura S, Matsumoto S, Yoh K, Ohmatsu H, Goto K. Second-line docetaxel for patients with platinum-refractory advanced non-small cell lung cancer and interstitial pneumonia. Cancer Chemother Pharmacol, 76:69-74, 2015

22. Watanabe N, Niho S, Kirita K, Umemura S, Matsumoto S, Yoh K, Ohmatsu H, Goto K. Vinorelbine and cisplatin in patients with advanced non-small cell lung cancer with interstitial pneumonia. Anticancer Res, 35:1697-1701, 2015

Department of Esophageal Surgery

Hiroyuki Daiko, Takeo Fujita

Introduction

The Esophageal Surgery Division deals with neoplasms arising from the esophagus. The surgical management of esophageal cancer has been the main clinical as well as research activity of this Division. In particular, the Division is striving to establish minimally invasive surgery that consists of neoadjuvant treatment followed by minimally invasive esophagectomy. The Division is conducting a study to define the role of surgery in the multimodal approach to the treatment of esophageal cancer, and is aiming for thoracolaparoscopic esophagectomy, which consists of thoracoscopic esophagectomy and laparoscopic reconstruction, to become a standard surgical procedure.

Routine activities

The Esophageal Surgery Division consists of two staff surgeons and four residents. An Esophageal Conference is held every Tuesday evening to discuss the diagnosis, staging, and treatment strategy for each patient and is attended by surgeons, medical oncologists, endoscopists, radiologists, radiation oncologists, and head and neck surgeons. Approximately four patients are operated upon every week. In 2014, 153 patients underwent esophagectomies. Transthoracic esophagectomies with extended lymph node dissection were performed on 39 non-treated cases. Thoracoscopic esophagectomies in the prone position with radical lymph node dissection were undertaken in 114 cases. A two-stage surgical procedure divided into resection and reconstruction for patients more than 80 years old or patients with multiple complications was undertaken in 12 cases. Postoperatively, within 30 days, 1 patient died due to complications after a salvage operation.

Clinical activities

Currently, the Division is examining the role of thoracolaparoscopic esophagectomy as a minimally invasive esophagectomy that consists of thoracoscopic esophagectomy and laparoscopic reconstruction. For patients without radical chemoradiotherapy, thoracoscopic esophagectomy in the prone position with radical lymph node dissection and laparoscopic reconstruction after esophagectomy for patients without a history of laparotomy are being attempted to become a standard surgical procedure for esophageal cancer.

For treating patients aged over 80 years or at high risk, a two-stage surgical procedure divided into resection and reconstruction is being attempted.

A randomized controlled phase III study comparing Cisplatin and 5-fluorouracil versus Cisplatin and 5-fluorouracil plus Docetaxel versus Cisplatin and 5-fluorouracil concurrent radiation as a neoadjuvant treatment for locally advanced esophageal cancer is ongoing.

A randomized controlled phase III study of minimally invasive versus open esophagectomy for thoracic esophageal cancer (JCOG1409, MONET trial) is ongoing.

Since 2000, the Division has started to perform salvage surgery for patients in whom definitive chemoradiotherapy has failed. The operative procedures and postoperative management have been refined gradually. The Division is also studying the role and efficacy of salvage surgery in the multimodal treatment of esophageal cancer.

Table 1. Type of Procedure

One-stage operation	141
Two-stage operation	12
Total number of esophagectomies	153
Rt-Transthoracic Esophagectomy	39
Thoracoscopic Esophagectomy	114
Others	35
Total	188

List of papers published in 2015

Journal

1. Fujita T, Daiko H. Optimal duration of prophylactic antimicrobial administration and risk of postoperative infectious events in thoracic esophagectomy with three-field lymph node dissection: short-course versus prolonged antimicrobial administration. Esophagus, 12:38-43, 2015

2. Daiko H, Fujita T. Laparoscopic assisted versus open gastric pull-up following thoracoscopic esophagectomy: A cohort study. Int J Surg, 19:61-66, 2015

3. Nozaki I, Kato K, Igaki H, Ito Y, Daiko H, Yano M, Udagawa H, Mizusawa J, Katayama H, Nakamura K, Kitagawa Y. Evaluation of safety profile of thoracoscopic esophagectomy for T1bN0M0 cancer using data from JCOG0502: a prospective multicenter study. Surg Endosc, 29:3519-3526, 2015

Department of Gastric Surgery

Takahiro Kinoshita, Hidehito Shibasaki, Akio Kaito, Toshirou Nishida, Takuya Hamakawa

Introduction

Our Division consists of three staff surgeons, one senior resident and six junior resident surgeons. Our managing of tumors includes common gastric adenocarcinoma, adenocarcinoma of the esophagogastric junction (AEG: Siewert type 2/3), and gastric submucosal tumors (GIST, etc.). Annually, 260-300 patients are operated on either by means of open surgery or laparoscopic surgery. Laparoscopic gastrectomy with radical node dissection was introduced in 2010, and now our department is one of the leading institutions in Japan. In 2014, about 80% of gastrectomies were performed under laparoscopy, and also robot-assisted surgery has been done as an advanced medical service system (endorsed by the government). The basis of our surgery is radical extirpation of cancer lesions, but at the same time, organ functions and better quality of life (QOL) should be maintained. In addition, we strive to obtain better clinical outcomes for patients with diseases with dismal prognoses (type 4 gastric cancer or with progressive metastasis) by surgery combined with a modern chemotherapy regimen, including molecular-targeting drugs in cooperation with medical oncologists.

Routine activities

Usually 12-14 patients are hospitalized and five to seven patients undergo operations per week. A clinical conference of our Division is held once a week to decide our treatment strategy. Further, a conference with internal medicine is held every Monday evening with doctors of the Department of Diagnostic Radiology, Gastrointestinal Endoscopy, and Gastrointestinal Oncology, discussing the accurate diagnosis of the patients with gastric tumors to decide the optimal treatment method for each patient. Every Tuesday morning, a small conference is held with medical oncologists to discuss border-line cases. In principle, patients with low-risk superficial gastric cancer lesions (cT1a) are treated by endoscopic submucosal dissection (ESD) following the criteria of the guideline. Some are required to undergo subsequent completion laparoscopic surgery with nodal dissection based on pathological findings of specimens obtained by ESD. Laparoscopic surgery covers distal, proximal, pylorus-preserving, and total gastrectomy. D2 dissection can also be done under laparoscopy, and its applicability for advanced cancer is under investigation. When the tumor infiltrates to adjacent organs, sometimes extended operations are chosen. Recently, due to the progress of modern chemotherapy regimen, down-staging from cStageIV is sometimes seen. For such patients, we selectively perform conversion surgery to achieve favorable outcomes. For AEGs, the transhiatal approach can be safely employed under laparoscopy with a better surgical view.

Research activities

We aggressively publish our clinical research data in domestic or international congresses. In addition, we participate in multi-institutional clinical trials conducted by the Japan Clinical Oncology Group (JCOG) – Gastric Surgery Study Group or other organizations. Patients with gastric cancer are, if eligible for each study, invited to take part in one of the ongoing clinical trials.

Clinical trials

The list of clinical trials in which we participated in 2015 is as below.

1) JCOG 1104 A phase II trial to define the optimal period of adjuvant S-1 chemotherapy for pathological stage II gastric cancer patients who underwent D2 gastrectomy

2) JCOG 1401 Nonrandomized confirmatory study of laparoscopic total/proximal gastrectomy for clinical stage I gastric cancer
3) A prospective study to evaluate safety, feasibility and economy of robot-assisted radical gastrectomy using da Vinci Surgical System (DVSS) (advanced medical service)
4) JLSSG 0901 A phase III randomized trial comparing open and laparoscopic distal gastrectomy for clinical stage II/III gastric cancer
5) A prospective randomized phase II trial comparing circular and linear stapled esophagojejunostomy after laparoscopic total/proximal gastrectomy (cooperation with Osaka University)
6) A prospective cohort study to evaluate the proper extent of lymph node dissection for esophagogastric junction cancer

Education

Resident doctors are trained to be specialized surgical oncologists with sufficient techniques and knowledge. Nowadays, opportunities to perform laparoscopic and open surgery are simultaneously given to them. We also place importance on the education of surgeons of other institutions. In 2015, surgeons from domestic and foreign hospitals (from China, Korea, Philippine, Spain and Germany) visited our division to learn surgical techniques.

Future prospects

We will keep striving to obtain better survival outcomes for the patients with far advanced diseases; for multidisciplinary therapy (chemotherapy, molecular-target agents or immune check-point inhibitor), collaborating with medical oncologists is essential. Additionally, we will continue to develop less-invasive as well as high-quality surgical methods (laparoscopic or robotic surgery), to increase patients' QOL and realize complete cures. It is also our obligation to expand our knowledge and experience globally as one of the most main countries in terms of gastric cancer occurrence.

Table 1. Number of patients

Gastric cancer	256
Others (GIST, etc.)	25

Table 2. Type of procedure

Open gastrectomy	60
Distal Gastrectomy	25
Pylorus-preserving Gastrectomy	2
Proximal Gastrectomy	4
Total Gastrectomy	22
Pancreaticoduodenectomy	0
Partial Gastrectomy	2
Others (bypass, exploration, etc.)	5
Laparoscopic Surgery (robot-assisted surgery)	221 (7)
Distal Gastrectomy	116 (6)
Pylorus-preserving Gastrectomy	9
Proximal Gastrectomy	16
Total Gastrectomy	24 (1)
Partial Gastrectomy	8
Others (bypass, exploration, etc.)	48

List of papers published in 2015

Journal

1. Kinoshita T, Kinoshita T, Saiura A, Esaki M, Sakamoto H, Yamanaka T. Multicentre analysis of long-term outcome after surgical resection for gastric cancer liver metastases. Br J Surg, 102:102-107, 2015

2. Nishida T, Doi T, Naito Y. Tyrosine kinase inhibitors in the treatment of unresectable or metastatic gastrointestinal stromal tumors. Expert Opin Pharmacother, 15:1979-1989, 2015

3. Fujii S, Fujihara A, Natori K, Abe A, Kuboki Y, Higuchi Y, Aizawa M, Kuwata T, Kinoshita T, Yasui W, Ochiai A. TEM1 expression in cancer-associated fibroblasts is correlated with a poor prognosis in patients with gastric cancer. Cancer Med, 4:1667-1678, 2015

4. Takahashi T, Nakajima K, Miyazaki Y, Miyazaki Y, Kurokawa Y, Yamasaki M, Miyata H, Takiguchi S, Nishida T, Mori M, Doki Y. Surgical strategy for the gastric gastrointestinal stromal tumors (GISTs) larger than 5 cm: laparoscopic surgery is feasible, safe, and oncologically acceptable. Surg Laparosc Endosc Percutan Tech, 25:114-118, 2015

5. Yanagimoto Y, Takahashi T, Muguruma K, Toyokawa T, Kusanagi H, Omori T, Masuzawa T, Tanaka K, Hirota S, Nishida T. Re-appraisal of risk classifications for primary gastrointestinal stromal tumors (GISTs) after complete resection: indications for adjuvant therapy. Gastric Cancer, 18:426-433, 2015

6. Hirota M, Nakajima K, Miyazaki Y, Takahashi T, Kurokawa Y, Yamasaki M, Miyata H, Takiguchi S, Nishida T, Mori M, Doki Y. Clinical outcomes of laparoscopic partial gastrectomy for gastric submucosal tumors. Asian J Endosc Surg, 8:24-28, 2015

7. Joensuu H, Rutkowski P, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Braconi C, Bordoni A, Magnusson MK, Sufliarsky J, Federico M, Jonasson JG, Hostein I, Bringuier PP, Emile JF. KIT and PDGFRA mutations and the risk of GI stromal tumor recurrence. J Clin Oncol, 33:634-642, 2015

8. Takiguchi S, Fujiwara Y, Yamasaki M, Miyata H, Nakajima K, Nishida T, Sekimoto M, Hori M, Nakamura H, Mori M, Doki Y. Laparoscopic intraoperative navigation surgery for gastric cancer using real-time rendered 3D CT images. Surg Today, 45:618-624, 2015

9. Akamaru Y, Takahashi T, Nishida T, Omori T, Nishikawa K, Mikata S, Yamamura N, Miyazaki S, Noro H, Takiguchi S, Mori M, Doki Y. Effects of daikenchuto, a Japanese herb, on intestinal motility after total gastrectomy: a prospective randomized trial. J Gastrointest Surg, 19:467-472, 2015

10. Nishida T, Matsushima T, Tsujimoto M, Takahashi T, Kawasaki Y, Nakayama S, Omori T, Yamamura M, Cho H, Hirota S, Ueshima S, Ishihara H. Cyclin-Dependent Kinase Activity Correlates with the Prognosis of Patients Who Have Gastrointestinal Stromal Tumors. Ann Surg Oncol, 22:3565-3573, 2015

11. Komatsu Y, Doi T, Sawaki A, Kanda T, Yamada Y, Kuss I, Demetri GD, Nishida T. Regorafenib for advanced gastrointestinal stromal tumors following imatinib and sunitinib treatment: a subgroup analysis evaluating Japanese patients in the phase III GRID trial. Int J Clin Oncol, 20:905-912, 2015

12. Nishida T. The role of endoscopy in the diagnosis of gastric gastrointestinal stromal tumors. Ann Surg Oncol, 22:2810-2811, 2015

13. Maki RG, Blay JY, Demetri GD, Fletcher JA, Joensuu H, Martín-Broto J, Nishida T, Reichardt P, Schöffski P, Trent JC. Key Issues in the Clinical Management of Gastrointestinal Stromal Tumors: An Expert Discussion. Oncologist, 20:823-830, 2015

14. Joensuu H, Martin-Broto J, Nishida T, Reichardt P, Schöffski P, Maki RG. Follow-up strategies for patients with gastrointestinal stromal tumour treated with or without adjuvant imatinib after surgery. Eur J Cancer, 51:1611-1617, 2015

15. Isosaka M, Niinuma T, Nojima M, Kai M, Yamamoto E, Maruyama R, Nobuoka T, Nishida T, Kanda T, Taguchi T, Hasegawa T, Tokino T, Hirata K, Suzuki H, Shinomura Y. A Screen for Epigenetically Silenced microRNA Genes in Gastrointestinal Stromal Tumors. PLoS One, 10:e0133754, 2015

16. Barrios CH, Blackstein ME, Blay JY, Casali PG, Chacon M, Gu J, Kang YK, Nishida T, Purkayastha D, Woodman RC, Reichardt P. The GOLD ReGISTry: a Global, Prospective, Observational Registry Collecting Longitudinal Data on Patients with Advanced and Localised Gastrointestinal Stromal Tumours. Eur J Cancer, 51:2423-2433, 2015

17. Natatsuka R, Takahashi T, Serada S, Fujimoto M, Ookawara T, Nishida T, Hara H, Nishigaki T, Harada E, Murakami T, Miyazaki Y, Makino T, Kurokawa Y, Yamasaki M, Miyata H, Nakajima K, Takiguchi S, Kishimoto T, Mori M, Doki Y, Naka T. Gene therapy with SOCS1 for gastric cancer induces G2/M arrest and has an antitumour effect on peritoneal carcinomatosis. Br J Cancer, 113:433-442, 2015

18. Komatsu Y, Ohki E, Ueno N, Yoshida A, Toyoshima Y, Ueda E, Houzawa H, Togo K, Nishida T. Safety, efficacy and prognostic analyses of sunitinib in the post-marketing surveillance study of Japanese patients with gastrointestinal stromal tumor. Jpn J Clin Oncol, 45:1016-1022, 2015

Department of Colorectal Surgery

Masaaki Ito, Akihiro Kobayashi, Yuji Nishizawa, Takeshi Sasaki, Norio Saito, Kenichi Koshi, Yuichiro Tsukada, Koji Ikeda, Naoki Sakuyama

Introduction

The Colorectal and Pelvic Surgery Division was established 17 years ago. Its main purpose is to bring together the Divisions that are composed of colorectal surgeons and urologists. Cooperation between these Divisions contributes not only to the establishment of effective operative techniques but also to an oncological consensus including consensus on the quality of life (QOL) and the various functions of patients with pelvic malignancies. New surgical procedures, such as nerve-sparing surgery, sphincter-saving surgery, bladder-sparing surgery, pouch surgery and minimally invasive surgery are being developed to prevent postoperative dysfunctions. These new approaches will contribute to better curability and QOL among patients with pelvic malignancies

Routine activities

The Department of Colorectal Surgery comprises 6 consultants (four colorectal surgeons and two urologists) and 11 residents. The outpatient clinic is open five days a week. More than 360 new patients with colorectal carcinomas and more than 150 new patients with other pelvic malignancies visited this Department during the last year. Treatment plans are discussed at a weekly conference on GI malignancies and at another weekly conference on pelvic malignancies. Many treatment modalities, such as local excision with or without adjuvant chemo- or radiotherapy and other minimally invasive forms of surgery using laparoscopy, have been introduced for the treatment of patients in the early stages of cancer. Laparoscopy-assisted operations (Lap-Ops) with wider lymphadenectomy of up to more than D2 are also increasingly being performed in patients with advanced colorectal carcinomas. Abdominoperineal resection (APR) has, in the past, been the standard surgery in patients with very low rectal cancer; however, partial anal sphincter preserving surgery such as intersphincteric resection (ISR) and direct CAA have been performed in more than 500 patients with very low rectal tumors and has resulted in cure, preservation of anal function, and better QOL.

Research activities

1) A prospective randomized trial for extending the indications for Lap-Op (JCOG0404 CRC Surg-LAP vs. Open). A total of 77 patients have been registered in this Department. This study has been completed.
2) Intersphincteric resection with or without neoadjuvant mFOLFOX6 study (NAIR Study)- A prospective multi-center trial -A Phase II/III randomized multicenter trial of intersphincteric resection (ISR) with or without preoperative chemotherapy for very low-lying rectal cancer. APR has been the standard surgery for very low rectal cancer located within five cm of the anal verge. However, a permanent colostomy causes severe impairment of QOL. This study was designed to evaluate the feasibility and the oncological and functional outcomes of ISR for treatment of very low rectal cancer. Curability with ISR was verified histologically, and acceptable oncological and functional outcomes were obtained in many patients. However, patients need to be informed preoperatively regarding the potential functional adverse effects after ISR. This study is in progress, and 50 patients have been registered.
3) Bladder-sparing surgery for locally advanced rectal cancer involving the prostate. Total pelvic exenteration (TPE) is the standard procedure in such patients. This study aims to evaluate

the feasibility of bladder-sparing surgery as an alternative to TPE. This procedure has been performed in 39 patients with primary or recurrent tumors and permits conservative surgery in selected patients with advanced rectal cancer involving the prostate without compromising local control. The QOL of these patients appears to be better. Evaluation on usefulness and safety of cysto-urethral anastomosis with additional ileal flap in patients with rectal cancer involving the prostate (Ileal flap study) is also in progress.

4) A prospective randomized trial for the feasibility and effect of lateral node dissection in low rectal cancer – (Total) Mesorectal Excision (ME) vs. Lateral Node Dissection with preservation of autonomic nerves (D3 with nerve-sparing) [JCOG0212 CRC Surg.]. In this study, 76 patients have been registered.
5) Local excision with postoperative chemoradiotherapy for T1・T2 rectal cancer. This study aims to evaluate preoperatively the feasibility and the oncologic outcome of local therapy for T1 and a part of T2 rectal cancer without lymph node metastases. In this study, 82 patients have been registered.
6) A prospective cohort study of Reduced Port Surgery for colorectal cancer. Registration of this study is closed.
7) Study on Robotic surgery for rectal cancer. This study is currently in progress.

Clinical trials

Other clinical trials are also in progress as follows:

- A Phase I/II trial of chemoradiotherapy concurrent with S-1 plus MMC in patients with clinical stage II/III squamous cell carcinoma of the anal canal (JCOG0903)
- A randomized study of conventional technique vs. no-touch isolation technique (JCOG1006)
- A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer (JCOG1007)
- A randomized Phase III study of mFOLFOX7 or CAPOX plus bevacizumab versus 5-fluorouracil/leucovorin or capecitabine plus bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer (JCOG1018)
- A randomized controlled trial comparing laparoscopic surgery with open surgery in palliative resection of primary tumor in incurable Stage IV colorectal cancer (JCOG1107)
- A Prospective Phase II Trial of Laparoscopic Surgery for Ultra-low Rectal Cancers within Five Centimeters from the Anus or Three Centimeters from the Dentate Line. Under the Japanese Society for Cancer of the Colon and Rectum (JSCCR)
- A prospective study of urinary and sexual dysfunction after surgery for rectal cancer
- A Phase II study of neoadjuvant mFOLFOX6 (+ cetuximab) in patients with resectable pelvic recurrences after rectal cancer surgery
- T-REX Study; the International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer (JSCCR)
- Development of LAP-instruments for colorectal surgery

Education

- Guiding university students in their studies
- Guiding colorectal surgeons for obtaining medical specialist

Future prospects

Establishment of less-invasive surgery for curing and function-preserving in cancer patients with colorectal malignances.

Table 1. Number of priniary colorectal patients (2015.1-2015.12)

Primary colorectal canter			Other cases
Colon	Rectum	Sub-total	
170	226	396	179

Table 2. Type of procedure

Operative Procedures (2015.1-2015.12)

Colon N=170 Laparoscopic (LAP): 146 Open: 24		
Sigmoidectomy	62	(LAP: 60)
	54	(LAP: 52)
Ileocecal resection	21	(LAP: 17)
Limited colectomy	14	(LAP: 10)
Hartmann procedure	1	
Low anterior resection	1	(LAP: 1)
Left (hemi) colectomy	5	(LAP: 4)
Stoma	7	
Others	5	(LAP: 2)

Rectum N=226 Laparoscopic (LAP): 188	Robot: 7	Open: 31	
Low anterior resection	99	(LAP: 87)	(Robot: 6)
Intersphincteric resection (ISR)	56	(LAP: 53)	
High anterior resection	24	(LAP: 23)	(Robot: 1)
Abdominoperineal resection (APR)	22	(LAP: 20)	
Hartmann procedure	4	(LAP: 3)	
Local excision	2		
Total pelvic exenteration	1		
Stoma	12		
Others	6	(LAP: 2)	

Table 3. Survival rates

Stage	Colon			Rectum		
	No. of pts	5-yr survival (%)		No. of pts	5-yr survival (%)	
		Overall	Cancer specific		Overall	Cancer specific
Stage 0	10	100	100	14	100	100
Stage Ⅰ	210	95.2	100	171	93.6	97.6
Stage Ⅱ	286	90.3	84.8	215	84.5	89.4
Stage Ⅲa	194	82.1	86.5	179	79.3	82.0
Stage Ⅲb	63	71.9	74.5	123	60.5	64.1
Stage Ⅳ	167	22.0	23.2	102	23.8	24.0

OP: 2000.1.1-2007.12

List of papers published in 2015

Journal

1. Shiomi A, Ito M, Maeda K, Kinugasa Y, Ota M, Yamaue H, Shiozawa M, Horie H, Kuriu Y, Saito N. Effects of a diverting stoma on symptomatic anastomotic leakage after low anterior resection for rectal cancer: a propensity score matching analysis of 1,014 consecutive patients. J Am Coll Surg, 220:186-194, 2015

2. Kawai T, Shin M, Nishizawa Y, Horise Y, Nishikawa A, Nakamura T. Mobile locally operated detachable end-effector manipulator for endoscopic surgery. Int J Comput Assist Radiol Surg, 10:161-169, 2015

3. Ohue M, Hamaguchi T, Ito Y, Sakai D, Noura S, Kinugasa Y, Fujita S, Shimada Y, Saito N, Moriya Y. A phase I trial of preoperative S-1 in combination with oxaliplatin and pelvic radiation for lower rectal cancer with T4 and lateral pelvic lymph node metastasis. Int J Clin Oncol, 20:338-344, 2015

4. Kobayashi S, Ito M, Yamamoto S, Kinugasa Y, Kotake M, Saida Y, Kobatake T, Yamanaka T, Saito N, Moriya Y. Randomized clinical trial of skin closure by subcuticular suture or skin stapling after elective colorectal cancer surgery. Br J Surg, 102:495-500, 2015

5. Yokota M, Kojima M, Higuchi Y, Nishizawa Y, Kobayashi A, Ito M, Saito N, Ochiai A. Spread of tumor microenvironment contributes to colonic obstruction through subperitoneal fibroblast activation in colon cancer. Cancer Sci, 106:466-474, 2015

6. Yokota M, Kobayashi A, Nomura S, Nishizawa Y, Ito M, Nagai K, Saito N. Patterns and treatment of recurrence following pulmonary resection for colorectal metastases. World J Surg, 39:1758-1766, 2015

7. Kondo A, Nishizawa Y, Akamoto S, Fujiwara M, Okano K, Suzuki Y. Internal inguinal hernia on the transplant side after kidney transplantation: a case report. Surg Case Rep, 1:108, 2015

Department of Gastrointestinal Oncology

Takayuki Yoshino, Atsushi Ohtsu, Toshihiko Doi, Takashi Kojima, Kouhei Shitara, Hideaki Bando, Yasutoshi Kuboki, Nozomu Fuse, Ken Hatogai, Sawako Miyoshi, Shota Fukuoka

Introduction

In 2015, approximately 650 gastrointestinal (GI) cancer patients were treated by staff oncologists and skilled residents in the Department of GI Oncology, which focuses on optimal chemotherapy W/ or W/O radiation for the treatment of GI cancers.

Routine activities

The Inter-Divisional tumor board conferences with the Surgical/Radiation Oncology Divisions are held regularly to review the current treatment for each patient and to discuss further treatment strategies. Basically, routine chemotherapy is done on an outpatient basis, and there are approximately 1,900 selected patients who need hospitalization for the purpose of planned therapy with chemotherapy or palliation. Our activities for each type of GI cancer in 2015 are shown in Table 1 (Number), Table 2 (Treatment), and Table 3 (Efficacy). There are ongoing clinical trials that consist of 45 Phase I trials including globally first-in-class (FIC), first-in-human (FIH), investigational new drugs (INDs) and 30 Phase II/III clinical trials to approve the INDs.

Research activities

Phase I

Our Department has focused more on early-stage clinical development of INDs. The number of patients enrolled for Phase I trials has been increasing recently. Importantly, the number of FIH trials and trials around the same time as Western countries is increasing. Several results of phase I trials, such as the oral pan-AKT inhibitor (MK-2206), LY2603618, a CHK1 inhibitor, in combination with gemcitabine, TAS-114, a dUTPase inhibitor in combination with S-1, and VEGF receptor/MET-targeted kinase inhibitor (TAS-115), were published or presented at international meetings.

Esophageal Cancer (EC)

A prognostic or predictive biomarker study in patients who underwent surgery or received chemoradiotherapy for clinical stage I esophageal squamous cell carcinoma (JCOG0502-AI) was completed. The results of the phase I/II trial of chemoradiotherapy with concurrent S-1 and cisplatin for clinical stage II/III esophageal carcinoma (JCOG 0604) was published. And the sub-analysis of the JCOG9907 study for the accuracy of preoperative diagnosis of lymph node metastasis and prognostic Factors in Patients Receiving Neoadjuvant 5-Fluorouracil plus Cisplatin for Advanced Esophageal Cancer were published.

Gastric Cancer (GC)

The results of a global randomized phase III trial comparing 2nd-line chemotherapy with ado-trastuzumab emtansine (T-DM1), an antibody-drug conjugate (ADC) for HER2 and taxanes agents for advanced GC were presented in ASCO-GI 2016. The phase II study of adjuvant chemotherapy of S-1 plus oxaliplatin for patients with stage III gastric cancer after D2 gastrectomy was published. Several sponsored-initiated trials to evaluate molecular targeting agents as well as immune checkpoint inhibitors are currently ongoing. An investigator-initiated trial of the phase 1 trial of sulfasalazine (SSZ), which targets cancer stem-like cell fraction, plus cisplatin for CD44v gastric cancer which refractory to cisplatin finished its enrollment. Results of comprehensive molecular profiling of advanced GC using next generation sequencing and immunohistochemistry were also published, which identified several possible candidate genes that could be targets for precision medicine. Since September 2015, we have initiated an immune monitoring study to evaluate several

immunological properties such as classification of lymphocyte or expression of immune checkpoint in tumor infiltrating lymphocyte and peripheral blood mononuclear cell (PBMC) before and after treatment, which will hopefully lead to personalized therapy in the field of immune therapy.

Colorectal Cancer (CRC)

We have established the SCRUM-Japan GI-SCREEN 2013-01-CRC (UMIN000016343), which is the nationwide cancer genome screening project by using the Oncomine Cancer Research Panel. We also started GI-SCREEN CRC-MSI, which is the multi-center project for screening the microsatellite instability (MSI) status of Japanese CRC patients. Based on the screening system of GI-SCREEN 2013-01-CRC, we are currently planning the investigator-initiated clinical trials for patients with BRAF non-V600E mutations, HER2 amplifications, and high tumor-infiltrating lymphocytes (TILs). The clinical evaluation study of cell-free DNA-based RAS gene testing by using BEAMing technology will soon be started.

Clinical trials

Esophageal Cancer (EC)

The phase III study comparing preoperative CDDP+5-FU (CF) versus docetaxel+CF versus CF-radiation followed by esophagectomy with D2-3 lymphadenectomy for locally advanced esophageal squamous cell cancer (JCOG1109) and the phase III study comparing docetaxel, CDDP and 5-FU with CDDP and 5-FU in patients with metastatic or recurrent esophageal cancer (JCOG1314) is ongoing. A multicenter phase I study of HSP105-derived peptide vaccine for patients with advanced esophageal cancer/colorectal cancer and phase II trial of BKM120 in patients with advanced esophagus cancer is ongoing. As in the single institutional clinical study, the phase II trial of definitive chemoprotontherapy in patients with clinical stage I/II/III esophageal carcinoma is ongoing.

Gastric Cancer (GC)

The results of the GATSBY trial, which compared 2nd-line T-DM1 and taxanes agents for HER2 positive gastric cancer, was presented in ASCO-GI 2016, which could not meet its primary endpoint. The enrollment for a multicenter global trial (JACOB) of pertuzumab was completed. Multicenter global phase III trials of molecular targeting agents (ENRICH, BRIGHTER) are ongoing. Several phase 2 or 3 trials to evaluate the efficacy of an anti-PD1 antibody are also ongoing (KEYNOTE-59, 61 and 62). Several phase I or II studies of newer agents including c-MET tyrosine kinase inhibitor of MET high GC, FGFR-inhibitor for FGFR high GC as well as combination therapy of immune checkpoint inhibitors are ongoing. Several investigator-initiated trials of a multicenter phase III trial comparing DCS to cisplatin plus S-1 (JCOG 1013), a multicenter phase II trial comparing 12 months of S-1 to 6 months of S-1 as an adjuvant chemotherapy (JCOG 1104) are ongoing. After confirmation of the mode of action of SSZ as a cancer stem cell inhibitor, a phase 1 trial of SSZ in combination with cisplatin for cisplatin refractory GC patients was also conducted.

Colorectal Cancer (CRC)

The results of a global randomized phase III trial comparing TAS-102 to best supportive care (RECOURSE) were published in the New England Journal of Medicine. We have completed the phase 1b/2 trial of the novel combination of TAS-102 plus bevacizumab as an investigator-initiated trial (IIT). The patients' registration of an international phase III trial, which investigates the survival benefits of the oral multi-target kinase inhibitor nintedanib with placebo in a salvage setting (LUME-COLON 1), were finished. We are participating in two different international phase 1b/2 trials that target patients with BRAF V600E mutated CRC, of which results were reported in the ESMO World Congress on Gastrointestinal Cancer 2015. We are now recruiting the phase 1b/2 trial of the novel combination of TAS-102 plus nintedanib as an IIT. The phase II and III clinical trials of the immune checkpoint inhibitor pembrolizumab, for patients with deficiency in mismatch repair (KEYNOTE-164, KEYNOTE-177), are ongoing. We have conducted two randomized, multicenter, phase III studies called ACHIEVE and ACHIEVE-2 trials, together with other collaborative

groups in the US, UK/Australia, Italy, Greece and France.

Education

Our residents learn the latest evidence-based medicine and apply this knowledge pragmatically to enhance care for patients with GI cancers, and eventually obtain qualifications as comprehensive GI oncologists through daily practice and direct training from our staff. Accordingly, our staff actively provide a wealth of valuable opportunities to polish their skills regarding various chemotherapies, especially in collaboration with the Department of Experimental Therapeutics as well as diagnostic and therapeutic endoscopies in collaboration with the Department of Digestive Endoscopy. We regularly held tumor-related board meetings and frequently have numerous face-to-face meetings with experts in different specialties. We instruct them how to conduct valuable clinical trials, how to have the chance to attend international academic conferences, and the best way to present academic meetings and work on many high-impact articles in scholarly journals. To date, our department has helped many residents to become 'true' skilled GI oncologists who play major roles at leading cancer centers across the country.

Future prospects

We continue to provide the best treatment for cancer patients, the best education for residents, and aim to perform the following activities:

1) To provide the latest, cutting-edge medicine to cancer patients and to foster the next generation of skilled GI oncologists.
2) To achieve medical innovation in Japan, we aim to play leading roles in the clinical developments of INDs by contributing to various types of clinical trials including FIC, FIH early trials, IITs with proof-of-concept, and international clinical trials.
3) To enhance our research activities, we will establish research networks with cutting-edge researchers in Japan as well as globally.

Table 1. Number of new patients

Esophageal	328
Gastric	240
Colorectal	335
Other type of tumors	58
Total	961

Table 2. Treatment

Esophageal Cancer	Chemotherapy (include CRT*)	185
Gastric Cancer	Chemotherapy	175
Colorectal Cancer	Chemotherapy	317

List of papers published in 2015

Journal

1. Fujii S, Fujihara A, Natori K, Abe A, Kuboki Y, Higuchi Y, Aizawa M, Kuwata T, Kinoshita T, Yasui W, Ochiai A. TEM1 expression in cancer-associated fibroblasts is correlated with a poor prognosis in patients with gastric cancer. Cancer Med, 4:1667-1678, 2015

2. Komatsu Y, Doi T, Sawaki A, Kanda T, Yamada Y, Kuss I, Demetri GD, Nishida T. Regorafenib for advanced gastrointestinal stromal tumors following imatinib and sunitinib treatment: a subgroup analysis evaluating Japanese patients in the phase III GRID trial. Int J Clin Oncol, 20:905-912, 2015

3. Bando H, Takebe N. Recent innovations in the USA National Cancer Institute-sponsored investigator initiated Phase I and II anticancer drug development. Jpn J Clin Oncol, 45:1001-1006, 2015

4. Doi T, Tamura K, Tanabe Y, Yonemori K, Yoshino T, Fuse N, Kodaira M, Bando H, Noguchi K, Shimamoto T, Ohtsu A. Phase 1 pharmacokinetic study of the oral pan-AKT inhibitor MK-2206 in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:409-416, 2015

5. Doi T, Yoshino T, Shitara K, Matsubara N, Fuse N, Naito Y, Uenaka K, Nakamura T, Hynes SM, Lin AB. Phase I study of LY2603618, a CHK1 inhibitor, in combination with gemcitabine in Japanese patients with solid tumors. Anticancer Drugs, 26:1043-1053, 2015

6. Kawazoe A, Shitara K, Fukuoka S, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yamanaka T, Doi T, Ohtsu A, Yoshino T. A retrospective observational study of clinicopathological features of KRAS, NRAS, BRAF and PIK3CA mutations in Japanese patients with metastatic colorectal cancer. BMC Cancer, 15:258, 2015

7. Kawazoe A, Shitara K, Fukuoka S, Noguchi M, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yoshino T, Ohtsu A, Doi T. Clinical outcomes in 66 patients with advanced gastric cancer treated in phase I trials: the NCCHE experience. Invest New Drugs, 33:664-670, 2015

8. Yoshino T, Yamazaki K, Gotoh M, Nasroulah F, Gao L, Yoshizuka N, Ohtsu A. Safety and Pharmacokinetics of Second-line Ramucirumab plus FOLFIRI in Japanese Patients with Metastatic Colorectal Carcinoma. Anticancer Res, 35:4003-4007, 2015

9. Yoshino T, Muro K, Yamaguchi K, Nishina T, Denda T, Kudo T, Okamoto W, Taniguchi H, Akagi K, Kajiwara T, Hironaka S, Satoh T. Clinical Validation of a Multiplex Kit for RAS Mutations in Colorectal Cancer: Results of the RASKET (RAS KEy Testing) Prospective, Multicenter Study. EBioMedicine, 2:317-323, 2015

10. Hecht JR, Mitchell EP, Yoshino T, Welslau M, Lin X, Chow Maneval E, Paolini J, Lechuga MJ, Kretzschmar A. 5-Fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) plus sunitinib or bevacizumab as first-line treatment for metastatic colorectal cancer: a randomized Phase IIb study. Cancer Manag Res, 7:165-173, 2015

11. Kondoh C, Shitara K, Nomura M, Takahari D, Ura T, Tachibana H, Tomita N, Kodaira T, Muro K. Efficacy of palliative radiotherapy for gastric bleeding in patients with unresectable advanced gastric cancer: a retrospective cohort study. BMC Palliat Care, 14:37, 2015

12. Kotaka M, Yoshino T, Oba K, Shinozaki K, Touyama T, Manaka D, Matsui T, Ishigure K, Hasegawa J, Inoue K, Goto K, Sakamoto J, Saji S, Ohtsu A, Watanabe T. Initial safety report on the tolerability of modified FOLFOX6 as adjuvant therapy in patients with curatively resected stage II or III colon cancer (JFMC41-1001-C2: JOIN trial). Cancer Chemother Pharmacol, 76:75-84, 2015

13. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A, RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med, 372:1909-1919, 2015

14. Oh DY, Doi T, Shirao K, Lee KW, Park SR, Chen Y, Yang L, Valota O, Bang YJ. Phase I Study of Axitinib in Combination with Cisplatin and Capecitabine in Patients with Previously Untreated Advanced Gastric Cancer. Cancer Res Treat, 47:687-696, 2015

15. Saito T, Kondo C, Shitara K, Ito Y, Saito N, Ikehara Y, Yatabe Y, Yamamichi K, Tanaka H, Nakanishi H. Comparison of intratumoral heterogeneity of HER2 expression between primary tumor and multiple organ metastases in gastric cancer: Clinicopathological study of three autopsy cases and one resected case. Pathol Int, 65:309-317, 2015

16. Satake H, Yano T, Muto M, Minashi K, Yoda Y, Kojima T, Oono Y, Ikematsu H, Aoyama I, Morita S, Miyamoto S, Fujii S, Yoshizawa A, Ochiai A, Hayashi R, Kaneko K. Clinical outcome after endoscopic resection for superficial pharyngeal squamous cell carcinoma invading the subepithelial layer. Endoscopy, 47:11-18, 2015

17. Tabernero J, Lenz HJ, Siena S, Sobrero A, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Yoshino T, Goldberg RM, Sargent DJ, Wagner A, Laurent D, Teufel M, Jeffers M, Grothey A, Van Cutsem E. Analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer: a retrospective, exploratory analysis of the CORRECT trial. Lancet Oncol, 16:937-948, 2015

18. Tabernero J, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, Ciuleanu TE, Portnoy DC, Van Cutsem E, Grothey A, Prausová J, Garcia-Alfonso P, Yamazaki K, Clingan PR, Lonardi S, Kim TW, Simms L, Chang SC, Nasroulah F, RAISE Study Investigators. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol, 16:499-508, 2015

19. Takahashi H, Kaniwa N, Saito Y, Sai K, Hamaguchi T, Shirao K, Shimada Y, Matsumura Y, Ohtsu A, Yoshino T, Doi T, Takahashi A, Odaka Y, Okuyama M, Sawada J, Sakamoto H, Yoshida T. Construction of possible integrated predictive index based on EGFR and ANXA3 polymorphisms for chemotherapy response in fluoropyrimidine-treated Japanese gastric cancer patients using a bioinformatic method. BMC Cancer, 15:718, 2015

20. Takebe N, Miele L, Harris PJ, Jeong W, Bando H, Kahn M, Yang SX, Ivy SP. Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update. Nat Rev Clin Oncol, 12:445-464, 2015

21. Taniguchi H, Yamazaki K, Yoshino T, Muro K, Yatabe Y, Watanabe T, Ebi H, Ochiai A, Baba E, Tsuchihara K, Japanese Society of Medical Oncology. Japanese Society of Medical Oncology Clinical Guidelines: RAS (KRAS/NRAS) mutation testing in colorectal cancer patients. Cancer Sci, 106:324-327, 2015

22. Ueda S, Satoh T, Gotoh M, Gao L, Doi T. A phase ib study of safety and pharmacokinetics of ramucirumab in combination with paclitaxel in patients with advanced gastric adenocarcinomas. Oncologist, 20:493-494, 2015

23. Kurose K, Ohue Y, Wada H, Iida S, Ishida T, Kojima T, Doi T, Suzuki S, Isobe M, Funakoshi T, Kakimi K, Nishikawa H, Udono H, Oka M, Ueda R, Nakayama E. Phase Ia Study of FoxP3+ CD4 Treg Depletion by Infusion of a Humanized Anti-CCR4 Antibody, KW-0761, in Cancer Patients. Clin Cancer Res, 21:4327-4336, 2015

24. Yoshida M, Muro K, Tsuji A, Hamamoto Y, Yoshino T, Yoshida K, Shirao K, Miyata Y, Takahari D, Takahashi T, Ohtsu A. Combination chemotherapy with bevacizumab and S-1 for elderly patients with metastatic colorectal cancer (BASIC trial). Eur J Cancer, 51:935-941, 2015

25. Nishio M, Horiike A, Nokihara H, Horinouchi H, Nakamichi S, Wakui H, Ohyanagi F, Kudo K, Yanagitani N, Takahashi S, Kuboki Y, Yamamoto N, Yamada Y, Abe M, Tahata T, Tamura T. Phase I study of the anti-MET antibody onartuzumab in patients with solid tumors and MET-positive lung cancer. Invest New Drugs, 33:632-640, 2015

26. Yoshino T, Komatsu Y, Yamada Y, Yamazaki K, Tsuji A, Ura T, Grothey A, Van Cutsem E, Wagner A, Cihon F, Hamada Y, Ohtsu A. Randomized phase III trial of regorafenib in metastatic colorectal cancer: analysis of the CORRECT Japanese and non-Japanese subpopulations. Invest New Drugs, 33:740-750, 2015

27. Geva R, Vecchione L, Kalogeras KT, Jensen BV, Lenz HJ, Yoshino T, Paez D, Montagut C, Souglakos J, Cappuzzo F, Cervantes A, Frattini M, Fountzilas G, Johansen JS, Høgdall EV, Zhang W, Yang D, Yamazaki K, Nishina T, Papamichael D, Vincenzi B, Macarulla T, Loupakis F, De Schutter J, Spindler KL, Pfeiffer P, Ciardiello F, Piessevaux H, Tejpar S. FCGR polymorphisms and cetuximab efficacy in chemorefractory metastatic colorectal cancer: an international consortium study. Gut, 64:921-928, 2015

28. Nagatsuma AK, Aizawa M, Kuwata T, Doi T, Ohtsu A, Fujii H, Ochiai A. Expression profiles of HER2, EGFR, MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma. Gastric Cancer, 18:227-238, 2015

29. Nishida Y, Kuwata T, Nitta H, Dennis E, Aizawa M, Kinoshita T, Ohtsu A, Ochiai A. A novel gene-protein assay for evaluating HER2 status in gastric cancer: simultaneous analyses of HER2 protein overexpression and gene amplification reveal intratumoral heterogeneity. Gastric Cancer, 18:458-466, 2015

30. Osera S, Yano T, Odagaki T, Oono Y, Ikematsu H, Ohtsu A, Kaneko K. Peritonitis related to percutaneous endoscopic gastrostomy using the direct method for cancer patients. Surg Endosc, 29:2941-2946, 2015

31. Satoh T, Lee KH, Rha SY, Sasaki Y, Park SH, Komatsu Y, Yasui H, Kim TY, Yamaguchi K, Fuse N, Yamada Y, Ura T, Kim SY, Munakata M, Saitoh S, Nishio K, Morita S, Yamamoto E, Zhang Q, Kim JM, Kim YH, Sakata Y. Randomized phase II trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer. Gastric Cancer, 18:824-832, 2015

32. Shitara K, Ohtsu A. Ramucirumab for gastric cancer. Expert Rev Gastroenterol Hepatol, 9:133-139, 2015

33. Sasaki T, Fuse N, Kuwata T, Nomura S, Kaneko K, Doi T, Yoshino T, Asano H, Ochiai A, Komatsu Y, Sakamoto N, Ohtsu A. Serum HER2 levels and HER2 status in tumor cells in advanced gastric cancer patients. Jpn J Clin Oncol, 45:43-48, 2015

34. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishihara S, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Boku N, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K, Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol, 20:207-239, 2015

35. Doi T, Yoshino T, Fuse N, Boku N, Yamazaki K, Koizumi W, Shimada K, Takinishi Y, Ohtsu A. Phase I study of TAS-102 and irinotecan combination therapy in Japanese patients with advanced colorectal cancer. Invest New Drugs, 33:1068-1077, 2015

36. Nishina T, Kato T, Yamazaki K, Yoshino T, Miyata Y, Esaki T, Moriwaki T, Boku N, Hyodo I. A phase II study of S-1, oxaliplatin, oral leucovorin, and bevacizumab combination therapy (SOLA) in patients with unresectable metastatic colorectal cancer. Cancer Chemother Pharmacol, 76:547-553, 2015

37. Kataoka K, Tokunaga M, Mizusawa J, Machida N, Katayama H, Shitara K, Tomita T, Nakamura K, Boku N, Sano T, Terashima M, Sasako M, Stomach Cancer Study Group/Japan Clinical Oncology Group. A randomized Phase II trial of systemic chemotherapy with and without trastuzumab followed by surgery in HER2-positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1301 (Trigger Study). Jpn J Clin Oncol, 45:1082-1086, 2015

38. Mizutani T, Tanaka M, Eba J, Mizusawa J, Fukuda H, Hanaoka N, Takeuchi M, Aoyama I, Kojima T, Takizawa K, Ono H, Muto M, Gastrointestinal Endoscopy Study Group of the Japan Clinical Oncology Group (JCOG). A Phase III study of oral steroid administration versus local steroid injection therapy for the prevention of esophageal stricture after endoscopic submucosal dissection (JCOG1217, Steroid EESD P3). Jpn J Clin Oncol, 45:1087-1090, 2015

Department of Endoscopy

Kazuhiro Kaneko, Tomonori Yano, Hiroaki Ikematsu, Yasuhiro Oono

Introduction

The Department of Endoscopy covers the fields of the gastrointestinal (GI) tract and head and neck regions. In 2015, approximately 12,000 examinations and treatments were performed. This is the highest number to date. A narrow band imaging (NBI) system and/or Blue LASER imaging (BLI) system has been included for routine examination in six endoscopy rooms since September 2009. The BLI system was introduced in 2013. Furthermore, endoscopic treatments such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), percutaneous endoscopic gastrostomy (PEG), endoscopic balloon dilation (EBD), radial incision and cutting (RIC), and photodynamic therapy (PDT) have been performed.

In addition, research studies have been conducted in various fields: endoscopic diagnosis and treatment, or prevention for cancer patients in the GI tract and head and neck. Many of the research projects are conducted as prospective clinical studies either in a single institution or in collaboration with other institutions. The present research activities mainly focus on the development of new instruments for endoscopic diagnosis and new endoscopic treatment modalities. In addition, molecular biology research is also performed using blood and tissue samples of patients in order to examine strategies to enable the early detection, prevention, or prediction of prognosis for treatment. These projects are conducted in collaboration with not only commercial companies but also the faculties of Technology and Science in certain universities.

Routine activities

Routine endoscopic examinations including magnifying NBI and endoscopic ultrasound are presently used for head and neck, esophageal, gastric, and colorectal cancers, and the NBI or BLI systems have become essential in detecting very early cancers and precursor lesions in these areas. With the NBI or BLI systems, a differential diagnosis between neoplasia and non-neoplasia can be performed without the need for any dye solution. Double-balloon enteroscopy and capsule endoscopy are mainly performed for examinations of the small intestine. Follow-up examinations after endoscopic treatment and chemotherapy are also performed in many cases, in addition to routine examinations.

With the recent progress in instruments and techniques, the number of endoscopic treatments has been increasing. EMR is indicated routinely for early GI tract cancers, and ESD is basically used not only for gastric cancers but also for esophageal or colorectal cancers. For the colon and rectum, colonoscopic day surgeries such as polypectomy and EMR are currently performed in one-third of all examinations. Furthermore, EMR and PDT are sometimes indicated as salvage treatments for local residual/recurrent tumors after chemoradiotherapy for esophageal cancer. PEG and EBD are valuable supporting techniques during the treatment of patients with head and neck, and esophageal cancers.

Research activities

Furthermore, molecular biological analysis of cancers of the esophagus, head and neck, stomach, and colorectum is under way. Importantly, analysis of the genetic polymorphism in the genes coding for alcohol dehydrogenase (ADH 1B) and aldehyde dehydrogenase (ALDH 2) regarding alcohol metabolism is performed as a useful novel strategic approach in the prevention of upper aerodigestive tract cancers. In addition, the relationships between the production of acetaldehyde and oral microflora after consumption of alcohol are being investigated

in our study group.

In contrast, developing research into novel endoscopy systems is being performed. Hypoxia imaging is detected for neoplastic lesions of the head and neck and alimentary tracts, with blue visualized images. The first in-human clinical trial of hypoxia imaging was finished, and we are preparing pharmaceutical approval. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm. This system is capable of penetrating through the gastrointestinal wall and obtaining images utilizing various spectrums. Furthermore, molecular imaging endoscopy with some agents such as small molecules, peptides, antibodies and nanoparticles has been developed in collaborate with some universities. With a low-temperature atmospheric pressure plasma system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnosis system using photosensitizing agents, such as hypericin and 5ALA, has been constructed. Moreover, a new clinical trial of a biodegradable (BD) stent has been performed for patients with benign esophageal stricture after curative treatment, such as ESD, surgery, and chemoradiotherapy.

Clinical trials

A wide range of many prospective clinical trials is ongoing into the endoscopic treatment of cancers of the esophagus, stomach, and colorectum, as follows: clinical trial of hypoxia imaging for neoplasia of the alimentary tract in a single unit; a phase II clinical trial for BD stent implantation for benign esophageal stricture; a clinical trial for photodynamic diagnosis using 5ALA; multicenter clinical trials of a follow-up study after EMR of m1-3 esophageal cancers; a phase I/II study of PDT using Laserphyrin in residual/recurrent cases followed by chemoradiation for esophageal cancers; a multicenter clinical study for enrollment of early gastric cancer following endoscopic treatment for an enrollment system using the Web; a multicenter clinical trial of ESD for undifferentiated gastric cancer (JCOG1009); a randomized controlled phase II/III study comparing EBD combined with steroid versus RIC combined with steroid for refractory anastomotic stricture after esophagectomy (JCOG1207); a multicenter clinical study of a learning curve trial using NBI; a multicenter clinical study regarding residual/recurrent rates and observation periods of endoscopic piecemeal mucosal resection (EPMR) for colorectal neoplastic lesions; and the Japan Polyp Study (JPS) for determination of observation periods after endoscopic treatment for colorectal polyps.

Education

The aim is cultivation of human resources in specializing in endoscopic diagnosis and treatment for alimentary tract cancer. Staff supervise individual residents. The importance of positiveness is highlighted in periodic case conferences and joint conferences among internal medicine, surgery and radiology staff. Staff supervise academic congress presentations and writing manuscripts after deciding upon individual themes, and detailed discussion is undertaken in the department conference. For residents interested in development research, opportunities to study are supported after graduation.

Future prospects

Existing endoscopic diagnosis for neoplasia of the alimentary tract is performed on the basis of the morphological features of the tumor. Molecular imaging endoscopy is a novel system to visualize cancer using a specific laser source under phosphor combined with cancer-specific agents. We can obtain new imaging, since the function or metabolic state in cancer cells is visualized. In additional modalities, there are hypoxia imaging endoscopy, photodynamic diagnosis and endomicroscopy. These modalities, especially including near infrared light, are anticipated to be next generation endoscopy, and we will undertake innovative development to produce new endoscopy.

Table 1. Number of patients

Number of patients Examined in 2011-2015

Section	2011	2012	2013	2014	2015
Upper gastrointestinal endoscopy	6,350	6,647	6,846	6,825	7,309
Endoscopic ultrasonography	70	54	43	47	43
Endoscopic mucosal resection (esophagus)	181	168	220	196	196
Endoscopic mucosal resection (stomach)	205	215	203	218	185
Endoscopic balloon dilation	644	711	824	654	657
Percutaneous endoscopic gastrostomy	215	171	196	236	191
Photodynamic therapy (esophagus)	48	39	32	35	23
Colonoscopy	1,550	2,302	2,368	2,417	2,308
Polypectomy/EMR	800	912	832	903	906
Narrow Band Imaging (head and neck)	95	106	80	41	48
Endoscopic mucosal resection (head and neck)	41	46	52	49	105

EMR, Endoscopic mucosal resection including ESD.

Table 2. Endoscopic procedures in 2015

		2011	2012	2013	2014	2015
Esophagus	EMR	100	89	65	60	59
	ESD	45	79	155	136	137
Stomach	EMR	9	3	0	1	9
	ESD	202	212	203	217	172
Colon and rectum	EMR*	744	834	725	913	906
	ESD	17	78	98	92	107
Head and neck	EMR	6	7	1	0	3
	ESD	35	33	51	49	102

EMR , endoscopic mucosal resection; ESD, endoscopic submucosal dissection; *, including polypectomy

List of papers published in 2015

Journal

1. Osera S, Ikematsu H, Odagaki T, Oono Y, Yano T, Kobayashi A, Ito M, Saito N, Kaneko K. Efficacy and safety of endoscopic radial incision and cutting for benign severe anastomotic stricture after surgery for lower rectal cancer (with video). Gastrointest Endosc, 81:770-773, 2015

2. Zako T, Yoshimoto M, Hyodo H, Kishimoto H, Ito M, Kaneko K, Soga K, Maeda M. Cancer-targeted near infrared imaging using rare earth ion-doped ceramic nanoparticles. Biomater Sci, 3:59-64, 2015

3. Satake H, Yano T, Yoda Y, Fujii S, Zenda S, Tomioka T, Shinozaki T, Miyazaki M, Kaneko K, Hayashi R. Feasibility of salvage endoscopic resection for patients with locoregional failure after definitive radiotherapy for pharyngeal cancer. Endosc Int Open, 3:E274-E280, 2015

4. Zako T, Ito M, Hyodo H, Yoshimoto M, Watanabe M, Takemura H, Kishimoto H, Kaneko K, Soga K, Maeda M. Extra-luminal detection of assumed colonic tumor site by near-infrared laparoscopy. Surg Endosc, 2015

5. Takizawa K, Ono H, Yamamoto Y, Katai H, Hori S, Yano T, Umegaki E, Sasaki S, Iizuka T, Kawagoe K, Shimoda T, Muto M, Sasako M. Incidence of lymph node metastasis in intramucosal gastric cancer measuring 30 mm or less, with ulceration; mixed, predominantly differentiated-type histology; and no lymphovascular invasion: a multicenter retrospective study. Gastric Cancer, 2015

6. Ikematsu H, Matsuda T, Osera S, Imajoh M, Kadota T, Morimoto H, Sakamoto T, Oono Y, Kaneko K, Saito Y. Usefulness of narrow-band imaging with dual-focus magnification for differential diagnosis of small colorectal polyps. Surg Endosc, 29:844-850, 2015

7. Wada Y, Kudo SE, Tanaka S, Saito Y, Iishii H, Ikematsu H, Igarashi M, Saitoh Y, Inoue Y, Kobayashi K, Hisabe T, Tsuruta O, Kashida H, Ishikawa H, Sugihara K. Predictive factors for complications in endoscopic resection of large colorectal lesions: a multicenter prospective study. Surg Endosc, 29:1216-1222, 2015

8. Oka S, Tanaka S, Saito Y, Iishi H, Kudo SE, Ikematsu H, Igarashi M, Saitoh Y, Inoue Y, Kobayashi K, Hisabe T, Tsuruta O, Sano Y, Yamano H, Shimizu S, Yahagi N, Watanabe T, Nakamura H, Fujii T, Ishikawa H, Sugihara K, Colorectal Endoscopic Resection Standardization Implementation Working Group of the Japanese Society for Cancer of the Colon and Rectum, Tokyo, Japan. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. Am J Gastroenterol, 110:697-707, 2015

9. Kanesaka T, Uedo N, Yao K, Ezoe Y, Doyama H, Oda I, Kaneko K, Kawahara Y, Yokoi C, Sugiura Y, Ishikawa H, Kato M, Takeuchi Y, Muto M, Saito Y. A significant feature of microvessels in magnifying narrow-band imaging for diagnosis of early gastric cancer. Endosc Int Open, 3:E590-E596, 2015

10. Mochizuki S, Uedo N, Oda I, Kaneko K, Yamamoto Y, Yamashina T, Suzuki H, Kodashima S, Yano T, Yamamichi N, Goto O, Shimamoto T, Fujishiro M, Koike K, SAFE Trial Study Group. Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. Gut, 64:397-405, 2015

11. Daiko H, Fujita T, Ohgara T, Yamazaki N, Fujii S, Ohno Y, Yano T. Minimally invasive hybrid surgery combined with endoscopic and thoracoscopic approaches for submucosal tumor originating from thoracic esophagus. World J Surg Oncol, 13:40, 2015

12. Satake H, Yano T, Muto M, Minashi K, Yoda Y, Kojima T, Oono Y, Ikematsu H, Aoyama I, Morita S, Miyamoto S, Fujii S, Yoshizawa A, Ochiai A, Hayashi R, Kaneko K. Clinical outcome after endoscopic resection for superficial pharyngeal squamous cell carcinoma invading the subepithelial layer. Endoscopy, 47:11-18, 2015

13. Osera S, Yano T, Odagaki T, Oono Y, Ikematsu H, Ohtsu A, Kaneko K. Peritonitis related to percutaneous endoscopic gastrostomy using the direct method for cancer patients. Surg Endosc, 29:2941-2946, 2015

14. Sasaki T, Fuse N, Kuwata T, Nomura S, Kaneko K, Doi T, Yoshino T, Asano H, Ochiai A, Komatsu Y, Sakamoto N, Ohtsu A. Serum HER2 levels and HER2 status in tumor cells in advanced gastric cancer patients. Jpn J Clin Oncol, 45:43-48, 2015

15. Oka S, Tamai N, Ikematsu H, Kawamura T, Sawaya M, Takeuchi Y, Uraoka T, Moriyama T, Kawano H, Matsuda T. Improved visibility of colorectal flat tumors using image-enhanced endoscopy. Dig Endosc, 271:35-39, 2015

Book

1. Muto M, Inoue H, Morita S, Monma K, Yano T, Katada C, Goda K, Tajiri H, Fujiwara J. Atlas of neoplastic lesions. In: Muto M, Yao K, Sano Y (eds), Atlas of Endoscopy with Narrow Band Imaging, Japan, Springer Japan, pp 79-129, 2015

Department of Hepatobiliary and Pancreatic Surgery

Masaru Konishi, Shinichiro Takahashi, Naoto Gotohda, Yuichiro Kato, Kazuhiko Kitaguchi, Yasunori Nishida, Yusuke Nakayama

Introduction

The recent development of various diagnostic techniques has led to the detection of an increasing number of early-stage and borderline malignancies, and for such patients, a limited resection preserving organ function is indicated. However, some diseases, such as invasive ductal pancreatic cancer, advanced gallbladder cancer, and hilar cholangiocarcinoma, remain a difficult challenge for surgeons and are still associated with dismal long-term prognoses. Recently, chemotherapy for hepatobiliary and pancreatic malignancies has been developed. In line with this development, several studies on adjuvant hemotherapy for malignancies with dismal prognoses have been conducted.

With the refinements in laparoscopic instruments and advances in surgical experience, laparoscopic surgery is a safe alternative for selected patients with hepatobiliary pancreatic neoplasms, and has fulfilled its indications. In our division, laparoscopic hepatectomies have been performed since 2002, and laparoscopic distal pancreatectomies since 2011.

Routine activities

Our group is composed of four attending surgeons, three chief residents, and four residents. The outpatient clinic is open five days a week. Staff meetings are held three times a week during which treatment strategies from medical and surgical points of view are discussed. A case conference on imaging diagnosis is conducted every Tuesday in cooperation with radiologists and medical oncologists, and a pathology conference is held every month with pathologists. In 2015, 253 patients with hepatobiliary and pancreatic diseases underwent surgical treatment including 51 laparoscopic hepatectomies and nine laparoscopic distal pancreatectomies.

Research activities

Sarcopenia is a newly identified marker of frailty. We assess whether preoperative sarcopenia has an impact on clinically relevant postoperative pancreatic fistula (POPF) formation. A total of 266 consecutive patients who underwent a pancreaticoduodenectomy (PD) between from 2010 and 2014 were enrolled in this retrospective study. Skeletal muscle mass was measured using preoperative computed tomography images. This study concluded that preoperative sarcopenia was identified as a strong and independent risk factor for clinically relevant POPF formation after PD.

Clinical trials

- JASPAC04 is a randomized phase II study on neoadjuvant chemotherapy using combination therapy with gemcitabine and S-1 vs. S-1 and concurrent radiotherapy in patients with resected pancreatic cancer. Recruitment started in 2014.
- JASPAC05 is a phase II study on neoadjuvant S-1 and concurrent radiotherapy for patients with borderline resectable pancreatic cancer. Recruitment started in 2012.
- JCOG1202 (ASCOT) is a phase III study to compare S-1 with surgery alone as adjuvant chemotherapy for patients with curatively resected biliary tract cancer including Intrahepatic cholangiocarcinoma, extrahepatic bile duct cancer, gallbladder cancer and ampullary cancer. Recruitment started in 2013.
- JCOG0605 is a randomized phase III trial to compare FOLFOX with surgery alone as adjuvant chemotherapy for patients with curatively resected liver metastasis from

colorectal cancer. Recruitment is on-going.

Education

'Board certified expert surgeons' is a high level of skill in the field of hepato-biliary-pancreatic surgery. To be qualified as a board certified surgeon, surgeons are required to perform a prescribed number of operations under the guidance of a board certified instructor. The residents of our department are training to get their certifications by the end of the chief resident course.

Table 1. Number of patients

Invasive pancreatic cancer	49
Other pancreatic neoplasms	25
Hepatocellular carcinoma	44
Hepatic metastases	55
Intrahepatic cholangiocarcinoma	8
Perihilar cholangiocarcinoma	11
Distal bile duct cancer	11
Ampullary cancer	8
Gallbladder cancer	4

Table 2. Type of procedure

Hepatectomy and pancreaticoduodenectomy	1
Pancreaticoduodenectomy	65
Distal pancreatectomy	17
Total pancreatectomy	6
Laparoscopic distal pancreatectomy	9
Hapatectomy with biliary reconstruction	13
Hapatectomy without biliary reconstruction	54
Laparoscopic hepatectomy	50
Others	38
Total	253

Table 3. Survival rates

Diagnosis	No. of pts	5-yr survival (%)
Invasive pancreatic cancer	364	24.6
Hepatocellular carcinoma	350	48.5
Hepatic metastases	575	51.7
Intrahepatic cholangiocarcinoma	60	39.0
Perihilar cholangiocarcinoma	121	42.0
Distal bile duct cancer	97	45.6
Ampullary cancer	68	52.1
Gallbladder cancer	82	47.1

List of papers published in 2015

Journal

1. Sugimoto M, Takahashi S, Kobayashi T, Kojima M, Gotohda N, Satake M, Ochiai A, Konishi M. Pancreatic perfusion data and post-pancreaticoduodenectomy outcomes. J Surg Res, 194:441-449, 2015

2. Kato Y, Takahashi S, Gotohda N, Konishi M. Risk factors for malignancy in branched-type intraductal papillary mucinous neoplasms of the pancreas during the follow-up period. World J Surg, 39:244-250, 2015

3. Kitaguchi K, Kato Y, Kojima M, Okubo S, Takahashi D, Okada R, Nakayama Y, Nishida Y, Gotohda N, Takahashi S, Konishi M. A resected case of intraductal tubulopapillary neoplasm of the pancreas: report of a case. Int Surg, 100:281-286, 2015

4. Kitaguchi K, Gotohda N, Yamamoto H, Kato Y, Takahashi S, Konishi M, Hayashi R. Intraoperative circulatory management using the FloTrac™ system in laparoscopic liver resection. Asian J Endosc Surg, 8:164-170, 2015

5. Beppu T, Wakabayashi G, Hasegawa K, Gotohda N, Mizuguchi T, Takahashi Y, Hirokawa F, Taniai N, Watanabe M, Katou M, Nagano H, Honda G, Baba H, Kokudo N, Konishi M, Hirata K, Yamamoto M, Uchiyama K, Uchida E, Kusachi S, Kubota K, Mori M, Takahashi K, Kikuchi K, Miyata H, Takahara T, Nakamura M, Kaneko H, Yamaue H, Miyazaki M, Takada T. Long-term and perioperative outcomes of laparoscopic versus open liver resection for colorectal liver metastases with propensity score matching: a multi-institutional Japanese study. J Hepatobiliary Pancreat Sci, 22:711-720, 2015

6. Takahara T, Wakabayashi G, Beppu T, Aihara A, Hasegawa K, Gotohda N, Hatano E, Tanahashi Y, Mizuguchi T, Kamiyama T, Ikeda T, Tanaka S, Taniai N, Baba H, Tanabe M, Kokudo N, Konishi M, Uemoto S, Sugioka A, Hirata K, Taketomi A, Maehara Y, Kubo S, Uchida E, Miyata H, Nakamura M, Kaneko H, Yamaue H, Miyazaki M, Takada T. Long-term and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study. J Hepatobiliary Pancreat Sci, 22:721-727, 2015

7. Okano K, Hirao T, Unno M, Fujii T, Yoshitomi H, Suzuki S, Satoi S, Takahashi S, Kainuma O, Suzuki Y. Postoperative infectious complications after pancreatic resection. Br J Surg, 102:1551-1560, 2015

8. Gotohda N, Yamanaka T, Saiura A, Uesaka K, Hashimoto M, Konishi M, Shimada K. Impact of energy devices during liver parenchymal transection: a multicenter randomized controlled trial. World J Surg, 39:1543-1549, 2015

Department of Hepatobiliary and Pancreatic Oncology

Masafumi Ikeda, Shuichi Mitsunaga, Izumi Ohno, Yusuke Hashimoto, Hideaki Takahashi, Kazuo Watanabe, Kumiko Umemoto

Introduction

The Department of Hepatobiliary and Pancreatic Oncology is responsible for the treatment and management of patients with hepatic, biliary, and pancreatic cancers. Our goal is to provide high-quality cancer treatment with adequate palliative care, and to develop novel and effective treatments through well-designed clinical trials and research.

Routine activities

Our Department is composed of five staff oncologists and two residents, with an average of 45 beds in the hospital. We conduct clinical rounds for admitted patients every morning and evening. Most new patients with unresectable hepatobiliary and pancreatic tumors are hospitalized for the diagnosis and treatment of tumors. The treatment strategies on individual patients are discussed in weekly tumor board conferences attended by medical oncologists, surgeons, radiologists, radiation oncologists, and pharmacists. Furthermore, we are also responsible for external or endoscopic abdominal ultrasonographic examinations, endoscopic or percutaneous ultrasound-guided biopsies of abdominal masses, local ablative therapy for liver tumors, endoscopic or percutaneous biliary drainage and stenting for obstructive jaundice.

Research activities

1) Hepatocellular carcinoma (HCC)

Sorafenib is the only available standard of care for advanced HCC. We conducted a randomized phase II trial of sorafenib plus hepatic arterial infusion chemotherapy with cisplatin vs. sorafenib alone in patients with advanced HCC, and the combination therapy yielded favorable overall survival as compared to sorafenib alone. A further phase III trial is planned to confirm these results.

2) Pancreatic cancer (PC)

Gemcitabine (Gem) plus nab-paclitaxel was approved for the treatment of advanced PC in December 2014, following the approval of FOLFIRINOX in December 2014. Gem plus nab-paclitaxel has been reported to be comparable on efficacy to and more feasible on adverse events than FOLFIRINOX. In our hospital, Gem plus nab-paclitaxel has been adapted as a first line treatment of advanced PC, and it has been elucidated to have a favorable efficacy and manageable toxicities in daily practice. It should be clarified which is the better treatment in advanced PC patients: Gem plus nab-paclitaxel or FOLFIRINOX by large-scale phase III trial.

The diagnostic value of serum microRNAs on a highly sensitive microarray was found in PC and biliary tract cancer (BTC). A combination strategy of the microRNA markers has been reported to be effective in diagnosis of resectable PC. In addition, the cachexia-related factors that deteriorate during chemotherapy for PC and are associated with poor overall survival have been identified to evaluate the efficacy of the anti-cachexic treatment and to develop the newly arriving anti-cachexic treatment.

Clinical trials

Thirty-six clinical trials (sponsored: 21 trials, investigator-initiated: 15 trials) are ongoing, and eight clinical trials (sponsored: six trials, investigator-initiated: five trials) are being planned for the upcoming year. Recently, immune checkpoint inhibitors are noticed in all cancer treatment, and sponsored trials of these agents or combination therapies with these agents are increasing in this field.

1) HCC

A randomized phase II trial comparing

sorafenib vs. observation in combination with transcatheter arterial chemoembolization (TACE) is ongoing. Some sponsored trials of sorafenib plus resminostat, sorafenib plus LY2157299, sorafenib plus BBI503 are ongoing as first line chemotherapy. As the second line setting, the enrollment of some clinical trials of nivolumab, regorafenib, ONO-7268MX1, ONO-7268MX2, and so forth, have been finished, but some clinical trials of tivantinib, ramucirumab, other immune checkpoint inhibitors, and so forth, are ongoing.

2) BTC

A randomized phase III trial comparing adjuvant S-1 with observation in patients with resected BTC (The Japan Clinical Oncology Group (JCOG) 1202) is ongoing. As first line chemotherapy, a randomized phase III trial comparing Gem plus S-1 with Gem plus cisplatin (JCOG1113) is ongoing, and Gem cisplatin plus nivolumab is planned. As advanced BTCs refractory to Gem, some sponsored trials of resminostat plus S-1, immune checkpoint inhibitors or these combinations are under way.

3) PC

A multicenter phase II trial of neoadjuvant S-1 and concurrent radiotherapy for borderline resectable PC (JASPAC05) is ongoing. A phase II trial of Gem plus Z-360 vs. Gem+Placebo, a phase I trial of Gem plus LY2157299 in chemo-naïve PC patients, a phase III trial of mixed agents of S-1 plus leucovorin (TAS-118) vs. S-1 in Gem refractory PC patients, and a phase II trial of GBS-01 in refractory PC patients to Gem-based and fluoropyrimidine-based regimen have been finished on the enrollments. Some sponsored trials of immune check point inhibitors are planned as second line chemotherapy for advanced PC.

Education

For our residents, one-to-one training is provided on the daily practice of management of inpatients and outpatients. In addition, the residents can learn the indication, administration and management of the adverse events of all cancer treatments from local treatments to systemic chemotherapy for hepatic, biliary, and pancreatic cancer patients and the accompanied procedures to make diagnosis and drainage for obstructive jaundice. In addition, the residents can make a presentation of their research in domestic and overseas' meetings and present a paper in English under the instruction of staff physicians.

Future prospects

The prognosis of patients with hepatic, biliary, and pancreatic cancers remains bleak, and standard treatments for theses cancer is limited. In Japan, the incidences of these cancer, especially HCC and BTC, are higher than those in Western countries. Therefore, we must conduct a lot of novel and promising clinical trials and research that take the lead worldwide. And it is necessary to develop biomarker research accompanying cancer treatment in cooperation with our cancer research center and pharmaceutical companies to identify the more effective and less toxic patient subgroups.

Table 1. Number of patients

Hepatocellular carcinoma	103
Biliary tract cancer	
Intrahepatic cholangiocarcinoma	32
Extrahepatic cholangiocarcinoma	30
Gallbladder cancer	27
Papilla of vater carcinoma	5
Pancreatic cancer	
Locally advanced disease	67
Metastatic disease	161
Other	27
Total	452

Table 2. Type of procedure

Hepatocellular carcinoma	
Radiofrequency ablation	81
Transarterial chemoembolization	190
Intra-arterial chemotherapy	56
Systemic chemotherapy	49
Proton beam radiotherapy	28
Biliary tract cancer	
Systemic chemotherapy	96
Radiotherapy	3
Pancreatic cancer	
Systemic chemotherapy	286
Chemoradiotherapy	3
Total	792

List of papers published in 2015

Journal

1. Miura T, Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Takahashi H, Furuse J, Inagaki M, Higashi S, Kato H, Terao K, Ochiai A. Characterization of patients with advanced pancreatic cancer and high serum interleukin-6 levels. Pancreas, 44:756-763, 2015

2. Ikeda M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Kondo S, Morizane C, Ueno H, Okusaka T. Chemotherapy for advanced poorly differentiated pancreatic neuroendocrine carcinoma. J Hepatobiliary Pancreat Sci, 22:623-627, 2015

3. Okusaka T, Ueno H, Morizane C, Kondo S, Sakamoto Y, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Ikeda M. Cytotoxic chemotherapy for pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci, 22:628-633, 2015

4. Takahashi H, Ikeda M, Kumada T, Osaki Y, Kondo S, Kusumoto S, Ohkawa K, Nadano S, Furuse J, Kudo M, Ito K, Yokoyama M, Okusaka T, Shimoyama M, Mizokami M. Multicenter cooperative case survey of hepatitis B virus reactivation by chemotherapeutic agents. Hepatol Res, 45:1220-1227, 2015

5. Ikeda M, Mitsunaga S, Ohno I, Hashimoto Y, Takahashi H, Watanabe K, Umemoto K, Okusaka T. Systemic chemotherapy for advanced hepatocellular carcinoma: past, present, and future. Diseases, 3:360-381, 2015

6. Okusaka T, Ikeda M, Fukutomi A, Ioka T, Furuse J, Ohkawa S, Isayama H, Boku N. Response to Y. Sasaki et al.: Is repeating FOLFIRINOX in the original dosage and treatment schedule tolerable in Japanese patients with pancreatic cancer? Cancer Sci, 106:1101-1102, 2015

7. Murakami H, Ikeda M, Okusaka T, Inaba Y, Iguchi H, Yagawa K, Yamamoto N. A Phase I study of MEDI-575, a PDGFRα monoclonal antibody, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:631-639, 2015

8. Fuchs CS, Azevedo S, Okusaka T, Van Laethem JL, Lipton LR, Riess H, Szczylik C, Moore MJ, Peeters M, Bodoky G, Ikeda M, Melichar B, Nemecek R, Ohkawa S, Świeboda-Sadlej A, Tjulandin SA, Van Cutsem E, Loberg R, Haddad V, Gansert JL, Bach BA, Carrato A. A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial. Ann Oncol, 26:921-927, 2015

9. Ohkawa S, Okusaka T, Isayama H, Fukutomi A, Yamaguchi K, Ikeda M, Funakoshi A, Nagase M, Hamamoto Y, Nakamori S, Tsuchiya Y, Baba H, Ishii H, Omuro Y, Sho M, Matsumoto S, Yamada N, Yanagimoto H, Unno M, Ichikawa Y, Takahashi S, Watanabe G, Wakabayashi G, Egawa N, Tsuda M, Hosotani R, Hamada C, Hyodo I. Randomised phase II trial of S-1 plus oxaliplatin vs S-1 in patients with gemcitabine-refractory pancreatic cancer. Br J Cancer, 112:1428-1434, 2015

10. Yamaue H, Tsunoda T, Tani M, Miyazawa M, Yamao K, Mizuno N, Okusaka T, Ueno H, Boku N, Fukutomi A, Ishii H, Ohkawa S, Furukawa M, Maguchi H, Ikeda M, Togashi Y, Nishio K, Ohashi Y. Randomized phase II/III clinical trial of elpamotide for patients with advanced pancreatic cancer: PEGASUS-PC Study. Cancer Sci, 106:883-890, 2015

11. Okusaka T, Aramaki T, Inaba Y, Nakamura S, Morimoto M, Moriguchi M, Sato T, Ikawa Y, Ikeda M, Furuse J. Phase I study of tivantinib in Japanese patients with advanced hepatocellular carcinoma: Distinctive pharmacokinetic profiles from other solid tumors. Cancer Sci, 106:611-617, 2015

12. Shinohara A, Ikeda M, Okuyama H, Kobayashi M, Funazaki H, Mitsunaga S, Shimizu S, Ohno I, Takahashi H, Ichida Y, Takahashi K, Okusaka T, Saitoh S. Efficacy of prophylactic minocycline treatment for skin toxicities induced by erlotinib plus gemcitabine in patients with advanced pancreatic cancer: a retrospective study. Am J Clin Dermatol, 16:221-229, 2015

13. Okusaka T, Ueno H, Ikeda M, Mitsunaga S, Ozaka M, Ishii H, Yokosuka O, Ooka Y, Yoshimoto R, Yanagihara Y, Okita K. Phase 1 and pharmacological trial of OPB-31121, a signal transducer and activator of transcription-3 inhibitor, in patients with advanced hepatocellular carcinoma. Hepatol Res, 45:1283-1291, 2015

14. Matsuyama M, Ishii H, Furuse J, Ohkawa S, Maguchi H, Mizuno N, Yamaguchi T, Ioka T, Ajiki T, Ikeda M, Hakamada K, Yamamoto M, Yamaue H, Eguchi K, Ichikawa W, Miyazaki M, Ohashi Y, Sasaki Y. Phase II trial of combination therapy of gemcitabine plus anti-angiogenic vaccination of elpamotide in patients with advanced or recurrent biliary tract cancer. Invest New Drugs, 33:490-495, 2015

15. Okita K, Izumi N, Ikeda K, Osaki Y, Numata K, Ikeda M, Kokudo N, Imanaka K, Nishiguchi S, Kondo S, Nishigaki Y, Shiomi S, Ueshima K, Isoda N, Karino Y, Kudo M, Tanaka K, Kaneko S, Moriwaki H, Makuuchi M, Okusaka T, Hayashi N, Ohashi Y, Kumada H, Peretinoin Study Group. Survey of survival among patients with hepatitis C virus-related hepatocellular carcinoma treated with peretinoin, an acyclic retinoid, after the completion of a randomized, placebo-controlled trial. J Gastroenterol, 50:667-674, 2015

16. Okuyama H, Ikeda M, Kuwahara A, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Senda S, Okusaka T. Prognostic factors in patients with hepatocellular carcinoma refractory or intolerant to sorafenib. Oncology, 88:241-246, 2015

Department of Urology

Yasuyuki Sakai, Yoshinobu Komai

Introduction

The Department of Urology has existed as part of the Department of Pelvic Surgery at the National Cancer Center Hospital East from 2003. This Department mainly treats diseases of the pelvic organs, including urogenital cancer, with the aim of preserving the sexual and/or voiding functions under minimally invasive surgery.

Routine activities

Outpatient activities: The outpatient clinic is open two days a week as a Urology Department. Flexible cystoscopy, abdominal ultrasonography, retrograde pyelography and some prostate biopsies are performed in the outpatient clinic. Superficial bladder cancer (G3, cis, or recurrent tumor) after TUR-Bt is treated by instillation of BCG into the bladder. Advanced urogenital cancers including metastatic prostate cancer are referred to the medical oncology division for chemotherapy or hormonal therapy. Extrinsic obstructions of the upper urinary tract that directly result from invasion of an adjacent malignancy or peritoneal metastasis are also treated. In most cases, internal stenting is better tolerated than percutaneous nephrostomy. 54 patients newly received ureteral stents and 18 underwent nephrostomy for obstructive uropathy in 2015. Inpatient activities: A daily conference is held with doctors of the Department of Pelvic Surgery on diagnosis and treatment of the patients with colorectal and urological cancer. We performedabout 28 combination surgeries with colorectal surgeons. In the department of urology, 103 general anaesthesia surgeries, 81 spinal anesthesia surgeries and 42 prostate biopsies were performed this year. Other: We have a conference on urogenital cancers every other week among medical oncologists, radiation oncologists, and pathologists. Neoadjuvant chemotherapy for muscle invasive bladder cancer, combination therapy of hormone and radiation for prostate cancer, treatment strategies for metastatic renal cell carcinoma and testicular cancer, and so on, are determined in the meeting.

Research activities

To facilitate laparoscopic off-clamp partial nephrectomy, we presented the "patient-specific 3D kidney image and 3D printed kidney model" at the 28th congress of the Japanese Society of Endourology, and this presentation was accepted as part of the content of the Audio-Visual Journal of the Japanese Urological Association. And at the 31st annual congress of the European Association of Urology, we presented a time-lapse movie as a novel informed consent tool. It was commended for the Best Poster Award. Total pelvic exenteration (TPE) is the standard procedure for locally advanced rectal cancer involving the prostate and seminal vesicles. We evaluated the feasibility of bladder-sparing surgery as an alternative to TPE. We performed concomitant prostatectomy and cysto-urethral anastomosis.

Clinical trials

1) A retrospective study of perioperative results in partial nephrectomy for renal cell carcinoma
2) An estimate of the prevalence of Lynch syndrome in upper urinary tract urothelial cancer
3) Development and validation of a nomogram to predict recurrences of upper urinary tract urothelial cancer in Japanese patients
4) A retrospective study of the utility and safety of Imidafenacin for overactive bladder, which occurs after urinary tract stenting for urinary obstruction by a progressive malignant tumor
5) A phase II clinical study of robotic-assisted

radical prostatectomy by the da Vinci S/Si Surgical System

6) A phase III study: BCG instillation for high-grade T1 bladder cancer (JCOG1019)

Education

We accepted one voluntary resident of urology in 2015 and educated the resident on urological surgery.

Future prospects

New laparoscopic transurethral surgical devices for bladder cancer are being developed in cooperation with another institution. Also, we aim for the safe introduction of laparoscopic total cystectomy and the safe adaptation expansion of robot-assisted laparoscopic surgery.

Table 1. Number of patients

	No.
Renal cell carcinoma	38
Upper urinary tract urothelial carcinoma	7
Bladder cancer	36
Prostate cancer	39
Testicular cancer	1

Table 2. Type of procedure

	No.
Radical nephrectomy (laparoscopic surgery/total)	19/25
Partial nephrectomy (laparoscopic surgery/total)	4/13
Nephroureterectomy (laparoscopic surgery/total)	6/7
Radical cystectomy (laparoscopic surgery/total)	1/14
TURBT	72
Radical prostatectomy (robotic-assisted laparoscopic surgery/total)	39/39

Department of Musculoskeletal Oncology and Rehabilitation

Fumihiko Nakatani

Introduction

The Department of Musculoskeletal Oncology and Rehabilitation of the National Cancer Center Hospital East (NCCHE) is a team consisting of a panel of orthopedic surgeons and rehabilitation professionals that started from 2012. We strive to provide expert interdisciplinary care for a variety of benign and malignant bone and soft tissue tumors and tumor-like conditions, and we also provide comprehensive rehabilitation services. Currently, we have a chief orthopedic surgeon and three rehabilitation staff engaging in the treatment of a variety of patients with the aid of other orthopedic staff from the NCCH.

Routine activities

Our outpatient service is open three days a week (Mondays, Wednesdays and Fridays) for patients with a variety of musculoskeletal tumors or cancer patients who need rehabilitation care. We also manage the patients with bone metastases or other orthopedic diseases as a result of consultation from other cancer specialists on a daily basis. To provide the prosthetic and orthotic care for our patients a special outpatient service is open every Friday. In cases of patients who need multidisciplinary approaches to their treatment, we offer appropriate referral to the NCCH for further treatment.

In 2015, we conducted 37 operations in total, consisting of 17 resections of soft tissue tumors, four osteosyntheses of pathological fractures from bone metastases, 13 operations for bone tumors and three operations for other tumors/reasons.

In September 2014, we opened a spacious rehabilitation unit with start-of-the-art equipment with the aim to reduce the common side effects of cancer treatment, including fatigue, weakness, poor endurance, pain, nausea, anxiety, depression and loss of confidence. As a result, we conducted rehabilitation for 1,127 patients in 2015 (Table 1).

Table 1. Characteristics and number of patients enrolled for rehabilitation.

Department	2012	2013	2014	2015
Hematology	39	24	11	68
Thoracic oncology	35	44	54	83
Thoracic surgery	29	13	30	119
Head and neck oncology	21	10	5	17
Gastrointestinal oncology	21	23	59	89
Esophageal surgery	19	34	60	200
Musculoskeletal oncology	17	52	23	42
Palliative medicine	15	18	2	66
Colorectal surgery	13	2	42	29
Hepatobiliary and pancreatic oncology	12	15	24	70
Breast and medical oncology	–	27	34	87
Head and neck surgery	–	13	97	134
Gastrointestinal surgery	–	–	–	32
Hepatobiliary and pancreatic surgery	–	–	–	48
Others	24	19	52	43
Total	146	245	493	1,127

Research activities

We have been focusing on regional cooperation with the local physiotherapists of Kashiwa City with the aim to provide cancer patients of the community with seamless rehabilitation care after invasive cancer operations. Until now, we have established the standard methods of physiotherapy and functional evaluations in common.

Clinical trials

We have been focusing on the standardization of multidisciplinary treatment for bone and soft tissue sarcomas through cooperation with the musculoskeletal oncology department of the NCCH. Two multi-institutional clinical trials are active as follows:

1) A multi-institutional phase III clinical trial of multidrug adjuvant chemotherapy for

osteosarcoma (JCOG 0905) has been ongoing since 2010.

2) A multi-institutional phase III clinical trial of adjuvant chemotherapy for high-grade soft part sarcoma (JCOG 1306) started in February 2014.

Education

We have undertaken several educational lectures for the medical staff to highlight the importance of rehabilitation for cancer treatment. We also provide some instructive lectures for the medical staff of the community.

Future prospects

Recent evolution of cancer treatment increases the demand for the orthopedic care and rehabilitation of cancer survivors. We must consistently focus on standardization for the methodology of rehabilitation for all cancer patients, which will be beneficial for the augmentation of quality of life for these patients.

List of papers published in 2015

Journal

1. Yamaga K, Kobayashi E, Kubota D, Setsu N, Tanaka Y, Minami Y, Tanzawa Y, Nakatani F, Kawai A, Chuman H. Pediatric myositis ossificans mimicking osteosarcoma. Pediatr Int, 57:996-999, 2015

2. Fujiwara T, Ogura K, Kobayashi E, Tanzawa Y, Nakatani F, Chuman H, Kawai A. Clinical Outcomes of Surgical Treatments for Primary Malignant Bone Tumors Arising in the Acetabulum. Sarcoma, 2015:430576, 2015

3. Fujiki M, Miyamoto S, Nakatani F, Kawai A, Sakuraba M. Rotationplasty with vascular reconstruction for prosthetic knee joint infection. Case Rep Orthop, 2015:241405, 2015

4. Miyamoto S, Fujiki M, Nakatani F, Sakisaka M, Sakuraba M. Free flow-through anterolateral thigh flap for complex knee defect including the popliteal artery. Microsurgery, 35:485-488, 2015

Department of Hematology

Kunihiro Tsukasaki, Sachiko Seo, Kensuke Narukawa, Rumiko Okamoto, Kota Ohashi

Introduction

The staff physicians and residents of the Department of Hematology carry out clinical and research activities related to multi-disciplinary treatment of patients with hematological malignancies that consist of more than 100 disease entities in the WHO classification (version 2008). Our Department focuses on early and late phases of clinical trials in collaboration with the Research Center for Innovative Oncology and the Japan Clinical Oncology Group (JCOG), respectively, especially on lymphoid malignancies.

Routine activities

The number of patients with newly diagnosed hematologic malignancies in our Department is increasing, and approximately 298 patients with newly diagnosed hematological malignancies including non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, macroglobulinemia, acute leukemia, myelodysplastic syndrome and chronic leukemia were cared for this year (Table 1). The Department is currently providing routine chemotherapy as an outpatient service to an increasing number of relatively aged patients with hematological malignancies. All patients undergoing intensive chemotherapy and autologous peripheral blood hematopoietic stem cell transplantation (APBSCT) (Table 2) are managed in laminar airflow rooms in the designated ward on the eighth floor. Besides managing patients, the Department also provides consultation on hematological abnormalities detected in Clinical Laboratories. A morning case conference on the inpatient care of our Department is held from Mondays to Friday, and a weekly case conference on new patients visiting our clinic is held on Thursday evenings. On Wednesday evenings, a weekly joint conference on lymphoid malignancies with expert pathologists and an educational cytology conference on bone marrow specimens are held. A joint morning journal club of our Department and the Department of Breast and Medical Oncology is held on Mondays and Fridays.

Research activities

Ancillary studies associated with retrospective case series and clinical trials at this Department have been continuously conducted focusing on several kinds on hematological malignancies and their complications. Recently, a nationwide survey of human T-lymphotropic virus type I (HTLV-1) associated adult T-cell leukemia-lymphoma (ATL) is ongoing by us under a grant for Cancer Research from the Ministry of Health, Labour and Welfare to elucidate the pathophysiology including geographical findings as compared to the surveys in 1980 to 1990.

Clinical trials

Clinical trials on hematological malignancies performed by our Department comprise protocols prepared in-house and participation in the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG-LSG), the Japan Adult Leukemia Study Group (JALSG) and others. The Department participated in pharmaceutical company-sponsored and investigator-initiated new-agent trials including international ones for hematological malignancies. The following JCOG clinical trials are ongoing: a randomized phase III trial of rituximab administered weekly or tri-weekly with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in patients with newly diagnosed CD20+ diffuse large B cell lymphoma (DLBCL) (JCOG0601) in which a dose-intense schedule of rituximab is evaluated; a randomized phase II trial comparing biweekly

rituximab-CHOP or biweekly rituximab-CHOP/cyclophosphamide, cytarabine, dexamethasone, etoposide and rituximab (CHASER) followed by high dose melphalan, cyclophosphamide, etoposide and dexamethasone (LEED) with APBSCT in patients with newly diagnosed poor risk CD20+ DLBCL (JCOG0908); a randomized phase II study of two induction treatments of melphalan, prednisolone, plus bortezomib (MPB), JCOG-MPB versus modified PETHEMA-MPB, in elderly patients or non-elderly patients refusing transplants with untreated symptomatic myeloma (JCOG1105); and a single armed phase III study of mLSG15 chemotherapy followed by allo-HSCT, comparing the results with historical control in JCOG9801 of mLSG15 alone to evaluate the promising efficacy of allo-HSCT, possibly associated with a graft-versus-ATL effect, especially in view of a comparison with intensive chemotherapy (JCOG0907). A phase III study evaluating the efficacy of the combination of interferon-alpha (IFN) and zidovudine (AZT) as compared to watchful-waiting for indolent ATL (JCOG1111) is ongoing under a highly advanced medical technology assessment system because IFN and AZT are not covered for ATL by National Health Insurance in Japan. A single armed phase III study of interim-PET response adapted a switch-strategy from ABVD to ABVD/DE-BEACOP for advanced Hodgkin Lymphoma (JCOG1305).

Table 1. Number of patients

Non-Hodgkin's lymphoma	150
Hodgkin's lymphoma	8
Acute lymphoid leukemia	7
Chronic lymphoid leukemia	4
Acute myeloid leukemia	16
Chronic myeloid leukemia	5
Myeloproliferative neoplasm(excluding CML)	10
Multiple myeloma	22
Myelodysplastic syndrome	12
Others	64
Total	298

Table 2. Type of procedure

PBSCT for non-Hodgkin's lymphoma in relapse	5
PBSCT for myeloma in remission	5
Total	10

List of papers published in 2015

Journal

1. Katsuya H, Ishitsuka K, Utsunomiya A, Hanada S, Eto T, Moriuchi Y, Saburi Y, Miyahara M, Sueoka E, Uike N, Yoshida S, Yamashita K, Tsukasaki K, Suzushima H, Ohno Y, Matsuoka H, Jo T, Amano M, Hino R, Shimokawa M, Kawai K, Suzumiya J, Tamura K, ATL–Prognostic Index Project. Treatment and survival among 1594 patients with ATL. Blood, 126:2570-2577, 2015

2. Yoshida N, Tsuzuki S, Karube K, Takahara T, Suguro M, Miyoshi H, Nishikori M, Shimoyama M, Tsukasaki K, Ohshima K, Seto M. STX11 functions as a novel tumor suppressor gene in peripheral T-cell lymphomas. Cancer Sci, 106:1455-1462, 2015

3. Miura S, Akazawa Y, Kurashige T, Tukasaki K, Kondo H, Yokota K, Mine M, Miyazaki Y, Sekine I, Nakashima M. The Nagasaki Atomic Bomb Survivors' Tumor Tissue Bank. Lancet, 386:1738, 2015

4. Yoshida N, Imaizumi Y, Utsunomiya A, Miyoshi H, Arakawa F, Tsukasaki K, Ohshima K, Seto M. Mutation Analysis for TP53 in Chronic-Type Adult T-Cell Leukemia/Lymphoma. J Clin Exp Hematop, 55:13-16, 2015

5. Seo S, Boeckh M, Storer BE, Schubert MM, Rotta M, Sandmaier BM, Mielcarek M. The association between donor and recipient statin use and infections after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant, 50:444-448, 2015

6. Erard V, Guthrie KA, Seo S, Smith J, Huang M, Chien J, Flowers ME, Corey L, Boeckh M. Reduced Mortality of Cytomegalovirus Pneumonia After Hematopoietic Cell Transplantation Due to Antiviral Therapy and Changes in Transplantation Practices. Clin Infect Dis, 61:31-39, 2015

7. Seo S, Renaud C, Kuypers JM, Chiu CY, Huang ML, Samayoa E, Xie H, Yu G, Fisher CE, Gooley TA, Miller S, Hackman RC, Myerson D, Sedlak RH, Kim YJ, Fukuda T, Fredricks DN, Madtes DK, Jerome KR, Boeckh M. Idiopathic pneumonia syndrome after hematopoietic cell transplantation: evidence of occult infectious etiologies. Blood, 125:3789-3797, 2015

8. Uy GL, Costa LJ, Hari PN, Zhang MJ, Huang JX, Anderson KC, Bredeson CN, Callander NS, Cornell RF, Perez MA, Dispenzieri A, Freytes CO, Gale RP, Garfall A, Gertz MA, Gibson J, Hamadani M, Lazarus HM, Kalaycio ME, Kamble RT, Kharfan-Dabaja MA, Krishnan AY, Kumar SK, Kyle RA, Landau HJ, Lee CH, Maiolino A, Marks DI, Mark TM, Munker R, Nishihori T, Olsson RF, Ramanathan M, Rodriguez TE, Saad AA, Savani BN, Schiller GJ, Schouten HC, Schriber JR, Scott E, Seo S, Sharma M, Ganguly S, Stadtmauer EA, Tay J, To LB, Vesole DH, Vogl DT, Wagner JL, Wirk B, Wood WA, D'Souza A. Contribution of chemotherapy mobilization to disease control in multiple myeloma treated with autologous hematopoietic cell transplantation. Bone Marrow Transplant, 50:1513-1518, 2015

Department of Dentistry

Tetsuhito Konishi , Toshiro Miyata, Tomoko Kaneda

Introduction

We aim to deal with the diverse intraoral complications associated with cancer treatment and to maintain and improve patients' quality of life (QOL) in the field of dentistry.

Cancer treatment is frequently associated with a variety of intraoral complications, such as mucositis, taste disorder, dry mouth, pain, and infection. In particular, in patients undergoing treatment for head and neck cancer (chemoradiotherapy, surgery) and hematopoietic stem cell transplantation, severe intraoral symptoms may occur, and strict infection control measures are needed.

When such measures are inadequate, composite complications may result in secondary complications such as eating disorders and undernutrition, and the oral cavity may serve as a source of systemic infections, which may lead to the need for deferring or discontinuing treatment, making continuation and completion of cancer treatment difficult.

To manage and prevent intraoral complications, we evaluate and stabilize the oral status before the initiation of cancer treatment. Proactive intervention by dentists or dental hygienists to educate the patients, their families, and the attending medical staff is extremely important.

Routine activities

We undertake efforts to prevent infection of wounds and aspiration pneumonia and to reduce other complications by oral hygiene management before and after surgery. To maintain postoperative functions of jaw defects, we are attempting to correct speech-language and eating functions by preparing appropriate artificial dentition and prostheses at an early stage, thereby improving the QOL of patients after treatment. For patients receiving chemotherapy and radiotherapy, we are supporting continuation and completion of treatment by taking measures to prevent infections arising from the dentistry realm and mucositis and by reducing pain. In regard to delayed complications, we are undertaking preventive and treatment activities for multiple dental caries, osteomyelitis of the jaw, and necrosis of the jaw bone. Patients treated over the long-term with zoledronic acid or denosumab may develop Medication-Related Osteonecrosis of the Jaw (MRONJ) as a result of contamination of the oral cavity and tooth extraction; thus, we are undertaking measures to prevent/treat this complication.

By participating in multidisciplinary conferences, we apply prevailing practices and information updates to future medical care support. In 2015, the numbers of new and revisiting patients were 1,006 and 8,375, respectively, and the total number of patients was 9,381. These numbers represent an approximately 1.8-fold increase as compared to those in the first year when dentists at the National Cancer Center Hospital East began to hold full-time positions. We believe that the importance of supportive care in cancer has been recognized.

Research activities

We are participating in a multicenter study being conducted to evaluate the effectiveness of proactive use of supportive care for preventing serious oral mucositis in patients with head and neck cancer undergoing chemoradiotherapy.

We are carrying out a study on multiple dental caries and radiation-induced osteomyelitis developing after radiotherapy for head and neck cancers. In addition, we are a part of the nutrition support team.

We cooperate with other facilities for the establishment of oral care programs for patients with head and neck cancers receiving chemoradiotherapy.

Department of Pediatric Oncology

Ako Hosono, Hiroshi Kawamoto, Naoko Yasui

Introduction

The Department of Pediatric Oncology was established in December 2011 to provide treatment for pediatric cancers including a wide variety of diseases such as hematologic malignancies comprising leukemia and lymphoma, embryonal tumors comprising neuroblastomas, nephroblastomas and hepatoblastomas, and mesenchymal tumors comprising Ewing sarcomas, rhabdomyosarcomas and osteosarcomas. Although they usually occur in children under the age of 15, they occasionally occur in adolescents and young adults (AYA). Most of the pediatric cancers are highly chemosensitive as well as radiosensitive. They are possibly curable in a certain situation where the intensity of multidisciplinary treatment and disease characteristics are balanced well. However, there are absolute refractory cases who need new treatments other than standard chemotherapy. Moreover, long-term survivors of pediatric cancers often suffer from complications secondary to chemotherapy and radiotherapy. The three major objectives of the Department of Pediatric Oncology in the NCCE are as follows: (1) To provide state-of-the-art treatment for AYA patients in collaboration with the Medical Oncology group. (2) To develop new treatments for pediatric cancer by sharing agents and knowledge with the Clinical Development Center. And (3) to provide less toxic proton-beam radiation therapy as one of the three proton centers for children in Japan. All three activities are currently on-going and several projects have already started (refer to "Research activities and clinical trials").

Routine activities

The pediatric outpatients service is open for three days a week, Monday, Wednesday and Friday, to treat newly diagnosed patients, patients who received chemotherapy in the outpatient setting and to provide follow-up treatment to patients who have completed an intensive treatment course. Also, the care of children receiving palliative treatment is carried out with the Palliative Care and Psycho-Oncology Group. Daily rounds and a conference are held every morning. We also attend conferences with the Medical Oncology, Orthopedic Surgery, Thoracic Surgery and Urology Department s at any time.

Research activities and clinical trials

As written above, several projects that are expected to achieve our objectives are ongoing. Proton-beam radiation therapy is currently provided as an Investigational Medical Care (Sensin-iryo). However, the medical costs related to the treatment with this system could possibly financially overburden patients and their families. To pursue the possibility of getting this technique approved under the Japanese Health Insurance system, we plan a clinical trial to gather data on safety for pediatric patients. Other projects include treatment development using relatively new off-label drugs as well as experimental agents such as peptide vaccines. One of the objectives of the following trials is gathering data on, and assessing the safety and efficacy data of, such off-label drugs and eventually getting them approved by the Ministry of Health, Labour and Welfare.

One clinical trial described below are currently active.

A phase I trial of immunotherapy using HLA-A2 and A24-restricted glypican-3 peptide vaccine for pediatric tumors.

Table 1. Number of patients

Benign bone tumors	8
Soft tissue sarcoma	2
Rhabdomyosarcoma	1
Ewing sarcoma	1
Leiomyosarcoma	2
Synovial sarcoma	1
Hepatoblastoma	2

Department of Anesthesiology and Intensive Care Unit

Hiroyuki Yamamoto, Aiko Ohshita, Katsuya Kobayashi, Kazuaki Hiraga, Kei Torigoe

Introduction

The Department of Anesthesiology and Intensive Care Unit (ICU) consists of five staff members (four Japanese Society of Anesthesiologists Board Certified Anesthesiologists and a Japanese Society of Anesthesiologists (JSA) Qualified Anesthesiologist) and two or three rotating residents. Each year, we provide more than 2,600 anesthesia services in eight operating rooms and over 1,300 patients have been admitted to the ICU. A large number of operations in the head and neck surgery division and procedures involving a thoracotomy for lung and esophageal cancer are one of the features of this hospital. Accordingly, a special anesthesia induction method for difficult airways and use of the one-lung ventilation technique are often necessary for anesthesiologists. Currently, our ICU admits mainly postsurgical patients who have undergone major abdominal, thoracic and complex surgical procedures, as well as patients who have suffered from serious preoperative complications. Increasingly complex procedures are being performed on more seriously ill patients with coronary disease, chronic obstructive pulmonary disease (COPD), neurological disorders and so on. The ICU needs to play an increasingly important role in postsurgical care for such patients. The goals of the Department of Anesthesiology and Intensive Care Unit are to provide anesthetic and perioperative care to patients, with their safety being the highest priority.

Routine activities

Five staff members (three full-time and two visiting anesthesiologists), four rotating residents and 12 part-time anesthesiologists cover eight operating rooms. A preanesthesia case presentation is held every morning to examine the case of the day and discuss the anesthesia problem and strategy for patients with various complications. In 2015, we provided 2,834 anesthesia services (Table 1). The annual number of patients admitted to the ICU was 1,347 and more than 95% of them were postsurgical patients (Table 2).

Research activities

The relationship between intraoperative blood loss and dry-side fluid management during liver resection was studied. Fluid management was performed based on the value of stroke volume variation (SVV) obtained by the FloTrac system, which has a strong correlation with central venous pressure (CVP). This technique demonstrated decreased intraoperative blood loss during liver resection.

Education

The Department of Anesthesiology and Intensive Care Unit has no resident. For rotating residents, we provide opportunities of epidural anesthesia, one-lung ventilation technique for thoracotomy, and difficult airway management including fiberoptic intubation. A Journal club is also held once a week in addition to the everyday morning conference. We support residents who hope to obtain the qualification of anesthesiologist or JSA Qualified Anesthesiologist during rotation periods.

Future prospects

In 2017, a new surgical and endoscopic center will be built, which has 12 operating rooms. We expect a 20 to 25% of increase in anesthesia cases. To accomplish this, an increase of the staff is essential. Next year, two staff anesthesiologists will join our department and we are preparing to increase the number of operations with these additional members.

Table 1. Number of Anesthesia Cases

Type of Surgery	2011	2012	2013	2014	2015
Head and Neck	424	454	423	409	443
Thoracic	466	473	501	520	561
Esophageal	126	182	201	215	199
Hepatobiliary and Pancreatic	269	231	253	282	260
Gastric	286	308	268	292	289
Colorectal	426	453	479	550	561
Urology	78	107	114	111	107
Orthopedic	—	22	43	34	33
Breast	291	309	325	315	347
Plastic and Reconstructive	—	3	8	20	34
Others	—	—	—	2	—
Total	2,366	2,542	2,668	2,697	2,834

Table 2. Number of Patients Admitted to the ICU

	2011	2012	2013	2014	2015
Number of Patients	1,228	1,412	1,458	1,348	1,347

Department of Palliative Medicine

Hiroya Kinoshita, Yoshihisa Matsumoto, Tomofumi Miura, Keita Tagami, Hanako Iwamoto, Yuki Sumazaki

Introduction

The purpose of our Department is to improve the quality of life for cancer patients and their family caregivers by management of irritable symptom burdens and establishment of a regional palliative care system. Therefore, we provide three palliative care services: 1) an outpatient clinic, 2) a supportive care team and 3) a palliative care unit.

Routine activities

1) Outpatient clinic

Patients with or without anti-cancer therapy consult our outpatient clinic for management of their symptoms or for support to decide where and how to spend their lives. The concept of early palliative care has gradually spread and consultations for patients undergoing anti-cancer therapy have been increasing.

2) Supportive care team

This team consist of a physician, psycho-oncologist, nurse, dietician, physiotherapist and speech-language-hearing therapist. Our supportive care team perform a multidisciplinary approach for inpatients with various sufferings in the oncology floor.

3) Palliative care unit

Our palliative care unit is the Japanese version of an acute palliative care unit (APCU). The features of APCU are multidimensional assessment, rapid symptom control and intensive psychosocial care with a shorter length of stay and lower death rate than in traditional PCU. Medical social workers greatly contribute to a transition to palliative home care and transfer to other hospitals.

Research activities

The aim of the research in our division is to establish a regional palliative care system and to integrate early palliative care with oncology. The following research is conducted:

1. System construction of screening and intervention for symptoms in patients with advanced cancer.
2. Development of the integration of early palliative care in metastatic lung cancer.
3. Surveys for patients about opioids adherence and for bereaved family members about opioids administration.
4. Registration for Japanese multicenter cohort studies and international multicenter projects.

Education

The purpose is to promote understanding about palliative care in cancer patients and their families for residents. Residents can train in home palliative care on request. To disseminate knowledge about primary palliative care, we held several workshops for medical staff in the National Cancer Center Hospital East (NCCHE) and for regional palliative care staff.

Future prospects

Our Department will continue the above activities and develop new research to improve quality of life (QOL) for cancer patients and their family caregivers.

List of papers published in 2015

Journal

1. Baba M, Maeda I, Morita T, Inoue S, Ikenaga M, Matsumoto Y, Sekine R, Yamaguchi T, Hirohashi T, Tajima T, Tatara R, Watanabe H, Otani H, Takigawa C, Matsuda Y, Nagaoka H, Mori M, Tei Y, Hiramoto S, Suga A, Kinoshita H. Survival prediction for advanced cancer patients in the real world: A comparison of the Palliative Prognostic Score, Delirium-Palliative Prognostic Score, Palliative Prognostic Index and modified Prognosis in Palliative Care Study predictor model. Eur J Cancer, 51:1618-1629, 2015

2. Hamano J, Morita T, Inoue S, Ikenaga M, Matsumoto Y, Sekine R, Yamaguchi T, Hirohashi T, Tajima T, Tatara R, Watanabe H, Otani H, Takigawa C, Matsuda Y, Nagaoka H, Mori M, Yamamoto N, Shimizu M, Sasara T, Kinoshita H. Surprise Questions for Survival Prediction in Patients With Advanced Cancer: A Multicenter Prospective Cohort Study. Oncologist, 20:839-844, 2015

3. Hamano J, Morita T, Ozawa T, Shishido H, Kawahara M, Aoki S, Demizu A, Goshima M, Goto K, Gyoda Y, Hashimoto K, Otomo S, Sekimoto M, Shibata T, Sugimoto Y, Matsunaga M, Takeda Y, Nagayama J, Kinoshita H. Validation of the Simplified Palliative Prognostic Index Using a Single Item From the Communication Capacity Scale. J Pain Symptom Manage, 50:542-547.e4, 2015

4. Maeda I, Morita T, Kinoshita H. Reply to H. Nakayama et al. J Clin Oncol, 33:2228-2229, 2015

5. Kizawa Y, Morita T, Miyashita M, Shinjo T, Yamagishi A, Suzuki S, Kinoshita H, Shirahige Y, Yamaguchi T, Eguchi K. Improvements in Physicians' Knowledge, Difficulties, and Self-Reported Practice After a Regional Palliative Care Program. J Pain Symptom Manage, 50:232-240, 2015

6. Miura T, Matsumoto Y, Hama T, Amano K, Tei Y, Kikuchi A, Suga A, Hisanaga T, Ishihara T, Abe M, Kaneishi K, Kawagoe S, Kuriyama T, Maeda T, Mori I, Nakajima N, Nishi T, Sakurai H, Morita T, Kinoshita H. Glasgow prognostic score predicts prognosis for cancer patients in palliative settings: a subanalysis of the Japan-prognostic assessment tools validation (J-ProVal) study. Support Care Cancer, 23:3149-3156, 2015

7. Umezawa S, Fujimori M, Matsushima E, Kinoshita H, Uchitomi Y. Preferences of advanced cancer patients for communication on anticancer treatment cessation and the transition to palliative care. Cancer, 121:4240-4249, 2015

8. Miura T, Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Takahashi H, Furuse J, Inagaki M, Higashi S, Kato H, Terao K, Ochiai A. Characterization of patients with advanced pancreatic cancer and high serum interleukin-6 levels. Pancreas, 44:756-763, 2015

9. Igarashi T, Abe K, Miura T, Tagami K, Motonaga S, Ichida Y, Hasuo H, Matsumoto Y, Saito S, Kinoshita H. Oxycodone frequently induced nausea and vomiting in oxycodone-naïve patients with hepatic dysfunction. J Palliat Med, 18:399, 2015

10. Kinoshita H, Maeda I, Morita T, Miyashita M, Yamagishi A, Shirahige Y, Takebayashi T, Yamaguchi T, Igarashi A, Eguchi K. Place of death and the differences in patient quality of death and dying and caregiver burden. J Clin Oncol, 33:357-363, 2015

Department of Psycho-Oncology Service

Asao Ogawa, Yoshio Iwata, Daisuke Fujisawa, Hiroyuki Nobata, Hiroko Tanaka, Junko Ueda, Rina Kakinuma, Tomoko Nishimura

Introduction

The Department of Psycho-Oncology Service, established in July 1996, aims to manage and alleviate emotional distress of cancer patients, their families and caring staff. The Department, adjunctive with the Psycho-oncology Division of the Research Center for Innovative Oncology, also aims to study the influence of psychosocial issues upon quality of life and survival of cancer patients. Management of elderly patients with cancer, who are frequently comorbid with cognitive impairment or dementia, is another focus of interest.

Routine activities

The Department of Psycho-Oncology Service is composed of two attending psychiatrists, three clinical psychologists, and two psychiatry residents. The clinical activities include psychiatric consultation, involving comprehensive assessment and addressing of psychiatric problems of cancer patients. The patients are either self-referred or referred by their oncologists in charge. The consultation data are shown in the Table. Psychiatric diagnosis is based on the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria. Consultation data also includes individuals who are family members of cancer patients.

A conference with the Supportive Care Team is held on Wednesdays, and a multicenter joint clinical teleconference involving six cancer center hospitals and three university hospitals is held on Thursdays. In 2014, the Supportive Care Center was developed. This center provides multi-professional attention to the individual's overall physical, psychosocial, and social needs, and cooperates with the Psycho-Oncology Division.

Table 1. Psychiatric consultation data (n=973; January-December, 2015)

Section		N (%)
Age	Mean ± SD (median, range) (yr)	64.4±12.8(67, 15 ～ 93)
Gender	(male/female)	637 (58.6%) / 450 (41.4%)
Inpatient / Outpatient		725(66.7%)/362(33.3%)
Cancer patient / Family member		1,051 (96.7%) / 36 (3.3%)
Cancer site	Head and Neck	193 (17.8%)
	Lung	154 (14.2%)
	Esophagus	119 (10.9%)
Stage	Ⅰ/Ⅱ/Ⅲ/Ⅳ/Recurrent	83(7.6%)/101 (9.3%)/128(11.8%)/416(38.3%)/ 180(16.6%)/
PS	0/1, 2/3, 4	348 (32.0%) /504 (46.4%)/235 (21.6%)
Psychiatric diagnosis	Delirium	270 (24.8%)
	Adjustment disorders	164 (15.1%)
	Major depression	62 (5.7%)
	Dementia	125 (11.5%)
	No diagnosis	180 (16.6%)

Supportive Care Team

Hiroya Kinoshita, Yoshihisa Matsumoto, Tomofumi Miura, Asao Ogawa, Yoshio Iwata, Naoko Kobayashi, Chiyuki Sasaki, Junya Ueno, Yoshie Iino, Kazuaki Hiraga, Daisuke Fujisawa, Hiroyuki Nobata, Keita Tagami, Yuki Sumazaki, Hanako Iwamoto, Lina Orikabe, Naoko Yoshino, Noriko Fujishiro, Junko Ueda, Rina Kakinuma, Tomoko Nishimura, Hideo Uesugi, Kumi Nakamura, Taichi Watanabe, Hatoe Sakamoto

Introduction

The Supportive Care Team (SCT), established in October 2005, primarily aims to improve care for cancer patients and families facing a life-threatening illness. The role of the SCT is to implement comprehensive cancer care by assessing unrelieved symptoms (physical and psychiatric) and unattended needs, as well as efficiently managing physical symptoms, providing psychological support, and coordinating services.

Routine activities

The SCT is an interdisciplinary team composed of palliative care physicians, psychiatrists, certified nurse specialists, certified nurses, clinical psychologists, pharmacy practitioners, registered dietitians and social workers. The SCT keeps regular contact with clinician-teams in charge, discusses patients' needs, and refers patients and families to the appropriate services. Interdisciplinary team conferences and SCT rounds are held on Wednesdays. The SCT consultation data are shown in the table.

Clinical trials

Please refer to the "Department of Psycho-Oncology Service, Research Center for Innovative Oncology" section and the "Department of Palliative Medcine" sections.

Table 1. Supportive Care Team consultation data (n=1,009; January-December, 2015)

		N (%)
Age	Mean ± SD (range) (yr)	63.8±13.2
Gender	(male/female)	629 (62%) / 380 (38%)
Service	Palliative care/ Psycho-oncology	284/ 725
Performance status	0/1/ 2/ 3/ 4	146 (14%) / 230 (23%) / 261 (26%) / 245 (24%) / 127 (13%)
Physical symptoms (moderate - severe)	Pain	516 (51%)
	Appetite loss	375 (37%)
	Fatigue	484 (48%)
	Respiratory distress	233 (23%)
Psychiatric diagnosis (primary diagnosis)	Delirium	235 (23%)
	Adjustment disorders	76 (8%)
	Dementia	93 (9%)
	Major depressive disorders	28 (3%)
Outcome	Discharge/ Hospital transfer	892 (89%) / 110 (11%)

List of papers published in 2015

Journal

Please refer to the "Psycho-Oncology Service" sections.

List of papers published in 2015

Journal

1. Mori M, Shimizu C, Ogawa A, Okusaka T, Yoshida S, Morita T. A National Survey to Systematically Identify Factors Associated With Oncologists' Attitudes Toward End-of-Life Discussions: What Determines Timing of End-of-Life Discussions? Oncologist, 20:1304-1311, 2015

2. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Ogawa A, Fujisawa D, Sone T, Yoshiuchi K, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Personality traits and coping styles explain anxiety in lung cancer patients to a greater extent than other factors. Jpn J Clin Oncol, 45:456-463, 2015

3. Umezawa S, Fujisawa D, Fujimori M, Ogawa A, Matsushima E, Miyashita M. Prevalence, associated factors and source of support concerning supportive care needs among Japanese cancer survivors. Psychooncology, 24:635-642, 2015

4. Yokomichi N, Morita T, Nitto A, Takahashi N, Miyamoto S, Nishie H, Matsuoka J, Sakurai H, Ishihara T, Mori M, Tarumi Y, Ogawa A. Validation of the Japanese Version of the Edmonton Symptom Assessment System-Revised. J Pain Symptom Manage, 50:718-723, 2015

Book

1. Ogawa A. Long-term cognitive function. In: Bruera E, Higginson IJ, von Gunten CF, Morita T (eds), Textbook of Palliative Medicine and Supportive Care, Second Edition, USA, CRC Press, pp 1269-1275, 2015

Department of Diagnostic Radiology

Masahiko Kusumoto, Ryoko Iwata, Yoshihiro Nakagami, Tatsushi Kobayashi, Kaoru Shimada, Kotaro Sekiya, Hirohumi Kuno

Introduction

The Department of Diagnostic Radiology is committed to improving health through excellence in image-oriented patient care and research. Our Department performs more than 96,000 inpatient and outpatient procedures annually. The department also conducts clinical scientific research as well as basic scientific studies, with the results translated directly into better patient care.

Routine activities

Our Department has four multi-slice computed tomography (CT) scanners including two area detector CT scanners and one Dual Source CT, two 3T magnetic resonance imaging (MRI) systems, one interventional radiology (IR) CT system, one Multi-axis c-arm CT system, two gamma cameras with the capacity for single photon emission CT (SPECT), two digital radiographic (DR) systems for fluoroscopy, two mammographies (MMG), and four computed radiographic (CR) systems. Our IR-CT systems use digital subtraction angiography with multi-detector computerized tomography (MDCT). One is equipped with a 320 multi-slice CT. A positron emission tomography (PET) scanner and baby cyclotron have been installed, and tumor imaging using 18F-FDG (fluorodeoxyglucose) has been performed. These all-digital image systems enhance the efficacy of routine examinations.

This department has seven consulting radiologists and 22 technologists. As part of our routine activities, every effort is made to produce an integrated report covering almost all examinations, such as MMG, contrast radiological procedures, CT, MRI, RI, PET, angiography and IR, mainly transarterial chemoembolization (TACE).

The number of cases examined in 2015 is shown in the Table below. Several conferences are routinely held at our department including pre- and postoperative conferences. Furthermore, our Department contributes to decide treatment strategy through the image presentation at the weekly tumor board conference (especially, Hepatobiliary-Pancreatic and Head-Neck regions).

Research activities

The research activities of the Department of Diagnostic Radiology focus on diagnostic imaging and IR. These activities consist of 1) Development of new CT/MRI technology and 2) Development of new Nuclear Medicine tracers. The department also conducts clinical scientific research as well as basic scientific studies, with the results translated directly into better patient care.

1) Development of new CT/MRI technology

In the study with dual energy CT, for the larynx, hypopharynx, thyroid cancers and lymph node metastasis, the possibility of a quantitative evaluation with iodine uptake value measuring and histogram generation using monochromatic imaging technique have been confirmed. The results of this preliminary study have suggested that the quantitative analysis of tumors may aid differential diagnosis and the lymph node metastasis detection.

In 320-row area-detector CT, it is found that the effect of SEMAR (single energy metal artifact reduction: the algorithm to reduce metal artifacts without increasing the X-ray dose) influenced by the location of metal materials at the scan. In addition, it has been confirmed that the location adjustment of the metal materials can increase the effect of SEMAR and CT image quality. Furthermore, in the other study with 320-row area-detector CT, using the area-detector CT features as a four dimensional CT, the relationship between the perfusion parameters of the pancreas and the frequency of the

post-operative complication have been investigated.

In the 3-Tesla MR study, the imaging quality of mandibular cross-sectional multiplanar reconstruction (CS-MPR) using 3D sequences has been improved by optimization of the 3D imaging process. This optimization provides more accurate evaluation of bone marrow invasion.

In another study using 3T-MRI, the vessels of the tongue have been visualized by bright-blood time with a 3D sequence. It is suggested that this bright-blood imaging technique will provide more sensitive lymph node metastasis detection because the tongue cancer invasion into the lingual vascular bundle is known as a predictor of lymph node metastasis.

2) Development of new Nuclear Medicine tracers

Small interfering RNAs (siRNAs) were discovered as a promising gene silencing tool in research and in the clinic, and we succeeded in radiolabeling siRNA last year. However, siRNA is unstable for RNase in the living body. Therefore, the transfection reagent is usually required when siRNA is given to the living body.

We compared the degree of resistance against RNaseA among unlabeled siRNA, naked radiolabeled siRNA and radiolabeled siRNA with the transfection reagent. For Radiolabeled siRNA with the transfection reagent, slightly less than 60% of the RNA remained at 60 minutes after adding RNaseA. On the other hand, for naked unlabeled siRNA, almost all siRNA was broken down at seven minutes after adding RNaseA. For naked radiolabeled siRNA only, slightly over 30% of the RNA remained at 60 minutes after adding RNaseA, although we did not use the transfection reagent.

The results suggest that our labeled siRNA is stable not only as a complex with transfection reagents but also as naked labeled siRNA and should be deliverable to the specific regions overexpressing the target gene.

Table 1. Number of Anesthesia Cases

	2011	2012	2013	2014	2015
Plain X-ray examination	35,032	39,128	38,722	42,672	43,652
Mammography (MMG)	2,434	2,380	2,354	2,310	2,368
Fluoroscopic Imaging	3,903	4,029	4,628	4,748	4,691
CT	21,967	24,101	28,963	30,088	34,867
MRI	5,708	5,619	5,657	5,675	5,875
RI (Scintiscan)	1,582	1,586	1,363	1,396	1,302
PET	2,239	2,284	2,208	2,332	2,481
Angiography	656	742	511	801	807
Total	73,521	79,869	84,406	90,022	96,043

List of papers published in 2015

Journal

1. Sugimoto M, Takahashi S, Kobayashi T, Kojima M, Gotohda N, Satake M, Ochiai A, Konishi M. Pancreatic perfusion data and post-pancreaticoduodenectomy outcomes. J Surg Res, 194:441-449, 2015

2. Murata S, Onozawa S, Mine T, Ueda T, Sugihara F, Yasui D, Kumita S, Satake M. Retrograde-outflow percutaneous isolated hepatic perfusion using cisplatin: A pilot study on pharmacokinetics and feasibility. Eur Radiol, 25:1631-1638, 2015

3. Kakinuma R, Muramatsu Y, Kusumoto M, Tsuchida T, Tsuta K, Maeshima AM, Asamura H, Moriyama N. Solitary pure ground-glass nodules 5 mm or smaller: frequency of growth. Radiology, 276:873-882, 2015

4. Watanabe Y, Kusumoto M, Yoshida A, Suzuki K, Asamura H, Tsuta K. Surgically resected solitary cavitary lung adenocarcinoma: association between clinical, pathologic, and radiologic findings and prognosis. Ann Thorac Surg, 99:968-974, 2015

5. Okada H, Kaneda T, Sekiya K, Kawashima Y, Suemitsu M, Hayakawa Y, Sakae T. Basic study of parametric X-ray radiation for clinical diagnosis using 125MeV linear particle accelerator. J Hard Tissue Biol, 24:299-302, 2015

6. Kaneda T, Sekiya K, Suemitsu M, Sakae T, Hayakawa Y, Kawashima Y, Hirahara N, Muraoka H, Ito K, Muramatsu T, Ishida M, Okada H. Preliminary clinical application study of parametric X-rays in diagnostic imaging. Int J Oral-Med Sci, 14:8-12, 2015

7. Sekiya K, Ishida M, Sekiya K, Suemitsu M, Hara Y, Kaneda T. A case of impacted tooth in the maxillary sinus: CT findings. Int J Oral-Med Sci, 13:128-130, 2015

Department of Radiation Oncology

Tetsuo Akimoto, Naoki Nakamura, Sadatomo Zenda, Masakatsu Onozawa, Satoko Arahira, Masamichi Toshima, Atsushi Motegi, Yasuhiro Hirano

Introduction

Radiotherapy (RT) plays an essential role in the management of cancer patients. It is used as (1) a curative treatment for many patients with loco-regional localized malignant disease, (2) integrated therapy combined with chemotherapy and/or surgery, and (3) palliative treatment for patients for whom curative treatment is not a treatment option. In radiotherapeutic approaches, the radiation dose to the loco-regional tumor must be as high as possible, while the dose to the surrounding normal tissues should be kept as low as possible in order to maintain the severity of radiation-related complications within an acceptable level.

The primary aim of the Department of Radiation Oncology is to develop high precision RT such as intensity modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), stereotactic body RT (SBRT) and proton beam therapy (PBT) and establish the definitive role of RT in cancer treatment. Another important goal is to establish standard treatments for various cancers and optimal irradiation techniques including total dose, fractionation and radiation fields.

Routine activities

At present, the staff of the Radiation Oncology Department consists of seven consultant physicians (radiation oncologists), 19 radiation technologists, four medical physicists, one nurse, and one clerk. We have more than 1,000 new cases for conventional RT and 300 or more new patients for proton beam therapy every year, and quality assurances of both conventional RT and PBT are performed by medical physicists and radiation technologists, and the conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. RT and PBT are routinely based on three-dimensional radiation therapy planning and PBT using RT-dedicated multi-detector-row helical computed tomography (CT) scanning in order to confirm a precise radiation dose to the targeted tumors. Respiratory-gating has been applied especially in radiotherapeutic management for patients with lung, esophagus and liver cancers.

Selection of treatment approaches is determined through clinical conferences between radiation oncologists, surgical oncologists and medical oncologists. Many clinical trials involving RT as the sole or combined treatment modalities for various cancers are now in progress.

The section is responsible for conventional (photon-electron) RT that consists of 4 linear accelerators, a CT simulator, four treatment planning computer workstations, and other important devices. IMRT and IGRT have been routinely applied for head and neck cancer and prostate cancer. The section is also responsible for PBT that is composed of seven operating staff members and one technician for fabricating the compensator and aperture; they are sent from manufacturing companies and work in collaboration with the other staff members of the Department. PBT consists of two treatment rooms and both rooms are routinely used for rotational gantry treatment. The Department ensures quality assurance and regular maintenance of the PBT machines for precise dose delivery and safe treatment.

Research activities

In the Radiation Oncology Department, the following research activities are in progress:

1) Establishment of optimal combined approaches including RT and chemotherapy for locally advanced head and neck cancer, non-small cell

lung cancer and esophageal cancer, and so on.
2) Establishment of clinical usefulness of IMRT for head and neck cancer, localized prostate cancer and cervical esophageal cancer.
3) Hypofractionated IMRT for localized prostate cancer.
4) Hypofractionated PBT for localized prostate cancer.
5) Evaluation of feasibility of PBT combined with chemotherapy for inoperable locally advanced non-small cell lung cancer and locally advanced esophageal cancer.
6) Evaluation of long-term complications after PBT for pediatric malignancies.
7) The role of gene polymorphism in development of acute and late radiation-related complications.
8) Exploration of biomarkers for head and neck cancer.
9) Radiobiological investigation of cellular response to radiation and proton beam.

Clinical trials

The following in-house and multi-institutional clinical trials are in progress:

1) The Japan Clinical Oncology Group (JCOG) 0701: Accelerated fractionation vs. conventional fractionation radiation therapy for glottic cancer of T1-2N0M0 phase III study.
2) JCOG0701-A1: Evaluation of single-nucleotide polymorphisms (SNPs) in development of acute and late complications after accelerated fractionation and/or conventional fractionation radiation therapy for glottic cancer of T1-2N0M0.
3) JCOG1015: A phase II study of intensity modulated radiation therapy (IMRT) with chemotherapy for loco-regionally advanced nasopharyngeal cancer (NPC).
4) Phase II study of PBT for malignant melanoma of nasal cavity.
5) Phase II trial of concurrent chemoradiotherapy with 5-FU plus cisplatin for resectable squamous cell carcinoma of cervical esophagus.
6) The Japanese Radiation Oncology Study Group (JROSG) phase II trial of IMRT with concurrent chemoradiotherapy for resectable squamous cell carcinoma of cervical esophagus.
7) JCOG1208: A non-randomized confirmatory study of intensity modulated radiation therapy (IMRT) for T1-2N0-1M0 oropharyngeal cancer.
8) JCOG1008: Phase II/III trial of postoperative chemoradiotherapy comparing 3-weekly cisplatin with weekly cisplatin in high-risk patients with squamous cell carcinoma of head and neck
9) Dose escalation study of PBT combined with concurrent chemotherapy for locally advanced esophageal cancer.
10) JCOG1408: Phase III study of SBRT for stage I non-small cell lung cancer.

Education

We established education and training systems for residents and junior radiation oncologists through clinical conferences and lectures on radiation oncology, physics and radiation biology. In addition, a training course about quality assurance of radiation therapy has been regularly held for medical physicists and radiological technologists.

Future prospects

We are now aiming at the establishment of a system that can provide high-quality and safe high-precision radiation therapy. In addition, we would like to promote research and development of innovative technologies regarding radiation therapy, radiation biology and medical physics.

Table 1. Number of patients treated with radiation therapy during 2011-2015

	2011	2012	2013	2014	2015
New patients	1,489	1,575	1,877	1,847	1,830
IMRT	147	225	256	279	280

Table: The changes in the number of patients treated with RT

List of papers published in 2015

Journal

1. Tahara M, Kiyota N, Mizusawa J, Nakamura K, Hayashi R, Akimoto T, Hasegawa Y, Iwae S, Monden N, Matsuura K, Fujii H, Onozawa Y, Homma A, Kubota A, Fukuda H, Fujii M. Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). Cancer Sci, 106:726-733, 2015

2. Hotta K, Kohno R, Nagafuchi K, Yamaguchi H, Tansho R, Takada Y, Akimoto T. Evaluation of monitor unit calculation based on measurement and calculation with a simplified Monte Carlo method for passive beam delivery system in proton beam therapy. J Appl Clin Med Phys, 16:228-238, 2015

3. Mizowaki T, Aoki M, Nakamura K, Yorozu A, Kokubo M, Karasawa K, Kozuka T, Nakajima N, Sasai K, Akimoto T. Current status and outcomes of patients developing PSA recurrence after prostatectomy who were treated with salvage radiotherapy: a JROSG surveillance study. J Radiat Res, 56:750-756, 2015

4. Hashimoto Y, Akimoto T, Iizuka J, Tanabe K, Mitsuhashi N. Correlation between the changes in the EPIC QOL scores and the dose-volume histogram parameters in high-dose-rate brachytherapy combined with hypofractionated external beam radiation therapy for prostate cancer. Jpn J Clin Oncol, 45:81-87, 2015

5. Motegi A, Kawashima M, Arahira S, Zenda S, Toshima M, Onozawa M, Hayashi R, Akimoto T. Accelerated radiotherapy for T1 to T2 glottic cancer. Head Neck, 37:579-584, 2015

6. Zenda S, Ishi S, Akimoto T, Arahira S, Motegi A, Tahara M, Hayashi R, Asanuma C. DeCoP, a Dermatitis Control Program using a moderately absorbent surgical pad for head and neck cancer patients receiving radiotherapy: a retrospective analysis. Jpn J Clin Oncol, 45:433-438, 2015

7. Zenda S, Kawashima M, Arahira S, Kohno R, Nishio T, Tahara M, Hayashi R, Akimoto T. Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up. Int J Clin Oncol, 20:447-454, 2015

Department of Pathology and Clinical Laboratories

Atsushi Ochiai, Takeshi Kuwata, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Masato Sugano, Chisako Yamauchi, Eiichi Yoshikawa, Shigehisa Yoshida, Masahiro Inoue, Masahiro Karibe, Seiji Iwasaki, Miki Goto, Masaki Takeda, Satoru Sunohara, Hiromi Kimura, Yasuharu Hashimoto, Yukihiro Okano, Akiko Yamada, Mari Hisano, Mika Sasanuma, Aya Koike, Takuya Yamaguchi, Takuya Aiba, Keiko Nakai, Ayumi Setsuta, Mayumi Motohashi, Ayumi Nakanishi, Sayuri Shibayama, Izumi Suzuki, Yasuko Yoshihara, Kazumi Yamaguchi, Rie Taniguchi, Sudo Kumiko, Saki Nakamura, Kazuki Motohashi, Atsushi Watanabe, Eriko Iwamoto, Yasuteru Yamagishi, Kazumi Tamura, Asami Sekine, Nagisa Bouno, Rie Kuroiwa, Masayuki Ito, Michiko Iida, Yuki Soeda, Megumi Michikawa, Tomoko Seto, Emiko Yoshikawa, Yoshiko Ohtake, Miwa Yamada, Megumi Yamaguchi

Introduction

The Department of Pathology and Clinical Laboratories (DPCL) has two divisions: Pathology Division (PD) and Clinical Laboratory Division (CLD). Both divisions play a fundamental role in routine hospital service and support research activities at the National Cancer Center Hospital East (NCCHE).

DPCL received ISO15189:2007 accreditation in 2012, and successfully transited to the newest version (ISO15189:2012) in 2014, ensuring quality control and quality assurance of testing, including the one for clinical trials, performed in the departments. In 2015, two sections, Physiology and Supporting laboratory testing in clinical studies, received ISO15189:2012, ensuring the quality control and quality assurance of the testing, including the ones for clinical trials, performed in the departments with global standards.

Routine activities

Primarily, the routine activity at the PD is surgical pathology. The Number of samples examined in the department in 2015 is listed in Table 1.

The CLD consists of seven sections: i) general laboratory medicine, ii) hematology, iii) biochemistry/serology, iv) Physiology, v) Bacteriology, vi) Blood transfusion and vii) Supporting laboratory tests in clinical studies. The numbers of tests performed in each division are listed in Table 2 and 3. The total number of tests performed in the DPCL in 2015 increased to 7.5% compared with the previous year; including a 94.4% and a 12.9% increase in the Blood transfusion and Serology sections, respectively.

Research activities

All of the pathologists were involved in research activities at RCIO (Research Center for Innovative Oncology). All the technologists working in the department are also highly motivated to develop advanced diagnostic technologies and various results are presented in several meetings.

Clinical trials

Practically, the CLD participated in all of the clinical trials operated at the NCCHE by providing laboratory data. The section for supporting laboratory testing in clinical studies was transferred to the DPCL in June 2014. The section, coordinating with the pathology and physiology sections, reinforces quality control and quality assurance for clinical tests performed in clinical trials at the NCCHE.

Education

Clinicopathological conferences are held regularly with each clinical department/section. In the PD, conference-style training sessions are open weekly for the residents.

Future prospects

Pathological diagnosis and laboratory tests

play a fundamental role not only in routine hospital work but also in medical research. As an ISO15189-certified clinical laboratory, the DPCL will be continuously involved in investigating new diagnostic technologies, developing new drugs and conducting translational/clinical research in the NCCHE.

Table 1. Number of pathology and cytology samples examined in Pathology Division in 2015

Department	Biopsy	Surgical	Cytology	Autopsy
Digestive Endoscopy	4,951	0	4	0
Gastrointestinal Oncology	154	0	74	0
Breast Surgery	593	358	132	0
Head and Neck Surgery	621	391	388	0
Thoracic Surgery	433	531	530	1
Thoracic Oncology	784	3	907	1
Hematology and medical oncology	545	3	209	2
Hepatobiliary and Pancreatic Oncology	489	1	450	0
Urology	264	103	736	0
Upper Abdominal Surgery	186	473	226	1
Radiation Oncology	149	3	4	0
Lower Abdominal Surgery	83	398	19	0
Orthopedics	43	16	1	0
Esophageal Surgery	8	182	19	0
Head and Neck Oncology	34	1	11	0
Obstetrics and Gynecology	18	0	199	0
Dental division	10	0	0	0
Anesthesiology	3	0	2	0
Dermatology	16	0	0	0
Plastic Surgery	2	5	2	0
Palliative medicine	1	1	4	0
Others	24	1	7	0
Total	9,411	2,469	3,924	5

Table 2. Number of laboratory tests examined in Clinical Laboratory Division in 2014 and 2015

	2014	2015
General laboratory medicine	48,199	48,199
Hematology	302,752	302,752
Biochemistry	1,970,515	1,970,515
Serology	164,382	270,112
Blood transfusion	10,720	11,438
Bacteriology	26,870	29,917
Physiology	22,730	24,703
Total	2,383,461	2,846,826

Table 3. Number of cases and samples prepared in Clinical Laboratory Division for clinical trials in 2015

	Cases	Samples
General laboratory test	3,204	5,972
Electrocardiogram (ECG)	998	1,397
Pathology	864	4,273

List of papers published in 2015

Journal

1. Fujii S, Fujihara A, Natori K, Abe A, Kuboki Y, Higuchi Y, Aizawa M, Kuwata T, Kinoshita T, Yasui W, Ochiai A. TEM1 expression in cancer-associated fibroblasts is correlated with a poor prognosis in patients with gastric cancer. Cancer Med, 4:1667-1678, 2015

2. Shinohara S, Kuroda K, Shimokawa H, Kuwata T, Takenaka M, Chikaishi Y, Oka S, Hirai A, Imanishi N, Uramoto H, Tanaka F. Pleural dissemination of a mixed ground-glass opacity nodule treated as a nontuberculous mycobacterial infection for 6 years without growing remarkably. J Thorac Dis, 7:E370-E373, 2015

3. Ishikawa T, Takahashi J, Kasai M, Shiina T, Iijima Y, Takemura H, Mizoguchi H, Kuwata T. Support system for pathologists and researchers. J Pathol Inform, 6:34, 2015

4. Neri S, Ishii G, Hashimoto H, Kuwata T, Nagai K, Date H, Ochiai A. Podoplanin-expressing cancer-associated fibroblasts lead and enhance the local invasion of cancer cells in lung adenocarcinoma. Int J Cancer, 137:784-796, 2015

5. Nishida Y, Kuwata T, Nitta H, Dennis E, Aizawa M, Kinoshita T, Ohtsu A, Ochiai A. A novel gene-protein assay for evaluating HER2 status in gastric cancer: simultaneous analyses of HER2 protein overexpression and gene amplification reveal intratumoral heterogeneity. Gastric Cancer, 18:458-466, 2015

6. Nagatsuma AK, Aizawa M, Kuwata T, Doi T, Ohtsu A, Fujii H, Ochiai A. Expression profiles of HER2, EGFR, MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma. Gastric Cancer, 18:227-238, 2015

7. Sasaki T, Fuse N, Kuwata T, Nomura S, Kaneko K, Doi T, Yoshino T, Asano H, Ochiai A, Komatsu Y, Sakamoto N, Ohtsu A. Serum HER2 levels and HER2 status in tumor cells in advanced gastric cancer patients. Jpn J Clin Oncol, 45:43-48, 2015

8. Nakamura K, Kuwata T, Shimoda T, Mizusawa J, Katayama H, Kushima R, Taniguchi H, Sano T, Sasako M, Fukuda H. Determination of the optimal cutoff percentage of residual tumors to define the pathological response rate for gastric cancer treated with preoperative therapy (JCOG1004-A). Gastric Cancer, 18:597-604, 2015

Department of Experimental Therapeutics

Toshihiko Doi, Kiyotaka Yoh, Yoichi Naito, Takahiro Kogawa, Hideaki Takahashi, Tomoko Yamazaki, Yasutoshi Kuboki

Introduction

The Exploratory Oncology Research & Clinical Trial Center (NCC-EPOC) Phase I Group has been organized to promote early drug development especially the first in human (FIH) trial in 2012. The phase I group consists of two sub-units (NCCE-Kashiwa and NCC-Tsukiji), which are organized by each hospital. The goal of both/each unit is to perform initial clinical evaluations of promising new anti-cancer compounds emerging from laboratories. Our phase I unit is the largest program in both Japan and Asia, and we contribute to the development of new cancer drugs through early phase trials.

In April 2013, the Department of Experimental Therapeutics was launched to strongly promote the EPOC missions as previously described. The members of the Department of Experimental Therapeutics consist of specialists in their oncology fields. Also, we have conducted/contributed to IIT using yet-to-be-approved new drug and academia seeds.

Routine activities

This Department plays an important role in new anti-cancer drug development in our center as well as in Japan. The top priority is to conduct the FIH trials, while we also perform the phase I trials for solid tumors (that is, all comers). Recently, we joined a global phase I trial to accelerate new drug development in Japan. Web- and tele-conferences are held with EU and US sites, and we are discussing patient enrollment as well as further developmental strategy. Routine web-conferences are also held between Kashiwa and Tsukiji campuses every Friday morning, and we are sharing information about adverse events, patient enrollments and are referring candidates to each other to accelerate enrollment. Several IIT-FIH using new class seeds are conducted by each unit and also yet-to-be-approved company agents

Research activities

The elucidation of the proof of concept is essential in new anti-cancer drug development especially in the early phase; we conduct several translational research projects in collaboration with the adjoining research institute. In the Kashiwa campus, comprehensive genomic analyses, which is known as the ABC-study, is ongoing to facilitate patient enrollment for new molecular targeted drugs under investigation. Also, a new immune-monitoring system for immune agents has been established in the hospital; the system is controlled by Professor Nishikawa.

Clinical trials

In 2015, 38 phase I trials were conducted. (Table 1).

Table 1. Phase 1 Trials in 2015

No	Target	FIH	Target	Enrollment in 2014	Status
1	CDK4/6		Solid tumors	0	Closed
2	PD-L1		Solid tumors	2	Ongoing
3	FGFR	○	Solid tumors	0	Closed
4	FGFR	○	Solid tumors	3	Ongoing
5	CSC		Solid tumors	8	Ongoing
6	immuno checkpoint		Solid tumors	15	Ongoing
7	AKT		Solid tumors	3	Ongoing
8	HSP90	○	Solid tumors	3	Ongoing
9	HER2	○	Solid tumors	3	Ongoing
10	Chk-1		Solid tumors	2	Ongoing
11	PI3K6mTOR		Solid tumors	0	Ongoing
12	PD1		Solid tumors	0	Closed
13	ADC	○	Solid tumors	0	2015.1 Enrollment start
14	c-Met		Solid tumors	11	Ongoing
15	5FU enhancer		Solid tumors	14	Closed
16	anti-cancer-stem cell		Solid tumors	0	Closed
17	PTK2		Solid tumors	0	Closed
18	FGFR		Solid tumors	3	Ongoing
19	EGFR		Solid tumors	6	Closed
20	*****		Solid tumors	1	Ongoing
21	TEM-1		Solid tumors	0	Closed
22	PI3K		Solid tumors	0	Ongoing
23	MEK		Solid tumors	0	Closed
24	c-Met		Solid tumors	3	Ongoing
25	c-Met		Solid tumors	4	Ongoing
26	****		Solid tumors	0	Closed
27	FGFR	○	Solid tumors	14	Ongoing
28	IGFIR		Solid tumors	16	Ongoing
29	****		Solid tumors	2	Closed
30	****		Solid tumors	2	Ongoing
31	PI3K	○	Solid tumors	2	Ongoing
32	AKT	○	Solid tumors	10	Ongoing
33	****		Solid tumors	2	Ongoing
34	****	○	Solid tumors	7	Ongoing
35	****		Solid tumors	1	Ongoing
36	mTOR		Solid tumors	6	Ongoing
37	****		Solid tumors	5	Ongoing
38	****		Solid tumors	1	Ongoing
			Total enrollment	149	

FIH: first in human trial

List of papers published in 2015

Journal

1. Watanabe N, Umemura S, Niho S, Kirita K, Matsumoto S, Yoh K, Ohmatsu H, Goto K. Docetaxel for platinum-refractory advanced thymic carcinoma. Jpn J Clin Oncol, 45:665-669, 2015

2. Fouad TM, Kogawa T, Liu DD, Shen Y, Masuda H, El-Zein R, Woodward WA, Chavez-MacGregor M, Alvarez RH, Arun B, Lucci A, Krishnamurthy S, Babiera G, Buchholz TA, Valero V, Ueno NT. Overall survival differences between patients with inflammatory and noninflammatory breast cancer presenting with distant metastasis at diagnosis. Breast Cancer Res Treat, 152:407-416, 2015

3. Fujii T, Le Du F, Xiao L, Kogawa T, Barcenas CH, Alvarez RH, Valero V, Shen Y, Ueno NT. Effectiveness of an Adjuvant Chemotherapy Regimen for Early-Stage Breast Cancer: A Systematic Review and Network Meta-analysis. JAMA Oncol, 1:1311-1318, 2015

4. Kai M, Kogawa T, Liu DD, Fouad TM, Kai K, Niikura N, Hsu L, Willey JS, Theriault RL, Valero V, Ueno NT. Clinical characteristics and outcome of bone-only metastasis in inflammatory and noninflammatory breast cancers. Clin Breast Cancer, 15:37-42, 2015

5. Hayashi N, Niikura N, Masuda N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M, Kondo N, Naito Y, Honda Y, Matsui A, Fujisawa T, Oshitanai R, Yasojima H, Yamauchi H, Saji S, Iwata H. Prognostic factors of HER2-positive breast cancer patients who develop brain metastasis: a multicenter retrospective analysis. Breast Cancer Res Treat, 149:277-284, 2015

6. Mukai H, Saeki T, Shimada K, Naito Y, Matsubara N, Nakanishi T, Obaishi H, Namiki M, Sasaki Y. Phase 1 combination study of eribulin mesylate with trastuzumab for advanced or recurrent human epidermal growth factor receptor 2 positive breast cancer. Invest New Drugs, 33:119-127, 2015

7. Yoshida T, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Ohe Y, Goto K. RECIST progression patterns during EGFR tyrosine kinase inhibitor treatment of advanced non-small cell lung cancer patients harboring an EGFR mutation. Lung Cancer, 90:477-483, 2015

8. Daga H, Takeda K, Okada H, Miyazaki M, Ueda S, Kaneda H, Okamoto I, Yoh K, Goto K, Konishi K, Sarashina A, Tanaka T, Kaiser R, Nakagawa K. Phase I study of nintedanib in combination with pemetrexed as second-line treatment of Japanese patients with advanced non-small cell lung cancer. Cancer Chemother Pharmacol, 76:1225-1233, 2015

9. Ono M, Tsuda H, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Kinoshita T, Fujiwara Y. Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers. Breast Cancer, 22:141-152, 2015

10. Yoshida T, Ishii G, Goto K, Neri S, Hashimoto H, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Iida S, Niimi A, Nagai K, Ohe Y, Ochiai A. Podoplanin-positive cancer-associated fibroblasts in the tumor microenvironment induce primary resistance to EGFR-TKIs in lung adenocarcinoma with EGFR mutation. Clin Cancer Res, 21:642-651, 2015

11. Yagishita S, Horinouchi H, Katsui Taniyama T, Nakamichi S, Kitazono S, Mizugaki H, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. Int J Radiat Oncol Biol Phys, 91:140-148, 2015

12. Miura T, Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Takahashi H, Furuse J, Inagaki M, Higashi S, Kato H, Terao K, Ochiai A. Characterization of patients with advanced pancreatic cancer and high serum interleukin-6 levels. Pancreas, 44:756-763, 2015

13. Fujii S, Fujihara A, Natori K, Abe A, Kuboki Y, Higuchi Y, Aizawa M, Kuwata T, Kinoshita T, Yasui W, Ochiai A. TEM1 expression in cancer-associated fibroblasts is correlated with a poor prognosis in patients with gastric cancer. Cancer Med, 4:1667-1678, 2015

14. Komatsu Y, Doi T, Sawaki A, Kanda T, Yamada Y, Kuss I, Demetri GD, Nishida T. Regorafenib for advanced gastrointestinal stromal tumors following imatinib and sunitinib treatment: a subgroup analysis evaluating Japanese patients in the phase III GRID trial. Int J Clin Oncol, 20:905-912, 2015

15. Sugiyama E, Umemura S, Nomura S, Kirita K, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Ohe Y, Goto K. Impact of single nucleotide polymorphisms on severe hepatotoxicity induced by EGFR tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring EGFR mutations. Lung Cancer, 90:307-313, 2015

16. Hishida T, Tsuboi M, Shukuya T, Takamochi K, Sakurai H, Yoh K, Ohashi Y, Kunitoh H. Multicenter observational cohort study of post-operative treatment for completely resected non-small-cell lung cancer of pathological stage I (T1 >2 cm and T2 in TNM classification version 6). Jpn J Clin Oncol, 45:499-501, 2015

17. Udagawa H, Ishii G, Morise M, Umemura S, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A, Ohe Y. Comparison of the expression levels of molecular markers among the peripheral area and central area of primary tumor and metastatic lymph node tumor in patients with squamous cell carcinoma of the lung. J Cancer Res Clin Oncol, 141:1417-1425, 2015

18. Koriyama H, Ishii G, Yoh K, Neri S, Morise M, Umemura S, Matsumoto S, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A. Presence of podoplanin-positive cancer-associated fibroblasts in surgically resected primary lung adenocarcinoma predicts a shorter progression-free survival period in patients with recurrences who received platinum-based chemotherapy. J Cancer Res Clin Oncol, 141:1163-1170, 2015

19. Doi T, Tamura K, Tanabe Y, Yonemori K, Yoshino T, Fuse N, Kodaira M, Bando H, Noguchi K, Shimamoto T, Ohtsu A. Phase 1 pharmacokinetic study of the oral pan-AKT inhibitor MK-2206 in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:409-416, 2015

20. Asao T, Nokihara H, Yoh K, Niho S, Goto K, Ohmatsu H, Kubota K, Yamamoto N, Sekine I, Kunitoh H, Fujiwara Y, Ohe Y. Phase II study of amrubicin at a dose of 45 mg/m2 in patients with previously treated small-cell lung cancer. Jpn J Clin Oncol, 45:941-946, 2015

21. Doi T, Yoshino T, Shitara K, Matsubara N, Fuse N, Naito Y, Uenaka K, Nakamura T, Hynes SM, Lin AB. Phase I study of LY2603618, a CHK1 inhibitor, in combination with gemcitabine in Japanese patients with solid tumors. Anticancer Drugs, 26:1043-1053, 2015

22. Kawazoe A, Shitara K, Fukuoka S, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yamanaka T, Doi T, Ohtsu A, Yoshino T. A retrospective observational study of clinicopathological features of KRAS, NRAS, BRAF and PIK3CA mutations in Japanese patients with metastatic colorectal cancer. BMC Cancer, 15:258, 2015

23. Kawazoe A, Shitara K, Fukuoka S, Noguchi M, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yoshino T, Ohtsu A, Doi T. Clinical outcomes in 66 patients with advanced gastric cancer treated in phase I trials: the NCCHE experience. Invest New Drugs, 33:664-670, 2015

24. Oh DY, Doi T, Shirao K, Lee KW, Park SR, Chen Y, Yang L, Valota O, Bang YJ. Phase I Study of Axitinib in Combination with Cisplatin and Capecitabine in Patients with Previously Untreated Advanced Gastric Cancer. Cancer Res Treat, 47:687-696, 2015

25. Ikeda M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Kondo S, Morizane C, Ueno H, Okusaka T. Chemotherapy for advanced poorly differentiated pancreatic neuroendocrine carcinoma. J Hepatobiliary Pancreat Sci, 22:623-627, 2015

26. Takahashi H, Kaniwa N, Saito Y, Sai K, Hamaguchi T, Shirao K, Shimada Y, Matsumura Y, Ohtsu A, Yoshino T, Doi T, Takahashi A, Odaka Y, Okuyama M, Sawada J, Sakamoto H, Yoshida T. Construction of possible integrated predictive index based on EGFR and ANXA3 polymorphisms for chemotherapy response in fluoropyrimidine-treated Japanese gastric cancer patients using a bioinformatic method. BMC Cancer, 15:718, 2015

27. Ueda S, Satoh T, Gotoh M, Gao L, Doi T. A phase ib study of safety and pharmacokinetics of ramucirumab in combination with paclitaxel in patients with advanced gastric adenocarcinomas. Oncologist, 20:493-494, 2015

28. Kurose K, Ohue Y, Wada H, Iida S, Ishida T, Kojima T, Doi T, Suzuki S, Isobe M, Funakoshi T, Kakimi K, Nishikawa H, Udono H, Oka M, Ueda R, Nakayama E. Phase Ia Study of FoxP3+ CD4 Treg Depletion by Infusion of a Humanized Anti-CCR4 Antibody, KW-0761, in Cancer Patients. Clin Cancer Res, 21:4327-4336, 2015

29. Nishio M, Horiike A, Nokihara H, Horinouchi H, Nakamichi S, Wakui H, Ohyanagi F, Kudo K, Yanagitani N, Takahashi S, Kuboki Y, Yamamoto N, Yamada Y, Abe M, Tahata T, Tamura T. Phase I study of the anti-MET antibody onartuzumab in patients with solid tumors and MET-positive lung cancer. Invest New Drugs, 33:632-640, 2015

30. Okusaka T, Ueno H, Morizane C, Kondo S, Sakamoto Y, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Ikeda M. Cytotoxic chemotherapy for pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci, 22:628-633, 2015

31. Takahashi H, Ikeda M, Kumada T, Osaki Y, Kondo S, Kusumoto S, Ohkawa K, Nadano S, Furuse J, Kudo M, Ito K, Yokoyama M, Okusaka T, Shimoyama M, Mizokami M. Multicenter cooperative case survey of hepatitis B virus reactivation by chemotherapeutic agents. Hepatol Res, 45:1220-1227, 2015

32. Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, Goto K. Beyond *ALK-RET*, *ROS1* and other oncogene fusions in lung cancer. Transl Lung Cancer Res, 4:156-164, 2015

33. Nagatsuma AK, Aizawa M, Kuwata T, Doi T, Ohtsu A, Fujii H, Ochiai A. Expression profiles of HER2, EGFR, MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma. Gastric Cancer, 18:227-238, 2015

34. Shinohara A, Ikeda M, Okuyama H, Kobayashi M, Funazaki H, Mitsunaga S, Shimizu S, Ohno I, Takahashi H, Ichida Y, Takahashi K, Okusaka T, Saitoh S. Efficacy of prophylactic minocycline treatment for skin toxicities induced by erlotinib plus gemcitabine in patients with advanced pancreatic cancer: a retrospective study. Am J Clin Dermatol, 16:221-229, 2015

35. Sasaki T, Fuse N, Kuwata T, Nomura S, Kaneko K, Doi T, Yoshino T, Asano H, Ochiai A, Komatsu Y, Sakamoto N, Ohtsu A. Serum HER2 levels and HER2 status in tumor cells in advanced gastric cancer patients. Jpn J Clin Oncol, 45:43-48, 2015

36. Okita K, Izumi N, Ikeda K, Osaki Y, Numata K, Ikeda M, Kokudo N, Imanaka K, Nishiguchi S, Kondo S, Nishigaki Y, Shiomi S, Ueshima K, Isoda N, Karino Y, Kudo M, Tanaka K, Kaneko S, Moriwaki H, Makuuchi M, Okusaka T, Hayashi N, Ohashi Y, Kumada H, Peretinoin Study Group. Survey of survival among patients with hepatitis C virus-related hepatocellular carcinoma treated with peretinoin, an acyclic retinoid, after the completion of a randomized, placebo-controlled trial. J Gastroenterol, 50:667-674, 2015

37. Okuyama H, Ikeda M, Kuwahara A, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Senda S, Okusaka T. Prognostic factors in patients with hepatocellular carcinoma refractory or intolerant to sorafenib. Oncology, 88:241-246, 2015

38. Doi T, Yoshino T, Fuse N, Boku N, Yamazaki K, Koizumi W, Shimada K, Takinishi Y, Ohtsu A. Phase I study of TAS-102 and irinotecan combination therapy in Japanese patients with advanced colorectal cancer. Invest New Drugs, 33:1068-1077, 2015

39. Kogawa T, Fouad TM, Wei C, Masuda H, Kai K, Fujii T, El-Zein R, Chavez-MacGregor M, Litton JK, Brewster A, Alvarez RH, Hortobagyi GN, Valero V, Theriault R, Ueno NT. Association of Body Mass Index Changes during Neoadjuvant Chemotherapy with Pathologic Complete Response and Clinical Outcomes in Patients with Locally Advanced Breast Cancer. J Cancer, 6:310-318, 2015

40. Enomoto Y, Kenmotsu H, Watanabe N, Baba T, Murakami H, Yoh K, Ogura T, Takahashi T, Goto K, Kato T. Efficacy and Safety of Combined Carboplatin, Paclitaxel, and Bevacizumab for Patients with Advanced Non-squamous Non-small Cell Lung Cancer with Pre-existing Interstitial Lung Disease: A Retrospective Multi-institutional Study. Anticancer Res, 35:4259-4263, 2015

41. Soria JC, Wu YL, Nakagawa K, Kim SW, Yang JJ, Ahn MJ, Wang J, Yang JC, Lu Y, Atagi S, Ponce S, Lee DH, Liu Y, Yoh K, Zhou JY, Shi X, Webster A, Jiang H, Mok TS. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol, 16:990-998, 2015

42. Takahashi A, Ishii G, Neri S, Yoshida T, Hashimoto H, Suzuki S, Umemura S, Matsumoto S, Yoh K, Niho S, Goto K, Ohmatsu H, Nagai K, Gemma A, Ohe Y, Ochiai A. Podoplanin-expressing cancer-associated fibroblasts inhibit small cell lung cancer growth. Oncotarget, 6:9531-9541, 2015

43. Watanabe N, Niho S, Kirita K, Umemura S, Matsumoto S, Yoh K, Ohmatsu H, Goto K. Second-line docetaxel for patients with platinum-refractory advanced non-small cell lung cancer and interstitial pneumonia. Cancer Chemother Pharmacol, 76:69-74, 2015

44. Watanabe N, Niho S, Kirita K, Umemura S, Matsumoto S, Yoh K, Ohmatsu H, Goto K. Vinorelbine and cisplatin in patients with advanced non-small cell lung cancer with interstitial pneumonia. Anticancer Res, 35:1697-1701, 2015

Office of Safety Management

Tomonori Yano, Keiji Okinaka, Masami Muto, Hisae Matsuhashi, Masahito Yonemura, Chika Hara

Introduction

The Office of Safety Management has been created as the department responsible for cross-organizational safety management in our hospital in order to practice best medical service and care for cancer patients.

Routine activities

This year, we organized the medical safety reporting system both in clinical practice and clinical trials to clarify the governance of the directors of our hospital as the top authority. And, we started the medical record survey of all in-hospital death cases, mortality and morbidity conferences, and prompt case study conferences in the hospital in order to correspond to the medical accident investigation system that started this October.

An infectious disease physician arrived at our hospital this year, and a support system for treatment of infectious diseases related to cancer itself or anti-cancer treatment was put in place. In addition, we also enhanced the infectious control abilities of staff at our hospital.

Research activities

The total number of cases reported was 2,832; from doctors: 296 cases (10%), from nurses: 2,169 cases (77%), from pharmacists: 209 cases (7%), from radiological technicians 70 cases (2%), from laboratory technicians: 22 cases (1%), from nutritionists: 20 cases (1%), from clerical staff: 15 cases (1%), and from others: 31 cases (1%).

Education

Medical safety

Training course of Team Strategies and Tools to Enhance Performance and Patient Safety (STEPPS), Training course of basic life support (BLS) and advanced cardiovascular life support (ACLS)

Infectious control

Countermeasures for tuberculosis, Countermeasures for flu

Future prospects

This year, we clarified the medical safety reporting system, and it resulted in an increase in the incident report number. We could improve the awareness of medical safety of all the staff. In addition, infectious disease physicians arrived at our hospital, making the office more efficient. Future goals, including for next year, are zero patient misidentifications, doubling of incident reporting from non-nursing staff, and prevention of infectious outbreaks, and we will continue to make every effort in order to achieve these goals.

Rare Cancer Center

(NCCH) Akira Kawai, Yoshitaka Narita, Shigenobu Suzuki, Seiichi Yoshimoto, Kan Yonemori, Mayu Yunokawa, Makoto Kodaira, Tatsunori Shimoi, Yasushi Goto, Yoshitaka Honma, Chigusa Morizane, Motokiyo Komiyama, Tomoyasu Kato, Hirokazu Chuuman, Yoshikazu Tanzawa, Eisuke Kobayashi, Makoto Endo, Naoya Yamazaki, Arata Tsutsumida, Akira Takahashi, Kenjiro Namikawa, Wataru Munakata, Chitose Ogawa, Ayumu Arakawa, Miyuki Sone, Shunsuke Sugawara, Hiroshi Igaki, Kana Takahashi, Akihiko Yoshida, Noboru Yamamoto, Shunsuke Kondo, Koichi Ichimura, Tadashi Kondo, Takahiro Higashi, Takuro Sakurai, Makiko Murase, Yoko Katoh, Natumi Takeuchi,
(NCCHE) Naoto Gotohda, Tetsuo Akimoto, Fumihiko Nakatani, Ako Hosono, Toshihiko Doi, Yoichi Naito, Junya Ueno

Introduction

The Rare Cancer Center was launched in December 2013 and officially opened in June 2014 as a multidisciplinary team to take measures against the innate problems associated with rare cancers. Based on discussions, rare cancers are defined as those with an incidence < 6/100,000/year. Although each rare cancer is rare in itself, when the number of each rare cancer is combined, it corresponds to up to 15% of all new cancer diagnoses. Information on rare cancers is scarce. Rare cancers are often inadequately diagnosed and treated in relation both to lack of knowledge and clinical expertise. Patients with rare cancers face great difficulty in having their diseases treated adequately.

Activities

The Rare Cancer Center plays a central role in the treating and managing of rare cancers in the National Cancer Center (NCC).

The mission statements of the Rare Cancer Center are as follows:

I) Establishing a vital network of diagnosis and treatment for rare cancers in the NCC Hospital and Hospital East.
II) Reviewing the problems associated with rare cancers in Japan and making proposals and taking up the issues as medical professionals.

To enable the Center to play its role, a total of 45 doctors, nurses and researchers dealing with rare cancers have joined as members of the Center. Each staff member of the Rare Cancer Center provides specialized, high-quality medical care to patients with rare cancers in cooperation with his/her Department staff.

The Rare Cancer Center provides consultation to the patients and relatives with rare cancers on the telephone (Rare Cancer Hotline). The number of telephone call was 3,006 cases in 2015. (Figure 1) The Center also provides comprehensive, scientifically based, up-to-date unbiased information about rare cancers to all patients, families and health professionals fighting against rare cancers via its website (Rare Cancer Center Homepage). The Rare Cancer Center organized the 1st International Cancer Research Symposium "Rare Cancers: Seeking Ideal Medical Care" on February 12 to 13, 2015. Also, staff of the Rare Cancer Center served as members of the committee on rare cancers (March to August 2015) set up by the Ministry of Health, Labour and Welfare.

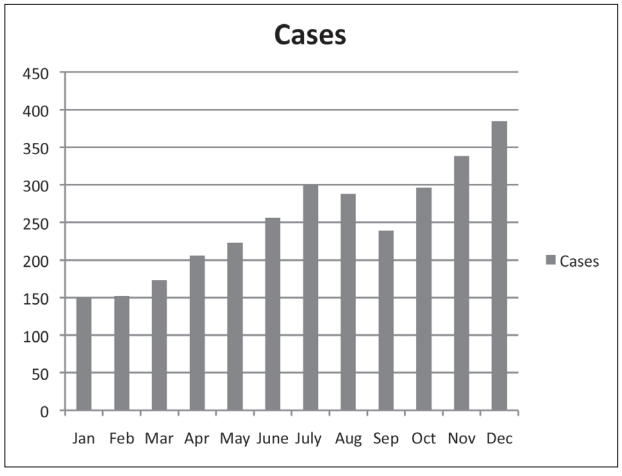


Figure 1. The Number of telephone calls to the Rare Cancer Hotline in 2015

List of papers published in 2015

Journal

1. Tahara M, Kiyota N, Mizusawa J, Nakamura K, Hayashi R, Akimoto T, Hasegawa Y, Iwae S, Monden N, Matsuura K, Fujii H, Onozawa Y, Homma A, Kubota A, Fukuda H, Fujii M. Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). Cancer Sci, 106:726-733, 2015

2. Kato T, Takashima A, Kasamatsu T, Nakamura K, Mizusawa J, Nakanishi T, Takeshima N, Kamiura S, Onda T, Sumi T, Takano M, Nakai H, Saito T, Fujiwara K, Yokoyama M, Itamochi H, Takehara K, Yokota H, Mizunoe T, Takeda S, Sonoda K, Shiozawa T, Kawabata T, Honma S, Fukuda H, Yaegashi N, Yoshikawa H, Konishi I, Kamura T, Gynecologic Oncology Study Group of the Japan Clinical Oncology Group. Clinical tumor diameter and prognosis of patients with FIGO stage IB1 cervical cancer (JCOG0806-A). Gynecol Oncol, 137:34-39, 2015

3. Hayashi N, Niikura N, Masuda N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M, Kondo N, Naito Y, Honda Y, Matsui A, Fujisawa T, Oshitanai R, Yasojima H, Yamauchi H, Saji S, Iwata H. Prognostic factors of HER2-positive breast cancer patients who develop brain metastasis: a multicenter retrospective analysis. Breast Cancer Res Treat, 149:277-284, 2015

4. Mukai H, Saeki T, Shimada K, Naito Y, Matsubara N, Nakanishi T, Obaishi H, Namiki M, Sasaki Y. Phase 1 combination study of eribulin mesylate with trastuzumab for advanced or recurrent human epidermal growth factor receptor 2 positive breast cancer. Invest New Drugs, 33:119-127, 2015

5. Yamazaki N, Kiyohara Y, Sugaya N, Uhara H. Phase I/II study of vemurafenib in patients with unresectable or recurrent melanoma with BRAF(V) (600) mutations. J Dermatol, 42:661-666, 2015

6. Yamazaki N, Tanaka R, Tsutsumida A, Namikawa K, Eguchi H, Omata W, Oashi K, Ogawa T, Hayashi A, Nakamura N, Tsuta K. BRAF V600 mutations and pathological features in Japanese melanoma patients. Melanoma Res, 25:9-14, 2015

7. Yamazaki N, Kiyohara Y, Uhara H, Fukushima S, Uchi H, Shibagaki N, Tsutsumida A, Yoshikawa S, Okuyama R, Ito Y, Tokudome T. Phase II study of ipilimumab monotherapy in Japanese patients with advanced melanoma. Cancer Chemother Pharmacol, 76:997-1004, 2015

8. Yamazaki N, Uhara H, Fukushima S, Uchi H, Shibagaki N, Kiyohara Y, Tsutsumida A, Namikawa K, Okuyama R, Otsuka Y, Tokudome T. Phase II study of the immune-checkpoint inhibitor ipilimumab plus dacarbazine in Japanese patients with previously untreated, unresectable or metastatic melanoma. Cancer Chemother Pharmacol, 76:969-975, 2015

9. Sakaizawa K, Ashida A, Uchiyama A, Ito T, Fujisawa Y, Ogata D, Matsushita S, Fujii K, Fukushima S, Shibayama Y, Hatta N, Takenouchi T, Uehara J, Okuyama R, Yamazaki N, Uhara H. Clinical characteristics associated with BRAF, NRAS and KIT mutations in Japanese melanoma patients. J Dermatol Sci, 80:33-37, 2015

10. Nakamura Y, Ohara K, Kishi A, Teramoto Y, Sato S, Fujisawa Y, Fujimoto M, Otsuka F, Hayashi N, Yamazaki N, Yamamoto A. Effects of non-amputative wide local excision on the local control and prognosis of in situ and invasive subungual melanoma. J Dermatol, 42:861-866, 2015

11. Sato S, Nakamura Y, Shimizu M, Yamada K, Teramoto Y, Yamazaki N, Yamamoto A. Giant pedunculated pilomatrix carcinoma on the upper limb: A rare clinical appearance. Eur J Dermatol, 25:91-92, 2015

12. Arita H, Narita Y, Matsushita Y, Fukushima S, Yoshida A, Takami H, Miyakita Y, Ohno M, Shibui S, Ichimura K. Development of a robust and sensitive pyrosequencing assay for the detection of *IDH1/2* mutations in gliomas. Brain Tumor Pathol, 32:22-30, 2015

13. Takami H, Yoshida A, Fukushima S, Arita H, Matsushita Y, Nakamura T, Ohno M, Miyakita Y, Shibui S, Narita Y, Ichimura K. Revisiting *TP53* Mutations and Immunohistochemistry-A Comparative Study in 157 Diffuse Gliomas. Brain Pathol, 25:256-265, 2015

14. Fukushima S, Yoshida A, Narita Y, Arita H, Ohno M, Miyakita Y, Ichimura K, Shibui S. Multinodular and vacuolating neuronal tumor of the cerebrum. Brain Tumor Pathol, 32:131-136, 2015

15. Murakami N, Yoshimoto S, Matsumoto F, Ueno T, Ito Y, Watanabe S, Kobayashi K, Harada K, Kitaguchi M, Sekii S, Takahashi K, Yoshio K, Inaba K, Morota M, Sumi M, Saito Y, Itami J. Severe gastrointestinal bleeding in patients with locally advanced head and neck squamous cell carcinoma treated by concurrent radiotherapy and Cetuximab. J Cancer Res Clin Oncol, 141:177-184, 2015

16. Ono M, Tsuda H, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Kinoshita T, Fujiwara Y. Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers. Breast Cancer, 22:141-152, 2015

17. Yamamoto H, Ando M, Aogi K, Iwata H, Tamura K, Yonemori K, Shimizu C, Hara F, Takabatake D, Hattori M, Asakawa T, Fujiwara Y. Phase I and pharmacokinetic study of trastuzumab emtansine in Japanese patients with HER2-positive metastatic breast cancer. Jpn J Clin Oncol, 45:12-18, 2015

18. Kinjo Y, Nonaka S, Oda I, Abe S, Suzuki H, Yoshinaga S, Maki D, Yoshimoto S, Taniguchi H, Saito Y. The short-term and long-term outcomes of the endoscopic resection for the superficial pharyngeal squamous cell carcinoma. Endosc Int Open, 3:E266-E273, 2015

19. Sone M, Nakajima Y, Woodhams R, Shioyama Y, Tsurusaki M, Hiraki T, Yoshimatsu M, Hyodoh H, Kubo T, Takeda S, Minakami H. Interventional radiology for critical hemorrhage in obstetrics: Japanese Society of Interventional Radiology (JSIR) procedural guidelines. Jpn J Radiol, 33:233-240, 2015

20. Asano N, Yoshida A, Ogura K, Kobayashi E, Susa M, Morioka H, Iwata S, Ishii T, Hiruma T, Chuman H, Kawai A. Prognostic Value of Relevant Clinicopathologic Variables in Epithelioid Sarcoma: A Multi-Institutional Retrospective Study of 44 Patients. Ann Surg Oncol, 22:2624-2632, 2015

21. Suzuki M, Shiraishi K, Yoshida A, Shimada Y, Suzuki K, Asamura H, Furuta K, Kohno T, Tsuta K. *HER2* gene mutations in non-small cell lung carcinomas: concurrence with *Her2* gene amplification and her2 protein expression and phosphorylation. Lung Cancer, 87:14-22, 2015

22. Miyamoto S, Fukunaga Y, Fujiki M, Nakatni F, Tanzawa Y, Sakuraba M. Accompanying artery of sciatic nerve as recipient vessel for free-flap transfer: a computed tomographic angiography study and case reports. Microsurgery, 35:284-289, 2015

23. Kikuta K, Kubota D, Yoshida A, Morioka H, Toyama Y, Chuuman H, Kawai A. An analysis of factors related to the tail-like pattern of myxofibrosarcoma seen on MRI. Skeletal Radiol, 44:55-62, 2015

24. Yagishita S, Horinouchi H, Katsui Taniyama T, Nakamichi S, Kitazono S, Mizugaki H, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. Int J Radiat Oncol Biol Phys, 91:140-148, 2015

25. Yoshida A, Asano N, Kawai A, Kawamoto H, Nakazawa A, Kishimoto H, Kushima R. Differential SALL4 immunoexpression in malignant rhabdoid tumours and epithelioid sarcomas. Histopathology, 66:252-261, 2015

26. Ogura K, Uehara K, Akiyama T, Iwata S, Shinoda Y, Kobayashi E, Saita K, Yonemoto T, Kawano H, Chuman H, Davis AM, Kawai A. Cross-cultural adaptation and validation of the Japanese version of the Toronto Extremity Salvage Score (TESS) for patients with malignant musculoskeletal tumors in the lower extremities. J Orthop Sci, 20:1098-1105, 2015

27. Ogura K, Fujiwara T, Yasunaga H, Matsui H, Jeon DG, Cho WH, Hiraga H, Ishii T, Yonemoto T, Kamoda H, Ozaki T, Kozawa E, Nishida Y, Morioka H, Hiruma T, Kakunaga S, Ueda T, Tsuda Y, Kawano H, Kawai A. Development and external validation of nomograms predicting distant metastases and overall survival after neoadjuvant chemotherapy and surgery for patients with nonmetastatic osteosarcoma: A multi-institutional study. Cancer, 121:3844-3852, 2015

28. Kimura H, Yamamoto N, Shirai T, Nishida H, Hayashi K, Tanzawa Y, Takeuchi A, Igarashi K, Inatani H, Shimozaki S, Kato T, Aoki Y, Higuchi T, Tsuchiya H. Efficacy of triplet regimen antiemetic therapy for chemotherapy-induced nausea and vomiting (CINV) in bone and soft tissue sarcoma patients receiving highly emetogenic chemotherapy, and an efficacy comparison of single-shot palonosetron and consecutive-day granisetron for CINV in a randomized, single-blinded crossover study. Cancer Med, 4:333-341, 2015

29. Ogura K, Miyamoto S, Sakuraba M, Fujiwara T, Chuman H, Kawai A. Intercalary reconstruction after wide resection of malignant bone tumors of the lower extremity using a composite graft with a devitalized autograft and a vascularized fibula. Sarcoma, 2015:861575, 2015

30. Joo MW, Shin SH, Kang YK, Kawai A, Kim HS, Asavamongkolkul A, Jeon DG, Kim JD, Niu X, Tsuchiya H, Puri A, Wang EH, Chung SH, Chung YG. Osteosarcoma in Asian Populations Over the Age of 40 Years: A Multicenter Study. Ann Surg Oncol, 22:3557-3564, 2015

31. Ogura K, Sakuraba M, Miyamoto S, Fujiwara T, Chuman H, Kawai A. Pelvic ring reconstruction with a double-barreled free vascularized fibula graft after resection of malignant pelvic bone tumor. Arch Orthop Trauma Surg, 135:619-625, 2015

32. Zhang L, Lyer AK, Yang X, Kobayashi E, Guo Y, Mankin H, Hornicek FJ, Amiji MM, Duan Z. Polymeric nanoparticle-based delivery of microRNA-199a-3p inhibits proliferation and growth of osteosarcoma cells. Int J Nanomedicine, 10:2913-2924, 2015

33. Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, Morioka H, Hiraga H, Hiruma T, Kunisada T, Matsumine A, Tanase T, Hasegawa T, Takahashi S. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol, 16:406-416, 2015

34. Takai E, Totoki Y, Nakamura H, Morizane C, Nara S, Hama N, Suzuki M, Furukawa E, Kato M, Hayashi H, Kohno T, Ueno H, Shimada K, Okusaka T, Nakagama H, Shibata T, Yachida S. Clinical utility of circulating tumor DNA for molecular assessment in pancreatic cancer. Sci Rep, 5:18425, 2015

35. Kataoka K, Nagata Y, Kitanaka A, Shiraishi Y, Shimamura T, Yasunaga J, Totoki Y, Chiba K, Sato-Otsubo A, Nagae G, Ishii R, Muto S, Kotani S, Watatani Y, Takeda J, Sanada M, Tanaka H, Suzuki H, Sato Y, Shiozawa Y, Yoshizato T, Yoshida K, Makishima H, Iwanaga M, Ma G, Nosaka K, Hishizawa M, Itonaga H, Imaizumi Y, Munakata W, Ogasawara H, Sato T, Sasai K, Muramoto K, Penova M, Kawaguchi T, Nakamura H, Hama N, Shide K, Kubuki Y, Hidaka T, Kameda T, Nakamaki T, Ishiyama K, Miyawaki S, Yoon SS, Tobinai K, Miyazaki Y, Takaori-Kondo A, Matsuda F, Takeuchi K, Nureki O, Aburatani H, Watanabe T, Shibata T, Matsuoka M, Miyano S, Shimoda K, Ogawa S. Integrated molecular analysis of adult T cell leukemia/lymphoma. Nat Genet, 47:1304-1315, 2015

36. Narita Y, Shibui S, Committee of Brain Tumor Registry of Japan Supported by the Japan Neurosurgical Society. Trends and outcomes in the treatment of gliomas based on data during 2001-2004 from the Brain Tumor Registry of Japan. Neurol Med Chir (Tokyo), 55:286-295, 2015

37. Narita Y. Bevacizumab for glioblastoma. Ther Clin Risk Manag, 11:1759-1765, 2015

38. Okita Y, Narita Y, Miyahara R, Miyakita Y, Ohno M, Shibui S. Health-related quality of life in long-term survivors with Grade II gliomas: the contribution of disease recurrence and Karnofsky Performance Status. Jpn J Clin Oncol, 45:906-913, 2015

39. Yoshida A, Kamata T, Iwasa T, Watanabe S, Tsuta K. Myocardial Sleeve Tissues in Surgical Lung Specimens. Am J Surg Pathol, 39:1427-1432, 2015

40. Katsuya Y, Yoshida A, Watanabe S, Tsuta K. Tumour-to-tumour metastasis from papillary thyroid carcinoma with BRAF mutation to lung adenocarcinoma with EGFR mutation: the utility of mutation-specific antibodies. Histopathology, 67:262-266, 2015

41. Kamata T, Yoshida A, Kosuge T, Watanabe S, Asamura H, Tsuta K. Ciliated muconodular papillary tumors of the lung: a clinicopathologic analysis of 10 cases. Am J Surg Pathol, 39:753-760, 2015

42. Hattori Y, Yoshida A, Yoshida M, Takahashi M, Tsuta K. Evaluation of androgen receptor and GATA binding protein 3 as immunohistochemical markers in the diagnosis of metastatic breast carcinoma to the lung. Pathol Int, 65:286-292, 2015

43. Komatsu Y, Doi T, Sawaki A, Kanda T, Yamada Y, Kuss I, Demetri GD, Nishida T. Regorafenib for advanced gastrointestinal stromal tumors following imatinib and sunitinib treatment: a subgroup analysis evaluating Japanese patients in the phase III GRID trial. Int J Clin Oncol, 20:905-912, 2015

44. Takami H, Yoshida A, Fukushima S, Arita H, Matsushita Y, Nakamura T, Ohno M, Miyakita Y, Shibui S, Narita Y, Ichimura K. Revisiting TP53 Mutations and Immunohistochemistry--A Comparative Study in 157 Diffuse Gliomas. Brain Pathol, 25:256-265, 2015

45. Tajima T, Kito F, Ohta T, Kawai A, Kondo T. Interactome analysis reveals molecular mechanisms underlying the association between selenium binding protein 1 expression and the malignant features of tumor cells. J Electrophoresis, 59:1-6, 2015

46. Uemura N, Kondo T. Current advances in esophageal cancer proteomics. Biochim Biophys Acta, 1854:687-695, 2015

47. Watanabe S, Hirano S, Mine S, Yoshida A, Motoi T, Ishii S, Naka G, Takeda Y, Igari T, Sugiyama H, Kobayashi N. A case of endobronchial NUT midline carcinoma with intraluminal growth. Anticancer Res, 35:1607-1612, 2015

48. Watanabe Y, Shiraishi K, Takahashi F, Yoshida A, Suzuki K, Asamura H, Takeuchi M, Furuta K, Tsuta K. Biomarker expression and druggable gene alterations for development of an appropriate therapeutic protocol for pulmonary adenosquamous carcinoma. Histopathology, 66:939-948, 2015

49. Inoue I, Higashi T, Iwamoto M, Heiney SP, Tamaki T, Osawa K, Inoue M, Shiraishi K, Kojima R, Matoba M. A national profile of the impact of parental cancer on their children in Japan. Cancer Epidemiol, 39:838-841, 2015

50. Iwamoto M, Higashi T, Miura H, Kawaguchi T, Tanaka S, Yamashita I, Yoshimoto T, Yoshida S, Matoba M. Accuracy of using Diagnosis Procedure Combination administrative claims data for estimating the amount of opioid consumption among cancer patients in Japan. Jpn J Clin Oncol, 45:1036-1041, 2015

51. Tsukada Y, Nakamura F, Iwamoto M, Nishimoto H, Emori Y, Terahara A, Higashi T. Are hospitals in Japan with larger patient volume treating younger and earlier-stage cancer patients? An analysis of hospital-based cancer registry data in Japan. Jpn J Clin Oncol, 45:719-726, 2015

52. Ikeda S, Ishikawa M, Kato T. Spontaneous ureteral rupture during concurrent chemoradiotherapy in a woman with uterine cervical cancer. Gynecol Oncol Rep, 13:18-19, 2015

53. Togami S, Sasajima Y, Kasamatsu T, Oda-Otomo R, Okada S, Ishikawa M, Ikeda S, Kato T, Tsuda H. Immunophenotype and human papillomavirus status of serous adenocarcinoma of the uterine cervix. Pathol Oncol Res, 21:487-494, 2015

54. Yoshida A, Yoshida H, Yoshida M, Mori T, Kobayashi E, Tanzawa Y, Yasugi T, Kawana K, Ishikawa M, Sugiura H, Maeda D, Fukayama M, Kawai A, Hiraoka N, Motoi T. Myoepithelioma-like Tumors of the Vulvar Region: A Distinctive Group of SMARCB1-deficient Neoplasms. Am J Surg Pathol, 39:1102-1113, 2015

55. Wakisaka N, Hasegawa Y, Yoshimoto S, Miura K, Shiotani A, Yokoyama J, Sugasawa M, Moriyama-Kita M, Endo K, Yoshizaki T. Primary Tumor-Secreted Lymphangiogenic Factors Induce Pre-Metastatic Lymphvascular Niche Formation at Sentinel Lymph Nodes in Oral Squamous Cell Carcinoma. PLoS One, 10:e0144056, 2015

56. Utsumi H, Honma Y, Nagashima K, Iwasa S, Takashima A, Kato K, Hamaguchi T, Yamada Y, Shimada Y, Kishi Y, Nara S, Esaki M, Shimada K. Bevacizumab and postoperative wound complications in patients with liver metastases of colorectal cancer. Anticancer Res, 35:2255-2261, 2015

57. AJCC Ophthalmic Oncology Task Force. International Validation of the American Joint Committee on Cancer's 7th Edition Classification of Uveal Melanoma. JAMA Ophthalmol, 133:376-383, 2015

58. Suzuki S, Aihara Y, Fujiwara M, Sano S, Kaneko A. Intravitreal injection of melphalan for intraocular retinoblastoma. Jpn J Ophthalmol, 59:164-172, 2015

59. Fujiwara T, Fujiwara M, Numoto K, Ogura K, Yoshida A, Yonemoto T, Suzuki S, Kawai A. Second primary osteosarcomas in patients with retinoblastoma. Jpn J Clin Oncol, 45:1139-1145, 2015

60. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Fujiwara Y, Tamura Y, Wakui H, Honda K, Mizugaki H, Kitazono S, Tanabe Y, Asahina H, Yamazaki N, Suzuki S, Matsuoka M, Ogita Y, Tamura T. Phase I and pharmacokinetics/pharmacodynamics study of the MEK inhibitor RO4987655 in Japanese patients with advanced solid tumors. Invest New Drugs, 33:641-651, 2015

61. Mizowaki T, Aoki M, Nakamura K, Yorozu A, Kokubo M, Karasawa K, Kozuka T, Nakajima N, Sasai K, Akimoto T. Current status and outcomes of patients developing PSA recurrence after prostatectomy who were treated with salvage radiotherapy: a JROSG surveillance study. J Radiat Res, 56:750-756, 2015

62. Hashimoto Y, Akimoto T, Iizuka J, Tanabe K, Mitsuhashi N. Correlation between the changes in the EPIC QOL scores and the dose-volume histogram parameters in high-dose-rate brachytherapy combined with hypofractionated external beam radiation therapy for prostate cancer. Jpn J Clin Oncol, 45:81-87, 2015

63. Motegi A, Kawashima M, Arahira S, Zenda S, Toshima M, Onozawa M, Hayashi R, Akimoto T. Accelerated radiotherapy for T1 to T2 glottic cancer. Head Neck, 37:579-584, 2015

64. Doi T, Tamura K, Tanabe Y, Yonemori K, Yoshino T, Fuse N, Kodaira M, Bando H, Noguchi K, Shimamoto T, Ohtsu A. Phase 1 pharmacokinetic study of the oral pan-AKT inhibitor MK-2206 in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:409-416, 2015

65. Zenda S, Ishi S, Akimoto T, Arahira S, Motegi A, Tahara M, Hayashi R, Asanuma C. DeCoP, a Dermatitis Control Program using a moderately absorbent surgical pad for head and neck cancer patients receiving radiotherapy: a retrospective analysis. Jpn J Clin Oncol, 45:433-438, 2015

66. Asao T, Nokihara H, Yoh K, Niho S, Goto K, Ohmatsu H, Kubota K, Yamamoto N, Sekine I, Kunitoh H, Fujiwara Y, Ohe Y. Phase II study of amrubicin at a dose of 45 mg/m2 in patients with previously treated small-cell lung cancer. Jpn J Clin Oncol, 45:941-946, 2015

67. Doi T, Yoshino T, Shitara K, Matsubara N, Fuse N, Naito Y, Uenaka K, Nakamura T, Hynes SM, Lin AB. Phase I study of LY2603618, a CHK1 inhibitor, in combination with gemcitabine in Japanese patients with solid tumors. Anticancer Drugs, 26:1043-1053, 2015

68. Kawazoe A, Shitara K, Fukuoka S, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yamanaka T, Doi T, Ohtsu A, Yoshino T. A retrospective observational study of clinicopathological features of KRAS, NRAS, BRAF and PIK3CA mutations in Japanese patients with metastatic colorectal cancer. BMC Cancer, 15:258, 2015

69. Davies BR, Guan N, Logie A, Crafter C, Hanson L, Jacobs V, James N, Dudley P, Jacques K, Ladd B, D'Cruz CM, Zinda M, Lindemann J, Kodaira M, Tamura K, Jenkins EL. Tumors with AKT1E17K Mutations Are Rational Targets for Single Agent or Combination Therapy with AKT Inhibitors. Mol Cancer Ther, 14:2441-2451, 2015

70. Kawazoe A, Shitara K, Fukuoka S, Noguchi M, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yoshino T, Ohtsu A, Doi T. Clinical outcomes in 66 patients with advanced gastric cancer treated in phase I trials: the NCCHE experience. Invest New Drugs, 33:664-670, 2015

71. Fujiwara Y, Nokihara H, Yamada Y, Yamamoto N, Sunami K, Utsumi H, Asou H, Takahashl O, Ogasawara K, Gueorguieva I, Tamura T. Phase 1 study of galunisertib, a TGF-beta receptor I kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1143-1152, 2015

72. Oh DY, Doi T, Shirao K, Lee KW, Park SR, Chen Y, Yang L, Valota O, Bang YJ. Phase I Study of Axitinib in Combination with Cisplatin and Capecitabine in Patients with Previously Untreated Advanced Gastric Cancer. Cancer Res Treat, 47:687-696, 2015

73. Horinouchi H, Yamamoto N, Fujiwara Y, Sekine I, Nokihara H, Kubota K, Kanda S, Yagishita S, Wakui H, Kitazono S, Mizugaki H, Tokudome T, Tamura T. Phase I study of ipilimumab in phased combination with paclitaxel and carboplatin in Japanese patients with non-small-cell lung cancer. Invest New Drugs, 33:881-889, 2015

74. Ikeda M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Kondo S, Morizane C, Ueno H, Okusaka T. Chemotherapy for advanced poorly differentiated pancreatic neuroendocrine carcinoma. J Hepatobiliary Pancreat Sci, 22:623-627, 2015

75. Murakami N, Kobayashi K, Nakamura S, Wakita A, Okamoto H, Tsuchida K, Kashihara T, Harada K, Yamada M, Sekii S, Takahashi K, Umezawa R, Inaba K, Ito Y, Igaki H, Itami J. A total EQD2 greater than 85 Gy for trachea and main bronchus D2cc being associated with severe late complications after definitive endobronchial brachytherapy. J Contemp Brachytherapy, 7:363-368, 2015

76. Watanabe T, Ueno H, Watabe Y, Hiraoka N, Morizane C, Itami J, Okusaka T, Miura N, Kakizaki T, Kakuya T, Kamita M, Tsuchida A, Nagakawa Y, Wilber H, Yamada T, Honda K. ACTN4 copy number increase as a predictive biomarker for chemoradiotherapy of locally advanced pancreatic cancer. Br J Cancer, 112:704-713, 2015

77. Takahashi H, Kaniwa N, Saito Y, Sai K, Hamaguchi T, Shirao K, Shimada Y, Matsumura Y, Ohtsu A, Yoshino T, Doi T, Takahashi A, Odaka Y, Okuyama M, Sawada J, Sakamoto H, Yoshida T. Construction of possible integrated predictive index based on EGFR and ANXA3 polymorphisms for chemotherapy response in fluoropyrimidine-treated Japanese gastric cancer patients using a bioinformatic method. BMC Cancer, 15:718, 2015

78. Kobayashi K, Murakami N, Wakita A, Nakamura S, Okamoto H, Umezawa R, Takahashi K, Inaba K, Igaki H, Ito Y, Shigematsu N, Itami J. Dosimetric variations due to interfraction organ deformation in cervical cancer brachytherapy. Radiother Oncol, 117:555-558, 2015

79. Yasui N, Yoshida A, Kawamoto H, Yonemori K, Hosono A, Kawai A. Clinicopathologic analysis of spindle cell/sclerosing rhabdomyosarcoma. Pediatr Blood Cancer, 62:1011-1016, 2015

80. Kikuta K, Morioka H, Kawai A, Kondo T. Global protein-expression profiling for reclassification of malignant fibrous histiocytoma. Biochim Biophys Acta, 1854:696-701, 2015

81. Kanda S, Horinouchi H, Fujiwara Y, Nokihara H, Yamamoto N, Sekine I, Kunitoh H, Kubota K, Tamura T, Ohe Y. Cytotoxic chemotherapy may overcome the development of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) therapy. Lung Cancer, 89:287-293, 2015

82. Ueda S, Satoh T, Gotoh M, Gao L, Doi T. A phase ib study of safety and pharmacokinetics of ramucirumab in combination with paclitaxel in patients with advanced gastric adenocarcinomas. Oncologist, 20:493-494, 2015

83. Yonemoto T, Hosono A, Iwata S, Kamoda H, Hagiwara Y, Fujiwara T, Kawai A, Ishii T. The prognosis of osteosarcoma occurring as second malignancy of childhood cancers may be favorable: experience of two cancer centers in Japan. Int J Clin Oncol, 20:613-616, 2015

84. Katsuya Y, Fujiwara Y, Sunami K, Utsumi H, Goto Y, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Takashima Y, Osawa S, Ohe Y, Tamura T, Hamada A. Comparison of the pharmacokinetics of erlotinib administered in complete fasting and 2 h after a meal in patients with lung cancer. Cancer Chemother Pharmacol, 76:125-132, 2015

85. Kurose K, Ohue Y, Wada H, Iida S, Ishida T, Kojima T, Doi T, Suzuki S, Isobe M, Funakoshi T, Kakimi K, Nishikawa H, Udono H, Oka M, Ueda R, Nakayama E. Phase Ia Study of FoxP3+ CD4 Treg Depletion by Infusion of a Humanized Anti-CCR4 Antibody, KW-0761, in Cancer Patients. Clin Cancer Res, 21:4327-4336, 2015

86. Ichikawa H, Yoshida A, Kanda T, Kosugi S, Ishikawa T, Hanyu T, Taguchi T, Sakumoto M, Katai H, Kawai A, Wakai T, Kondo T. Prognostic significance of promyelocytic leukemia expression in gastrointestinal stromal tumor; integrated proteomic and transcriptomic analysis. Cancer Sci, 106:115-124, 2015

87. Kitazono S, Fujiwara Y, Nakamichi S, Mizugaki H, Nokihara H, Yamamoto N, Yamada Y, Inukai E, Nakamura O, Tamura T. A phase I study of resminostat in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 75:1155-1161, 2015

88. Arita H, Narita Y, Yoshida A, Hashimoto N, Yoshimine T, Ichimura K. *IDH1/2* mutation detection in gliomas. Brain Tumor Pathol, 32:79-89, 2015

89. Kitazono S, Fujiwara Y, Tsuta K, Utsumi H, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Sasada S, Watanabe S, Asamura H, Tamura T, Ohe Y. Reliability of Small Biopsy Samples Compared With Resected Specimens for the Determination of Programmed Death-Ligand 1 Expression in Non--Small-Cell Lung Cancer. Clin Lung Cancer, 16:385-390, 2015

90. Kurihara H, Hamada A, Yoshida M, Shimma S, Hashimoto J, Yonemori K, Tani H, Miyakita Y, Kanayama Y, Wada Y, Kodaira M, Yunokawa M, Yamamoto H, Shimizu C, Takahashi K, Watanabe Y, Fujiwara Y, Tamura K. ^{64}Cu-DOTA-trastuzumab PET imaging and HER2 specificity of brain metastases in HER2-positive breast cancer patients. EJNMMI Res, 5:8, 2015

91. Hattori Y, Yoshida A, Sasaki N, Shibuki Y, Tamura K, Tsuta K. Desmoplastic small round cell tumor with sphere-like clusters mimicking adenocarcinoma. Diagn Cytopathol, 43:214-217, 2015

92. Fujita H, Yoshida A, Taniguchi H, Katai H, Sekine S. Adult-onset inflammatory myofibroblastic tumour of the stomach with a TFG-ROS1 fusion. Histopathology, 66:610-612, 2015

93. Mizugaki H, Yamamoto N, Fujiwara Y, Nokihara H, Yamada Y, Tamura T. Current Status of Single-Agent Phase I Trials in Japan: Toward Globalization. J Clin Oncol, 33:2051-2061, 2015

94. Mizugaki H, Yamamoto N, Nokihara H, Fujiwara Y, Horinouchi H, Kanda S, Kitazono S, Yagishita S, Xiong H, Qian J, Hashiba H, Shepherd SP, Giranda V, Tamura T. A phase 1 study evaluating the pharmacokinetics and preliminary efficacy of veliparib (ABT-888) in combination with carboplatin/paclitaxel in Japanese subjects with non-small cell lung cancer (NSCLC). Cancer Chemother Pharmacol, 76:1063-1072, 2015

95. Kobayashi E, Setsu N. Osteosclerosis induced by denosumab. Lancet, 385:539, 2015

96. Motonaga M, Yamamoto N, Makino Y, Ando-Makihara R, Ohe Y, Takano M, Hayashi Y. Phase I dose-finding and pharmacokinetic study of docetaxel and gefitinib in patients with advanced or metastatic non-small-cell lung cancer: evaluation of drug-drug interaction. Cancer Chemother Pharmacol, 76:713-721, 2015

97. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Honda K, Tamura Y, Wakui H, Sasaki T, Yusa W, Fujino K, Tamura T. A phase 1 study of lenvatinib, multiple receptor tyrosine kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1153-1161, 2015

98. Nishio M, Horiike A, Murakami H, Yamamoto N, Kaneda H, Nakagawa K, Horinouchi H, Nagashima M, Sekiguchi M, Tamura T. Phase I study of the HER3-targeted antibody patritumab (U3-1287) combined with erlotinib in Japanese patients with non-small cell lung cancer. Lung Cancer, 88:275-281, 2015

99. Nishio M, Horiike A, Nokihara H, Horinouchi H, Nakamichi S, Wakui H, Ohyanagi F, Kudo K, Yanagitani N, Takahashi S, Kuboki Y, Yamamoto N, Yamada Y, Abe M, Tahata T, Tamura T. Phase I study of the anti-MET antibody onartuzumab in patients with solid tumors and MET-positive lung cancer. Invest New Drugs, 33:632-640, 2015

100. Yamaga K, Kobayashi E, Kubota D, Setsu N, Tanaka Y, Minami Y, Tanzawa Y, Nakatani F, Kawai A, Chuman H. Pediatric myositis ossificans mimicking osteosarcoma. Pediatr Int, 57:996-999, 2015

101. Guo J, Yonemori K, Le Marchand L, Turesky RJ. Method to Biomonitor the Cooked Meat Carcinogen 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine in Dyed Hair by Ultra-Performance Liquid Chromatography-Orbitrap High Resolution Multistage Mass Spectrometry. Anal Chem, 87:5872-5877, 2015

102. Okusaka T, Ueno H, Morizane C, Kondo S, Sakamoto Y, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Ikeda M. Cytotoxic chemotherapy for pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci, 22:628-633, 2015

103. Fujiwara T, Ogura K, Kobayashi E, Tanzawa Y, Nakatani F, Chuman H, Kawai A. Clinical Outcomes of Surgical Treatments for Primary Malignant Bone Tumors Arising in the Acetabulum. Sarcoma, 2015:430576, 2015

104. Hara M, Nakashima T, Harashima H, Ryushima Y, Shimizu C, Kodaira M, Yunokawa M, Yamamoto H, Hashimoto J, Tanabe Y, Bun S, Makino Y, Iwase H, Fujiwara Y, Tamura K, Hayashi Y. Efficacy and safety of aprepitant and dexamethasone in the prevention of nausea and vomiting from neoadjuvant or adjuvant anthracyclines and cyclophosphamide combination therapy in patients with breast cancer. J Pharm Health Care Sci, 41:603-611, 2015

105. Fujiki M, Miyamoto S, Nakatani F, Kawai A, Sakuraba M. Rotationplasty with vascular reconstruction for prosthetic knee joint infection. Case Rep Orthop, 2015:241405, 2015

106. Miyamoto S, Fujiki M, Nakatani F, Sakisaka M, Sakuraba M. Free flow-through anterolateral thigh flap for complex knee defect including the popliteal artery. Microsurgery, 35:485-488, 2015

107. Blake EA, Kodama M, Yunokawa M, Ross MS, Ueda Y, Grubbs BH, Matsuo K. Feto-maternal outcomes of pregnancy complicated by epithelial ovarian cancer: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol, 186:97-105, 2015

108. Shoji H, Yamada Y, Okita N, Takashima A, Honma Y, Iwasa S, Kato K, Hamaguchi T, Shimada Y. Amplification of FGFR2 Gene in Patients with Advanced Gastric Cancer Receiving Chemotherapy: Prevalence and Prognostic Significance. Anticancer Res, 35:5055-5061, 2015

109. Igaki H, Magome T, Sakuramachi M, Nomoto A, Sakumi A, Kitaguchi M, Haga A, Itami J, Nakagawa K. Patterns of recurrence in malignant glioma patients: association with subventricular zone and radiotherapy dose. Jacobs J Radiat Oncol, 2:020, 2015

110. Hanakita S, Koga T, Shin M, Igaki H, Saito N. The long-term outcomes of radiosurgery for arteriovenous malformations in pediatric and adolescent populations. J Neurosurg Pediatr, 16:222-231, 2015

111. Takahashi N, Yamada Y, Furuta K, Nagashima K, Kubo A, Sasaki Y, Shoji H, Honma Y, Iwasa S, Okita N, Takashima A, Kato K, Hamaguchi T, Shimada Y. Association between serum ligands and the skin toxicity of anti-epidermal growth factor receptor antibody in metastatic colorectal cancer. Cancer Sci, 106:604-610, 2015

112. Kokudo N, Hasegawa K, Akahane M, Igaki H, Izumi N, Ichida T, Uemoto S, Kaneko S, Kawasaki S, Ku Y, Kudo M, Kubo S, Takayama T, Tateishi R, Fukuda T, Matsui O, Matsuyama Y, Murakami T, Arii S, Okazaki M, Makuuchi M. Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). Hepatol Res, 45:2015

113. Eba J, Shimokawa T, Nakamura K, Shibata T, Misumi Y, Okamoto H, Yamamoto N, Ohe Y, Lung Cancer Study Group of the Japan Clinical Oncology Group. A Phase II/III study comparing carboplatin and irinotecan with carboplatin and etoposide for the treatment of elderly patients with extensive-disease small-cell lung cancer (JCOG1201). Jpn J Clin Oncol, 45:115-118, 2015

114. Tamura Y, Fujiwara Y, Yamamoto N, Nokihara H, Horinouchi H, Kanda S, Goto Y, Kubo E, Kitahara S, Tsuruoka K, Tsuta K, Ohe Y. Retrospective analysis of the efficacy of chemotherapy and molecular targeted therapy for advanced pulmonary pleomorphic carcinoma. BMC Res Notes, 8:800, 2015

115. Miyashita M, Kawakami S, Kato D, Yamashita H, Igaki H, Nakano K, Kuroda Y, Nakagawa K. The importance of good death components among cancer patients, the general population, oncologists, and oncology nurses in Japan: patients prefer "fighting against cancer". Support Care Cancer, 23:103-110, 2015

116. Matsumoto K, Katsumata N, Shibata T, Satoh T, Saitou M, Yunokawa M, Takano T, Nakamura K, Kamura T, Konishi I. Phase II trial of oral etoposide plus intravenous irinotecan in patients with platinum-resistant and taxane-pretreated ovarian cancer (JCOG0503). Gynecol Oncol, 136:218-223, 2015

117. Yagishita S, Horinouchi H, Sunami KS, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T, Ohe Y. Impact of KRAS mutation on response and outcome of patients with stage III non-squamous non-small cell lung cancer. Cancer Sci, 106:1402-1407, 2015

118. Yunokawa M, Tsuta K, Tanaka T, Nara E, Koizumi F, Ito J, Sekine S, Fujiwara Y, Tamura K. Back with a vengeance: microvascular tumor embolism. Am J Med, 128:834-836, 2015

119. Takami H, Fukushima S, Fukuoka K, Suzuki T, Yanagisawa T, Matsushita Y, Nakamura T, Arita H, Mukasa A, Saito N, Kanamori M, Kumabe T, Tominaga T, Kobayashi K, Nagane M, Iuchi T, Tamura K, Maehara T, Sugiyama K, Nakada M, Kanemura Y, Nonaka M, Yokogami K, Takeshima H, Narita Y, Shibui S, Nakazato Y, Nishikawa R, Ichimura K, Matsutani M. Human chorionic gonadotropin is expressed virtually in all intracranial germ cell tumors. J Neurooncol, 124:23-32, 2015

120. Ichimura K, Narita Y, Hawkins CE. Diffusely infiltrating astrocytomas: pathology, molecular mechanisms and markers. Acta Neuropathol, 129:789-808, 2015

121. Mimori T, Kobayashi S, Tanaka A, Sasada S, Yoshida A, Izumo T, Sasaki N, Tsuchida T, Tsuta K. Novel use for an EGFR mutation-specific antibody in discriminating lung adenocarcinoma from reactive pneumocyte hyperplasia. Histopathology, 66:816-823, 2015

122. Geisenberger C, Mock A, Warta R, Rapp C, Schwager C, Korshunov A, Nied AK, Capper D, Brors B, Jungk C, Jones D, Collins VP, Ichimura K, Backlund LM, Schnabel E, Mittelbron M, Lahrmann B, Zheng S, Verhaak RG, Grabe N, Pfister SM, Hartmann C, von Deimling A, Debus J, Unterberg A, Abdollahi A, Herold-Mende C. Molecular profiling of long-term survivors identifies a subgroup of glioblastoma characterized by chromosome 19/20 co-gain. Acta Neuropathol, 130:419-434, 2015

123. Takahashi RU, Miyazaki H, Takeshita F, Yamamoto Y, Minoura K, Ono M, Kodaira M, Tamura K, Mori M, Ochiya T. Loss of microRNA-27b contributes to breast cancer stem cell generation by activating ENPP1. Nat Commun, 6:7318, 2015

124. Watanabe Y, Kusumoto M, Yoshida A, Suzuki K, Asamura H, Tsuta K. Surgically resected solitary cavitary lung adenocarcinoma: association between clinical, pathologic, and radiologic findings and prognosis. Ann Thorac Surg, 99:968-974, 2015

125. Ono R, Hasegawa D, Hirabayashi S, Kamiya T, Yoshida K, Yonekawa S, Ogawa C, Hosoya R, Toki T, Terui K, Ito E, Manabe A. Acute megakaryoblastic leukemia with acquired trisomy 21 and GATA1 mutations in phenotypically normal children. Eur J Pediatr, 174:525-531, 2015

126. Iwakawa R, Kohno T, Totoki Y, Shibata T, Tsuchihara K, Mimaki S, Tsuta K, Narita Y, Nishikawa R, Noguchi M, Harris CC, Robles AI, Yamaguchi R, Imoto S, Miyano S, Totsuka H, Yoshida T, Yokota J. Expression and clinical significance of genes frequently mutated in small cell lung cancers defined by whole exome/RNA sequencing. Carcinogenesis, 36:616-621, 2015

127. Kato M, Manabe A, Saito AM, Koh K, Inukai T, Ogawa C, Goto H, Tsuchida M, Ohara A. Outcome of pediatric acute lymphoblastic leukemia with very late relapse: a retrospective analysis by the Tokyo Children's Cancer Study Group (TCCSG). Int J Hematol, 101:52-57, 2015

128. Yasui N, Kawamoto H, Fujiwara M, Aihara Y, Ogawa C, Hosono A, Suzuki S. High-dose chemotherapy for high-risk retinoblastoma: clinical course and outcome of 14 cases in the National Cancer Center, Japan. Bone Marrow Transplant, 50:221-224, 2015

129. Nagatsuma AK, Aizawa M, Kuwata T, Doi T, Ohtsu A, Fujii H, Ochiai A. Expression profiles of HER2, EGFR, MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma. Gastric Cancer, 18:227-238, 2015

130. Sasaki T, Fuse N, Kuwata T, Nomura S, Kaneko K, Doi T, Yoshino T, Asano H, Ochiai A, Komatsu Y, Sakamoto N, Ohtsu A. Serum HER2 levels and HER2 status in tumor cells in advanced gastric cancer patients. Jpn J Clin Oncol, 45:43-48, 2015

131. Fujiwara Y, Yonemori K, Shibata T, Okita N, Ushirozawa N. Japanese universal health care faces a crisis in cancer treatment. Lancet Oncol, 16:251-252, 2015

132. Ohmoto A, Maeshima AM, Taniguchi H, Tanioka K, Makita S, Kitahara H, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Histopathological analysis of B-cell non-Hodgkin lymphomas without light chain restriction by using flow cytometry. Leuk Lymphoma, 56:3301-3305, 2015

133. Maeshima AM, Taniguchi H, Nomoto J, Makita S, Kitahara H, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Clinicopathological features of classical Hodgkin lymphoma in patients ≥ 40 years old, with special reference to composite cases. Jpn J Clin Oncol, 45:921-928, 2015

134. Miyagi Maeshima A, Taniguchi H, Makita S, Kitahara H, Miyamoto K, Fukuhara S, Munakata W, Suzuki T, Maruyama D, Kobayashi Y, Tobinai K. Histopathological Characteristics of Lymphomas in the Upper Aerodigestive Tract. A Single-Institute Study in Japan. J Clin Exp Hematop, 55:7-11, 2015

135. Ogura M, Uchida T, Terui Y, Hayakawa F, Kobayashi Y, Taniwaki M, Takamatsu Y, Naoe T, Tobinai K, Munakata W, Yamauchi T, Kageyama A, Yuasa M, Motoyama M, Tsunoda T, Hatake K. Phase I study of OPB-51602, an oral inhibitor of signal transducer and activator of transcription 3, in patients with relapsed/refractory hematological malignancies. Cancer Sci, 106:896-901, 2015

136. Aoki T, Kokudo N, Komoto I, Takaori K, Kimura W, Sano K, Takamoto T, Hashimoto T, Okusaka T, Morizane C, Ito T, Imamura M. Streptozocin chemotherapy for advanced/metastatic well-differentiated neuroendocrine tumors: an analysis of a multi-center survey in Japan. J Gastroenterol, 50:769-775, 2015

Book

1. Sone M, Arai Y. Section B. Coils and Plugs - 5. Gelfoam. In: Marcelo G, Riccardo L, Gary PS (eds), Embolization Therapy: Principles and Clinical Applications, Netherland, Wolters Kluwer, 2015

137. Doi T, Yoshino T, Fuse N, Boku N, Yamazaki K, Koizumi W, Shimada K, Takinishi Y, Ohtsu A. Phase I study of TAS-102 and irinotecan combination therapy in Japanese patients with advanced colorectal cancer. Invest New Drugs, 33:1068-1077, 2015

138. Tanaka Y, Kobayashi Y, Maeshima AM, Oh SY, Nomoto J, Fukuhara S, Kitahara H, Munakata W, Suzuki T, Maruyama D, Tobinai K. Intravascular large B-cell lymphoma secondary to lymphoplasmacytic lymphoma: a case report and review of literature with clonality analysis. Int J Clin Exp Pathol, 8:3339-3343, 2015

139. Ito J, Yoshida A, Maeshima AM, Nakagawa K, Watanabe S, Kobayashi Y, Fukuhara S, Tsuta K. Concurrent thymoma, thymic carcinoma, and T lymphoblastic leukemia/lymphoma in an anterior mediastinal mass. Pathol Res Pract, 211:693-696, 2015

Department of Radiology

Yoshihisa Muramatsu, Mitsuhiro Yoshida, Kazuyoshi Yamano, Kazutoshi Yokoyama, Koichi Nemoto, Takaki Ariji, Kuniji Naoi, Keisuke Takahashi, Naotaka Yamazawa, Satoe Kito, Hiroyuki Ohta, Hajime Ohyoshi, Kaoru Ikeno, Tsunemichi Akita, Keiichi Nomura, Hiroyuki Shitara, Daiki Kumagai, Fuminori Shimizu, Shogo Amano, Asami Tanaka, Ryuzo Uehara, Tatsuya Mogaki, Hiromi Baba, Shota Hosokawa, Kaori Yanagisawa, Syun Aoyagi, Yukihiro Matsukawa, Yuto Iwabuchi, Yuki Tanaka, Toshiyuki Shibuya, Kazuto Kano, Hikaru Sugahara, Hiroyuki Asai, Fumiya Tanaka, Toshiya Rachi, Daiki Kanke, Taku Tochinai, Yohei Takeda, Makoto Gohdo, Tomohiro Ohishi, Hiroshi Tsuruoka, Moeka Funakoshi, Hikari Inagawa, Hirokazu Kobayashi

Routine activities and research activities

Subsequent to the previous year, the number of radiographic examinations and radiation therapies in 2015 increased, as shown in Table 1.

Due to the increase in the number of clinical trials, the number of computed tomography (CT) examinations significantly increased. By reinforcing the medical cooperation service, the number of online reserved PET-CT examinations and Low-dose lung cancer CT screenings for working people has increased.

In the photon radiation therapy section, stereotactic irradiation targeting the liver was launched. By using a linear gold marker, CT image acquisition under respiratory gating and respiratory-gated irradiation was possible. In the proton therapy section, line scanning irradiation, which provides dose administration localized to a small area, has been launched.

Triennial inspections and checks under the "Law concerning Prevention of Radiation Hazards due to Radioisotopes, etc." were completed without any problems being highlighted.

Research findings

In collaboration with manufacturers (CH26088), to study dose simulation in CT examinations, the simulation environment was constructed at a level approximately 10% that of the actual measurement.

By participating in the Ishigaki section (Grants-in-Aid for Scientific Research: No.25713028), software that manages the exposure dose of radiological examinations is under development. For intensity-modulated radiation therapy (IMRT), as a verification of the dose accuracy of the plan, a treatment planning system based on independent software and a 3D radiation counter were proposed.

These achievements were presented at the study group and in papers of both domestic and overseas scientific societies.

Education

Radiological technologists whose experience was less than three years were given the opportunity to rotate between the radiation diagnostics department and the radiation therapy department, which helped them study a variety of radiation technologies.

All staff are actively involved in efforts to raise awareness such as highlighting the fact that radiation technology is a work in progress; this was reported through multipoint conferencing. As for medical safety education and associated activities, a movie, which prepares for shock caused by contrast medium, was filmed, a magnetic field experience program was carried out with new employees as targets and use of an assessment sheet for radiation therapy patients was started. Also, two radiological technologists obtained overseas training grants, and visited London in the UK and Texas in the United States. Three radiological technologists studied on a master's course and one studied on a graduate school doctoral course in 2015. One of them received a master's degree. In addition to that, we also accepted and educated 12 trainees from three universities in radiological technology.

Future prospects

On the basis of medical safety, we plan to provide more efficient, high-accuracy radiation inspection and radiation treatment. Because international clinical trials are increasing, verifying the quality management of medical equipment in accordance with international approaches is necessary. Introducing the information and communication technology (ICT) as the recording evaluation and storage means in accordance with legal provisions, we will facilitate the conversion to electronic media from paper media.

Table 1. Transition of Number of Radiological Examination and Radiation Therapy by Year.

Number of Cases	2011	2012	2013	2014	2015
Plain X-ray examination	35,032	39,128	38,722	42,672	43,652
Mammography (MMG)	2,434	2,380	2,354	2,310	2,368
"Fluoroscopic Imaging (GI-series, etc.)	3,903	4,029	4,628	4,748	4,691
CT	21,967	24,101	28,963	31,995	34,867
MRI	5,708	5,619	5,657	5,675	5,875
RI (Scintiscan)	1,582	1,586	1,363	1,396	1,302
PET	2,239	2,284	2,208	2,332	2,481
Angiography	656	742	511	801	807
Radiation therapy	16,798	19,254	32,453	29,510	30,633
Proton therapy	4,941	5,910	11,460	9,513	9,047
Total	95,260	105,033	128,319	130,952	135,723

List of papers published in 2015

Journal

1. Fujii K, Nomura K, Muramatsu Y, Takahashi K, Obara S, Akahane K, Satake M. Evaluation of organ doses in adult and paediatric CT examinations based on Monte Carlo simulations and in-phantom dosimetry. Radiat Prot Dosimetry, 165:166-171, 2015

2. Kakinuma R, Moriyama N, Muramatsu Y, Gomi S, Suzuki M, Nagasawa H, Kusumoto M, Aso T, Muramatsu Y, Tsuchida T, Tsuta K, Maeshima AM, Tochigi N, Watanabe S, Sugihara N, Tsukagoshi S, Saito Y, Kazama M, Ashizawa K, Awai K, Honda O, Ishikawa H, Koizumi N, Komoto D, Moriya H, Oda S, Oshiro Y, Yanagawa M, Tomiyama N, Asamura H. Ultra-high-resolution computed tomography of the lung: image quality of a prototype scanner. PLoS One, 10:e0137165, 2015

3. Kakinuma R, Moriyama N, Muramatsu Y, Gomi S, Suzuki M, Nagasawa H, Kusumoto M, Aso T, Muramatsu Y, Tsuchida T, Tsuta K, Maeshima AM, Tochigi N, Watanabe SI, Sugihara N, Tsukagoshi S, Saito Y, Kazama M, Ashizawa K, Awai K, Honda O, Ishikawa H, Koizumi N, Komoto D, Moriya H, Oda S, Oshiro Y, Yanagawa M, Tomiyama N, Asamura H. Correction: Ultra-high-resolution computed tomography of the lung: image quality of a prototype scanner. PLoS One, 10:e0145357, 2015

4. Maedera F, Inoue K, Sugino M, Sano R, Shimizu H, Tsuruoka H, Fukushi M. Cesium concentrations in shell of japanese mitten crab around Fukushima Daiichi Nuclear Power Plant. Radiation Emergency Medicine, 4:60-67, 2015

Book

1. Tsuruoka H, Inoue K, Sakano Y, Hamada M, Shimizu H, Fukushi M. Variation of radiocesium concentrations in cedar pollen in the Okutama area since the Fukushima Daiichi Nuclear Power Plant accident. In: Radiat Prot Dosimetry, pp 219-222, 2015

Clinical Laboratories

Atsushi Ochiai, Takeshi Kuwata, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Masato Sugano, Chisako Yamauchi, Eiichi Yoshikawa, Shigehisa Yoshida, Masahiro Inoue, Masahiro Karibe, Seiji Iwasaki, Miki Goto, Masaki Takeda, Satoru Sunohara, Hiromi Kimura, Yasuharu Hashimoto, Yukihiro Okano, Akiko Yamada, Mari Hisano, Mika Sasanuma, Aya Koike, Takuya Yamaguchi, Takuya Aiba, Keiko Nakai, Ayumi Setsuta, Mayumi Motohashi, Ayumi Nakanishi, Sayuri Shibayama, Izumi Suzuki, Yasuko Yoshihara, Kazumi Yamaguchi, Rie Taniguchi, Kumiko Sudo, Saki Nakamura, Kazuki Motohashi, Atsushi Watanabe, Eriko Iwamoto, Yasuteru Yamagishi, Kazumi Tamura, Asami Sekine, Nagisa Bouno, Rie Kuroiwa, Masayuki Ito, Michiko Iida, Yuki Soeda, Megumi Michikawa, Tomoko Seto, Emiko Yoshikawa, Yoshiko Ohtake, Miwa Yamada, Megumi Yamaguchi

Introduction

The Department of Pathology and Clinical Laboratories (DPCL) has two divisions: Pathology Division (PD) and Clinical Laboratory Division (CLD). Both divisions play a fundamental role in routine hospital service and support research activities at the National Cancer Center Hospital East (NCCHE).

DPCL received ISO15189:2007 accreditation in 2012, and successfully transited to the newest version (ISO15189:2012) in 2014, ensuring quality control and quality assurance of testing, including the one for clinical trials, performed in the departments. In 2015, two sections, Physiology and Supporting laboratory testing in clinical studies, received ISO15189:2012, ensuring the quality control and quality assurance of the testing, including the ones for clinical trials, performed in the departments with global standards.

Routine activities

Primarily, the routine activity at the PD is surgical pathology. The Number of samples examined in the department in 2015 is listed in Table 1.

The CLD consists of seven sections: i) general laboratory medicine, ii) hematology, iii) biochemistry/serology, iv) Physiology, v) Bacteriology, vi) Blood transfusion and vii) Supporting laboratory tests in clinical studies. The numbers of tests performed in each division are listed in Table 2 and 3. The total number of tests performed in the DPCL in 2015 increased to 7.5% compared with the previous year; including a 94.4% and a 12.9% increase in the Blood transfusion and Serology sections, respectively.

Research activities

All of the pathologists were involved in research activities at RCIO (Research Center for Innovative Oncology). All the technologists working in the department are also highly motivated to develop advanced diagnostic technologies and various results are presented in several meetings.

Clinical trials

Practically, the CLD participated in all of the clinical trials operated at the NCCHE by providing laboratory data. The section for supporting laboratory testing in clinical studies was transferred to the DPCL in June 2014. The section, coordinating with the pathology and physiology sections, reinforces quality control and quality assurance for clinical tests performed in clinical trials at the NCCHE.

Education

Clinicopathological conferences are held regularly with each clinical department/section. In the PD, conference-style training sessions are open weekly for the residents.

Future prospects

Pathological diagnosis and laboratory tests

play a fundamental role not only in routine hospital work but also in medical research. As an ISO15189-certified clinical laboratory, the DPCL will be continuously involved in investigating new diagnostic technologies, developing new drugs and conducting translational/clinical research in the NCCHE.

Table 1. Number of pathology and cytology samples examined in Pathology Division in 2015

Department	Biopsy	Surgical	Cytology	Autopsy
Digestive Endoscopy	4,951	0	4	0
Gastrointestinal Oncology	154	0	74	0
Breast Surgery	593	358	132	0
Head and Neck Surgery	621	391	388	0
Thoracic Surgery	433	531	530	1
Thoracic Oncology	784	3	907	1
Hematology and medical oncology	545	3	209	2
Hepatobiliary and Pancreatic Oncology	489	1	450	0
Urology	264	103	736	0
Upper Abdominal Surgery	186	473	226	1
Radiation Oncology	149	3	4	0
Lower Abdominal Surgery	83	398	19	0
Orthopedics	43	16	1	0
Esophageal Surgery	8	182	19	0
Head and Neck Oncology	34	1	11	0
Obstetrics and Gynecology	18	0	199	0
Dental division	10	0	0	0
Anesthesiology	3	0	2	0
Dermatology	16	0	0	0
Plastic Surgery	2	5	2	0
Palliative medicine	1	1	4	0
Others	24	1	7	0
Total	9,411	2,469	3,924	5

Table 2. Number of laboratory tests examined in Clinical Laboratory Division in 2014 and 2015

	2014	2015
General laboratory medicine	48,199	48,199
Hematology	302,752	302,752
Biochemistry	1,970,515	1,970,515
Serology	164,382	270,112
Blood transfusion	10,720	11,438
Bacteriology	26,870	29,917
Physiology	22,730	24,703
Total	2,383,461	2,846,826

Table 3. Number of cases and samples prepared in Clinical Laboratory Division for clinical trials in 2015

	Cases	Samples
General laboratory test	3,204	5,972
Electrocardiogram (ECG)	998	1,397
Pathology	864	4,273

Surgical Center

Masaru Konishi, Hiroyuki Yamamoto, Emiko Kanazawa

Introduction

The Surgical Center performs function-preserving operations for ordinary cancer patients as much as possible in consideration of patient quality of life (QOL), but depending on the case, the extended surgery is done to cure localized highly progressive cancers. Thoracoscopic and laparoscopic surgery are routinely indicated for the treatment of various cancer patients.

Routine activities

In 2015, 3,115 cases underwent surgical treatment including 2,834 general anesthesia cases. This total was an increase of 210 over 2014.

To preserve organ functions, limited resection or reconstructive operation is indicated in our hospital. These procedures include vertical partial laryngectomy for voice preservation, breast-conserving surgery, total mastectomy with breast reconstruction, pancreas-sparing duodenectomy, partial anal sphincter preserving surgery and bladder-sparing surgery.

With the refinements in laparoscopic instruments and advances in surgical experience, laparoscopic surgery is a safe alternative for selected patients with malignant neoplasms, and has fulfilled its indications. In our hospital, laparoscopic surgery has been introduced in the esophageal, thoracic, gastric, colorectal, hepatobiliary, pancreatic, and urology divisions. A robotic surgical system had been used to provide less invasive surgery since 2014. The system was indicated for prostate, rectal and gastric cancer.

Education

We place importance on the education of young surgeons. All surgical groups have their own training programs for resident surgeons. Many surgeons from domestic or foreign hospitals have visited our center to learn surgical techniques.

Table 1. Total number of operations

Anesthesia	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
General	119	141	145	143	127	163	162	171	153	160	148	158	1,790
General and epidural	92	83	105	105	76	99	85	79	70	93	82	75	1,044
Lumbar	4	9	8	6	10	7	5	2	6	10	12	8	87
Local	14	18	16	11	22	13	11	17	17	13	22	20	194
Total	229	251	274	265	235	282	263	269	246	276	264	261	3,115

Supportive Care Center

Koichi Goto

Introduction

Our Department was established as an organization to provide, in addition to conventional consultation support, positive and comprehensive support from a variety of professional occupations for actual or potential, physical, mental, and social problems that cancer patients and their families have to confront. The main activities are establishment of a continuous support system for patients and families, enhancement of a home care support system, and promotion of community cooperation for establishing early palliative care.

Routine activities

1) Consultation support/community medicine cooperation

In 2015, we received 5,179 new consultations. Among them, 4,151 (80.2%) were from patients who had received medical treatment from our hospital, or their families, and 1,028 (20.6%) were from patients who had received medical treatment at other medical institutions, or their families, or local medical welfare workers (Table 1).

In this year, to improve QOL during cancer treatment, we started new educational services for cancer patients such as an oral care program, a skin and nail care program, and a physical rehabilitation program. We provide these new additional services taking into account the difficulties faced by patients.

The new building, which is named NEXT, for enlarged operating and endoscopic rooms is under construction in our hospital. Therefore, to acquire more new patients, we have started new case conferences held in communities in order to build face-to-face relationships between the physicians of our hospital and local physicians.

2) Continuous nursing support

For outpatients, we provide continuous nursing support. In 2015, we provided continuous support and consultation services to about 2,600 patients, mainly in the areas of thoracic and gastrointestinal oncology.

In order to promote self-care by inpatients and/or their families, as well as to secure appropriate social resources, we provide medical and social support with a view to home care even from an early time of hospitalization. We carried out a screening program for about 2,250 patients who needed social support and provided them with appropriate support.

In order to sustain seamless medical and social support, we strengthen cooperation with home-visit nursing stations to deal with the problems faced by home care patients and/or their families, mainly related to medical management. In 2015, we carried out interventions such as approximately 1,030 phone-calls and face-to-face consultations.

Table 1. Details of the consultation support provided in 2015

	Number	%
New consultations	5,179	
Total number	16,843	
Purpose of new support request		
Support for nursing hospital selection	3,030	58.5
Consultation about treatment and diagnosis	670	12.9
Consultation about social problems	584	11.3
Consultation about physical symptoms	46	0.9
Consultation for caregivers	44	0.8
Mental problems	37	0.7
Others	768	14.8
Responsible hospital		
Our hospital	4,151	80.2
Other hospitals	831	16.0
Others	197	3.8
Treatment state		
Before diagnosis	209	4.0
Before first treatment	1,029	19.9
During chemotherapy	1,450	28.0
After treatment/during follow-up	930	18.0
Only palliative care	1,401	27.1
Dead (Bereaved family)	10	0.2
Others	150	2.9

Section of Radiation Safety and Quality Assurance

Tetsuo Akimoto, Hidenobu Tachibana, Kenji Hotta, Hiromi Baba, Koichi Nemoto

Introduction

Radiation therapy technologies have improved recently and will continue to progress. However, while advanced technology has provided higher accuracy and precision in radiotherapy, it has introduced more complex situations and difficulties in performing the treatment adequately. Radiotherapy errors can occur at several time points from planning through treatment. The accuracy and precision of dose delivery in radiation therapy is important because there is evidence that a 7-10% change in the dose to the target volume may result in a significant change in tumor control probability. "Quality assurance in radiotherapy" is for all procedures that ensure consistency of the medical prescription, and safe fulfillment of that prescription, as regards the dose to the target volume, together with the minimal dose to normal tissue, minimal exposure of personnel and adequate patient monitoring aimed at determining the end result of the treatment.

The primary aim of the Section of Radiation Safety and Quality Assurance is to develop quality assurance programs for photon and proton therapy machines as well as to check that quality requirements in photon and proton therapy products are met and to adjust and correct performance if the requirements are found not to have been met. The second aim is to install and establish advanced technologies in clinical practices in the radiation oncology department. Other goals are to develop high-precision radiotherapy as intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), respiratory-gating radiation therapy, marker-tracking radiation therapy, image-guided radiation therapy (IGRT), stereotactic RT and proton beam therapy (PBT) in cancer treatment.

Routine activities

At present, the staff of the Section of Radiation Safety and Quality Assurance consists of one radiation oncologists, three medical physicists and one radiological technologist. We have more than 1,000 new patients for photon and proton therapy every year. The section is responsible for four linear accelerators, two CT simulators and four different treatment planning systems in photon/electron therapy. In proton therapy, one accelerator, two treatment units, and one planning system are managed.

Quality assurance programs have been established for photon and proton therapy by the medical physicists. The daily, monthly and annual programs are performed by the medical physicists and radiological technologists. In addition, the medical physicists perform radiotherapy planning for IMRT/VMAT in prostate and head and neck sites, stereotactic RT in the liver and lungs, and proton therapy in the head and neck, esophagus, lung, liver, prostate and infants. The medical physicists support conventional radiotherapy planning and also check the quality and safety for all treatment plans.

Research activities

In the Radiation Safety and Quality Assurance Section, the following research activities are on-going:

1) Design and development of new proton beam irradiation system
2) Design and development of monitor unit calculation for proton therapy
3) Design and development of a Monte Carlo-based dose calculation algorithm for proton therapy
4) Design and development of a CT-based image guided and adaptive proton therapy system.

5) Design and development of four-dimensional planning for motion synchronized dose delivery for photon therapy.
6) Design and development of CT-pulmonary ventilation imaging
7) Design and development of quality assurance system for gated radiotherapy
8) Multi-institutional study of independent MU/Dose verification for conventional, stereotactic RT, IMRT, VMAT as well as for Vero, CyberKnife and Tomotherapy in photon therapy

Clinical trials

The following multi-institutional clinical trials are ongoing:

1) Establishment of safety for radiotherapy planning of photon therapy

Education

We established an on-the job-training program for quality assurance programs for a photon linear accelerator and over 100 medical physicists and radiological technologists have taken the educational program. We held a meeting for independent MU/dose verification and over 180 medical physicists and radiological technologists participated in the meeting. We trained graduated students from Tsukuba University and Komazawa University for a quality assurance program in photon therapy.

Future prospects

We maintain the quality of photon/electron and proton therapy machines and also establish new technologies to improve patient outcomes. In addition, we will work on radiotherapy as well as radiology including establishment of a quality assurance program for diagnostic instruments and management of radioactive materials.

List of papers published in 2015

Journal

1. Kohno R, Yamaguchi H, Motegi K, Tanaka F, Akita T, Nagata Y, Hotta K, Miyagishi T, Nishioka S, Dohmae T, Akimoto T. Position verification of the RADPOS 4-D *in-vivo* dosimetry system. Int J Med Phys Clin Eng Radiat Oncol, 4:318-325, 2015
2. Hotta K, Kohno R, Nagafuchi K, Yamaguchi H, Tansho R, Takada Y, Akimoto T. Evaluation of monitor unit calculation based on measurement and calculation with a simplified Monte Carlo method for passive beam delivery system in proton beam therapy. J Appl Clin Med Phys, 16:228-238, 2015

Nutrition Management Office

Haruka Citose, Yumi Ochiai, Takako Kuroda, Marie Ohishi, Kana Shiraiwa, Taichi Watanabe, Keiko Asano, Rumi Noda, Ayuko Umezawa, Yoshio Shimokawa, Hideki Takano, Koichi Abe, Takahiro Takahashi, Tatsuya Hirakawa, Satoshi Watanabe, Hideki Ogiwara, Akio Sairennji

Introduction

In 2015, we focused on the activities of the NST (nutrition support team). Increasing the number of consultations was an effort to improve quality. We received an increase in health care fees.

Routine activities

Dietary meals totaled 327,706 in 2015, and we gave nutrition-related dietary advice to 2,612 persons. There have been 1,577 new requests for consultations with the NST, an average of 131 per month (Table 1). The total number of consultations in 2015 was 2,094. 2015 saw 50% growth against the previous year.

Cooking classes for cancer prevention were held three times as planned.

Cooking classes to cope with cancer symptoms have been held 167 times since the beginning of the program.

Research activities

We are doing a "study on the effectiveness of rehabilitation and nutrition therapy in perioperative hepatobiliary surgery". The "Impact on the development and postoperative complications of obesity in colon cancer patients of a preoperative weight loss program" is also carried out. These studies were to verify the effect of preoperative nutritional guidance. And, through team medical practices, we are aiming to participate in a total treatment plan.

In other research, there is a diet support research for cancer survivors.

Table 1. Number of NST Collsultaticns in 2015 (New request number)

Clinical Departments	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sept	Oct	Nov	Dec	Total
Head and Neck Surgery	6	5	7	10	5	6	5	3	4	7	8	10	76
Head and Neck Medical Oncology	7	11	14	13	10	13	11	7	10	9	9	10	124
Gastrointestinal Oncology	4	4	5	1	3	4	1	2	1	3	3	4	35
Colorectal Surgery	4	2	1	0	2	0	3	4	2	4	2	4	28
Gastrointestinal Oncology	27	25	28	29	29	34	35	34	32	37	28	30	368
Hepatobiliary and Pancreatic Surgery	0	0	1	6	2	3	1	1	2	0	0	2	18
Hepatobiliary & Pancreatic Oncology	9	16	15	5	14	18	23	23	18	18	21	21	201
Thoracic Surgery	0	1	2	5	5	2	1	2	5	2	2	1	28
Thoracic Oncology	26	28	33	33	32	25	21	25	23	21	26	21	314
Urology	1	1	0	0	0	2	1	0	1	0	0	0	6
Hematology	9	14	14	15	19	22	20	18	25	23	21	21	221
Breast and Medical Oncology	7	7	11	9	7	10	12	13	11	15	7	17	126
Palliative Medicine	1	1	5	2	0	0	0	0	1	0	0	0	10
Other departments	2	2	2	2	1	2	2	3	4	1	1	0	22
Total	103	117	138	130	129	141	136	135	139	140	128	141	1,577

Education

In the field of human resources development, we have a strong commitment to education and training and have conducted eight university courses for registered dietitians within universities. By strengthening our cooperation with universities, our aim is to enhance research activities in the future through the development of human resources.

Future prospects

Regarding the cooking classes that we have worked on over many years, we will consider a better plan to offer the classes in a way to meet the needs of patients and their families, and locals. In addition, we plan to hold numerous lectures for local residents. We will plan these together with the government. We want to disseminate information and understanding of said information about diets that influence cancer therapy and cancer prevention among a lot of people .

Office of Cancer Registry

Hironobu Ohmatsu, Takashi Kojima, Tokiko Inagaki, Yumi Ishii, Maiko Miura, Yayoi Ohtsuka

Introduction

In September 2014, the "Health Information Management Office" was separated into the Medical Information Management Office and the Office of Cancer Registry. The Office of Cancer Registry is a department for executing a hospital-based cancer registry.

Routine activities

Diagnostic cases registered in 2014 in the hospital cancer registry (the first visit of cancer patients diagnosed from January to December in our hospital) were 5,796 (of which, initial treatment conducted in our hospital: 3,833 cases: in our hospital diagnosis only: 150 cases; after the start of treatment in another hospital: 941 cases; and diagnosis and treatment in another hospital (including a second opinion): 872 cases). The number of new registrations shows that the number of female patients has been consistently less over time than male patients due to irregular situations according to department (see Table 1).

Table 1. The number of cancer registrations of NCCH-East

Year	Male	Female	Total
2000	3,054	1,625	4,679
2011	3,145	1,733	4,878
2012	3,435	1,749	5,184
2013	3,996	2,043	6,039
2014	3,753	2,043	5,796

The number of new registrations according to the place of residence was 786 in Kashiwa City, 461 in Matsudo City, 353 in Nagareyama City ... (see Table 2)

Table 2. The number of new registrations according to the place of residence

	Residence (city)	No. of registrations
1	Kashiwa	786
2	Matsudo	461
3	Nagareyama	353
4	Noda	343
5	Abiko	257

Last year, for the first time, the hospital cancer registry aggregate results (2014 cases) were published in the internal server of the hospital because it is seen as basic data that can help in medical care, research and the management analysis. In the future, we aim to publish these results every year.

Medical Information Management Office

Hironobu Ohmatsu, Tokiko Inagaki

Introduction

The Medical Information Management Office is a department for managing the medical records of hospitals by professional medical information management officers.

Routine activities

- Auditing Discharge Summary (quantitative inspection)
  Data on discharge summaries should be entered and approved by the attending physician (Table 1). We inspected and checked the summaries and, where required, gave some advice for correct input.
- Maintenance of disease codes based on ICD-10
- Analysis of medical contents on DPC (Diagnostic Procedure Combination) and recommendation for efficiency.

Table 1. Submitting rate of dischatge summary

2012	2013	2014	2015*
79%	81%	98%	91%

* Definition was changed from "entered" to "entered and approved" from May 2015.

Future prospects

We would like to make recommendations and proposals of good and effective medical care based on DPC data. Each department has held the "DPC round".

Department of Pharmacy

Shinichiro Saito, Kunio Takahashi, Toshikatsu Kawasaki, Yasuhiko Ichida, Tomoyuki Akimoto, Reiko Matsui, Hisanaga Nomura, Yasuaki Ryushima, Naoko Yoshino, Minako Yoshida, Hideki Funasaki, Yoshiki Kojima, Daisuke Kanou, Yousuke Maki, Nobuo Mochizuki, Kenji Kawasumi, Tomoka Okano, Shinya Motonaga, Ryoko Udagawa, Hiroko Ouchi, Tomoko Morita, Mai Itagaki, Shinya Suzuki, Takeshi Koike, Misaki Kobayashi, Motoko Kaneko, Akira Shinohara, Takahiro Outa, Daisuke Hisamatsu, Ayumi Yamaguchi, Takayuki Sano

Introduction

The main objectives of our Department of Pharmacy are: 1) To promote clinical studies to create new evidence-based data; 2) To provide chemotherapy based on the most updated evidence-based data; and 3) To pursue patient-centered pharmaceutical care.

Our residents' training program started in 2006. In 2015, five residents joined our Department. Presently, we have a total of 24 residents. In addition, our Department has accepted seven trainees from other institutions for our oncology pharmacist training programs. Through 2015, which is two terms of the training courses, we have educated eight pharmacy students and two advanced-training pharmacy students.

The Department of Pharmacy provides various important services: controlling inventory; dispensing medications; preparing i.v. solutions for chemotherapy, which include the aseptic mixing of antineoplastic agents; collecting and providing drug information; managing therapeutic drug monitoring; checking treatment regimens for each patient's chemotherapy; and providing pharmaceutical management and counseling.

Our Department reviews the drugs taken by patients before and during their hospitalization. In inpatient care, the Department assigns pharmacists to provide medication counseling and drug information for healthcare providers and patients, to pursue effective pharmaceutical care. In outpatient care, the Department provides a pharmacy outpatient service in which pharmacists check patients for adverse reactions and doses of antineoplastic agents, especially in the case of oral anticancer medications. We then assess the necessity of supportive-care medications and suggest them to physicians. The pharmacy outpatient service also reviews the drugs taken by all patients to evaluate when patients have to stop their anticoagulants before their operation or when they have to stop to take metformin before examinations with iodinated-contrast material. Pharmacists are on duty at the Outpatient Chemotherapy Center as dedicated staff members. The pharmacists provide a Chemotherapy Hotline Service, which is a direct line for our outpatients who have any problems concerning their chemotherapy treatment. In the Outpatient Chemotherapy Center, pharmacists are always available to provide drug information for healthcare providers and patients. We also manage investigational drugs.

New developments

Checking home medication, that is, medication reconciliation, is one of the core services in the pharmacy division. At the National Cancer Center Hospital East, pharmacists used to perform the service from a dispensing room window. However, the working place has changed from the dispensing room window to hospital wards, because patients had a long waiting time and underwent the burden of having their brought-in medicine checked. According to the change of working place, ward pharmacists have checked brought-in home medication in the ward since February 5th, 2015. The change of service location does not only reduce the burden of patients having to wait, but also reduces the nurses' work burden. In addition, the number of brought-in medicine checks has increased, and this enhances the clinical pharmacy service in the inpatient division.

Table 1. Pharmacy Achievement

	2012	2013	2014	2015
Number of Prescriptions				
Prepared in hospital pharmacy				
Total	90,392	97,444	105,477	102,757
Inpatients	84,800	91,549	99,367	99,390
Outpatients	5,592	5,895	6,110	3,367
Taken to outside pharmacies	59,722	64,123	70,879	77,546
(% of prescriptions filled outside)	(91.4%)	(91.6%)	(92.1%)	(95.8%)
Injections				
Total	160,105	158,557	164,485	167,973
Inpatients	126,428	125,106	131,278	132,252
Outpatients	33,677	33,451	33,207	35,721
Number of Prescriptions				
(Investigational new drugs)	4,584	5,110	6,792	6,308
Aseptic Preparation of Injection Mixture				
Anticancer drugs	38,663	42,735	47,362	55,049
Others	3,994	4,204	5,633	5,145
Number of medication counseling sessions (for inpatients)				
Patient	6,418	7,248	7,512	5,232
counseling sessions that earned a counseling fee	7,139	5,005	7,916	6,860
Number of medication counseling sessions (for outpatients)				
in the Outpatient Chemotherapy Center	8,965	10,073	9,765	12,651
in the pharmacy outpatient service	1,782	2,375	3,493	4,621
in the 'Nexavar' outpatient service	381	202	270	241
Number of calls on the Chemotherapy Hotline	1,665	2,087	2,258	2,399
Number of checking home medications	6,017	6,506	7,087	9,524
Number of insurance-reimbursement claims for dedicated clinical-pharmacist services		8,094	25,592	26,479

List of papers published in 2015

Journal

1. Shinohara A, Ikeda M, Okuyama H, Kobayashi M, Funazaki H, Mitsunaga S, Shimizu S, Ohno I, Takahashi H, Ichida Y, Takahashi K, Okusaka T, Saitoh S. Efficacy of prophylactic minocycline treatment for skin toxicities induced by erlotinib plus gemcitabine in patients with advanced pancreatic cancer: a retrospective study. Am J Clin Dermatol, 16:221-229, 2015

Department of Nursing

Chie Asanuma

Introduction

Guided by the principle that nurses are active team members in state-of-the-art cancer treatment and participate in the development of cancer nursing at the core hospital providing cancer nursing care in Japan, the Department of Nursing of the National Cancer Center Hospital East works based on the following basic policies:

1) To provide nursing care founded on trust and reassurance, respecting the dignity of life and the rights of patients;
2) To pursue the essential values of nursing and practice scientific and creative nursing;
3) To facilitate clinical studies and disseminate new information concerning cancer nursing; and
4) To promote development of leadership skills.

In addition, the Department of Nursing is involved in and contributing to hospital management, working to help find a better balance between the provision of quality medical and nursing services and the efficiency of business.

Routine activities

1) Nursing Activities

Backed by the consciousness and a sense of responsibility of the nurses at the Hospital East, the Department of Nursing has been striving to support the progress of medicine and to provide safe and reliable nursing care meeting the needs of patients and their families in the best possible way. To this end, the Department has been making efforts to develop institutional systems, improve work practice, promote team medicine, promote regional healthcare collaboration, and develop and recruit human resources, so that it can actively be involved in hospital management and provide quality medical and nursing services through linkage, cooperation, and collaboration, across the borders of different vocations.

The average number of inpatients, bed utilization rate, bed availability, average length of stay, number of outpatients, number of chemotherapy patients at the Outpatient Treatment Center, number of operations, and other performance indicators all exceeded the records in the previous year.

The increase in the number of patients saw a response in the increase in nurses, outpatient and ward clerks, and nursing assistants, as well as delegation of work responsibilities among different vocations, sharing of work responsibilities, and improvement of work practice, which resulted in remarkable improvements in efficiency, safety, and cost performance.

2) Educational Activities

The in-house education program of our hospital is characterized by the two-tier structure consisting of "basic education" providing basic knowledge and skills in nursing and "specialist education in cancer nursing" for the practice of cancer nursing. On the foundation of the basic knowledge and skills in nursing, the in-house education program trains nurses who can deliver "nursing offering peace of mind," where patients and their families may choose treatment and care through their own decisions, while nurses use their excellent expertise and skills to alleviate pain. The nurses trained in this way are sent to work in clinical settings.

In addition, in-house programs for nurse administrators, researchers, and educators are also offered, as well as active support got the participation in overseas training and outside training for the nurses who want further advancement.

Training programs are also offered to the nurses from other organizations, such as "Delirium Program Training," "Communication Training," and

"Cancer Nursing Training," achieving qualitative improvement and career advancement of nurses both in and outside of the hospital.

3) Certified Nurse Specialists and Certified Nurses

One certified nurse specialist in cancer, one certified nurse in skin and excretory care, and one certified nurse in palliative care were newly qualified in 2015. At present, there are eight certified nurse specialists in two areas and 31 certified nurses in eight areas working in various nursing units, serving as role models in nursing practice in respective specialties. They are also working in cross-organizational roles as the members of medical teams, such as infection control, palliative care, and nutrition support teams.

The scheme for in-house certified nurses in anticancer IV was created to enhance the specialty of nurses and expand their work responsibilities for the purpose of reducing the workload of physicians so that they could concentrate on their work. In the third year of implementation, this scheme has qualified 55 in-house certified nurses. The scheme for in-house certified nurses in radiotherapy intravenous injection, launched last year, qualified four in-house certified nurses, who are working actively in clinical practice.

"Delirium Program Training," "Communication Training," "Cancer Nursing Training," and other training programs were offered to nurses from other organizations, and were attended by many nurses from across the country. The in-house education programs of our hospital are also made available to the nurses from five national hospitals in Chiba Prefecture and other hospitals in the country. These have been attended by 244 nurses in total, achieving qualitative improvement and career advancement of nurses both in and outside of the hospital.

4) Operation of Certified Nurse Education Courses and Training of Certified Nurses

The training course for certification in palliative care, established in 2013 after obtaining facility accreditation as an educational institution for certified nurses from the Japanese Nursing Association, has seen successful graduation of 11 trainees in the first batch and 18 in the second. At present, it is attended by 22 trainees in the third batch.

The 29 trainees in the first and second graduating classes passed the examination for certified nurses in palliative care, and are working as role models in palliative care at various medical institutions.

Following the training course for certification in palliative care, the certified nurse training course in chemotherapy is in the process of preparation, scheduled for opening in July 2016.

Research activities

Including three presentations at overseas venues, 30 presentations were made at academic conferences. Three of these studies were supported by subsidies from outside organizations. The increase in the number of presentations in nursing study, the acquisition of study funds from outside sources, and the improvement of the quality of study owe a lot to the support of the clinical trial support team consisting of physicians and other members from the Hospital East, as well as the nursing study support team consisting of certified nurse specialists and certified nurses. These support teams are providing assistance and stimulating the inquiring minds of nurses, who are courageously tackling the clinical problems.

The publication of 26 articles in journals and the issuance of the book "Communication Skills Using NURSE," edited by the Department of Nursing of the Hospital East, were the products of our research activities in clinical practice.

We strive for further improvement of the quality of our nursing study, so that we can create and disseminate new approaches to evidence-based cancer nursing at the National Cancer Center Hospital East.

Future prospects

Our tasks for 2016 include making a further leap forward as a research core hospital and obtaining the accreditation as a specific function hospital providing advanced, pioneering medical care. In conjunction with the construction of the NEXT building, we also expect the addition of more

operating rooms and endoscopy rooms and the construction of ICUs. The Department of Nursing of the Hospital East, as a component in team medicine, plans to provide advanced, pioneering medical care expected of a research core hospital/specific function hospital; to promote clinical study and trials; and to reinforce the system for patient safety. At the same time, we strive for appropriate training, recruitment, and placement of nurses, which are the basis for the improvement of the quality of nursing and the innovations in nursing in response to the progress of medicine.

As we understand the critical importance of stable business operations in realizing the ideals and missions of the National Cancer Center, the Department of Nursing of the Hospital East works in cooperation and collaboration with other departments to facilitate management improvements.

Clinical Research Support office

Akihiro Sato, Miki Fukutani, Sakiko Kuroda, Takako Tomizawa, Kayo Toyosaki, Masako Nakamoto, Kana Fukui, Masato Yonemura, Hiromi Hasegawa, Yoshihiro Aoyagi, Seiko Matsuda, Kaori Tobayama, Ayako Sugama, Tsukiko Higuchi, Wataru Okamoto, Akiko Nakayama, Izumi Miki, Tomohisa Sudo, Yuuko Tagami

Introduction

The Research Management and Data Management Section supports the investigator-initiated clinical trial program in the NCCHE though the clinical datacenter, study management, site visit monitoring, safety information management, and bio statistics.

The Bio Bank and TR Support Section supports Translational Research including a genome-wide screening network program through study management and data management.

Routine activities

Data Management Section
-Database and CRF form design
-Registration
-Data management
-System administration
-Bio statistics
Research Management Section
-Study management
-Site visit monitoring
-Safety information management
-Medical writing
Bio Bank and TR Support Section
-Study management for TR
-Data management for TR
-Research concierges for Bio Bank

Clinical trials

Data Management and Research Management sections
- In 2015, five IND trials started enrollment.
- A total of 86 patients were enrolled

Bio Bank and TR Support Section
- In 2015, five TR trials were conducted.
- A total of 1,783 patients were enrolled

Education

On-the-job-training for new staff.

Support the education program for clinical trial methodology and GCP in the NCC.

Co-host the GCP training seminar with other ARO.

Future prospects

Preparation for conducting global IIT IND trials.

Certified nurse curriculum

Toshirou Nishida, Asuko Sekimoto

Curriculum for certified nurses

In March 2015, 18 students of the second-generation class completed the accredited curriculum (palliative care), and 16 students passed the certified nurse qualification examination sponsored by the Japanese Nursing Association. Consequently, 27 students, including the students of the inaugural class, registered as palliative care certified nurses in July 2015.

In July 2015, 22 students entered our nursing institute, and are presently in the third-generation class.

In October 2015, 22 students of the fourth-generation class passed the entrance examination at the competition ratio of 1.5 (compared to 1.2 last year).

Since April, 2015, our institute has improved as a means of education that aims toward the practice of well-grounded cancer chemotherapy nursing and as a point of feedback to a system in cutting-edge fields in cancer medical research. On November 10, 2015, we were authorized by the Japanese Nursing Association as a certified nurse educational institution (cancer chemotherapy nursing), and thereafter, started admitting trainees to our institute in December. Eleven applied for the entrance exam, which has a quota of 15, and eight applicants passed.

In February 2015, the follow-up training for the first graduating class was held, and 80 people, including certified nurses of the hospital, participated.

Image for the future

Through our curricula, we shall improve on the latest and professional knowledge, as well as improve skills for cancer medical care and cancer nursing and provide further contributions to reflect our in-service education, its procedure, and the system concerned. We shall introduce our current certified nurse curriculum to society to help secure staff resources as well as support for future career development.

Research Institute

Preface

The National Cancer Center Research Institute (NCCRI) was established in 1962 as one of the main parts of the National Cancer Center (NCC), and has been driving cancer research in Japan ever since. The NCC was designated a National Research and Development Agency in April 2015. Since then, there has been more demand than ever to promote research and development and to maximize results. To meet such demand, the NCCRI has been collaborating closely with the NCC Hospitals, the Exploratory Oncology Research & Clinical Trial Center, the Research Center for Cancer Prevention and Screening (the Center for Public Health Sciences from January 2016), and the Center for Cancer Control and Information Services, and thereby has tried to maximize the transition "from bench to bedside".

In addition to 19 divisions, the NCCRI also contains the Fundamental Innovative Oncology Center (FIOC), which is a core facility for the entire NCC. The FIOC consists of 15 departments, and it runs the NCC BioBank, provides specialized techniques, and also facilitates collaborative work with various private sectors outside the NCC. As of March 2016, the NCCRI has 83 research staff, 79 postdoctoral fellows and 131 graduate students/supporting staff, all of whom are dedicated to a wide range of cancer research including prevention of cancer, elucidating inter- or intra-tumor heterogeneity, identification of therapeutic targets and preclinical studies for novel anti-cancer reagents.

Outstanding achievements in 2015 in the NCCRI include the following:

1) Large-scale genomic analyses on biliary tract cancer
2) Discovery of the relationship between the expression level of a microRNA and resistance against anti-cancer drugs
3) Identification of stem cells in Barrett's esophagus lesions.
4) Development of a novel modality by the use of synthetic lethality for tumors with *CBP* mutations.
5) Large-scale genomic analyses on ampullary carcinoma.

The NCCI also actively participates in, and leads worldwide cancer research collaborations including the International Cancer Genome Consortium (ICGC) and the International Human Epigenome Consortium (IHEC). We are also collaborating with the Early Detection Research Network (EDRN) of the National Cancer Institute (NCI) of the United States.

As described above, through enhancing high-quality research and interaction with other institutes, the NCCRI is eagerly generating novel modalities to prevent and conquer cancer.

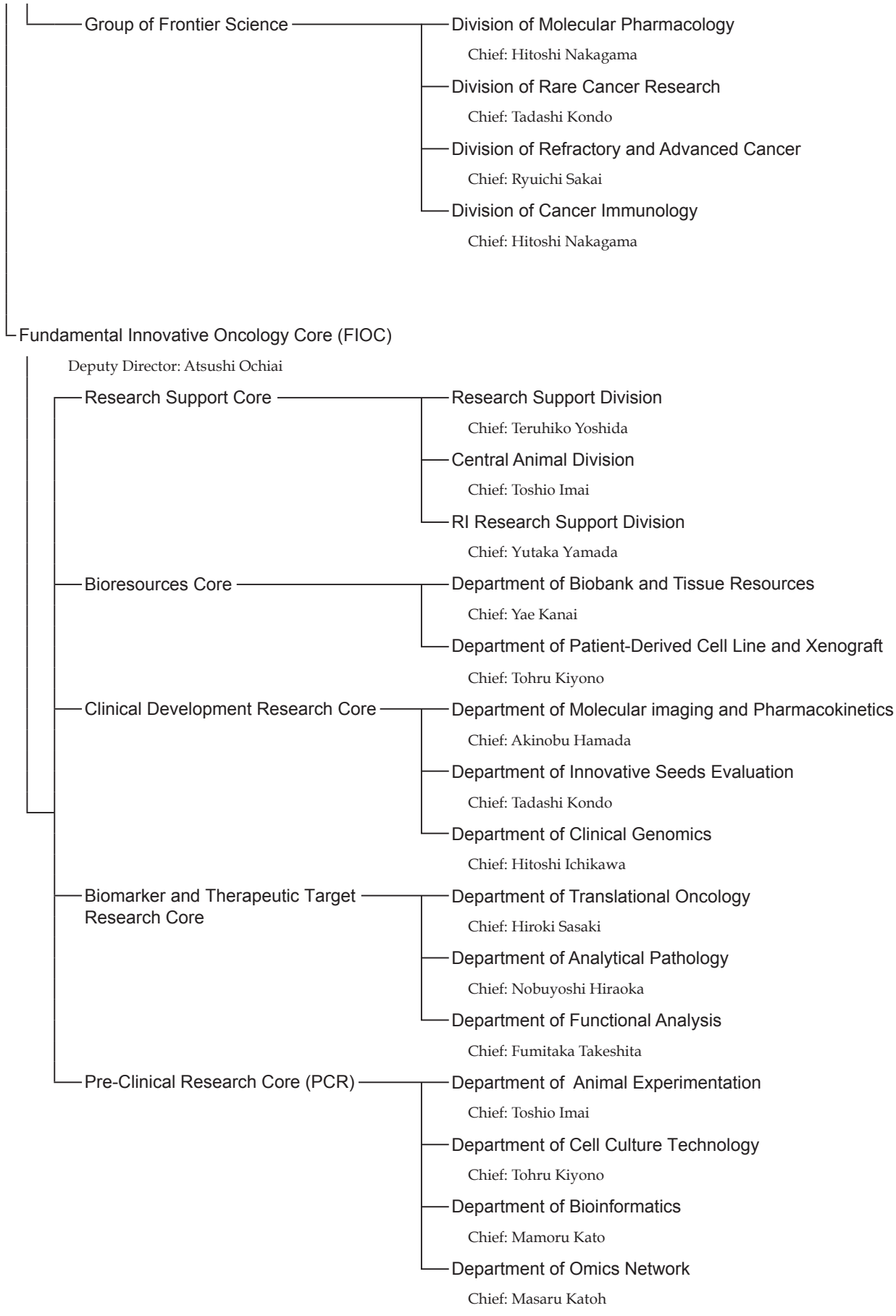
Hiroyuki Mano, M.D., Ph.D.
Director, National Cancer Center Research Institute

Organization

President:
Tomomitsu Hotta

Director:
Hitoshi Nakagama

- Group for Cancer Development and Progression
  - Division of Molecular Pathology
    Chief: Yae Kanai
  - Division of Genetics
    Chief: Teruhiko Yoshida
  - Division of Carcinogenesis and Prevention
    Senior Chief: Toru Kiyono
    Chief: Hitoshi Nakagama
  - Division of Cancer Biology
    Chief: Hirofumi Arakawa
- Group for Research of Molecular Functions and Targets
  - Division of Hematological Malignancy
    Chief: Issay Kitabayashi
  - Division of Cancer Stem Cell
    Chief: Kenkichi Masutomi
  - Division of Cancer Differentiation
    Chief: Koji Okamoto
- Group for Development of Molecular Diagnostics and Individualized Therapy
  - Division of Epigenomics
    Chief: Toshikazu Ushijima
  - Division of Cancer Genomics
    Chief: Tatsuhiro Shibata
  - Division of Genome Biology
    Chief: Takashi Kohno
  - Division of Brain Tumor Translational Research
    Chief: Koichi Ichimura
- Group for Translational Research
  - Division of Chemotherapy and Clinical Research
    Senior Chief: Tesshi Yamada
    Chief: Vacant
  - Division of Cancer Pathophysiology
    Chief: Yasuhito Uezono
  - Division of Molecular and Cellular Medicine
    Senior Chief: Takahiro Ochiya
    Chief: Kazunori Aoki


Group of Frontier Science
Division of Molecular Pharmacology
Chief: Hitoshi Nakagama
Division of Rare Cancer Research
Chief: Tadashi Kondo
Division of Refractory and Advanced Cancer
Chief: Ryuichi Sakai
Division of Cancer Immunology
Chief: Hitoshi Nakagama
Fundamental Innovative Oncology Core (FIOC)
Deputy Director: Atsushi Ochiai
Research Support Core
Research Support Division
Chief: Teruhiko Yoshida
Central Animal Division
Chief: Toshio Imai
RI Research Support Division
Chief: Yutaka Yamada
Bioresources Core
Department of Biobank and Tissue Resources
Chief: Yae Kanai
Department of Patient-Derived Cell Line and Xenograft
Chief: Tohru Kiyono
Clinical Development Research Core
Department of Molecular imaging and Pharmacokinetics
Chief: Akinobu Hamada
Department of Innovative Seeds Evaluation
Chief: Tadashi Kondo
Department of Clinical Genomics
Chief: Hitoshi Ichikawa
Biomarker and Therapeutic Target Research Core
Department of Translational Oncology
Chief: Hiroki Sasaki
Department of Analytical Pathology
Chief: Nobuyoshi Hiraoka
Department of Functional Analysis
Chief: Fumitaka Takeshita
Pre-Clinical Research Core (PCR)
Department of Animal Experimentation
Chief: Toshio Imai
Department of Cell Culture Technology
Chief: Tohru Kiyono
Department of Bioinformatics
Chief: Mamoru Kato
Department of Omics Network
Chief: Masaru Katoh

Activities of the Divisions

Division of Molecular Pathology

Yae Kanai, Eri Arai, Masahiro Gotoh, Ying Tian, Yoshimasa Saito, Takuya Yotani, Yuriko Yamada, Koji Tsumura, Ayako Shibuya, Nanako Itoh, Toshihide Muramatsu, Toshiya Nakaoka, Michiko Suzuki

Introduction

On the basis of findings from routine diagnostic pathology work, we develop scientific ideas and follow them up using a molecular pathological approach to understand the molecular basis of diseases and mechanisms determining clinicopathological heterogeneity of cancers. Our Division mainly consists of researchers who also belong to academia and industry. Therefore, we focus on industrial‐academic‐government cooperation to yield potential benefits for cancer patients.

Research activities

Activities in the International Human Epigenome Consortium (IHEC)

We have participated in IHEC as a principal investigator supported by the Core Research for Evolutional Science and Technology (CREST) project by the Japan Agency for Medical Research and Development (AMED). We have worked in collaboration with research groups in Kyushu University and the University of Tokyo to reveal the epigenome landscape, whole-genome bisulfite sequencing using post-bisulfite adaptor tagging, chromatin immunoprecipitation sequencing, RNA sequencing and whole-genome sequencing using normal hepatocytes purified from partial hepatectomy specimens of six Japanese patients. CpG methylation levels were generally low in the region 200 bp upstream from the transcription start site (TSS200), the first coding exon and the CpG island. Considerable CHG and CHH methylation was observed. Personal differentially methylated regions (pDMRs) were observed less frequently in TSS200, the first coding exon and the CpG island. Histone modification profiles of pDMRs differed considerably among samples. pDMRs were observed around the TSSs of genes whose expression levels are reportedly regulated by CpG methylation. pDMRs were frequently observed in the vicinity of single-nucleotide variations and insertions/deletions, suggesting the possibility of cis-acting genome-epigenome interaction. Genetic variations may induce epigenetic variations and generate individual differences in the phenotypes of normal hepatocytes through variations in expression.

Epigenome maps are now being obtained from hepatocytes purified from diseased liver tissue with hepatitis C virus or hepatitis B virus-infection and epithelial cells purified from the stomach, colon and urogenital organs for IHEC activities. Such data we obtain will be made available by the National Bioscience Database Center (http://humandbs.biosciencedbc.jp/en/) and the IHEC database (http://epigenomesportal.ca/ihec/). Accurate epigenome profiling of normal cells will allow the identification of disease-specific epigenome profiles, thus facilitating a potential breakthrough in the prevention, diagnosis and therapy of diseases.

From November 16-18, 2015, AMED and our CREST team had the pleasure to host this year's annual meeting of IHEC and to welcome IHEC members from around the world to Tokyo, Japan. The three-day meeting offered various sessions including country updates, workgroup meetings and talks by both IHEC members and invited scientists on their latest findings in epigenomics. This year's meeting marked the highest number of attendees yet in the series of IHEC conferences.

Multilayer omics analysis in human cancers for personalized medicine

CpG-island methylator phenotype (CIMP)-positive clear cell renal cell carcinomas (RCCs), which we have originally identified, are characterized by

accumulation of DNA hypermethylation of CpG islands, clinicopathological aggressiveness and poor patient outcome. To clarify the molecular pathways participating in CIMP-positive renal carcinogenesis, genome (whole-exome and copy number), transcriptome and proteome (two-dimensional image converted analysis of liquid chromatography-mass spectrometry) analyses were performed using tissue specimens of CIMP-negative and CIMP-positive clear cell RCCs and corresponding specimens of non-cancerous renal cortex in a collaborative joint research project. Genes encoding microtubule-associated proteins, such as *DNAH2, DNAH5, DNAH10, RP1* and

Figure 1. Participants (upper) and discussion (lower) in IHEC Science Day and Annual Meeting in Tokyo (November 16-18, 2015).

HAUS8, showed a high incidence of mutations in CIMP-positive RCCs, whereas CIMP-negative RCCs lacked distinct genetic characteristics. Alterations of mRNA or protein expression were significantly accumulated in signaling pathways participating in the spindle checkpoint. All CIMP-positive RCCs showed overexpression of Aurora kinases, *AURKA* and *AURKB*, which are key players in the spindle checkpoint and this overexpression was mainly attributable to the increased copy number. These data suggest that abnormalities of the spindle checkpoint pathway participate in CIMP-positive renal carcinogenesis, and that *AURKA* and *AURKB* may be potential therapeutic targets in more aggressive CIMP-positive RCCs.

In order to make DNA methylation diagnosis applicable to clinical use, a high performance liquid chromatography (HPLEC)-based and scaled-down methylated DNA detection device, which can be introduced into clinical laboratories of each hospital and even into small clinics, is now being developed by a joint research program with Sekisui Medical Co., Ltd. This joint R&D was introduced in several newspapers and other media in 2015. We are now attempting to use this device for carcinogenetic risk estimation, liquid biopsy diagnosis, prognostication and companion diagnosis for molecular targeted therapy in cancers derived from various organs.

Clinicopathological studies of human cancers based on the practice of diagnostic pathology

Using morphological, histological, immunohistochemical and molecular pathological approaches, diagnostic and prognostic criteria, which are applicable to histological specimens, were explored. We collect tissue samples for the National Cancer Center Biobank and contribute to joint research through providing clinicopathological information.

Future prospects

We will continuously perform joint research using tissue specimens pathologically examined by ourselves with both academia and industry to develop new strategies for cancer prevention, diagnosis and therapy.

List of papers published in 2015

Journal

1. Arai E, Gotoh M, Tian Y, Sakamoto H, Ono M, Matsuda A, Takahashi Y, Miyata S, Totsuka H, Chiku S, Komiyama M, Fujimoto H, Matsumoto K, Yamada T, Yoshida T, Kanai Y. Alterations of the spindle checkpoint pathway in clinicopathologically aggressive CpG island methylator phenotype clear cell renal cell carcinomas. Int J Cancer, 137:2589-2606, 2015

2. Yamanoi K, Arai E, Tian Y, Takahashi Y, Miyata S, Sasaki H, Chiwaki F, Ichikawa H, Sakamoto H, Kushima R, Katai H, Yoshida T, Sakamoto M, Kanai Y. Epigenetic clustering of gastric carcinomas based on DNA methylation profiles at the precancerous stage: its correlation with tumor aggressiveness and patient outcome. Carcinogenesis, 36:509-520, 2015

3. Sato T, Soejima K, Arai E, Hamamoto J, Yasuda H, Arai D, Ishioka K, Ohgino K, Naoki K, Kohno T, Tsuta K, Watanabe S, Kanai Y, Betsuyaku T. Prognostic implication of PTPRH hypomethylation in non-small cell lung cancer. Oncol Rep, 34:1137-1145, 2015

4. Robles AI, Arai E, Mathé EA, Okayama H, Schetter AJ, Brown D, Petersen D, Bowman ED, Noro R, Welsh JA, Edelman DC, Stevenson HS, Wang Y, Tsuchiya N, Kohno T, Skaug V, Mollerup S, Haugen A, Meltzer PS, Yokota J, Kanai Y, Harris CC. An Integrated Prognostic Classifier for Stage I Lung Adenocarcinoma Based on mRNA, microRNA, and DNA Methylation Biomarkers. J Thorac Oncol, 10:1037-1048, 2015

5. Sakamoto A, Hino S, Nagaoka K, Anan K, Takase R, Matsumori H, Ojima H, Kanai Y, Arita K, Nakao M. Lysine Demethylase LSD1 Coordinates Glycolytic and Mitochondrial Metabolism in Hepatocellular Carcinoma Cells. Cancer Res, 75:1445-1456, 2015

6. Narukawa T, Hara T, Arai E, Komiyama M, Kawahara T, Kanai Y, Fujimoto H. Tumour multifocality and grade predict intravesical recurrence after nephroureterectomy in patients with upper urinary tract urothelial carcinoma without a history of bladder cancer. Jpn J Clin Oncol, 45:488-493, 2015

7. Hashimoto T, Ogawa R, Matsubara A, Taniguchi H, Sugano K, Ushiama M, Yoshida T, Kanai Y, Sekine S. Familial adenomatous polyposis-associated and sporadic pyloric gland adenomas of the upper gastrointestinal tract share common genetic features. Histopathology, 67:689-698, 2015

8. Matsubara A, Ogawa R, Suzuki H, Oda I, Taniguchi H, Kanai Y, Kushima R, Sekine S. Activating GNAS and KRAS mutations in gastric foveolar metaplasia, gastric heterotopia, and adenocarcinoma of the duodenum. Br J Cancer, 112:1398-1404, 2015

9. Yoshida M, Sekine S, Ogawa R, Yoshida H, Maeshima A, Kanai Y, Kinoshita T, Ochiai A. Frequent MED12 mutations in phyllodes tumours of the breast. Br J Cancer, 112:1703-1708, 2015

10. Terai H, Soejima K, Yasuda H, Sato T, Naoki K, Ikemura S, Arai D, Ohgino K, Ishioka K, Hamamoto J, Kanai Y, Betsuyaku T. Long-term exposure to gefitinib induces acquired resistance through DNA methylation changes in the EGFR-mutant PC9 lung cancer cell line. Int J Oncol, 46:430-436, 2015

11. Hiraoka N, Ino Y, Yamazaki-Itoh R, Kanai Y, Kosuge T, Shimada K. Intratumoral tertiary lymphoid organ is a favourable prognosticator in patients with pancreatic cancer. Br J Cancer, 112:1782-1790, 2015

12. Shirota T, Ojima H, Hiraoka N, Shimada K, Rokutan H, Arai Y, Kanai Y, Miyagawa S, Shibata T. Heat shock protein 90 is a potential therapeutic target in cholangiocarcinoma. Mol Cancer Ther, 14:1985-1993, 2015

13. Yoshida M, Ogawa R, Yoshida H, Maeshima A, Kanai Y, Kinoshita T, Hiraoka N, Sekine S. TERT promoter mutations are frequent and show association with MED12 mutations in phyllodes tumors of the breast. Br J Cancer, 113:1244-1248, 2015

14. Hayashi T, Horiuchi A, Sano K, Kanai Y. Yaegashi N, Aburatani H, Konishi I. Biological characterization of soft tissue sarcomas. Ann Transl Med,3: 368,2015

15. Oguro S, Ino Y, Shimada K, Hatanaka Y, Matsuno Y, Esaki M, Nara S, Kishi Y, Kosuge T, Hiraoka N. Clinical significance of tumor-infiltrating immune cells focusing on BTLA and Cbl-b in patients with gallbladder cancer. Cancer Sci, 106:1750-1760, 2015

16. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, Hama N, Hosoda F, Urushidate T, Ohashi S, Hiraoka N, Ojima H, Shimada K, Okusaka T, Kosuge T, Miyagawa S, Shibata T. Genomic spectra of biliary tract cancer. Nat Genet, 47:1003-1010, 2015

17. Springer S, Wang Y, Dal Molin M, Masica DL, Jiao Y, Kinde I, Blackford A, Raman SP, Wolfgang CL, Tomita T, Niknafs N, Douville C, Ptak J, Dobbyn L, Allen PJ, Klimstra DS, Schattner MA, Schmidt CM, Yip-Schneider M, Cummings OW, Brand RE, Zeh HJ, Singhi AD, Scarpa A, Salvia R, Malleo G, Zamboni G, Falconi M, Jang JY, Kim SW, Kwon W, Hong SM, Song KB, Kim SC, Swan N, Murphy J, Geoghegan J, Brugge W, Fernandez-Del Castillo C, Mino-Kenudson M, Schulick R, Edil BH, Adsay V, Paulino J, van Hooft J, Yachida S, Nara S, Hiraoka N, Yamao K, Hijioka S, van der Merwe S, Goggins M, Canto MI, Ahuja N, Hirose K, Makary M, Weiss MJ, Cameron J, Pittman M, Eshleman JR, Diaz LA, Papadopoulos N, Kinzler KW, Karchin R, Hruban RH, Vogelstein B, Lennon AM. A combination of molecular markers and clinical features improve the classification of pancreatic cysts. Gastroenterology, 149:1501-1510, 2015

18. Sekiguchi M, Kushima R, Oda I, Suzuki H, Taniguchi H, Sekine S, Fukagawa T, Katai H. Clinical significance of a papillary adenocarcinoma component in early gastric cancer: a single-center retrospective analysis of 628 surgically resected early gastric cancers. J Gastroenterol, 50:424-434, 2015

19. Yamada M, Sakamoto T, Otake Y, Nakajima T, Kuchiba A, Taniguchi H, Sekine S, Kushima R, Ramberan H, Parra-Blanco A, Fujii T, Matsuda T, Saito Y. Investigating endoscopic features of sessile serrated adenomas/polyps by using narrow-band imaging with optical magnification. Gastrointest Endosc, 82:108-117, 2015

20. Oguro S, Esaki M, Kishi Y, Nara S, Shimada K, Ojima H, Kosuge T. Optimal indications for additional resection of the invasive cancer-positive proximal bile duct margin in cases of advanced perihilar cholangiocarcinoma. Ann Surg Oncol, 22:1915-1924, 2015

21. Fujimoto A, Furuta M, Shiraishi Y, Gotoh K, Kawakami Y, Arihiro K, Nakamura T, Ueno M, Ariizumi S, Nguyen HH, Shigemizu D, Abe T, Boroevich KA, Nakano K, Sasaki A, Kitada R, Maejima K, Yamamoto Y, Tanaka H, Shibuya T, Shibata T, Ojima H, Shimada K, Hayami S, Shigekawa Y, Aikata H, Ohdan H, Marubashi S, Yamada T, Kubo M, Hirano S, Ishikawa O, Yamamoto M, Yamaue H, Chayama K, Miyano S, Tsunoda T, Nakagawa H. Whole-genome mutational landscape of liver cancers displaying biliary phenotype reveals hepatitis impact and molecular diversity. Nat Commun, 6:6120, 2015

22. Watanabe T, Ueno H, Watabe Y, Hiraoka N, Morizane C, Itami J,Okusaka T, Miura N, Kakizaki T, Kakuya T, Kamita M, TsuchidaA, Nagakawa Y, Wilber H, Yamada T, Honda K. ACTN4 copy number increase as a predictive biomarker for chemoradiotherapy of locally advanced pancreatic cancer. Br J Cancer,112:704-713, 2015

Division of Genetics

Teruhiko Yoshida, Hiromi Sakamoto, Hitoshi Zembutsu, Bunsyo Shiotani, Norihisa Saeki, Chihiro Udagawa, Marianne Hanae Mazevet, Mineko Ushiama, Yoko Odaka, Misuzu Tsukamoto, Sachiyo Mitani, Fumiko Chiwaki, Rie Komatsuzaki, Masumi Shimizu, Noriko Abe, Sayaka Mito, Shizuka Shinohara, Hitomi Gunji, Tomoko Ikegami, Akiko Sakamoto, Aya Imai, Naoya Hayashida

Introduction

In 2015, the major research themes of the Division were 1) molecular understanding of cancer susceptibility; 2) pharmacogenomics research on cancer treatment and 3) molecular understanding of DNA damage response. Dr. Shiotani joined the Division as a new Senior Staff Scientist in April 2015 to lead theme 3) above.

Research activities

1) LMO1 was identified as a neuroblastoma (NB)-susceptibility gene by a genome-wide association study in our previous study. Based on microarray expression analyses on LMO1-knockdown NB cells, several microRNAs were found suppressed and some of them, including the let-4 family miRNAs, showed cell-growth inhibition activities when introduced into NB cells. The results suggest that LMO1 contributes to tumorigenesis through down-regulation of tumor-suppressing microRNAs.

2) In the pharmacogenomics research, the prospective multi-center study of CYP2D6-Tamoxifen has completed its patient recruitment. The manuscript is in preparation. Other on-going projects have shown solid progress in the validation study for genetic markers of gemcitabine-induced neutropenia; some of the candidate SNPs were replicated successfully in the samples of the National Cancer Center biobank. The biomarker for Herceptin-induced cardiotoxicity has been searched by whole-exome sequencing analysis. Targeted sequencing has been performed on cancer-related genes to identify biomarkers for sensitivity to cytotoxic anticancer drugs using a PDX model. Serum biomarker screening for BRCTF1-targeted therapy has identified three candidate biomarkers.

3) ATR is a master checkpoint kinase orchestrating DNA damage response to maintain genome integrity and is a promising target in cancer chemotherapy. An analog sensitive (AS-ATR) was identified out of 60 candidates, which showed their kinase activity in the presence of both natural ATP and an analog ATP. A system is being developed utilizing AS-ATR and analog ATP for comprehensive identification of direct ATR substrates.

4) The Integrated Disease Omics Project supported by the National Institute of Biomedical Innovation (NiBio) finished in March 2015. Two staff of the Division are expected to continue to play a leading role in the Project for the development and public release of the Disease Omics database. Data cleaning and registration in the database have been the major focus of the painstaking efforts.

Education

A postdoctoral fellow was employed and an undergraduate student has been trained since 2015.

Future prospects

In addition to the research projects described above, the staff of the Division have engaged in the services of the genome core facility and biobank. In particular, the duties of the genome core facility have included the genetic test of hereditary cancer syndromes for the outpatient genetic counseling clinic in the National Cancer Center Hospital. On

the other hand, original research activities are being centered in the research themes 2) and 3). Because the staff leading the themes have stayed in the Division only from 1 to 2 years, further development is expected in the coming few years.

List of papers published in 2015

Journal

1. Zembutsu H. Pharmacogenomics toward personalized tamoxifen therapy for breast cancer. Pharmacogenomics, 16:287-296, 2015

2. Hashimoto T, Ogawa R, Matsubara A, Taniguchi H, Sugano K, Ushiama M, Yoshida T, Kanai Y, Sekine S. Familial adenomatous polyposis-associated and sporadic pyloric gland adenomas of the upper gastrointestinal tract share common genetic features. Histopathology, 67:689-698, 2015

3. Kumamoto K, Ishida H, Ohsawa T, Ishibashi K, Ushiama M, Yoshida T, Iwama T. Germline and somatic mutations of the APC gene in papillary thyroid carcinoma associated with familial adenomatous polyposis: Analysis of three cases and a review of the literature. Oncol Lett, 10:2239-2243, 2015

4. Saeki N, Ono H, Sakamoto H, Yoshida T. Down-regulation of Immune-related Genes by PSCA in Gallbladder Cancer Cells Implanted into Mice. Anticancer Res, 35:2619-2625, 2015

5. Matsunuma R, Niida H, Ohhata T, Kitagawa K, Sakai S, Uchida C, Shiotani B, Matsumoto M, Nakayama KI, Ogura H, Shiiya N, Kitagawa M. UV Damage-Induced Phosphorylation of HBO1 Triggers CRL4DDB2-Mediated Degradation To Regulate Cell Proliferation. Mol Cell Biol, 36:394-406, 2015

6. Tanaka Y, Aoyagi K, Minashi K, Komatsuzaki R, Komatsu M, Chiwaki F, Tamaoki M, Nishimura T, Takahashi N, Oda I, Tachimori Y, Arao T, Nishio K, Kitano S, Narumi K, Aoki K, Fujii S, Ochiai A, Yoshida T, Muto M, Yamada Y, Sasaki H. Discovery of a Good Responder Subtype of Esophageal Squamous Cell Carcinoma with Cytotoxic T-Lymphocyte Signatures Activated by Chemoradiotherapy. PLoS One, 10:e0143804, 2015

7. Saeki N, Ono H, Yanagihara K, Aoyagi K, Sasaki H, Sakamoto H, Yoshida T. rs2294008T, a risk allele for gastric and gallbladder cancers, suppresses the PSCA promoter by recruiting the transcription factor YY1. Genes Cells, 20:382-391, 2015

8. Yamanoi K, Arai E, Tian Y, Takahashi Y, Miyata S, Sasaki H, Chiwaki F, Ichikawa H, Sakamoto H, Kushima R, Katai H, Yoshida T, Sakamoto M, Kanai Y. Epigenetic clustering of gastric carcinomas based on DNA methylation profiles at the precancerous stage: its correlation with tumor aggressiveness and patient outcome. Carcinogenesis, 36:509-520, 2015

9. Saeki N, Komatsuzaki R, Chiwaki F, Yanagihara K, Sasaki H. A GSDMB enhancer-driven HSV thymidine kinase-expressing vector for controlling occult peritoneal dissemination of gastric cancer cells. BMC Cancer, 15:439, 2015

10. Suzuki M, Chiwaki F, Sawada Y, Ashikawa M, Aoyagi K, Fujita T, Yanagihara K, Komatsu M, Narita M, Suzuki T, Nagase H, Kushima R, Sakamoto H, Fukagawa T, Katai H, Nakagama H, Yoshida T, Uezono Y, Sasaki H. Peripheral opioid antagonist enhances the effect of anti-tumor drug by blocking a cell growth-suppressive pathway *in vivo*. PLoS One, 10:e0123407, 2015

11. Budhathoki S, Iwasaki M, Yamaji T, Sasazuki S, Takachi R, Sakamoto H, Yoshida T, Tsugane S. Dietary heterocyclic amine intake, NAT2 genetic polymorphism, and colorectal adenoma risk: the colorectal adenoma study in Tokyo. Cancer Epidemiol Biomarkers Prev, 24:613-620, 2015

12. Fujita T, Chiwaki F, Takahashi RU, Aoyagi K, Yanagihara K, Nishimura T, Tamaoki M, Komatsu M, Komatsuzaki R, Matsusaki K, Ichikawa H, Sakamoto H, Yamada Y, Fukagawa T, Katai H, Konno H, Ochiya T, Yoshida T, Sasaki H. Identification and Characterization of CXCR4-Positive Gastric Cancer Stem Cells. PLoS One, 10:e0130808, 2015

13. Iwakawa R, Kohno T, Totoki Y, Shibata T, Tsuchihara K, Mimaki S, Tsuta K, Narita Y, Nishikawa R, Noguchi M, Harris CC, Robles AI, Yamaguchi R, Imoto S, Miyano S, Totsuka H, Yoshida T, Yokota J. Expression and clinical significance of genes frequently mutated in small cell lung cancers defined by whole exome/RNA sequencing. Carcinogenesis, 36:616-621, 2015

Division of Carcinogenesis and Prevention (Viral Carcinogenesis and Prevention Group)

Tohru Kiyono, Takashi Yugawa, Tomomi Nakahara, Kenji Yamada, Ghani Farhana Ishrat, Takako Ishiyama, Katsuyuki Tanaka, Chiho Kohno, Shin-ichi Ohno, Yuki Inagawa, Kasumi Ohtsubo, Akiko Noguchi, Etsuko Kabasawa

Introduction

Approximately 15% of human cancers have a viral etiology, and seven viruses have been elucidated as being associated with human cancers. Among these recognized viruses, research in the Division of Carcinogenesis and Cancer Prevention is mainly focused on the molecular mechanisms of persistent infection and oncogenesis of human papillomaviruses (HPVs). A subset of HPVs including types 16 and 18 are closely associated with human cancers and have thus been called high-risk HPVs (HR-HPVs). Persistent infection of the HR-HPVs is a major cause of cervical cancer and a subset of head and neck cancer. Our goal is to develop non-invasive therapies to prevent and cure HPV-associated cancers. We have developed a tissue culture model recapitulating the viral persistence as well as viral oncogene, E6 and E7, -induced cancer development. By using these tissue culture models, we are currently studying (1) mechanism of the viral genome replication and (2) the roles of E6, E7 and cellular oncogenes in multistep carcinogenesis.

Routine activities

To clarify molecular mechanisms of oncogenesis by viral and cellular oncogenes and inactivation of tumor suppressors, we are establishing ex vivo carcinogenesis models for cervical cancer and other cancers by transducing abnormalities of genes found in cancer into normal cells-of-origin of each cancer. To develop an anti-HPV drug, we are studying molecular mechanisms of HPV genome replication, a key aspect of the viral persistence.

Research activities

1) Molecular mechanism of HPV genome maintenance and anti-HPV drug development.

The HPV genome undergoes three phases of replication: initial amplification, maintenance replication and productive amplification in the viral life cycle. Upon infection, HPV establishes its genome as a nuclear episome through initial amplification and about 50 to 100 copies of the viral episomes are stably maintained in basal cells of the infected lesions such as cervical intraepithelial neoplasm (CIN). In terminally differentiating compartments of the lesions, HPV genome are drastically increased through productive amplification and incorporated in progeny virions. In a previous study, we demonstrated that the viral helicase E1 is dispensable for maintenance replication but indispensable for the initial and productive amplification of the HPV16 genome. In a recent study, we found that expression of HPV16 E1 results in activation of DNA damage response (DDR) which leads to activation of NF-κB pathway in human cervical keratinocytes (HCKs) stably maintaining HPV16 genome. The activation of NF-κB pathway suppressed the E1-dependent replication of HPV genome by promoting its proteosomal degradation. Furthermore, NF-κB activities are constitutively higher in HPV containing-cell lines derived from CIN biopsies than in normal HCKs and inhibition or activation of NF-κB resulted in an increase or decrease of HPV copy numbers, respectively. Thus, E1 and NF-κB may constitute a negative feedback that mediates transition from initial amplification to maintenance replication and also sustains an E1-independent replication during the viral persistence. We also developed HCKs maintaining recombinant "reporter" HPV16 genomes expressing a secreted luciferase and verified that luciferase activities in cultural medium collates with the viral copy numbers. By using this reporter system, we are

working on identifying NF-κB target genes that enables intervention in viral persistence as well as developing drug screening to eradicate HPV genomes. Once an HPV genome is integrated in the form that E6 and E7 genes can be highly expressed in the basal cells, these oncogenes cooperatively immortalize and transform cells so as to induce CIN2/3 lesions. Recent genome editing technology with nucleases such as Zinc finger nuclease and clustered regularly interspaced short palindromic repeats (CRISPR) / CRISPR-associated (Cas) made it possible to directly target an HPV genome whether or not it is integrated. With the CRISPR/Cas system, we are developing targeting vector to knock down E6/E7 regions of HPV16 and 18.

2) *In vitro* human carcinogenesis model

p63, a member of the p53 family, is frequently overexpressed in squamous cell carcinomas (SCCs). Paradoxically, growing evidence points out the association of p63 loss with metastasis appearance and poor prognosis in SCCs, although the underlying molecular mechanism and its functional relevance to carcinogenesis remains largely unclear. We have previously demonstrated that p63 represses NOTCH1 gene expression to support the self-renewing capacity of normal human keratinocytes, and its overexpression enhances tumorigenicity. We also identified the novel NOTCH-ROCK pathway as a critical regulator for keratinocyte differentiation downstream of p63. Recently, we revealed that MYC overexpression rescues the proliferative ability of p63-deficient cells. Using our *in vitro* human multistep carcinogenesis model, we found that knock-down of p63 increased invasiveness through the NOTCH-ROCK pathway in a three-dimensional culture system. We aim to develop a novel therapeutic strategy to target poorly differentiated SCCs based on their cancer biology.

Using a novel culture method based on the finding of the NOTCH-ROCK pathway, normal bile duct epithelial cells and duodenal epithelial cells were isolated and immortalized. These cells have been used to model ampullary cancer.

Education

One Ph.D. student and one MD/Ph.D. student in local universities worked as trainees in our lab and had cancer research training. One post-doctoral researcher has been currently training in a cancer research field with us since April.

Future prospects

The current HPV vaccines have no therapeutic effect upon pre-existing CIN lesions. To clear HPV infection from CIN lesions, a possible strategy is eradication of HPV genomes with a specific inhibitor of HPV replication or elimination of HPV-infected cells with surgery or by induction of cell death with a drug or therapeutic vaccine. Further understanding of molecular mechanisms underlying the viral persistence through an E1-NFκB negative feedback will promote development of anti-HPV drug and possible immuno-therapies by enhancing presentation of the viral specific antigens in persistently infected basal cells.

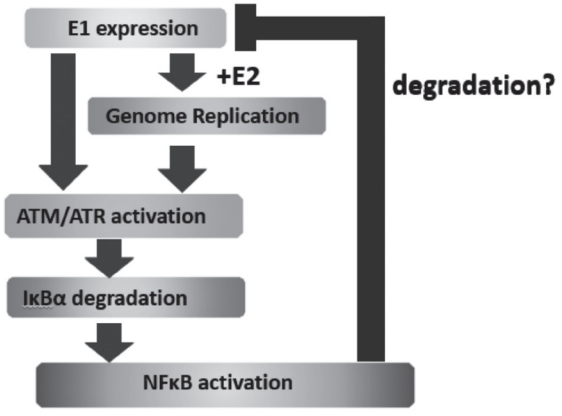


Figure 1. Regulation of HPV genome replication

List of papers published in 2015

Journal

1. Hata R, Izukuri K, Kato Y, Sasaki S, Mukaida N, Maehata Y, Miyamoto C, Akasaka T, Yang X, Nagashima Y, Takeda K, Kiyono T, Taniguchi M. Suppressed rate of carcinogenesis and decreases in tumour volume and lung metastasis in CXCL14/BRAK transgenic mice. Sci Rep, 5:9083, 2015

2. Kuroda K, Kiyono T, Eitsuka T, Isogai H, Takahashi K, Donai K, Isogai E, Fukuda T. Establishment of cell lines derived from the genus Macaca through controlled expression of cell cycle regulators. J Cell Biochem, 116:205-211, 2015

3. Kuroda K, Kiyono T, Isogai E, Masuda M, Narita M, Okuno K, Koyanagi Y, Fukuda T. Immortalization of fetal bovine colon epithelial cells by expression of human cyclin D1, mutant cyclin dependent kinase 4, and telomerase reverse transcriptase: an *in vitro* model for bacterial infection. PLoS One, 10:e0143473, 2015

4. Nakahara T, Tanaka K, Ohno S, Egawa N, Yugawa T, Kiyono T. Activation of NF-κB by human papillomavirus 16 E1 limits E1-dependent viral replication through degradation of E1. J Virol, 89:5040-5059, 2015

5. Nakamura T, Iwase A, Bayasula B, Nagatomo Y, Kondo M, Nakahara T, Takikawa S, Goto M, Kotani T, Kiyono T, Kikkawa F. CYP51A1 induced by growth differentiation factor 9 and follicle-stimulating hormone in granulosa cells is a possible predictor for unfertilization. Reprod Sci, 22:377-384, 2015

6. Ohira M, Iwasaki Y, Tanaka C, Kuroki M, Matsuo N, Kitamura T, Yukuhiro M, Morimoto H, Pang N, Liu B, Kiyono T, Amemiya M, Tanaka K, Yoshida K, Sugimoto N, Ohshima T, Fujita M. A novel anti-microtubule agent with carbazole and benzohydrazide structures suppresses tumor cell growth *in vivo*. Biochim Biophys Acta, 1850:1676-1684, 2015

7. Sugimoto N, Maehara K, Yoshida K, Yasukouchi S, Osano S, Watanabe S, Aizawa M, Yugawa T, Kiyono T, Kurumizaka H, Ohkawa Y, Fujita M. Cdt1-binding protein GRWD1 is a novel histone-binding protein that facilitates MCM loading through its influence on chromatin architecture. Nucleic Acids Res, 43:5898-5911, 2015

8. Ichioka M, Mita S, Shimizu Y, Imada K, Kiyono T, Bono Y, Kyo S. Dienogest, a synthetic progestin, down-regulates expression of CYP19A1 and inflammatory and neuroangiogenesis factors through progesterone receptor isoforms A and B in endometriotic cells. J Steroid Biochem Mol Biol, 147:103-110, 2015

9. Takeshima H, Niwa T, Takahashi T, Wakabayashi M, Yamashita S, Ando T, Inagawa Y, Taniguchi H, Katai H, Sugiyama T, Kiyono T, Ushijima T. Frequent involvement of chromatin remodeler alterations in gastric field cancerization. Cancer Lett, 357:328-338, 2015

Division of Carcinogenesis and Prevention (Environmental Carcinogenesis and Prevention Group)

Yukari Totsuka, Michihiro Mutoh, Ken-ichi Yoshioka, Gen Fujii, Sachiko Dobashi, Masanori Goto, Haruna Sato, Nozomi Akiba, Wakana Onuma, Takahiro Hamoya, Yuri Fukushi, Shuuya Tamura, Yuko Atsumi, Yusuke Minakawa, Atsuhiro Shimizu, Tetsuya Mukasa

Introduction

Cancer is a disease associated with aging and environmental risk factors. It is well known that chemical substances form DNA adducts, which are considered to be a 'trigger' of mutagenesis. As cancer risk elevates in association with aging, genomic destabilization frequently arises in the cells of the elderly, which is associated with the impairment of DNA repair functions. The aims of our research projects are exploration of novel cancer etiology via identification of DNA adducts that are important for human cancer development, and clarification of the mechanisms for genomic instability associated with aging. On the other hand, cancer chemoprevention is one of the preemptive approaches that is strongly expected to reduce cancer morbidity and mortality. We are working to develop novel candidates for cancer chemopreventive agents and aim for their practical application using the concept of drug repositioning.

Research activities

1) Exploration of cancer etiology using comprehensive DNA adduct analysis

Nanosized-magnetite (MGT) showed genotoxicity in both *in vitro* and *in vivo* assay systems. Based on the mutational spectrum observed in the lungs of mice exposed to MGT, it was suggested that inflammatory responses exist behind the genotoxicity. To further clarify mechanisms underlying the genotoxicity, a comprehensive DNA adduct (DNA adductome) analysis was conducted using DNA samples derived from the lungs of mice exposed to MGT. Principal component analysis (PCA) against a subset of DNA adducts was applied and several adducts, which are deduced to be formed by inflammation or oxidative stress, as is the case of etheno-deoxycytidine (ε dC), revealed higher contributions to MGT exposure. From these observations, it is suggested that inflammatory responses might be involved in the genotoxicity induced by MGT in the lungs of mice.

2) Regulations for genome stability and the associated anti-cancer and aging effects

Senescent cells are usually defective in DNA damage repair, and hence widely accumulate irreparable DNA double strand breaks (DSBs). Such repair deficiency is associated with the decrease of histone H2AX that is required for efficient DSB repair and hence for genome stability. We showed that cells with largely down-regulated H2AX were defective in repairing DNA-replication stress-associated DSBs but still could repair directly caused DSBs through transient H2AX stabilization. H2AX stabilization upon DSB formation was mediated by the ATM kinase, sirtuin protein SIRT6, and ISWI family chromatin remodeler SNF2H.

3) Prevention of colorectal cancer

Familial adenomatous polyposis (FAP) patients are a well-known high-risk group with colorectal cancer (CRC). We are evaluating the usefulness and safety of thorough endoscopic polypectomy and of cancer chemopreventive agents in FAP patients. Based on these findings, we are trying to clarify the underlying mechanism of colorectal carcinogenesis in a laboratory study. Moreover, we are searching for novel chemopreventive agents against CRC using animal models of FAP.

Education

Ten undergraduate and graduate students in local universities worked as trainees in our lab and had cancer research training.

Future prospects

- Establish a novel cancer prevention strategy based on the exploration of cancer etiology and mechanisms
- Develop novel candidates for cancer chemopreventive agents and aim for their practical application

List of papers published in 2015

Journal

1. Ishino K, Kato T, Kato M, Shibata T, Watanabe M, Wakabayashi K, Nakagama H, Totsuka Y. Comprehensive DNA adduct analysis reveals pulmonary inflammatory response contributes to genotoxic action of magnetite nanoparticles. Int J Mol Sci, 16:3474-92, 2015.
2. Shimizu S, Ishigamori R, Fujii G, Takahashi M, Onuma W, Terasaki M, Yano T, Mutoh M. Involvement of NADPH oxidases in suppression of cyclooxygenase-2 promoter-dependent transcriptional activities by sesamol. J Clin Biochem Nutr, 56:118-122, 2015.
3. Mutoh M, Ishikawa H.Metformin use and lung cancer risk--letter. Cancer Prev Res (Phila), 8:760, 2015.
4. Shimizu S, Miyamoto S, Fujii G, Nakanishi R, Onuma W, Ozaki Y, Fujimoto K, Yano T, Mutoh M. Suppression of intestinal carcinogenesis in *Apc*-mutant mice by limonin. J Clin Biochem Nutr, 57:39-43, 2015.
5. Komiya M, Fujii G, Miyamoto S, Takahashi M, Ishigamori R, Onuma W, Ishino K, Totsuka Y, Fujimoto K, Mutoh M. Suppressive effects of the NADPH oxidase inhibitor apocynin on intestinal tumorigenesis in obese KK-A^y and *Apc* mutant Min mice. Cancer Sci, 106:1499-1505, 2015.
6. Shiotani A, Ishikawa H, Mutoh M, Takeshita T, Nakamura T, Morimoto K, Sakai T, Wakabayashi K, Sakai T, Matuura N. Genetic polymorphisms in A*DH1B* and A*LDH2* are associated with colorectal tumors in Japan. J Cancer Therapy, 6:1054-1062, 2015.
7. Atsumi Y, Minakawa Y, Ono M, Dobashi S, Shinohe K, Shinohara A, Takeda S, Takagi M, Takamatsu N, Nakagama H, Teraoka H, Yoshioka K. ATM and SIRT6/SNF2H Mediate Transient H2AX Stabilization When DSBs Form by Blocking HUWE1 to Allow Efficient γH2AX Foci Formation. Cell Rep, 13:2728-2740, 2015
8. Yoshioka K, Atsumi Y, Nakagama H, Teraoka H. Development of cancer-initiating cells and immortalized cells with genomic instability. World J Stem Cells, 7:483-489, 2015
9. Fujimoto K, Fujii G, Sakurai H, Yoshitome H, Mutoh M, Wada M. Intestinal Peyer's patches prevent tumorigenesis in $Apc^{Min/+}$ mice. J Clin Biochem Nutr, 56:43-48, 2015.
10. Fujimoto K, Fujii G, Taniguchi K, Yasuda K, Matsuo Y, Hashiyama A, Mutoh M, Tanaka H, Wada M, Involvement of trefoil factor family 2 in the enlargement of intestinal tumors in $Apc^{Min/+}$ mice. Biochem Biophys Res Commun, 463:859-863, 2015.

Book

1. Miyamoto S, Fujii G, Komiya M, Terasaki M, Mutoh M. Potential for sesame seed-derived factors to prevent colorectal cancer. In: Ullah MF, Ahmad A (eds), Critical dietary factors in cancer chemoprevention, Switzerland, Springer Publishers (Basel, Switzerland), pp 183-197, 2015

Division of Cancer Biology

Hirofumi Arakawa, Yasuyuki Nakamura, Masayuki Tsuneki, Hiroki Kamino, Yoko Sagami, Ruri Nakanishi, Natsuki Kinoshita, Chieko Haga, Ayami Kawashima, Katsuko Honjo, Tomonori Aikawa

Introduction

The scope of the research at the Division of Cancer Biology is broad, covering numerous areas including the cloning of genes involved in carcinogenesis, biological and structural analyses of proteins, analyses of animal models, and the development of new strategies for cancer therapy. In particular, the roles of the Mieap-regulated mitochondrial quality control and cancer-specific unhealthy mitochondria in tumorigenesis have been studied to uncover the mechanisms of cancer initiation, growth, invasion and metastasis, based on which new cancer preventive, diagnostic, and therapeutic strategies could be developed.

Research activities

Mieap-regulated mitochondrial quality control

Mieap controls mitochondrial quality via two distinct novel mechanisms. One of the mechanisms has been designated MALM for Mieap-induced accumulation of lysosome-like organelles within mitochondria (*PLoS ONE* 6: e16054, 2011). In this mechanism, Mieap induces the accumulation of intramitochondrial lysosomal proteins in order to eliminate oxidized mitochondrial proteins in response to mitochondrial damage. This leads to a decrease in reactive oxygen species generation and an increase in mitochondrial Adenosine TriPhosphate (ATP) synthesis activity, implying MALM plays a role in repairing unhealthy mitochondria.

BNIP3 and NIX, mitochondrial outer membrane proteins, two Mieap-interacting proteins mediate the translocation of lysosomal proteins from cytosol into mitochondria during MALM by forming an unknown pore in the mitochondrial double membrane (*PLoS ONE* 7: e30767, 2012). 14-3-3 γ mediates the degradation of oxidized mitochondrial proteins within mitochondria during MALM (*Scientific Reports* 2: 379, 2012).

Alternatively, the other mechanism has been designated MIV for Mieap-induced vacuole (*PLoS ONE* 6: e16060, 2011). When MALM is inhibited, Mieap induces a vacuole-like structure, MIV. The MIV engulfs the damaged mitochondria and accumulates lysosomes, leading to the degradation of unhealthy mitochondria. MIV likely represents a novel mechanism for mitochondrial autophagy, also called "mitophagy". Therefore, Mieap controls mitochondrial quality by repairing or eliminating unhealthy mitochondria via MALM or MIV generation, respectively (Figure 1).

Mieap-regulated mitochondrial quality control is frequently inactivated in human cancer

The accumulation of unhealthy mitochondria results in mitochondrial dysfunction, which has been implicated in aging, degenerative diseases and cancer. The Mieap-regulated mitochondrial quality control (MQC) was found to be frequently inactivated by p53 mutations or Mieap/BNIP3 promoter methylation in more than 70% of primary cancer tissues of colorectal cancer patients, leading to accumulation of unhealthy mitochondria and a high level of mitochondria reactive oxygen species generation (ROS).

The elevated mitochondrial ROS causes oxidative damage to DNA, RNA, protein and lipid and so on. This induces genomic instability. The mitochondrial ROS contribute to tumor growth, epithelial-to-mesenchymal transition, cancer invasion, cancer metastasis, tumor angiogenesis through the activation of HIF-1, NF-kB, MMPs, AKT, Erk1/2, JNK and so on. Therefore, the Mieap-regulated mitochondrial quality control is a tumor suppressor for colorectal cancer (Figure 2).

In order to further evaluate the clinical significance of the Mieap-regulated MQC in human cancer, the status of p53, Mieap, and BNIP3 are

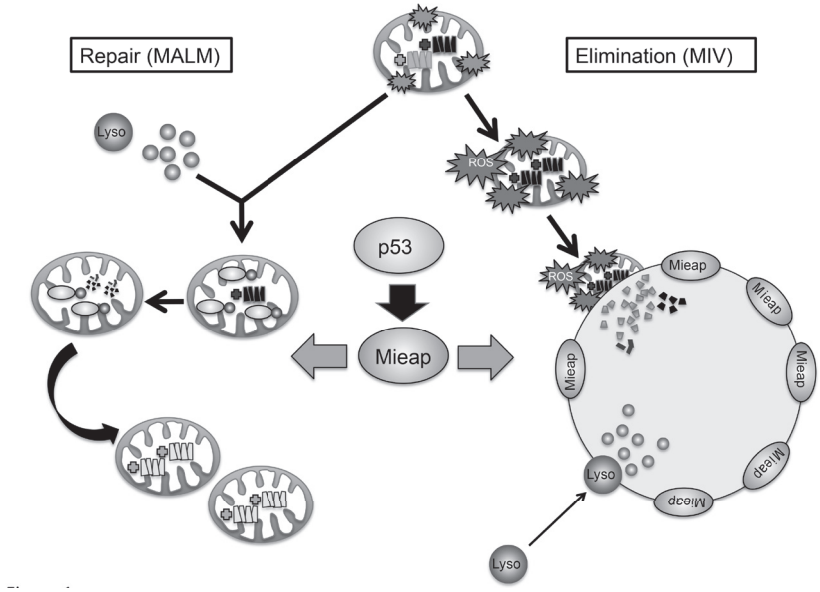


Figure 1. Mieap-regulated mitochondrial quality control

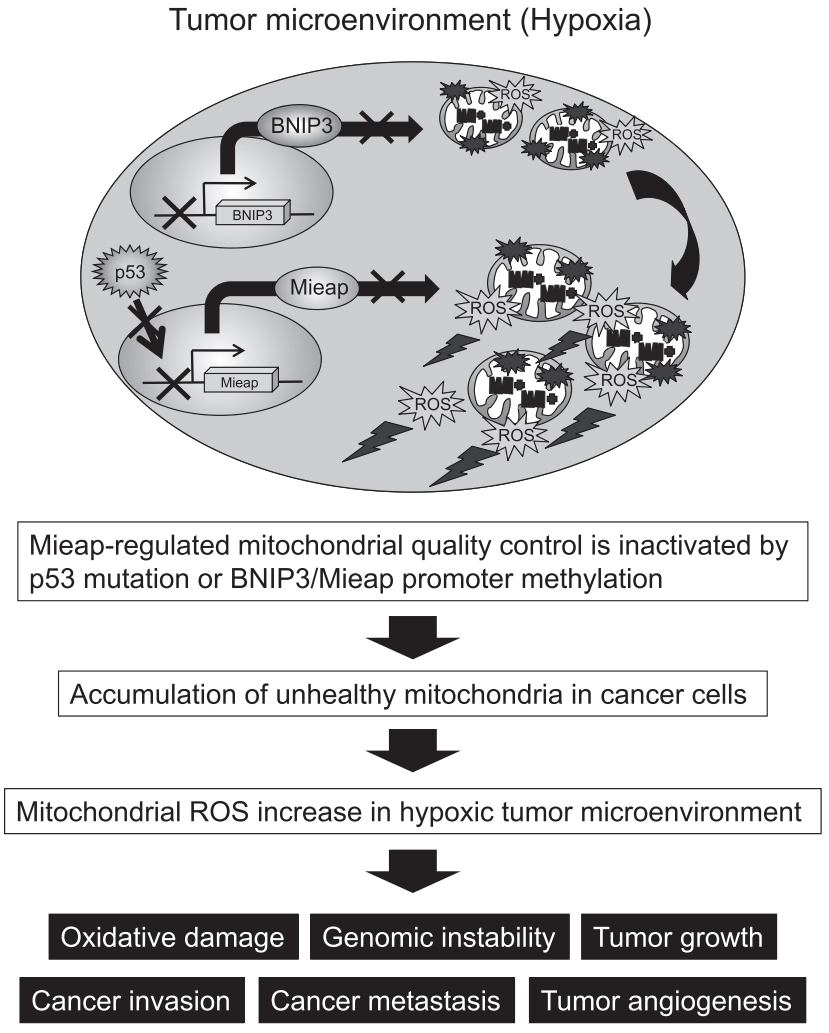


Figure 2. Alteration of Mieap-regulated mitochondrial quality control in cancer

being examined in primary cancer tissues of breast, gastric, pancreatic, lung and liver cancer patients.

Mieap-deficient cancer animal model

To clarify the in vivo role of the Mieap-regulated MQC in tumorignenesis, Mieap knockout mice were generated in the Division. Using the Mieap knockout mice, the Mieap-deficient $Apc^{Min/+}$ mice were also generated and analyzed in order to elucidate the role of Mieap in colorectal cancer tumorigenesis.

Interestingly, the Mieap-deficient $Apc^{Min/+}$ mice exhibited remarkably reduced lifespans compared with those of $Apc^{Min/+}$ mice. Furthermore, a substantial increase in the number and size of intestinal polyps was found in the Mieap-deficient $Apc^{Min/+}$ mice. Histopathologically, intestinal tumors in the Mieap-deficient $Apc^{Min/+}$ mice clearly exhibited advanced grades of adenoma and adenocarcinomas. Unhealthy mitochondria dramatically accumulated in the tumor cells and generated a high level of ROS in the Mieap-deficient $Apc^{Min/+}$ mice. These results suggest that the Mieap-regulated mitochondrial quality control pathway has a critical role in the suppression of intestinal tumor in vivo.

In addition to the colorectal cancer model, the Mieap-deficient pancreatic and gastric cancer models are being prepared at the Division.

Development of new cancer preventive/diagnostic/therapeutic methods through targeting cancer-specific unhealthy mitochondria

Unhealthy mitochondria are dramatically and specifically accumulated in cancer cells due to inactivation of the Mieap-regulated MQC. Therefore, the Division's working hypothesis proposes that cancer-specific unhealthy mitochondria owing to inactivation of the Mieap-regulated MQC may be very attractive and are promising targets for development of new cancer preventive/diagnostic/therapeutic methods. Now, in order to identify new cancer preventive/diagnostic/therapeutic targets, the nature and characteristics of these cancer-specific unhealthy mitochondria are being explored by metabolome, transcriptome, proteome analyses in the Division.

Education

To gain understanding and skill for cancer research, students attend lectures and seminars, and attend and/or practice research meetings, journal clubs, scientific meetings, and so forth. These practices will enable students to develop the ability to conduct their studies as an independent cancer researcher in the future. To obtain the high-level skills to carry out experiments that are required for cancer research, students belong to one of our research groups, and conduct their own studies under the guidance of the instructor and/or staff. Students perform various experiments involved in genetics, gene technology, biochemistry, cellular biology, molecular biology, physiology, experimental animal, pathology, genomic/epigenomic/proteomic analysis, imaging, next generation sequencing, and so forth.

Future prospects

Analyses of clinical cancer tissues and various cancer-mouse models enable us to understand the actual role of the Mieap-regulated mitochondrial quality control in human cancer formation, progression, invasion and metastasis. Finally, we will be able to establish a solid foundation for development of new strategies for cancer prevention, diagnosis, and therapy in the future.

List of papers published in 2015

Journal

1. Tsuneki M, Nakamura Y, Kinjo T, Nakanishi R, Arakawa H. Mieap suppresses murine intestinal tumor via its mitochondrial quality control. Sci Rep, 5:12472, 2015

Division of Hematological Malignancy

Issay Kitabayashi, Kazutsune Yamagata, Takuo Katsumoto, Yutaka Shima, Yoko Ogawara, Emi Takamatsu, Yuuki Kagiyama, Mai Suzuki, Shuhei Fujita, Makoto Nakagawa, Yukiko Aikawa, Mika Shino, Rieko Furuya

Introduction

Acute myeloid leukemia (AML) is the most common leukemia in Japan and the U.S. With current standard chemotherapy, approximately 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. However, many of the AML patients have a relapse and only 25-30% of young adults and fewer than 10% of older patients survive longer than 5 years, suggesting the presence of AML stem cells that are resistant to chemotherapy. Thus, AML stem cell eradication is thought to be crucial for the cure to AML. Chromosome abnormalities, which results in the generation of specific fusion genes, are observed in ~50% of AML patients. AML associated with fusion genes involving MLL, MOZ, CALM or NUP98 have an extremely poor outcome. Normal cytogenetics portend average-risk AML. Recent genome analysis revealed that mutations in NPM, IDH1/IDH2/TET2, DNMT3a and FLT3 genes are often simultaneously observed in patients with normal cytogenetics. Our research purpose is to establish new therapeutic methods by identifying molecular targets that are essential for the maintenance of AML cells, especially AML stem cells.

Research activities

AML is a clonal malignant disorder derived from a small number of leukemic stem cells (LSCs). *MLL* gene rearrangements are found in AML associated with poor prognosis. The upregulation of *Hox* genes is critical for LSC induction and maintenance, but is unlikely to support malignancy and the high LSC frequency observed in MLL leukemias. The present study shows that MLL fusion proteins interact with the transcription factor PU.1 to activate the transcription of *CSF-1R*, which is critical for LSC activity. AML is cured by either deletion of *PU.1*, or ablation of cells expressing CSF-1R. Kinase inhibitors specific for CSF-1R prolong survival time. These findings indicate that PU.1-mediated upregulation of CSF-1R is a critical effector of *MLL* leukemogenesis.

IDH1 and IDH2 mutations occur frequently in AML and other cancers. The mutant IDH enzymes convert α-ketoglutarate (α-KG) to the oncometabolite 2-hydroxyglutarate (2-HG), which dysregulates a set of α-KG-dependent dioxygenases. To determine whether mutant IDH enzymes are valid targets for cancer therapy, we created a mouse model of AML in which mice were transplanted with *nucleophosmin1 (NPM1)*+/- hematopoietic stem/progenitor cells co-transduced with four mutant genes (*NPMc, IDH2/R140Q, DNMT3A/R882H,* and *FLT3/ITD*) which often occur simultaneously in human AML patients. Conditional deletion of *IDH2/R140Q* blocked 2-HG production and maintenance of leukemia stem cells, resulting in survival of the AML mice. IDH2/R140Q was necessary for the engraftment or survival of $NPMc^+$ cells in vivo. Gene expression analysis indicated that NPMc increased expression of Hoxa9. IDH2/R140Q also increased the level of Meis1 and activated the hypoxia pathway in AML cells. IDH2/R140Q decreased the 5hmC modification and expression of some differentiation-inducing genes (*Ebf1* and *Spib*). Taken together, our results indicated that IDH2 mutation is critical for the development and maintenance of AML stem-like cells, and they provided a preclinical justification for targeting mutant IDH enzymes as a strategy for anticancer therapy.

List of papers published in 2015

Journal

1. Ogawara Y, Katsumoto T, Aikawa Y, Shima Y, Kagiyama Y, Soga T, Matsunaga H, Seki T, Araki K, Kitabayashi I. IDH2 and NPM1 mutations cooperate to activate Hoxa9/Meis1 and hypoxia pathways in acute myeloid leukemia. Cancer Res, 75:2005-2016, 2015

2. Aikawa Y, Yamagata K, Katsumoto T, Shima Y, Shino M, Stanley ER, Cleary ML, Akashi K, Tenen DG, Kitabayashi I. Essential role of PU.1 in maintenance of mixed lineage leukemia-associated leukemic stem cells. Cancer Sci, 106:227-236, 2015

3. Kato T, Sakata-Yanagimoto M, Nishikii H, Ueno M, Miyake Y, Yokoyama Y, Asabe Y, Kamada Y, Muto H, Obara N, Suzukawa K, Hasegawa Y, Kitabayashi I, Uchida K, Hirao A, Yagita H, Kageyama R, Chiba S. Hes1 suppresses acute myeloid leukemia development through FLT3 repression. Leukemia, 29:576-585, 2015

Division of Cancer Stem Cell

Kenkichi Masutomi, Yoshiko Maida, Mami Yasukawa, Marco Ghilotti, Satoko Yamaguchi, Mihoko Tsurumaki, Akiya Tatsumi

Introduction

Research in the Division of Cancer Stem Cell is focused on deciphering the mechanisms that establish and maintain cancer stem cells and to develop novel therapeutic approaches to treat cancer stem cells. In particular, the Division studies the molecular links between a) telomerase and RNA-dependent RNA polymerase (RdRP); b) telomerase and cancer stem cells; and c) RdRP and anticancer drugs.

Telomerase and RNA-dependent RNA polymerase

Telomerase is a ribonucleoprotein complex that elongates telomeres. Human TERT is known as the catalytic subunit of the enzyme. TERT acts as an RNA-dependent DNA polymerase (RdDP) and synthesizes telomere DNA from a non-coding RNA template human *TERC*. Although the major function of TERT is believed to be telomere elongation, emerging evidence indicates that TERT exhibits various functions beyond telomere maintenance. We reported that TERT has an RdRP activity and mediates post-transcriptional gene silencing through the production of endogenous siRNAs[1] (Figure 1). The RdRP enzyme complex is distinct from telomerase; TERT assembles with BRG1 and nucleostemin (NS), and the TERT-BRG1-NS complex (TBN complex) exerts RdRP activity[2]. We found that the TBN complex regulates miRNA expression, presumably at the transcriptional level[3] (Figure 2). To further investigate biological functions of TERT-RdRP, we generated a new anti-TERT monoclonal antibody and established an RdRP assay using TERT immune complexes isolated from cell lysate (IP-RdRP assay)[2]. We confirmed that TERT protein levels and TERT-associated RdRP activity are positively correlated in human cancer cell lines.

RdRPs in yeast and worms regulate centromeric heterochromatin formation, and RdRPs are required for proper chromosome segregation during mitosis in these organisms. The RNA-directed RNA polymerase complex (RDRC) contributes to the regulation, and the complex contains RdRP and RNA helicase. Because TERT has RdRP activity, and BRG1 has helicase activity, we speculated that the TBN complex might have similar functions with the RDRC. We confirmed that TERT-RdRP suppresses transcription from heterochromatic regions at centromeres and transposons, and suppression of TERT-RdRP complex results in the increase of the cells arrested in mitosis, binucleate cells and the heterochromatic transcription[2]. These observations indicate that TERT-RdRP contributes to mitotic progression through the regulation of heterochromatin maintenance (Figure 2). Our findings suggest that inhibitors for the novel functions of TERT may prove useful in targeting cancer cells.

Telomerase and cancer stem cells

Previous studies indicated that TERT has activities beyond telomere maintenance, and it is speculated that the constitutive expression of TERT not only stabilizes telomere length and facilitates cell immortalization but also contributes to tumor susceptibility and alters stem cell cycling *in vivo* even when telomere lengths are not limited. We found that the TBN complex participates in the regulation of tumor initiating cells (TICs) phenotypes through telomere-independent mechanisms[4] (Figure 2). We also confirmed that the cells that constitutively express NS exhibited increased beta-catenin signaling and elevated MYC, OCT3/4, KLF4 and TWIST expression. Moreover, cells that constitutively express elevated levels of TERT, BRG1 and NS exhibit increased CD133 and

CD44 expression and enhanced tumorigenicity at limiting cell numbers. These observations indicate that the TBN complex is essential for the maintenance of TICs.

RdRP and anticancer drugs

Ovarian cancer is the most lethal of all gynecological malignancies in Japan. The majority of ovarian cancers are diagnosed at an advanced stage. Currently, platinum-based chemotherapy is the standard first-line treatment for advanced ovarian cancer patients; however, chemoresistance is a major obstacle for long-term survival after initial treatment[5]. Using platinum-sensitive and platinum-resistant ovarian cancer cell lines, we screened a series of anti-cancer compounds for growth suppression of platinum-resistant ovarian cancer cell lines[5]. We found that eribulin mesylate (eribulin) effectively inhibits growth of platinum-resistant ovarian cancer cells. Although, it has been confirmed that eribulin exerts its anticancer effect by blocking the elongation of microtubules, we found that eribulin specifically inhibits the RdRP activity of TERT *in vitro*, suggesting TERT-RdRP as a novel molecular target of the drug beyond tubulin. This hypothesis was further supported by the results showing that 1) eribulin-sensitive ovarian cancer cell lines express high levels of TERT, and 2) suppression of TERT expression reduced sensitivity to eribulin. The eribulin-sensitive cell lines have enhanced cancer stem cell (CSC)-like traits, the characteristics related to TERT, as well. Our study demonstrated that eribulin might be a promising therapeutic agent for platinum-resistant ovarian cancer.

References

1) Maida Y, *et al*. An RNA-dependent RNA polymerase formed by TERT and the RMRP RNA. *Nature*, 461:230-235, 2009.
2) Maida Y, *et al*. Involvement of telomerase reverse transcriptase in heterochromatin maintenance. *Mol. Cell. Biol*., 34:1576-93, 2014.
3) Lassmann T, *et al*. Telomerase reverse transcriptase regulates microRNAs. *Int J Mol Sci*, 16:1192-1208, 2015.
4) Okamoto N, *et al*. Maintenance of tumor initiating cells of defined genetic composition by nucleostemin. *Proc. Natl. Acad. Sci. U S A*, 108:20388-20393, 2011.
5) Yamaguchi S, *et al*. Eribulin mesylate targets human telomerase reverse transcriptase in ovarian cancer cells. *PLOS ONE*, 9:e112438, 2014.

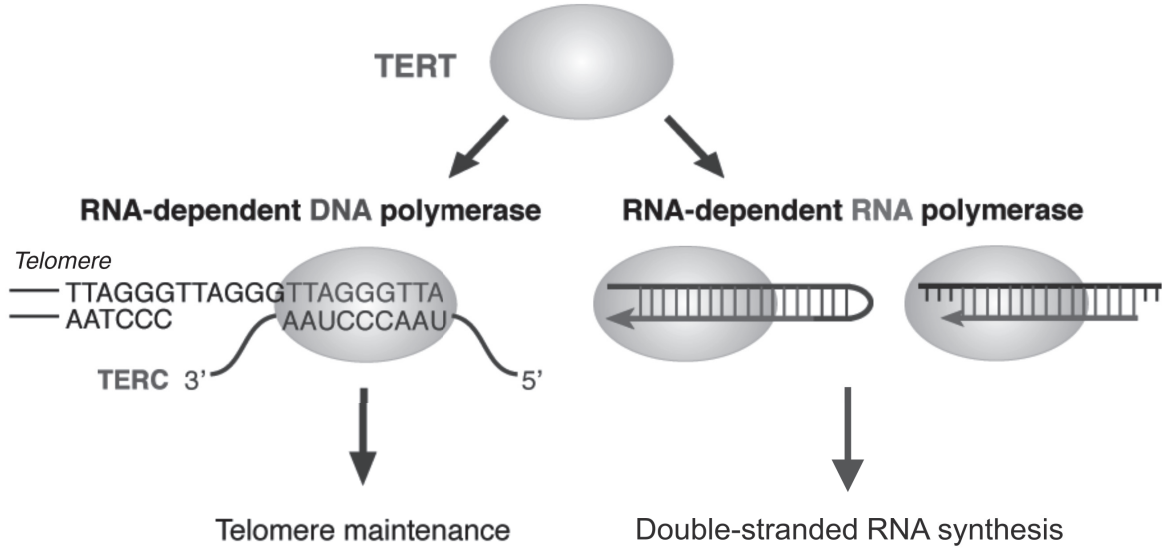


Figure 1. TERT exerts RdRP activity

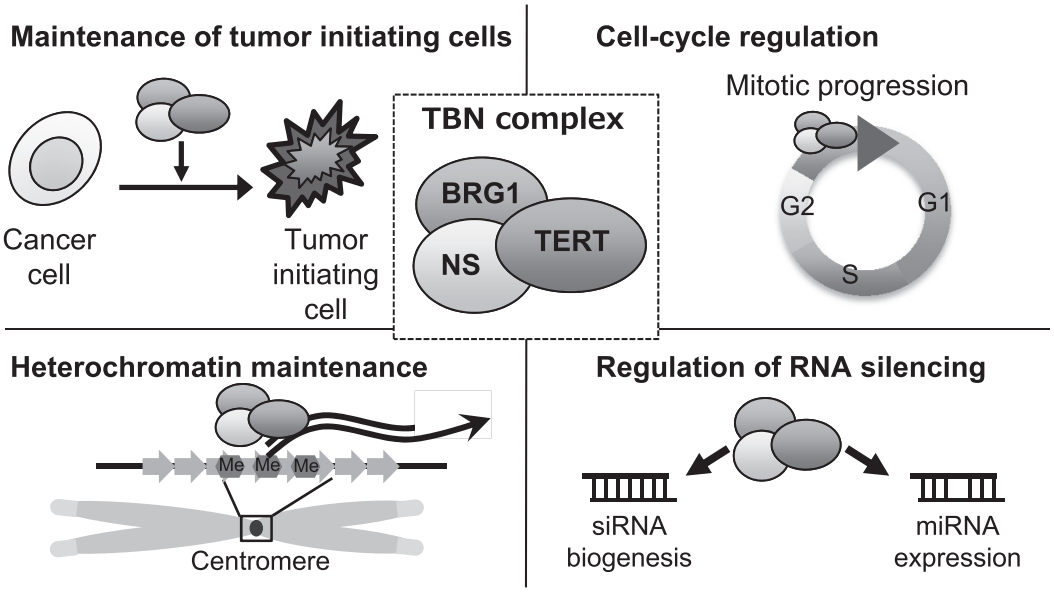


Figure 2. Various functions of the TBN complex

List of papers published in 2015

Journal

1. Lassmann T, Maida Y, Tomaru Y, Yasukawa M, Ando Y, Kojima M, Kasim V, Simon C, Daub CO, Carninci P, Hayashizaki Y, Masutomi K. Telomerase reverse transcriptase regulates microRNAs. Int J Mol Sci, 16:1192-1208, 2015
2. Maida Y, Masutomi K. Telomerase reverse transcriptase moonlights: Therapeutic targets beyond telomerase. Cancer Sci, 106:1486-1492, 2015

Division of Cancer Differentiation

Koji Okamoto, Daisuke Shiokawa, Hirokazu Ohata, Toshiaki Miyazaki, Manami Miura, Naoko Osada, Kenta Takahashi, Rie Uchino, Wakako Hara, Ai Sato, Hiroaki Sakai, Seiko Ogawa

Introduction

It is proposed that cancer stem cells (CSCs) are responsible for the malignant traits of refractory cancer, that is, the ability to generate metastatic foci and chemoresistance. Our group mainly focuses on studying CSCs from colon cancer and ovarian cancer. We aim to find out the weaknesses of CSCs that are cultivated in vitro from various clinical specimens, and to exploit them for clinical purposes. In addition, we use the established CSCs to generate patient-derived xenograft tumors in order to understand the mechanisms of chemoresistance (Figure 1).

Routine activities

A weekly conference is held with members of the Division of Cancer Differentiation

Research activities

1) Biological characterization of cancer stem cells in vitro from human refractory cancer

Recently, we isolated and expanded CSCs in vitro from human colon cancer and serous ovarian cancer. Using the cultivated CSCs, we demonstrated that activation of mTORC1 is responsible for proliferation and maintenance of stemness of colon CSCs. Furthermore, we revealed that reactive oxygen species (ROS) produced by NADPH oxidase contribute to the activation of mTORC1. In addition, we compared the metastatic and non-metastatic CSCs through microarray and metabolome analyses, and identified genes and metabolites that are specifically expressed at high levels in metastatic liver. We are now examining if they are linked to any functional roles in liver metastasis of colon cancer. In addition to colon CSCs, we also investigated regulatory pathways of ovarian CSCs. We showed that ALDH1 is specifically expressed in ovarian CSCs. Further, we demonstrated the functional importance of ALDH for their proliferation.

2) Establishment of PDX models of refractory cancer through transplantation of CSCs into mice

Using xenograft tumors through transplantation of colon and ovarian CSCs into immuno-compromised MOG mice, we established chemoresistance models in vivo, in which mice carrying the tumors were treated with chemotherapeutic agents. By applying single-cell gene expression analyses, the cellular heterogeneity of xenograft tumors and identity of chemo-resistant cells were examined.

Education

Teaching students (one undergraduate student, four graduate students)

Future prospects

We will pursue biological characterization of CSCs derived from refractory cancer. We will aim to translate the acquired knowledge for CSCs into clinical practices.

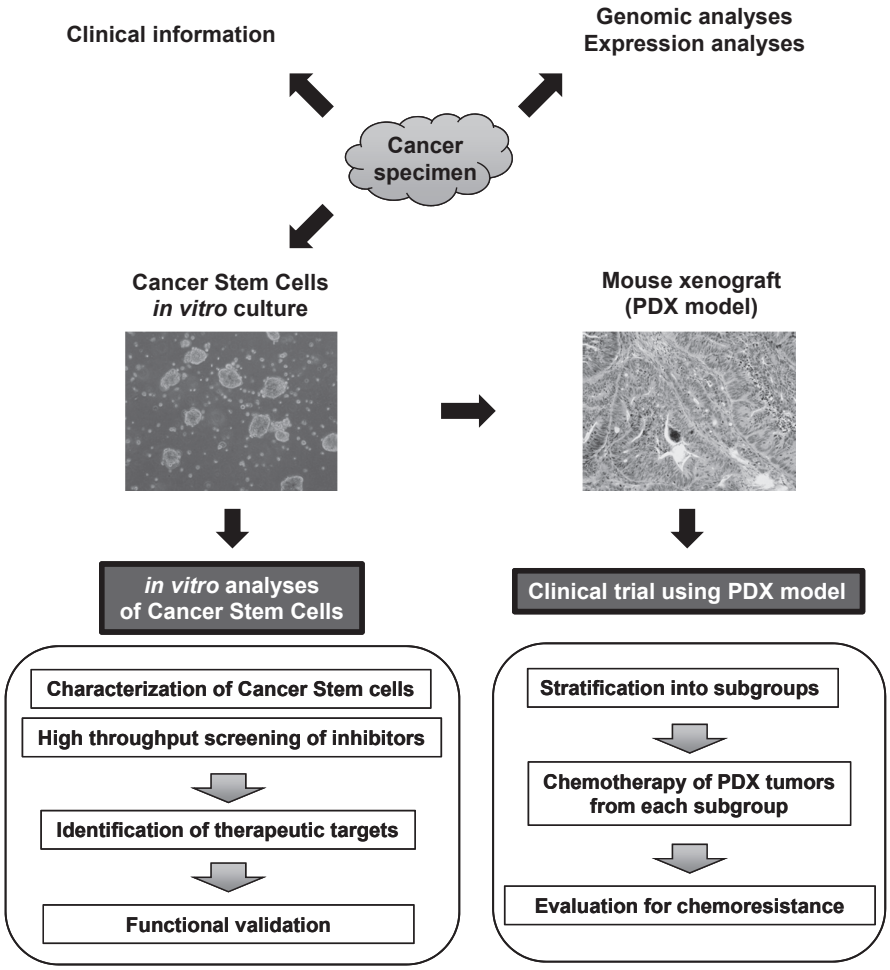


Figure 1. In vitro cultivation of Cancer Stem Cells and PDX models

List of papers published in 2015

Journal

1. Ujihira T, Ikeda K, Suzuki T, Yamaga R, Sato W, Horie-Inoue K, Shigekawa T, Osaki A, Saeki T, Okamoto K, Takeda S, Inoue S. MicroRNA-574-3p, identified by microRNA library-based functional screening, modulates tamoxifen response in breast cancer. Sci Rep, 5:7641, 2015
2. Miyazaki T, Ikeda K, Sato W, Horie-Inoue K, Okamoto K, Inoue S. MicroRNA library-based functional screening identified androgen-sensitive miR-216a as a player in bicalutamide resistance in prostate cancer. J Clin Med, 4:1853-1865, 2015

Division of Epigenomics

Toshikazu Ushijima, Satoshi Yamashita, Hideyuki Takeshima, Naoko Hattori, Masahiro Maeda, Emi Kubo, Naoko Iida, Akiko Mori, Kana Kimura, Kanako Sakashita, Naoko Kobayashi, Yuko Miyaji, Aya Nakajima, Mika Wakabayashi

Introduction

This Division has been focusing on the epigenetic mechanisms of carcinogenesis, and has identified many aberrantly methylated genes in various cancers, including gastric cancers, esophageal squamous cell carcinomas (ESCCs), neuroblastomas, breast cancers, pancreatic cancers, lung cancers, ovarian cancers, and melanomas. This has led to identification of novel tumor-suppressor genes, development of a powerful prognostic marker in neuroblastomas, and establishment of the concept of an "epigenetic field for cancerization (field defect)". This Division continues its activities in 1) developing clinically useful biomarkers, a novel approach to cancer prevention, and epigenetic therapy, and 2) revealing molecular mechanisms of aberrant DNA methylation induction.

Research activities

1) Identification of Novel Epigenetic Alterations

Identification of tumor-suppressor genes silenced by aberrant DNA methylation is important. This year, *SMARCA1*, encoding an ISWI-type chromatin remodeling factor, was identified as a tumor-suppressor gene inactivated by either aberrant DNA methylation or somatic mutation in gastric cancer. It was also revealed that genetic and epigenetic alterations of *SMARCA1* were induced at an early stage of carcinogenesis and were frequently involved in the formation of a field defect.

The recent development of personal sequencers and bead array technology has made it possible to conduct integrated analysis of genetic and epigenetic alterations in multiple cancer samples. This year, integrated analysis was conducted in 50 primary gastric cancers. It was revealed that about 40% of gastric cancer cases had no genetic alterations of known cancer-related genes, but frequently had epigenetic alterations of various genes involved in cancer-related pathways, such as WNT signaling and p53 signaling pathways.

2) Development of Biomarkers

This Division previously revealed that the degree of accumulated aberrant DNA methylation in normal-appearing gastric mucosae is expected to be a useful diagnostic marker to predict gastric cancer risk. To bring this concept into clinical practice, a multicenter prospective cohort study has been conducted for the prediction of metachronous gastric cancer risk after endoscopic resection. This year, an intermediate analysis was conducted, and it was revealed that cases with higher DNA methylation levels of *miR-124a-3* had a higher risk of developing metachronous gastric cancers (a multivariate-adjusted HR = 2.30 (95% CI = 1.03 to 5.10), $p = 0.042$) (Figure 1). Based on these results, we started a multicenter prospective cohort study for the prediction of gastric cancer risk in healthy volunteers who underwent eradication of *Helicobacter pylori (H. pylori)*, the almost exclusive cause of gastric cancers.

To establish clinically useful biomarkers to predict the response to cancer therapy is very important. This year, it was revealed that esophageal squamous cell carcinoma cases with DNA methylation of *ZNF695* benefitted from chemoradiotherapy treatment.

3) Development of epigenetic therapy

A combination of epigenetic modifications specifically present in cancer cells is a possible target in developing cancer cell-specific epigenetic therapy. This year, it was revealed that the combination of DNA methylation and trimethylation of histone H3 lysine 27 (H3K27me3) existed specifically in cancer

cells, and it was suggested that this combination is a possible target for cancer cell-specific epigenetic therapy.

Future prospects

Based on these results, this Division will 1) continue multicenter prospective cohort studies for the prediction of gastric cancer risk, 2) conduct the development of epigenetic therapy in gastric cancers and neuroblastomas, and 3) reveal the molecular mechanisms of how aberrant DNA methylation is induced by chronic inflammation.

Other activities

This Division assisted 1) epigenetic and genetic analyses of primary cancer samples in several translational research programs conducted in the National Cancer Center and other institutions, and 2) epigenetic analysis in various animal models.

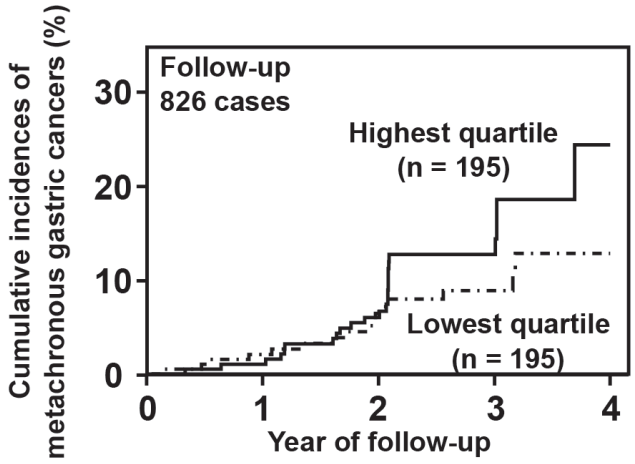


Figure 1. Prediction of gastric cancer risk by DNA methylation.

List of papers published in 2015

Journal

1. Wei FZ, Cao Z, Wang X, Wang H, Cai MY, Li T, Hattori N, Wang D, Du Y, Song B, Cao LL, Shen C, Wang L, Wang H, Yang Y, Xie D, Wang F, Ushijima T, Zhao Y, Zhu WG. Epigenetic regulation of autophagy by the methyltransferase EZH2 through an MTOR-dependent pathway. Autophagy, 11:2309-2322, 2015

2. Yoda Y, Takeshima H, Niwa T, Kim JG, Ando T, Kushima R, Sugiyama T, Katai H, Noshiro H, Ushijima T. Integrated analysis of cancer-related pathways affected by genetic and epigenetic alterations in gastric cancer. Gastric Cancer, 18:65-76, 2015

3. Takeshima H, Niwa T, Takahashi T, Wakabayashi M, Yamashita S, Ando T, Inagawa Y, Taniguchi H, Katai H, Sugiyama T, Kiyono T, Ushijima T. Frequent involvement of chromatin remodeler alterations in gastric field cancerization. Cancer Lett, 357:328-338, 2015

4. Asada K, Nakajima T, Shimazu T, Yamamichi N, Maekita T, Yokoi C, Oda I, Ando T, Yoshida T, Nanjo S, Fujishiro M, Gotoda T, Ichinose M, Ushijima T. Demonstration of the usefulness of epigenetic cancer risk prediction by a multicentre prospective cohort study. Gut, 64:388-396, 2015

5. Takahashi T, Yamahsita S, Matsuda Y, Kishino T, Nakajima T, Kushima R, Kato K, Igaki H, Tachimori Y, Osugi H, Nagino M, Ushijima T. *ZNF*695 methylation predicts a response of esophageal squamous cell carcinoma to definitive chemoradiotherapy. J Cancer Res Clin Oncol, 141:453-463, 2015

6. Takeshima, Hideyuki. Identification of coexistence of DNA methylation and H3K27me3 specifically in cancer cells as a promising target for epigenetic therapy. Carcinogenesis, 36:192-201, 2015

7. Descalzi G, Ikegami D, Ushijima T, Nestler EJ, Zachariou V, Narita M. Epigenetic mechanisms of chronic pain. Trends Neurosci, 38:237-246, 2015

8. Yamaguchi T, Mukai H, Yamashita S, Fujii S, Ushijima T. Comprehensive DNA methylation and extensive mutation analyses of HER2-positive breast cancer. Oncology, 88:377-384, 2015

9. Shimazu T, Asada K, Charvat H, Kusano C, Otake Y, Kakugawa Y, Watanabe H, Gotoda T, Ushijima T, Tsugane S. Association of gastric cancer risk factors with DNA methylation levels in gastric mucosa of healthy Japanese: a cross-sectional study. Carcinogenesis, 36:1291-1298, 2015

Division of Cancer Genomics

Tatsuhiro Shibata, Fumie Hosoda, Yasushi Totoki, Shinichi Yachida, Yasuhito Arai, Natsuko Hama, Hiromi Nakamura, Hirofumi Rokutan, Erina Takai, Koichi Ogura, Akihiro Oomoto, Mihoko Adachi, Masami Suzuki, Hiroko Shimizu, Shoko Ohashi, Wataru Omata, Wakako Mukai, Erika Arakawa, Keiko Igarashi, Risa Usui, Hiroki Sato, Machiko Watanabe

Introduction

The Division of Cancer Genomics focuses on comprehensive characterization of the cancer genome on the basis of tumor pathology and aims to make a "breakthrough" by identifying novel cancer-related genes, including potential therapeutic targets and biomarkers, and to understand the cancer genome as heterogeneous but *intervention-able* "biological systems" that contribute to the pathogenesis of cancer. This Division has also been participating in the international consortium (International Cancer Genome Consortium; ICGC), contributing to the core facility of the center, and developing new informatics tools for data analysis from various types of next-generation high-performance sequencers (NGS).

Research activities

1) Comprehensive molecular genetic characterization of Asian cancer genomes

Biliary tract cancer (BTC) is an intractable cancer, with limited therapeutic options, in which the molecular mechanisms underlying tumor development remain poorly understood. We performed whole-exome and transcriptome analysis of 260 biliary tract cancers, including 145 intrahepatic and 86 extrahepatic cholangiocarcinoma and 29 gallbladder cancers as a Japan ICGC project. We uncovered spectra of molecular alterations that included new potential therapeutic targets and unique immune-signatures, confirmed genetic differences in distinct subtypes and demonstrated that approximately 40% of cases harbored potentially targetable genetic aberrations (Figure 1). Notably, FGFR2 kinase fusion genes are identified as one of the high-potential therapeutic targets in BTC, and we have started-up BT-SCRUM (genomic screening consortium for biliary tract cancer) for the prospective study of genotype-based molecular therapy through collaboration with the Department of Hepatobiliary and Pancreatic Oncology.

We performed whole genome sequencing of adult T cell leukemia/lymphoma cases and identified somatic mutations, genomic rearrangements including fusion genes and human T cell leukemia virus type-1 (HTLV-1) genome integrations. We found many gene loci where genome deletions occurred frequently, including NRXN3, IMMP2L, DPYD and IKZF2, and in-frame fusion genes including CTLA4-CD28 and ICOS-CD28. We also found that all cases have one or more (up to three) HTLV-1 genome integration sites and some integrated HTLV-1 genomes had large deletions.

We have performed large-scale whole transcriptome and whole exome sequencing of gastric cancer as a Japan ICGC project. The whole transcriptome analysis identified multiple novel fusion genes including protein kinases. The whole exome analysis of 68 mucinous gastric carcinomas identified a characteristic mutational profile and driver mutations including potential therapeutic target genes.

We established international multicenter collaboration and conducted in-depth analysis of the genomic abnormalities of ampullary carcinomas. Whole exome sequencing and subsequent targeted deep sequencing led to the identification of a tumor suppressor gene, ELF3, characteristic of ampullary carcinomas.

2) New technological developments for next-generation genome medicine

Liquid biopsy

We developed a new mutation call program that can detect somatic mutations in samples with low (≧ 2%) tumor content such as circulating cell-free DNA (cfDNA) using deep sequencing. We performed targeted deep sequencing of 60 genes of cfDNA in 48 patients of pancreatic ductal adenocarcinoma (PDAC) and identified potentially targetable somatic mutations in 14 of 48 patients (29.2%) (Figure 2). We also analyzed somatic copy number alterations using our in-house algorithm and detected potentially targetable amplifications. Assessment of mutations and copy number alterations in plasma cfDNA may provide a prognostic and diagnostic tool to assist decisions regarding optimal therapeutic strategies for PDAC patients.

Microbiome

We are clarifying the relationships between the luminal microbiota and colorectal cancers and the mechanisms of potential contribution of the microbiome in colorectal cancer development.

Germline evaluation

We have examined the genetic polymorphisms of 147 drug metabolism-related genes in 75 ALK-positive lung cancer patients treated with crizotinib. We found possible functional SNPs in two genes, showing statistically significant differences between the patients with or without severe adverse effects. By whole exome sequencing of germline DNA, pancreatic cancer susceptibility genes in Japanese familial pancreatic cancer patients have been identified.

Education

Six young researchers, one cancer specialist training doctor, and one visiting researcher have been trained in this Division. Three young bioinformaticians have been trained and two of them prepared for papers as the first author.

Future prospects

By utilizing current and cutting-edge sequencing technologies (for example, single cell sequencing), this Division will actively investigate cancer genomics from both basic (new biomarkers including therapeutic targets, epigenomics, metagenomics and immune-genomics) and translational research (preclinical research, liquid clinical sequencing, PGx and germline evaluation) viewpoints. Especially tighter collaboration with cancer-immunology groups by applying single cell immune-profiling and TCR repertoire sequencing will be achieved. This Division will also contribute to the development of bioinformatics tools and human resources for analyzing large cancer genomics data.

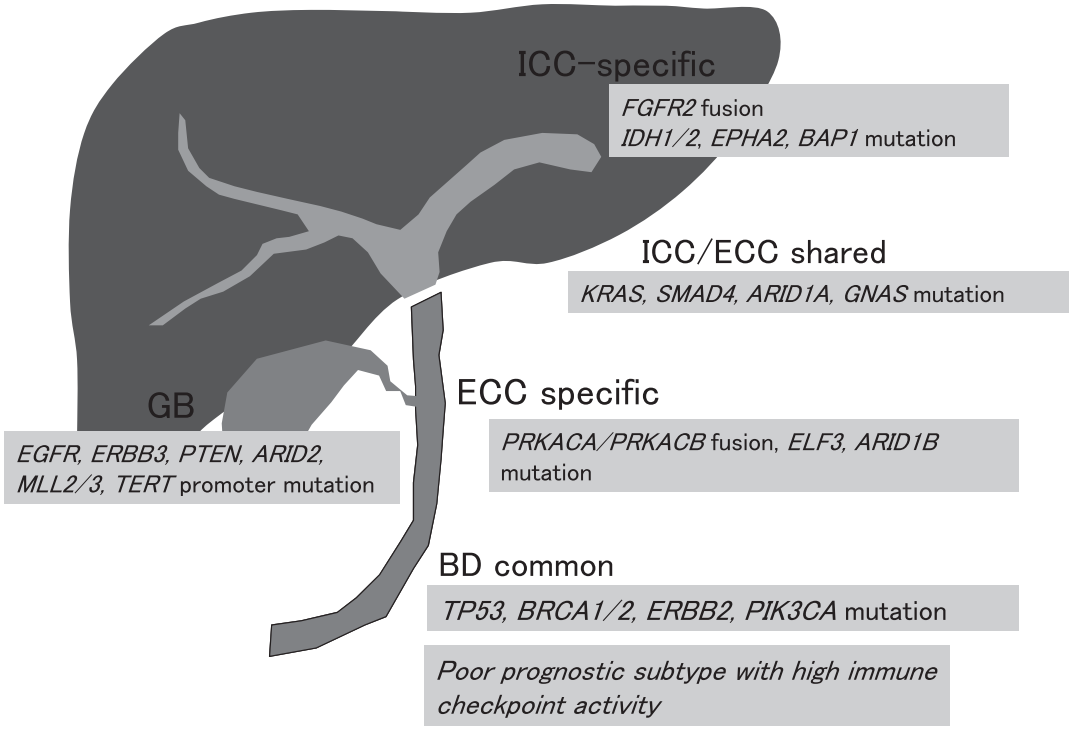


Figure 1. Subtype-specific omics (genome + RNA) signatures in BTC

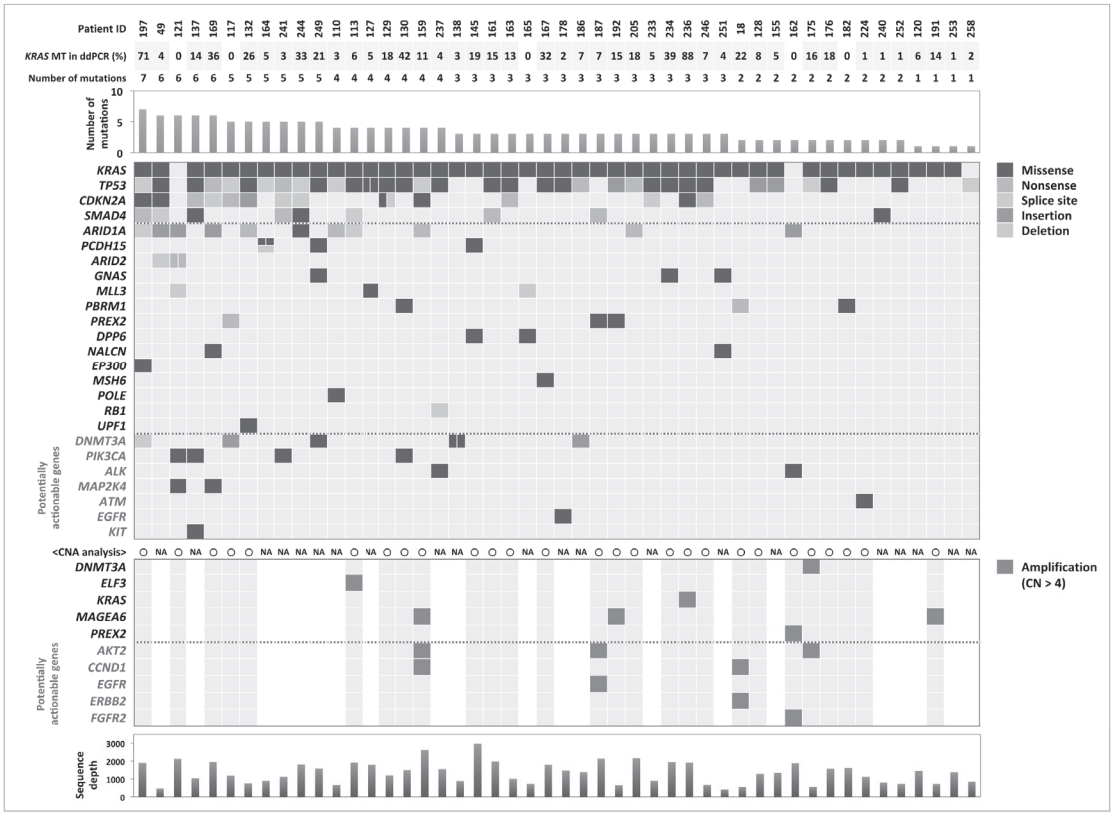


Figure 2. Somatic mutations and amplification detected by targeted sequencing of plasma cell-free DNA in 48 patients with pancreatic cancer

List of papers published in 2015

Journal

1. Wild CP, Bucher JR, de Jong BWD, Dillner J, von Gertten C, Groopman JD, Herceg Z, Holmes E, Holmila R, Olsen JH, Ringborg U, Scalbert A, Shibata T, Smith MT, Ulrich C, Vineis P, McLaughlin J. Translational cancer research: balancing prevention and treatment to combat cancer globally. J Natl Cancer Inst, 107:353, 2015

2. Fujimoto A, Furuta M, Shiraishi Y, Gotoh K, Kawakami Y, Arihiro K, Nakamura T, Ueno M, Ariizumi S, Nguyen HH, Shigemizu D, Abe T, Boroevich KA, Nakano K, Sasaki A, Kitada R, Maejima K, Yamamoto Y, Tanaka H, Shibuya T, Shibata T, Ojima H, Shimada K, Hayami S, Shigekawa Y, Aikata H, Ohdan H, Marubashi S, Yamada T, Kubo M, Hirano S, Ishikawa O, Yamamoto M, Yamaue H, Chayama K, Miyano S, Tsunoda T, Nakagawa H. Whole-genome mutational landscape of liver cancers displaying biliary phenotype reveals hepatitis impact and molecular diversity. Nat Commun, 6:6120, 2015

3. Kanamori M, Higa T, Sonoda Y, Murakami S, Dodo M, Kitamura H, Taguchi K, Shibata T, Watanabe M, Suzuki H, Shibahara I, Saito R, Yamashita Y, Kumabe T, Yamamoto M, Motohashi H, Tominaga T. Activation of the NRF2 pathway and its impact on the prognosis of anaplastic glioma patients. Neuro Oncol, 17:555-565, 2015

4. Hosoda F, Arai Y, Okada N, Shimizu H, Miyamoto M, Kitagawa N, Katai H, Taniguchi H, Yanagihara K, Imoto I, Inazawa J, Ohki M, Shibata T. Integrated genomic and functional analyses reveal glyoxalase I as a novel metabolic oncogene in human gastric cancer. Oncogene, 34:1196-1206, 2015

5. Asano N, Yoshida A, Ogura K, Kobayashi E, Susa M, Morioka H, Iwata S, Ishii T, Hiruma T, Chuman H, Kawai A. Prognostic Value of Relevant Clinicopathologic Variables in Epithelioid Sarcoma: A Multi-Institutional Retrospective Study of 44 Patients. Ann Surg Oncol, 22:2624-2632, 2015

6. Takai E, Totoki Y, Nakamura H, Morizane C, Nara S, Hama N, Suzuki M, Furukawa E, Kato M, Hayashi H, Kohno T, Ueno H, Shimada K, Okusaka T, Nakagama H, Shibata T, Yachida S. Clinical utility of circulating tumor DNA for molecular assessment in pancreatic cancer. Sci Rep, 5:18425, 2015

7. Kataoka K, Nagata Y, Kitanaka A, Shiraishi Y, Shimamura T, Yasunaga J, Totoki Y, Chiba K, Sato-Otsubo A, Nagae G, Ishii R, Muto S, Kotani S, Watatani Y, Takeda J, Sanada M, Tanaka H, Suzuki H, Sato Y, Shiozawa Y, Yoshizato T, Yoshida K, Makishima H, Iwanaga M, Ma G, Nosaka K, Hishizawa M, Itonaga H, Imaizumi Y, Munakata W, Ogasawara H, Sato T, Sasai K, Muramoto K, Penova M, Kawaguchi T, Nakamura H, Hama N, Shide K, Kubuki Y, Hidaka T, Kameda T, Nakamaki T, Ishiyama K, Miyawaki S, Yoon SS, Tobinai K, Miyazaki Y, Takaori-Kondo A, Matsuda F, Takeuchi K, Nureki O, Aburatani H, Watanabe T, Shibata T, Matsuoka M, Miyano S, Shimoda K, Ogawa S. Integrated molecular analysis of adult T cell leukemia/lymphoma. Nat Genet, 47:1304-1315, 2015

8. Shibata T. Current and future molecular profiling of cancer by next-generation sequencing. Jpn J Clin Oncol, 45:895-899, 2015

9. Mutation Consequences and Pathway Analysis working group of the International Cancer Genome Consortium. Pathway and network analysis of cancer genomes. Nat Methods, 12:615-621, 2015

10. Murakami S, Ninomiya W, Sakamoto E, Shibata T, Akiyama H, Tashiro F. SRY and OCT4 Are Required for the Acquisition of Cancer Stem Cell-Like Properties and Are Potential Differentiation Therapy Targets. Stem Cells, 33:2652-2663, 2015

11. Ishino K, Kato T, Kato M, Shibata T, Watanabe M, Wakabayashi K, Nakagama H, Totsuka Y. Comprehensive DNA adduct analysis reveals pulmonary inflammatory response contributes to genotoxic action of magnetite nanoparticles. Int J Mol Sci, 16:3474-3492, 2015

12. Basturk O, Hong SM, Wood LD, Adsay NV, Albores-Saavedra J, Biankin AV, Brosens LA, Fukushima N, Goggins M, Hruban RH, Kato Y, Klimstra DS, Klöppel G, Krasinskas A, Longnecker DS, Matthaei H, Offerhaus GJ, Shimizu M, Takaori K, Terris B, Yachida S, Esposito I, Furukawa T, Baltimore Consensus Meeting. A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. Am J Surg Pathol, 39:1730-1741, 2015

13. Springer S, Wang Y, Dal Molin M, Masica DL, Jiao Y, Kinde I, Blackford A, Raman SP, Wolfgang CL, Tomita T, Niknafs N, Douville C, Ptak J, Dobbyn L, Allen PJ, Klimstra DS, Schattner MA, Schmidt CM, Yip-Schneider M, Cummings OW, Brand RE, Zeh HJ, Singhi AD, Scarpa A, Salvia R, Malleo G, Zamboni G, Falconi M, Jang JY, Kim SW, Kwon W, Hong SM, Song KB, Kim SC, Swan N, Murphy J, Geoghegan J, Brugge W, Fernandez-Del Castillo C, Mino-Kenudson M, Schulick R, Edil BH, Adsay V, Paulino J, van Hooft J, Yachida S, Nara S, Hiraoka N, Yamao K, Hijioka S, van der Merwe S, Goggins M, Canto MI, Ahuja N, Hirose K, Makary M, Weiss MJ, Cameron J, Pittman M, Eshleman JR, Diaz LA, Papadopoulos N, Kinzler KW, Karchin R, Hruban RH, Vogelstein B, Lennon AM. A combination of molecular markers and clinical features improve the classification of pancreatic cysts. Gastroenterology, 149:1501-1510, 2015

14. Shibayama Y, Fujimori T, Nguyen G, Hirose T, Totsune K, Ichihara A, Kitada K, Nakano D, Kobori H, Kohno M, Masaki T, Suzuki Y, Yachida S, Nishiyama A. (Pro)renin receptor is crucial for Wnt/β-catenin-dependent genesis of pancreatic ductal adenocarcinoma. Sci Rep, 5:8854, 2015

15. Takai E, Yachida S. Genomic alterations in pancreatic cancer and their relevance to therapy. World J Gastrointest Oncol, 7:250-258, 2015

16. Shirota T, Ojima H, Hiraoka N, Shimada K, Rokutan H, Arai Y, Kanai Y, Miyagawa S, Shibata T. Heat shock protein 90 is a potential therapeutic target in cholangiocarcinoma. Mol Cancer Ther, 14:1985-1993, 2015

17. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, Hama N, Hosoda F, Urushidate T, Ohashi S, Hiraoka N, Ojima H, Shimada K, Okusaka T, Kosuge T, Miyagawa S, Shibata T. Genomic spectra of biliary tract cancer. Nat Genet, 47:1003-1010, 2015

18. Takenaka M, Saito M, Iwakawa R, Yanaihara N, Saito M, Kato M, Ichikawa H, Shibata T, Yokota J, Okamoto A, Kohno T. Profiling of actionable gene alterations in ovarian cancer by targeted deep sequencing. Int J Oncol, 46:2389-2398, 2015

19. Iwakawa R, Kohno T, Totoki Y, Shibata T, Tsuchihara K, Mimaki S, Tsuta K, Narita Y, Nishikawa R, Noguchi M, Harris CC, Robles AI, Yamaguchi R, Imoto S, Miyano S, Totsuka H, Yoshida T, Yokota J. Expression and clinical significance of genes frequently mutated in small cell lung cancers defined by whole exome/RNA sequencing. Carcinogenesis, 36:616-621, 2015

Division of Genome Biology

Takashi Kohno, Naoto Tsuchiya, Hideaki Ogiwara, Motonobu Saito, Kouya Shiraishi, Kuniko Sunami, Ken Ishida, Mariko Sasaki, Yoko Shimada, Yoshitaka Seki, Kazuaki Takahashi, Yuko Fujiwara, Takayuki Honda, Yoshie Iga, Ayaka Otsuka, Takashi Nakaoku, Yusuke Sugiyama, Yujin Ishihara, Mei Tanabe, Mokuri Masuda, Takashi Mitachi, Tomoaki Yoshizawa, Jun Yokota

Introduction

Somatic mutations in the cancer genome and inter-individual variations in the human genome are critical to improving cancer medicine. Our Division aims to find "seeds" that are applicable for development of novel strategies for the treatment and prevention of cancer through identifying and understanding the biological relationship of their seeds with cancer pathogenesis caused by somatic mutations and/or genetic polymorphisms of the patients. In order to attain our goal, we are working together with the National Cancer Center (NCC) staff from the hospital, evaluation system of postgraduate clinical training (EPOC) and the Research Center for Cancer Prevention and Screening to fight lung cancer, the most common cause of cancer-related death in the world.

Routine activities

A weekly research seminar and journal club are held with all the members of the division.

Research activities

1) Genes for personalized cancer medicine

Whole exome sequencing using 200 lung adenocarcinomas (LADC) demonstrated that cases with driver fusion genes showed a distinct profile with a smaller number of somatic mutations in cancer-related genes than those in the others. It was also found that genes encoding chromatin-remodeling factors are frequently mutated in the LADCs, which are negative for driver oncogene mutations, providing a novel concept that regulation of epigenetic status has an important role in lung carcinogenesis. In relation to this, a synthetic lethal screen against histone modification enzyme CBP, which are highly mutated in a certain kind of cancers, identified a novel molecular target, whose inhibition will be expected to eliminate CBP-deficient cancers. Therefore, development of compounds that specifically inhibit the function of a target molecule is now being conducted in collaboration with a pharmaceutical company. Whole RNA sequencing of 32 invasive mucinous adenocarcinomas (IMAs) identified the NRG fusion genes as a novel oncogenic fusion in IMA. It was clarified that a gene product of NER fusion is involved in the augmentation of stemness in lung cancer cells. A genome-wide association study (GWAS) led us to identify a novel LADC susceptibility locus. An international and pan-Japan collaborative GWAS study uncovered the relationship between telomere length and lung cancer risk. International collaboration is still under way to further identify genetic factors involved not only in susceptibility but also in prognosis of lung cancer.

2) Research for the development of nucleic acid drugs based on the properties of miRNA

NEK9 was previously identified by an miR-22 target screen as a regulator for cell cycle progression in p53-deficient cancer cells. Depletion of NEK9 selectively repressed the proliferation on p53 mutant cancer cells both in vivo and in vitro. Screening of molecules that are critical regulators in the NEK9 network is being conducted to establish the strategy for selective elimination of p53 deficient cancer cells. It was uncovered that tumor-suppressive miR-101 is a critical factor for precise activation of an intrinsic p53 tumor-suppressor network. Reduced-expression of miR-101 in p53 wild-type LADCs exhibited significant poor prognosis, suggesting that administration of miR-101 into cancer tissues is

a potential approach for the development of nucleic acid drug.

Clinical trials

A phase II clinical trial, which investigates the therapeutic effect of a RET-tyrosine kinase inhibitor, vandetanib, was conducted by identifying >20 RET-fusion positive lung cancers among >1,500 non-small cell lung carcinoma cases in 190 hospitals. The genetic screening was done by the LC-SCRUM-Japan (Lung Cancer Genomic Screening Project for Individualized Medicine in Japan) consortium.

Education

Supervising research and presentation skills for students and young researchers

Future prospects

Our Division aims to establish novel strategies for personalized cancer medicine, including prevention, diagnosis and therapy, through the finding of unique "seeds", which are identified by genetic and biological analyses using cancer cells and clinical samples. A nationwide clinical trial of RET-tyrosine kinase inhibitor will confirm the efficacy of RET-tyrosine kinase inhibitor for the treatment RET-fusion LADC. Furthermore, understanding biological roles of novel molecular targets, including chromatin-remodeling factors, histone modifiers and cell cycle regulators, which are identified by synthetic lethal screen and comprehensive genome analyses, provide unique and/or novel concepts for the development of cancer therapy. In addition, practical application of miRNAs as diagnostic biomarkers will be expected in the near future.

List of papers published in 2015

Journal

1. Suzuki M, Shiraishi K, Yoshida A, Shimada Y, Suzuki K, Asamura H, Furuta K, Kohno T, Tsuta K. *HER2* gene mutations in non-small cell lung carcinomas: concurrence with *Her2* gene amplification and her2 protein expression and phosphorylation. Lung Cancer, 87:14-22, 2015

2. Yagishita S, Horinouchi H, Katsui Taniyama T, Nakamichi S, Kitazono S, Mizugaki H, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. Int J Radiat Oncol Biol Phys, 91:140-148, 2015

3. Simó-Riudalbas L, Pérez-Salvia M, Setien F, Villanueva A, Moutinho C, Martínez-Cardús A, Moran S, Berdasco M, Gomez A, Vidal E, Soler M, Heyn H, Vaquero A, de la Torre C, Barceló-Batllori S, Vidal A, Roz L, Pastorino U, Szakszon K, Borck G, Moura CS, Carneiro F, Zondervan I, Savola S, Iwakawa R, Kohno T, Yokota J, Esteller M. KAT6B Is a Tumor Suppressor Histone H3 Lysine 23 Acetyltransferase Undergoing Genomic Loss in Small Cell Lung Cancer. Cancer Res, 75:3936-3945, 2015

4. Robles AI, Arai E, Mathé EA, Okayama H, Schetter AJ, Brown D, Petersen D, Bowman ED, Noro R, Welsh JA, Edelman DC, Stevenson HS, Wang Y, Tsuchiya N, Kohno T, Skaug V, Mollerup S, Haugen A, Meltzer PS, Yokota J, Kanai Y, Harris CC. An Integrated Prognostic Classifier for Stage I Lung Adenocarcinoma Based on mRNA, microRNA, and DNA Methylation Biomarkers. J Thorac Oncol, 10:1037-1048, 2015

5. Alagoz M, Katsuki Y, Ogiwara H, Ogi T, Shibata A, Kakarougkas A, Jeggo P. SETDB1, HP1 and SUV39 promote repositioning of 53BP1 to extend resection during homologous recombination in G2 cells. Nucleic Acids Res, 43:7931-7944, 2015

6. Suzuki A, Matsushima K, Makinoshima H, Sugano S, Kohno T, Tsuchihara K, Suzuki Y. Single-cell analysis of lung adenocarcinoma cell lines reveals diverse expression patterns of individual cells invoked by a molecular target drug treatment. Genome Biol, 16:66, 2015

7. Yagishita S, Horinouchi H, Sunami KS, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T, Ohe Y. Impact of KRAS mutation on response and outcome of patients with stage III non-squamous non-small cell lung cancer. Cancer Sci, 106:1402-1407, 2015

8. Kohno T, Saito M. Comparisons between mouse and human studies will help the prevention, diagnosis, and treatment of the deadliest type of lung cancer. J Thorac Oncol, 10:551-552, 2015

9. Ryan BM, Robles AI, McClary AC, Haznadar M, Bowman ED, Pine SR, Brown D, Khan M, Shiraishi K, Kohno T, Okayama H, Modali R, Yokota J, Harris CC. Identification of a functional SNP in the 3'UTR of CXCR2 that is associated with reduced risk of lung cancer. Cancer Res, 75:566-575, 2015

10. Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, Goto K. Beyond *ALK-RET, ROS1* and other oncogene fusions in lung cancer. Transl Lung Cancer Res, 4:156-164, 2015

11. Takenaka M, Saito M, Iwakawa R, Yanaihara N, Saito M, Kato M, Ichikawa H, Shibata T, Yokota J, Okamoto A, Kohno T. Profiling of actionable gene alterations in ovarian cancer by targeted deep sequencing. Int J Oncol, 46:2389-2398, 2015

12. George J, Lim JS, Jang SJ, Cun Y, Ozretic L, Kong G, Leenders F, Lu X, Fernandez-Cuesta L, Bosco G, Muller C, Dahmen I, Jahchan NS, Park KS, Yang D, Karnezis AN, Vaka D, Torres A, Wang MS, Korbel JO, Menon R, Chun SM, Kim D, Wilkerson M, Hayes N, Engelmann D, Putzer B, Bos M, Michels S, Vlasic I, Seidel D, Pinther B, Schaub P, Becker C, Altmuller J, Yokota J, Kohno T, Iwakawa R, Tsuta K, Noguchi M, Muley T, Hoffmann H, Schnabel PA, Petersen I, Chen Y, Soltermann A, Tischler V, Choi C, Kim YH, Massion PP, Zou Y, Jovanovic D, Kontic M, Wright GM, Russell PA, Solomon B, Koch I, Lindner M, Muscarella LA, la Torre A, Field JK, Jakopovic M, Knezevic J, Castanos-Velez E, Roz L, Pastorino U, Brustugun OT, Lund-Iversen M, Thunnissen E, Kohler J, Schuler M, Botling J, Sandelin M, Sanchez-Cespedes M, Salvesen HB, Achter V, Lang U, Bogus M, Schneider PM, Zander T, Ansen S, Hallek M, Wolf J, Vingron M, Yatabe Y, Travis WD, Nurnberg P, Reinhardt C, Perner S, Heukamp L, Buttner R, Haas SA, Brambilla E, Peifer M, Sage J, Thomas RK. Comprehensive genomic profiles of small cell lung cancer. Nature, 524:47-53, 2015

13. Saito M, Shimada Y, Shiraishi K, Sakamoto H, Tsuta K, Totsuka H, Chiku S, Ichikawa H, Kato M, Watanabe S, Yoshida T, Yokota J, Kohno T. Development of lung adenocarcinomas with exclusive dependence on oncogene fusions. Cancer Res, 75:2264-2271, 2015

14. Amornwichet N, Oike T, Shibata A, Nirodi CS, Ogiwara H, Makino H, Kimura Y, Hirota Y, Isono M, Yoshida Y, Ohno T, Kohno T, Nakano T. The *EGFR* mutation status affects the relative biological effectiveness of carbon-ion beams in non-small cell lung carcinoma cells. Sci Rep, 5:11305, 2015

15. Iwakawa R, Kohno T, Totoki Y, Shibata T, Tsuchihara K, Mimaki S, Tsuta K, Narita Y, Nishikawa R, Noguchi M, Harris CC, Robles AI, Yamaguchi R, Imoto S, Miyano S, Totsuka H, Yoshida T, Yokota J. Expression and clinical significance of genes frequently mutated in small cell lung cancers defined by whole exome/RNA sequencing. Carcinogenesis, 36:616-621, 2015

16. Machiela MJ, Hsiung CA, Shu XO, Seow WJ, Wang Z, Matsuo K, Hong YC, Seow A, Wu C, Hosgood HD, Chen K, Wang JC, Wen W, Cawthon R, Chatterjee N, Hu W, Caporaso NE, Park JY, Chen CJ, Kim YH, Kim YT, Landi MT, Shen H, Lawrence C, Burdett L, Yeager M, Chang IS, Mitsudomi T, Kim HN, Chang GC, Bassig BA, Tucker M, Wei F, Yin Z, An SJ, Qian B, Lee VHF, Lu D, Liu J, Jeon HS, Hsiao CF, Sung JS, Kim JH, Gao YT, Tsai YH, Jung YJ, Guo H, Hu Z, Hutchinson A, Wang WC, Klein RJ, Chung CC, Oh IJ, Chen KY, Berndt SI, Wu W, Chang J, Zhang XC, Huang MS, Zheng H, Wang J, Zhao X, Li Y, Choi JE, Su WC, Park KH, Sung SW, Chen YM, Liu L, Kang CH, Hu L, Chen CH, Pao W, Kim YC, Yang TY, Xu J, Guan P, Tan W, Su J, Wang CL, Li H, Sihoe ADL, Zhao Z, Chen Y, Choi YY, Hung JY, Kim JS, Yoon HI, Cai Q, Lin CC, Park IK, Xu P, Dong J, Kim C, He Q, Perng RP, Kohno T, Kweon SS, Chen CY, Vermeulen RCH, Wu J, Lim WY, Chen KC, Chow WH, Ji BT, Chan JKC, Chu M, Li YJ, Yokota J, Li J, Chen H, Xiang YB, Yu CJ, Kunitoh H, Wu G, Jin L, Lo YL, Shiraishi K, Chen YH, Lin HC, Wu T, Wong MP, Wu YL, Yang PC, Zhou B, Shin MH, Fraumeni JFJ, Zheng W, Lin D, Chanock SJ, Rothman N, Lan Q. Genetic variants associated with longer telomere length are associated with increased lung cancer risk among never-smoking women in Asia: a report from the female lung cancer consortium in Asia. Int J Cancer, 137:311-319, 2015

17. Seki Y, Mizukami T, Kohno T. Molecular process producing oncogene fusion in lung cancer cells by illegitimate repair of DNA double-strand breaks. Biomolecules, 5:2464-2476, 2015

Division of Brain Tumor Translational Research

Koichi Ichimura, Shintaro Fukushima, Kai Yamasaki, Kohei Fukuoka, Hirokazu Takami, Taishi Nakamura, Shunichiro Miki, Yuko Matsushita, Hideyuki Arita, Yuki Yomoda, Yumiko Miyamoto, Emiko Yamamoto

Introduction

Our laboratory focuses on translational research on various types of malignant brain tumors. Extensive genomic studies in recent years dramatically improved our understanding of the molecular mechanisms of brain tumors. It is highly anticipated that the new WHO Classification for central nervous system tumors (revised 4th edition) will incorporate molecular diagnostics as a part of criteria in some tumors. Through a nationwide multi-center collaboration including the Japan Clinical Oncology Group (JCOG), the Japan Children's Cancer Group (JCCG), the Japan Pediatric Molecular Neuro-oncology Group (JPMNG) and the Intracranial Germ Cell Tumor Consortium (iGCT), we are setting up and standardizing a robust molecular classification and a diagnostic system. This will enable more accurate and objective diagnosis of brain tumors and increase the efficacy of clinical trials. We are also developing a novel molecular-targeted therapy against TERT, which is very frequently mutated in the promoter region in adult gliomas. Through our research, we aim to establish a molecular diagnostic system for adult and pediatric brain tumors in Japan and utilize it for better stratification and assessment, as well as to develop a novel targeted therapy for one of the most therapy-resistant tumors of humans.

Routine activities

In collaboration with the Department of Neurosurgery and Neuro-oncology in the National Cancer Center Hospital, we routinely perform molecular diagnosis for all gliomas operated on in the National Cancer Center. Tumor tissues are snap-frozen immediately after removal at the operation theater and the samples are subjected to DNA extraction and analysis for mutations of IDH1, IDH2, TERT promoter, H3F3A and BRAF, as well as methylation of MGMT by using pyrosequencing in a single experiment. The results are reported back to clinics within two weeks of the operation to aid treatment decisions for the patient. Co-deletion of 1p/19q, which is a hallmark of oligodendroglioma, is examined using a customized FISH protocol or MLPA.

Research activities

1) Development of a novel molecular classification and optimal molecular tests for adult gliomas

We have previously discovered that the three major classes of adult glioma have distinct molecular profiles: oligodendroglioma, a chemo-sensitive glioma with relatively long survival, is characterized by combined IDH mutations, TERT promoter mutations and 1p/19q co-deletion; astrocytoma, less chemo-sensitive with significantly shorter survival than oligodendroglioma, harbors IDH mutation but not TERT mutation nor 1p/19q co-deletion; glioblastoma, the most therapy-resistant tumors with the poorest prognosis, often have TERT promoter mutations but seldom IDH mutations or 1p/19q co-deletion. We have performed a multicenter study to develop a novel molecular classification system utilizing the statuses of these molecular markers. We have studied more than 1,000 adult gliomas collected from 18 centers and showed that the combination of these markers defines 4 molecular subgroups with significantly different overall survival. In order to meet the requirement in the revised WHO Classification for central nervous system tumors, in which molecular tests will be mandatory to make diagnosis of astrocytomas and oligodendrogliomas, we are currently setting up robust and practicable molecular tests for clinical use in collaboration with industry.

2) Development of a novel targeted therapy for glioblastoma

A novel targeted therapy against TERT is being developed for glioblastoma in collaboration with the Division of Cancer Stem Cell at the National Cancer Center Research Institute. We have performed a series of pre-clinical experiments to investigate the efficacy of anti-TERT therapy. The results showed that glioblastoma cell lines that have TERT mutations are highly sensitive to the TERT inhibitor, and the survival of mice transplanted with TERT-mutated glioblastoma cell lines in the brain was significantly prolonged.

3) Genomic analysis of intracranial germ cell tumors

Intracranial germ cell tumors are the second most common pediatric brain tumors in Japan. We have established the Intracranial Germ Cell Tumor Genome Analysis Consortium (iGCT Consortium), a nationwide collaborative network to study germ cell tumors, through which tumor samples of more than 240 cases from 22 centers have been collected. We have previously performed a whole exome and targeted sequencing in 197 germ cell tumors of CNS or testicular origin, the results of which showed a high prevalence of mutations affecting the MAPK and/or PI3K pathway. We have now analyzed the genome-wide DNA methylation status as well as transcriptome and are investigating the potential cell of origin and mechanism of GCT development.

4) Molecular diagnosis of pediatric brain tumors

In order to build a central molecular diagnosis service for pediatric brain tumors nationwide, we have established JPMNG. More than 100 ependymomas collected through JPMNG have so far been analyzed and molecularly diagnosed using an Illumina HumanMethylation 450 BeadChip and a custom FISH protocol. Based on these results, we are now in collaboration with the German Cancer Research Center (DKFZ) as a part of an international effort to build up a consensus on molecular classification of ependymomas. A practical molecular diagnostic scheme for pediatric gliomas is also being set up. We also act as one of the central molecular diagnostic laboratories to perform molecular testing and classification for clinical trials and other clinical research conducted under JCCG.

Clinical trials

We continue to offer an MGMT methylation test for the patients enrolled in the EGGTRIAL, a clinical trial to evaluate the feasibility of the treatment strategy for elderly (70 or older) glioblastoma patients based on the MGMT status, in which those with methylated MGMT will only be given TMZ chemotherapy while those with unmethylated MGMT will only receive radiation therapy. In this trial, tumor specimens are sent to our laboratory from the participating centers immediately after the operation. For them, we perform an MGMT methylation test using our custom-designed pyrosequencing assay. Up to the end of 2015, 68 patients were tested for MGMT methylation. Registration continues in 2016. We are also preparing a clinical trial to test the efficacy of the TERT-targeted drug for recurrent glioblastomas, for which full support from the Center for Research Administration and Support at the National Cancer Center for the clinical trial has been approved.

Education

Three postgraduate students, three Research Residents, one Clinical Resident did research work during 2015 at the Division of Brain Tumor Translational Research.

Future prospects

As one of the leading translational research centers on malignant brain tumors in Japan, we continue to organize nationwide collaboration and perform research. We offer a central molecular diagnostic service in a number of clinical trials and clinical research. We develop novel targeted therapies, rigorously validated in pre-clinical settings and plan clinical trials. We also support young dedicated clinician investigators and help them with their PhD projects. Our goal is to be able to offer better patient care and treatment for brain tumor sufferers and help develop world-class neuro-oncology research in Japan.

List of papers published in 2015

Journal

1. Arita H, Narita Y, Matsushita Y, Fukushima S, Yoshida A, Takami H, Miyakita Y, Ohno M, Shibui S, Ichimura K. Development of a robust and sensitive pyrosequencing assay for the detection of *IDH1/2* mutations in gliomas. Brain Tumor Pathol, 32:22-30, 2015

2. Takami H, Yoshida A, Fukushima S, Arita H, Matsushita Y, Nakamura T, Ohno M, Miyakita Y, Shibui S, Narita Y, Ichimura K. Revisiting *TP53* Mutations and Immunohistochemistry-A Comparative Study in 157 Diffuse Gliomas. Brain Pathol, 25:256-265, 2015

3. Fukushima S, Yoshida A, Narita Y, Arita H, Ohno M, Miyakita Y, Ichimura K, Shibui S. Multinodular and vacuolating neuronal tumor of the cerebrum. Brain Tumor Pathol, 32:131-136, 2015

4. Arita H, Narita Y, Yoshida A, Hashimoto N, Yoshimine T, Ichimura K. *IDH1/2* mutation detection in gliomas. Brain Tumor Pathol, 32:79-89, 2015

5. Takami H, Fukushima S, Fukuoka K, Suzuki T, Yanagisawa T, Matsushita Y, Nakamura T, Arita H, Mukasa A, Saito N, Kanamori M, Kumabe T, Tominaga T, Kobayashi K, Nagane M, Iuchi T, Tamura K, Maehara T, Sugiyama K, Nakada M, Kanemura Y, Nonaka M, Yokogami K, Takeshima H, Narita Y, Shibui S, Nakazato Y, Nishikawa R, Ichimura K, Matsutani M. Human chorionic gonadotropin is expressed virtually in all intracranial germ cell tumors. J Neurooncol, 124:23-32, 2015

6. Ichimura K, Narita Y, Hawkins CE. Diffusely infiltrating astrocytomas: pathology, molecular mechanisms and markers. Acta Neuropathol, 129:789-808, 2015

7. Geisenberger C, Mock A, Warta R, Rapp C, Schwager C, Korshunov A, Nied AK, Capper D, Brors B, Jungk C, Jones D, Collins VP, Ichimura K, Backlund LM, Schnabel E, Mittelbron M, Lahrmann B, Zheng S, Verhaak RG, Grabe N, Pfister SM, Hartmann C, von Deimling A, Debus J, Unterberg A, Abdollahi A, Herold-Mende C. Molecular profiling of long-term survivors identifies a subgroup of glioblastoma characterized by chromosome 19/20 co-gain. Acta Neuropathol, 130:419-434, 2015

Division of Chemotherapy and Clinical Research

Tesshi Yamada, Mitsuko Masutani, Masaya Ono, Kazufumi Honda, Mari Masuda, Hiroaki Fujimori-Sakuma, Nami Miura, Ayako Mimata, Masahiro Kamita, Shoji Imamichi, Yuka Sasaki, Hiroko Ito, Junhui Wang, Haruyo Tozaki, Yuko Miyamoto, Naoko Goto, Takako Sakamoto, Keiko Takeuchi, Nobuhiko Nishijima, Takanori Kakuya, Makoto Kobayashi, Hirokazu Shoji, Teppei Sugano, Takahisa Hirai, Tasuku Itoh, Miyuki Hozumi, Sota Kikuhara, Kumiko Kinoshita, Noriko Shibata, Akira Sato, Gui Zhen Chen

Introduction

The Division has been devoted to the clinical application/translation of basic research findings obtained through the comprehensive genomics and proteomics approaches.

Therapeutic targets in the Wnt signaling pathway: feasibility of targeting TNIK in colorectal cancer

Wnt signaling is a major force driving colorectal carcinogenesis, but no molecular targeting therapy has yet been established. In the majority of colorectal cancers, the β-catenin destruction complex is not properly formed due to premature termination of the APC (adenomatous polyposis coli) protein (Figure 1), and only the molecules downstream of APC can be considered as targets for Wnt signal blockage. TRAF2 and NCK-interacting protein kinase (TNIK) is a regulator of the β-catenin and TCF4 (T-cell factor-4) transcription complex, the most downstream component of Wnt signaling. TNIK is essential for the full activation of Wnt signal, and colorectal cancer cells are highly dependent on TNIK expression. We have reported some of our research data as evidence for the legitimacy of targeting TNIK in our recent review articles.

Plasma biomarker for detection of early stage pancreatic cancer and risk factors for pancreatic malignancy using antibodies for apolipoprotein-AII isoforms

We previously reported that circulating apolipoprotein AII (apoAII) isoforms apoAII-ATQ/AT (C-terminal truncations of the apoAII homo-dimer) decline significantly in pancreatic cancer and thus might serve as plasma biomarkers for the early detection of this disease. We report here the development of novel enzyme-linked immunosorbent assays (ELISAs) for measurement of apoAII-ATQ/AT and their clinical applicability for early detection of pancreatic cancer.

Plasma and serum concentrations of apoAII-ATQ/AT were measured in three independent cohorts, which comprised healthy control subjects and patients with pancreatic cancer and gastroenterologic diseases (n = 1,156, two Japanese cohorts and one US cohort). These cohorts included 151 cases of stage I/II pancreatic cancer. Significant reductions in apoA2-ATQ/AT levels were recognized in patients with pancreatic cancer in comparison with healthy controls in both independent Japanese cohorts ($P = 1.34 \times 10^{-18}$ and 5.09×10^{-39}). Areas under the receiver operating characteristic curve (AUCs) were > 0.92 for distinguishing patients with stage-I/II pancreatic cancer from healthy controls in the Japanese cohorts. The AUCs of apoA2-ATQ/AT to distinguish patients with pancreatic cancer from healthy controls were higher than those of CA19-9 in both Japanese cohorts. Better discrimination of pancreatic cancer was also observed with apoA2-ATQ/AT than with CA19-9 in the blind test using the pancreatic cancer reference set of NCI EDRN (US National Cancer Institute's Early Detection Research Network) data; combining apoA2-ATQ/AT with CA19-9 led to significantly improved AUC compared to CA19-9 alone. ApoAII-ATQ/AT is a potential biomarker for screening patients for the early stage of pancreatic cancer and identifying patients at risk for pancreatic malignancy.

ACTN4 copy number as a predictive biomarker for chemoradiotherapy of locally advanced pancreatic cancer

The copy number increase (CNI) of *ACTN4* is well known to be a good prognostic biomarker

for some cancers. We evaluated the copy number of *ACTN4* in 91 biopsy specimens of LAPC before treatment using fluorescence in situ hybridisation (FISH) to determine if it could be used as a predictive biomarker for selection of the therapeutic strategy of LAPC. There were no statistically significant differences in overall survival (OS) or progression free survival (PFS) of LAPC between patients treated with chemotherapy alone or with CRT. In a subgroup analysis of patients treated with CRT, patients with a CNI of *ACTN4* had a worse prognosis of OS than patients with a normal copy number (NCN) of *ACTN4* (P = 0.0005 log-rank test). However, OS in the subgroup treated with chemotherapy alone was not significantly different between patients with a CNI and an NCN of *ACTN4*. We concluded that the copy number of *ACTN4* is a predictive biomarker for the decision of a personalized therapeutic strategy for LAPC.

The alternatively spliced actinin-4 variant as a prognostic marker for metastasis in small-cell lung cancer

The alternatively spliced actinin-4 variant (ACTN4va) is expressed in small-cell lung cancer (SCLC) and is thought to be a potential diagnostic marker. However, ACTN4va expression has not been examined in transbronchial biopsy specimens. We retrospectively examined the relationship between ACTN4va expression, clinical factors and survival in 104 consecutive newly diagnosed SCLC patients. Of the 104 screened cases, 83 (median age = 69 years; transbronchial biopsy, 71) were included in our study. Survival was significantly different in the group with no distant metastasis (1996 vs. 422 days, respectively; $P = 0.000115$) but was not significantly different with regard to ACTN4va expression in the group with distant metastasis (293 vs. 254 days, respectively; $P = 0.678$). ACTN4va expression was identifiable in small biopsy samples. ACTN4va expression was also significantly related to distant metastasis and could stratify SCLC patients according to prognosis.

Proteomic analysis of ligamentum flavum from patients with lumbar spinal stenosis

We report a first proteomic analysis of ligamentum flavum from patients with lumbar spinal stenosis. We analyzed 73 ligamentum flavum tissues from patients with lumbar spinal stenosis and lumbar disc herniation, and detected 316 peptides differentially expressed between them using our originally developed proteomic analyzing system 2DICAL (2-dimensional image converted analysis of LC/MS). From the differentially expressed peptides, we found several proteins important for the pathogenesis of ligamentum flavum and confirmed the expression difference by SRM (selected reaction monitoring)/MRM (Multiple Reaction Monitoring) and immunohistochemical study.

ATM and SIRT6/SNF2H Mediate Transient H2AX Stabilization When DSBs Form by Blocking HUWE1 to Allow Efficient gammaH2AX Foci Formation

H2AX was rapidly induced in response to DNA double-strand breaks (DSBs), thereby enabling γ H2AX foci formation and DSB repair. Such rapid H2AX induction resulted from continuous protein production. Synthesized H2AX was ordinarily degraded through the proteasome pathway mediated by the E3 ubiquitin ligase HUWE1. However, this process was transiently halted in response to DSBs, which was mediated by ATM and involved the dissociation of HUWE1 from poly-ubiquitinated H2AX. The serine-139 residue of H2AX was required for such transient H2AX expression and γ H2AX foci formation. Intriguingly, such H2AX expression was required for proper DSB repair even in H2AX-expressing cancer cells, as well as in H2AX-diminished quiescent cells. We contributed the paper for finding HUWE1 by 2DICAL.

Boron-captured neutron therapy

The development of accelerator-based BNCT (boron neutron-capture therapy) system is an ongoing collaborative project of the NCC (National Cancer Center) and industries. For biological evaluation of the safety and effectiveness of this BNCT system, the experimental systems are being set up using mouse models. Melanoma cell lines were evaluated as grafted tumor models in nude mice and further optimized for validation of BNCT effectiveness. The ICP-AES (Inductively

Coupled Plasma Atomic Emission Spectroscopy) procedure to measure the dynamic changes of ^{10}B-para-boronophenylalamine (BPA) in the blood and tumor tissues has been optimized. Biology of boron neutron-capture reaction (BNCR) has been also studied as a collaborative experimental research project of Kyoto University Reactor (KUR). Using SAS (human squamous cell carcinomas derived) cell line, cellular responses, DNA damage induction including γ H2AX foci induction and apoptosis were characterized after BNCR using comprehensive molecular approaches.

A comprehensive analysis of radiosensitization targets

A comprehensive genome-wide screening of targets using lenti virus shRNA library for radiosensitization was conducted with a functional cluster analysis. From the validated targets, we have focused on the DNA methyltransferase 3B (*DNMT3B*) gene, because expression of this gene often showed aberrant overexpression in various types of cancers. The radiosensitization by *DNMT3B* RNAi was caused through impairment of ionizing radiation (IR)-induced HP1 β foci formation, defective γ H2AX signaling and consequent attenuated DNA damage responses after IR. DNMT3B was found to interact with HP1 β in an untreated condition; however, after IR, DNMT3B no longer interacts with HP1 β and is associated with H2AX, suggesting that DNMT3B/H2AX interaction is required for an efficient H2AX accumulation after IR. This study suggests that comprehensive screening with cluster analysis is useful to identify the radiosensitization targets.

The studies on PARP and PARG inhibitors as anti-cancer drug

Poly(ADP-ribose) polymerase (PARP) is frequently upregulated in cancers and is involved in DNA repair. The action mechanism of PARP inhibitors, now approved as an anti-cancer drug, has been further investigated. Dysfunction of poly(ADP-ribose) glycohydrolase (PARG), a main enzyme for poly(ADP-ribose) degradation, suppresses DNA repair and poly(ADP-ribose) accumulation within the cells induces cell death. Development of PARG inhibitors as a potential anti-cancer target has been conducted as a collaboration study. Through comprehensive screening approaches, the genes that affect lethality under PARG functional inhibition have been identified and the mechanism of the synthetic lethality has been investigated.

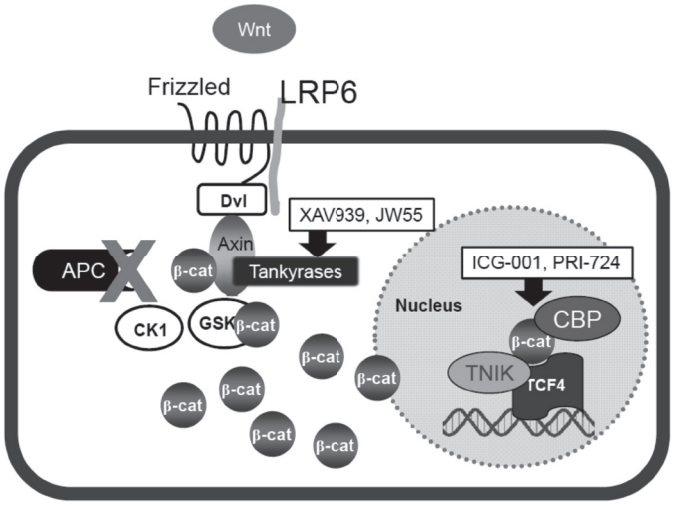


Figure 1. Pharmacological blocking of Wnt signaling has been considered an attractive therapeutic approach for colorectal cancer. TRAF2 and NCK-interacting protein kinase (TNIK) has been identified as a regulatory component of the T-cell factor-4 (TCF4) and β-catenin (β-cat) transcriptional complex. TNIK regulates Wnt signaling in the most downstream part of the pathway, and its inhibition is expected to block the signal even in colorectal cancer cells with *APC* gene mutation.

List of papers published in 2015

Journal

1. Okamoto N, Suzuki H, Kawahara K, Honda K, Miura N, Hirashima T, Tamiya M, Morishita N, Shiroyama T, Tanaka A, Tani E, Hamaguchi M, Kitani M, Yamada T, Kawase I. The alternatively spliced actinin-4 variant as a prognostic marker for metastasis in small-cell lung cancer. Anticancer Res, 35:1663-1667, 2015

2. Miyanaga A, Masuda M, Tsuta K, Kawasaki K, Nakamura Y, Sakuma T, Asamura H, Gemma A, Yamada T. Hippo pathway gene mutations in malignant mesothelioma: revealed by RNA and targeted exon sequencing. J Thorac Oncol, 10:844-851, 2015

3. Fukumoto M, Kurisu S, Yamada T, Takenawa T. α-Actinin-4 enhances colorectal cancer cell invasion by suppressing focal adhesion maturation. PLoS One, 10:e0120616, 2015

4. Arai E, Gotoh M, Tian Y, Sakamoto H, Ono M, Matsuda A, Takahashi Y, Miyata S, Totsuka H, Chiku S, Komiyama M, Fujimoto H, Matsumoto K, Yamada T, Yoshida T, Kanai Y. Alterations of the spindle checkpoint pathway in clinicopathologically aggressive CpG island methylator phenotype clear cell renal cell carcinomas. Int J Cancer, 137:2589-2606, 2015

5. Honda K, Kobayashi M, Okusaka T, Rinaudo JA, Huang Y, Marsh T, Sanada M, Sasajima Y, Nakamori S, Shimahara M, Ueno T, Tsuchida A, Sata N, Ioka T, Yasunami Y, Kosuge T, Miura N, Kamita M, Sakamoto T, Shoji H, Jung G, Srivastava S, Yamada T. Plasma biomarker for detection of early stage pancreatic cancer and risk factors for pancreatic malignancy using antibodies for apolipoprotein-AII isoforms. Sci Rep, 5:15921, 2015

6. Masuda M, Sawa M, Yamada T. Therapeutic targets in the Wnt signaling pathway: Feasibility of targeting TNIK in colorectal cancer. Pharmacol Ther, 156:1-9, 2015

7. Atsumi Y, Minakawa Y, Ono M, Dobashi S, Shinohe K, Shinohara A, Takeda S, Takagi M, Takamatsu N, Nakagama H, Teraoka H, Yoshioka K. ATM and SIRT6/SNF2H Mediate Transient H2AX Stabilization When DSBs Form by Blocking HUWE1 to Allow Efficient γH2AX Foci Formation. Cell Rep, 13:2728-2740, 2015

8. Wang J, Abe M, Sasamoto E, Maeda D, Sugimoto Y, Miki Y, Masutani M. Suppression of γ-irradiation-induced deletion mutations under Parp-1 deficiency in mice. Scholars Acad J Biosci, 3:998-1004, 2015

9. Fujimori H, Sato A, Kikuhara S, Wang J, Hirai T, Sasaki Y, Murakami Y, Okayasu R, Masutani M. A comprehensive analysis of radiosensitization targets; functional inhibition of DNA methyltransferase 3B radiosensitizes by disrupting DNA damage regulation. Sci Rep, 5:18231, 2015

10. Kishi Y, Fujihara H, Kawaguchi K, Yamada H, Nakayama R, Yamamoto N, Fujihara Y, Hamada Y, Satomura K, Masutani M. PARP Inhibitor PJ34 Suppresses Osteogenic Differentiation in Mouse Mesenchymal Stem Cells by Modulating BMP-2 Signaling Pathway. Int J Mol Sci, 16:24820-24838, 2015

11. Sato A, Itoh T, Imamichi S, Kikuhara S, Fujimori H, Hirai T, Saito S, Sakurai Y, Tanaka H, Nakamura H, Suzuki M, Murakami Y, Baiseitov D, Berikkhanova K, Zhumadilov Z, Imahori Y, Itami J, Ono K, Masunaga S, Masutani M. Proteomic analysis of cellular response induced by boron neutron capture reaction in human squamous cell carcinoma SAS cells. Appl Radiat Isot, 106:213-219, 2015

12. Kamita M, Mori T, Sakai Y, Ito S, Gomi M, Miyamoto Y, Harada A, Niida S, Yamada T, Watanabe K, Ono M. Proteomic analysis of ligamentum flavum from patients with lumbar spinal stenosis. Proteomics, 15:1622-1630, 2015

13. Watanabe T, Ueno H, Watabe Y, Hiraoka N, Morizane C, Itami J, Okusaka T, Miura N, Kakizaki T, Kakuya T, Kamita M, Tsuchida A, Nagakawa Y, Wilber H, Yamada T, Honda K. ACTN4 copy number increase as a predictive biomarker for chemoradiotherapy of locally advanced pancreatic cancer. Br J Cancer, 112:704-713, 2015

14. Masuda M, Yamada T. Signaling pathway profiling by reverse-phase protein array for personalized cancer medicine. Biochim Biophys Acta, 1854:651-657, 2015

15. Shiba S, Morizane C, Hiraoka N, Sasaki M, Koga F, Sakamoto Y, Kondo S, Ueno H, Ikeda M, Yamada T, Shimada K, Kosuge T, Okusaka T. Pancreatic neuroendocrine tumors: A single-center 20-year experience with 100 patients. Pancreatology, 16:99-105, 2015

Book

1. Wang J, Sato A, Fujimori H, Miki Y, Masutani M. PARP and carcinogenesis. In: Curtin N, Sharma R (eds), PARP inhibitors for cancer therapy, Switzerland, Humana Press, pp 99-124, 2015

Division of Cancer Pathophysiology

Yasuhito Uezono, Kanako Miyano, Seiji Shiraishi, Sadamoto Zenda, Junko Ezuka, Yukiko Araki, Kiyoshi Terawaki, Katsuya Ohbuchi, Chika Miyagi, Koichiro Minami, Tohru Yokoyama, Satoshi Murakami, Hideya Kokubun, Yoshiyuki Meguro, Akinobu Yokoyama, Hitomi Nishimura, Moeko Eto, Megumi Kawaida, Shiori Sato, Etsuko Nemoto, Hoko Ohguri, Tomoko Matsude, Takamichi Arima, Hirotsugu Kuwata, Yusuke Hamada, Tomoyuki Takahashi, Mio Sekiguchi, Airi Mizukami

Introduction

Since its establishment in January 2009, the Division of Cancer Pathophysiology has focused on two major research issues regarding 1) the improvement of the quality of life (QOL) of patients with cancer suffering from severe or intolerable pain, and 2) the prevention and development of novel treatments for cancer cachexia symptoms. Based on the 2nd Basic Plan to Promote Cancer Control Programs established in Japan in 2012, basic to clinical, and also clinical to basic translational collaborative research with the clinical laboratory groups comprises our main research protocols and has been ongoing. Since 2015, the Chief of this Division holds both the posts in Exploratory Oncology Research and Clinical Trial Center (for phase I clinical study) and Innovation Center for Supportive, Palliative and Psychosocial Care (for phase II and III clinical studies), to accelerate the development of novel drugs for cancer patients.

Routine activities

A weekly conference/research seminar is held with all members including students at the Division of Cancer Pathophysiology.

Research activities

1) Translational research to innovate new strategies to improve pain analgesia in cancer patients

The aim of our studies is to develop new therapies for chemotherapy-induced peripheral neuropathy, and refractory cancer pain, both of which make QOL of cancer patients even worse. One of the targets is oral stomatitis induced by chemotherapy and/or radiotherapy.

The cancer patients who undergo chemotherapy, radiotherapy and terminal palliative care often have a wide range of stomatitis, which induces severe pain and limits the fundamental basics of life such as eating, drinking and talking. On the clinical side, the local anesthetic lidocaine is normally used for the relief of pain in cancer patients with stomatitis. However, lidocaine removes not only pain but also the ability to discriminate taste and texture, since it non-selectively suppresses the activation of all neurons by blocking the voltage-gated Na+ channels. Therefore, a novel analgesic drug, which selectively blocks the pain-related neuron alone, is required to allow patients to eat without losing or changing the taste and texture. Since last year, we have been focusing on a "compound X" as a novel analgesic drug for stomatitis, and evaluated the intensity of oral pain using newly established stomatitis model animals. With the model, as expected, lidocaine not only inhibited pain but also caused numbness in normal oral mucosa. On the contrary, the compound X suppressed the pain in the ulcer without effects on normal tissues. Further, the analgesic effect of the compound X persisted longer than that of lidocaine. Based on our basic research results, we have been developing "the new pain-killer compound X, which can remove the oral pain without changing the texture and taste of food" for cancer patients with severe painful stomatitis, by intellectually and financially supporting the Project Promoting Support for Drug Discovery, Japan Agency for Medical Research and Development.

The second target is severe pain such as one with bone-metastasized patients. We showed that a platelet-activating factor (PAF) receptor antagonist produced profound and long lasting anti-allodynia effects in several different neuropathic pain models in mice. We have demonstrated that

the PAF antagonist showed extremely excellent analgesic effects on both the bone-metastasized cancer pain model and also the chemotherapy-induced peripheral neuropathy model. Further, we discovered that knocking out of inducible PAF synthase type 2 inhibited pain with siRNA technology in mouse models and also the type 2 PAF synthase knockout mice model. These results demonstrated that PAF seems to produce and maintain persistent pain. We now are collaborating with the members of the Department of Lipid Signaling, National Center for Global Health and Medicine to find novel PAF receptor and PAF synthase antagonists.

2) Prevention and decrease of the cachexic symptoms or chemotherapy-induced side effects and also prolonging survival in a mice model of human aging by Japanese traditional KAMPO medicines

We established novel cancer cachexia animal models and then undertook molecular and cellular analyses to identify the mechanisms of action of the expected compounds to improve QOL of patients suffering from cancer cachexia. We found that a Japanese Kampo (traditional Oriental) medicine "rikkunshito" usually administered for the prevention of gastritis, nausea and vomiting, improved the symptoms of cancer cachexia. In addition to rikkunshito, we analyzed and summarized the action mechanisms of other traditional Japanese Kampo medicines to improve chemotherapy-induced side effects such as pain and allodynia.

In addition, we demonstrated that rikkunshito prolonged survival in mouse models of human aging by activation of ghrelin signaling, suggesting that potentiation of this signal with rikkunshito may be useful to extend health and lifespan.

Education

We have three graduate students and 11 students.

Future prospects

The goal of the Division of Cancer Pathophysiology is to improve the QOL of cancer patients.

List of papers published in 2015

Journal

1. Okura D, Horishita T, Ueno S, Yanagihara N, Sudo Y, Uezono Y, Minami T, Kawasaki T, Sata T. Lidocaine preferentially inhibits the function of purinergic P2X7 receptors expressed in *Xenopus* oocytes. Anesth Analg, 120:597-605, 2015

2. Miyano K, Minami K, Yokoyama T, Ohbuchi K, Yamaguchi T, Murakami S, Shiraishi S, Yamamoto M, Matoba M, Uezono Y. Tramadol and its metabolite M1 selectively suppress transient receptor potential ankyrin 1 activity, but not transient receptor potential vanilloid 1 activity. Anesth Analg, 120:790-798, 2015

3. Kubota K, Ohtake N, Ohbuchi K, Mase A, Imamura S, Sudo Y, Miyano K, Yamamoto M, Kono T, Uezono Y. Hydroxy-α sanshool induces colonic motor activity in rat proximal colon: a possible involvement of KCNK9. Am J Physiol Gastrointest Liver Physiol, 308:G579-G590, 2015

4. Suzuki M, Chiwaki F, Sawada Y, Ashikawa M, Aoyagi K, Fujita T, Yanagihara K, Komatsu M, Narita M, Suzuki T, Nagase H, Kushima R, Sakamoto H, Fukagawa T, Katai H, Nakagama H, Yoshida T, Uezono Y, Sasaki H. Peripheral opioid antagonist enhances the effect of anti-tumor drug by blocking a cell growth-suppressive pathway *in vivo*. PLoS One, 10:e0123407, 2015

5. Hitomi S, Ono K, Miyano K, Ota Y, Uezono Y, Matoba M, Kuramitsu S, Yamaguchi K, Matsuo K, Seta Y, Harano N, Inenaga K. Novel methods of applying direct chemical and mechanical stimulation to the oral mucosa for traditional behavioral pain assays in conscious rats. J Neurosci Methods, 239:162-169, 2015

6. Hisaoka-Nakashima K, Miyano K, Matsumoto C, Kajitani N, Abe H, Okada-Tsuchioka M, Yokoyama A, Uezono Y, Morioka N, Nakata Y, Takebayashi M. Tricyclic antidepressant amitriptyline-induced glial cell line-derived neurotrophic factor production involves pertussis toxin-sensitive $G\alpha_{i/o}$ activation in astroglial cells. J Biol Chem, 290:13678-13691, 2015

7. Minami K, Sudo Y, Miyano K, Murphy RS, Uezono Y. μ-Opioid receptor activation by tramadol and O-desmethyltramadol (M1).

J Anesth, 29:475-479, 2015

8. Kitagawa H, Munekage M, Matsumoto T, Sadakane C, Fukutake M, Aoki K, Watanabe J, Maemura K, Hattori T, Kase Y, Uezono Y, Inui A, Hanazaki K. Pharmacokinetic profiles of active ingredients and its metabolites derived from rikkunshito, a ghrelin enhancer, in healthy Japanese volunteers: a crossover, randomized study. PLoS One, 10:e0133159, 2015

9. Yoshimura M, Uezono Y, Ueta Y. Anorexia in human and experimental animal models: physiological aspects related to neuropeptides. J Physiol Sci, 65:385-395, 2015

10. Kono T, Shimada M, Yamamoto M, Kaneko A, Oomiya Y, Kubota K, Kase Y, Lee K, Uezono Y. Complementary and synergistic therapeutic effects of compounds found in Kampo medicine: analysis of daikenchuto. Front Pharmacol, 6:159, 2015

11. Minami K, Ogata J, Uezono Y. What is the main mechanism of tramadol? Naunyn Schmiedebergs Arch Pharmacol, 388:999-1007, 2015

12. Kono T, Suzuki Y, Mizuno K, Miyagi C, Omiya Y, Sekine H, Mizuhara Y, Miyano K, Kase Y, Uezono Y. Preventive effect of oral goshajinkigan on chronic oxaliplatin-induced hypoesthesia in rats. Sci Rep, 5:16078, 2015

Division of Molecular and Cellular Medicine (Ochiya Group)

Takahiro Ochiya, Yusuke Yamamoto, Ryou-u Takahashi, Takeshi Katsuda, Yusuke Yoshioka, Ayako Inoue, Kana Kurosaki, Mayuko Yamamura, Luc Nicolas Gailhouste, Ai Hironaka, Satomi Fukuda, Takumi Sonoda, Hiroko Tadokoro, Juntaro Matsuzaki, Akira Yokoi, Yutaka Nezu, Mizuyo Arashi, Naomi Nomura, Teruko Yamaguchi, Kazumi Nagao, Satoko Takizawa, Yutaka Naito, Maki Abe, Kurataka Otsuka, Nao Nishida, Tsukasa Kadota, Makiko Ichikawa, Naoomi Tominaga, Liew Lee Chuen, Hayato Kurata, Yumi Kawamura

Introduction

The focus of the Division of Molecular and Cellular Medicine lies in the development of novel treatments and diagnosis against cancer. The specific activities are as follows: 1) studies on microRNA (miRNA) regulation in cancer cells and development of RNA interference (RNAi)-based therapeutics; 2) an exosome as a novel diagnosis and therapeutic tool against cancer; 3) the study of stem cells and their therapeutic applications.

Research activities

1) Studies on miRNA regulation in cancer cells and development of RNAi-based therapeutics.

RNAi-based therapeutics is a promising approach as a novel and potentially more effective treatment for cancer, and miRNA is one of the targets involved in the regulation of tumor-related genes（Urata, Sci Rep, Osaki Ther Deliv）.

By screening with the natural substance library, three compounds were identified as inducers of miR-200c in breast cancer cells (Hagiwara, Sci Rep).

The up-regulation of miR-200c suppressed the invasiveness of cancer cells mediated by ZEB1 inhibition and E-cadherin induction. We identified an miR-197/CKS1B/STAT3-mediated PD-L1 network in chemoresistant NSCLC. miR-197 is downregulated in platinum-resistant NSCLC specimens, resulting in the promotion of chemoresistance, tumorigenicity, and pulmonary metastasis in vitro and in vivo (Fujita, Mol Ther).

We previously demonstrated that silencing of RPN2 efficiently reduced resistance to docetaxel in human breast cancer cells. Recently, we also reported the clinical and functional correlations of RPN2 expression in lung cancer (Fujita, Int J Mol Sci, Fujita, Oncotarget). Higher RPN2 expression was significantly correlated with poor prognosis (Ono, Pathol Int). In July 2015, an investigator-initiated clinical trial (first-in-human phase I study) with intratumoral administration of RPN2-siRNA for treatment-resistant breast cancer was started at the National Cancer Center (NCC) Hospital.

2) Exosomes as a novel diagnosis and therapeutic tool against cancer

The circulating exosomes could be found in a variety of body fluids including serum, plasma, urine, saliva, and breast milk (Nishida-Aoki, CMLS). The existence of circulating exosomes in the blood of cancer patients has raised the possibility that exosomes may serve as a novel diagnostic marker.

To more precisely understand the functions of circulating miRNAs and extracellular vesicles in cancer biology, we developed a mouse model for brain metastasis using breast cancer cells and identified cancer-derived extracellular vesicles containing mir-181c, which trigger the breakdown of the blood-brain barrier (BBB). Importantly, miR-181c promotes the destruction of BBB through the abnormal localization of actin via the downregulation of its target gene, PDPK1, whose degradation leads to the downregulation of phosphorylated cofilin and the resultant activated cofilin-induced modulation of actin dynamics (Tominaga, Nat. Commun.).

Also, we have conducted a proteomics approach to reveal a molecular mechanism in which miRNA is transferred into extracelluar vesicles and identified Annexin A2 as a key player in this approach (Hagiwara, FEBS lett.).

We showed that suppression of autophagy by extracellular vesicles promotes myofibroblast

differentiation in chronic obstructive pulmonary disease (COPD) pathogenesis (Fujita, J Extracell Vesicles). These findings prompted us to consider the application of exosomes in diagnosis and therapy against cancer development (Tominaga, Adv Drug Deliv Rev; Fujita, Trends Mol Med; Lener, J Extracell Vesicles).

3) Molecular analysis of cancer stem cells governing breast cancer generation and related miRNAs

While cancer stem cell (CSC) properties such as tumorigenicity and drug resistance are a major focus in current cancer research, the molecular mechanisms for the regulation of CSC properties are not fully understood. MicroRNA (miRNA) is identified as the targets involved in the regulation of CSC properties (Osaki, Ther Deliv; Takahashi Cancers (Basel)). We identified microRNA-27b (miR-27b) as a key regulator for the generation of a side-population in breast cancer cells that showed CSC properties, and also found that the anti-type II diabetes (T2D) drug metformin reduced this side-population via miR-27b-mediated repression of ENPP1, which is involved in T2D development (Takahashi, Nat. Commun.). We found that some specific miRNAs played an important role in the acquisition of CSC properties. Therefore, these results suggest that conventional cancer therapy with modulation of the expression of miRNA may eradicate CSC fraction and improve the treatment of cancer patients.

4) Chemical reprogramming of adult hepatocytes modelling for hepatocellular carcinomas

We are interested in modelling hepatocellular carcinomas utilizing chemically-induced liver progenitor cells. Recently, we have developed a highly efficient strategy for small molecular cocktail-enabled mature hepatocytes to reprogram bi-potential liver progenitor cells. Also, we have established an orthotopic transplantation method for reprogrammed liver progenitor cells that showed remarkably high repopulation rates. Combining these techniques, our main focus is on the elucidation of the multi-step carcinogenesis process of normal liver cells to hepatocellular carcinomas.

List of papers published in 2015

Journal

1. Hagiwara K, Katsuda T, Gailhouste L, Kosaka N, Ochiya T. Commitment of Annexin A2 in recruitment of microRNAs into extracellular vesicles. FEBS Lett, 589:4071-4078, 2015

2. Naito Y, Tanaka Y, Ochiya T. microRNAs and Hepatitis B. Adv Exp Med Biol, 888:389-399, 2015

3. Lener T, Gimona M, Aigner L, Börger V, Buzas E, Camussi G, Chaput N, Chatterjee D, Court FA, Del Portillo HA, O'Driscoll L, Fais S, Falcon-Perez JM, Felderhoff-Mueser U, Fraile L, Gho YS, Görgens A, Gupta RC, Hendrix A, Hermann DM, Hill AF, Hochberg F, Horn PA, de Kleijn D, Kordelas L, Kramer BW, Krämer-Albers EM, Laner-Plamberger S, Laitinen S, Leonardi T, Lorenowicz MJ, Lim SK, Lötvall J, Maguire CA, Marcilla A, Nazarenko I, Ochiya T, Patel T, Pedersen S, Pocsfalvi G, Pluchino S, Quesenberry P, Reischl IG, Rivera FJ, Sanzenbacher R, Schallmoser K, Slaper-Cortenbach I, Strunk D, Tonn T, Vader P, van Balkom BW, Wauben M, Andaloussi SE, Théry C, Rohde E, Giebel B. Applying extracellular vesicles based therapeutics in clinical trials - an ISEV position paper. J Extracell Vesicles, 4:30087, 2015

4. Fujita Y, Araya J, Ochiya T. Extracellular vesicles in smoking-related lung diseases. Oncotarget, 6:43144-43145, 2015

5. Fujita Y, Kuwano K, Ochiya T. Development of small RNA delivery systems for lung cancer therapy. Int J Mol Sci, 16:5254-5270, 2015

6. Fujita Y, Yagishita S, Takeshita F, Yamamoto Y, Kuwano K, Ochiya T. Prognostic and therapeutic impact of RPN2-mediated tumor malignancy in non-small-cell lung cancer. Oncotarget, 6:3335-3345, 2015

7. Nishida-Aoki N, Ochiya T. Interactions between cancer cells and normal cells via miRNAs in extracellular vesicles. Cell Mol Life Sci, 72:1849-1861, 2015

8. Ishikawa T, Kobayashi M, Yanagi S, Kato C, Takashima R, Kobayashi E, Hagiwara K, Ochiya T. Human Induced Hepatic Lineage-Oriented Stem Cells: Autonomous Specification of Human iPS Cells toward Hepatocyte-Like Cells without Any Exogenous Differentiation Factors. PLoS One, 10:e0123193, 2015

9. Tominaga N, Kosaka N, Ono M, Katsuda T, Yoshioka Y, Tamura K, Lötvall J, Nakagama H, Ochiya T. Brain metastatic cancer cells release microRNA-181c-containing extracellular vesicles capable of destructing blood-brain barrier. Nat Commun, 6:6716, 2015

10. Takahashi RU, Miyazaki H, Ochiya T. The roles of microRNAs in breast cancer. Cancers (Basel), 7:598-616, 2015

11. Sugimachi K, Matsumura T, Hirata H, Uchi R, Ueda M, Ueo H, Shinden Y, Iguchi T, Eguchi H, Shirabe K, Ochiya T, Maehara Y, Mimori K. Identification of a bona fide microRNA biomarker in serum exosomes that predicts hepatocellular carcinoma recurrence after liver transplantation. Br J Cancer, 112:532-538, 2015

12. Fujita Y, Yagishita S, Hagiwara K, Yoshioka Y, Kosaka N, Takeshita F, Fujiwara T, Tsuta K, Nokihara H, Tamura T, Asamura H, Kawaishi M, Kuwano K, Ochiya T. The clinical relevance of the miR-197/CKS1B/STAT3-mediated PD-L1 network in chemoresistant non-small-cell lung cancer. Mol Ther, 23:717-727, 2015

13. Osaki M, Okada F, Ochiya T. miRNA therapy targeting cancer stem cells: a new paradigm for cancer treatment and prevention of tumor recurrence. Ther Deliv, 6:323-337, 2015

14. Akagi T, Kato K, Kobayashi M, Kosaka N, Ochiya T, Ichiki T. On-chip immunoelectrophoresis of extracellular vesicles released from human breast cancer cells. PLoS One, 10:e0123603, 2015

15. Takahashi RU, Miyazaki H, Takeshita F, Yamamoto Y, Minoura K, Ono M, Kodaira M, Tamura K, Mori M, Ochiya T. Loss of microRNA-27b contributes to breast cancer stem cell generation by activating ENPP1. Nat Commun, 6:7318, 2015

16. Fujita T, Chiwaki F, Takahashi RU, Aoyagi K, Yanagihara K, Nishimura T, Tamaoki M, Komatsu M, Komatsuzaki R, Matsusaki K, Ichikawa H, Sakamoto H, Yamada Y, Fukagawa T, Katai H, Konno H, Ochiya T, Yoshida T, Sasaki H. Identification and Characterization of CXCR4-Positive Gastric Cancer Stem Cells. PLoS One, 10:e0130808, 2015

17. Matsumura T, Sugimachi K, Iinuma H, Takahashi Y, Kurashige J, Sawada G, Ueda M, Uchi R, Ueo H, Takano Y, Shinden Y, Eguchi H, Yamamoto H, Doki Y, Mori M, Ochiya T, Mimori K. Exosomal microRNA in serum is a novel biomarker of recurrence in human colorectal cancer. Br J Cancer, 113:275-281, 2015

18. Ochiya T, Takenaga K, Asagiri M, Nakano K, Satoh H, Watanabe T, Imajoh-Ohmi S, Endo H. Efficient inhibition of tumor angiogenesis and growth by a synthetic peptide blocking S100A4-methionine aminopeptidase 2 interaction. Mol Ther Methods Clin Dev, 2:15008, 2015

19. Ono M, Tsuda H, Kobayashi T, Takeshita F, Takahashi RU, Tamura K, Akashi-Tanaka S, Moriya T, Yamasaki T, Kinoshita T, Yamamoto J, Fujiwara Y, Ochiya T. The expression and clinical significance of ribophorin II (RPN2) in human breast cancer. Pathol Int, 65:301-308, 2015

20. Fujita Y, Kosaka N, Araya J, Kuwano K, Ochiya T. Extracellular vesicles in lung microenvironment and pathogenesis. Trends Mol Med, 21:533-542, 2015

21. Tominaga N, Katsuda T, Ochiya T. Micromanaging of tumor metastasis by extracellular vesicles. Semin Cell Dev Biol, 40:52-59, 2015

22. Tokuhisa M, Ichikawa Y, Kosaka N, Ochiya T, Yashiro M, Hirakawa K, Kosaka T, Makino H, Akiyama H, Kunisaki C, Endo I. Exosomal miRNAs from peritoneum lavage fluid as potential prognostic biomarkers of peritoneal metastasis in gastric cancer. PLoS One, 10:e0130472, 2015

23. Izumi H, Tsuda M, Sato Y, Kosaka N, Ochiya T, Iwamoto H, Namba K, Takeda Y. Bovine milk exosomes contain microRNA and mRNA and are taken up by human macrophages. J Dairy Sci, 98:2920-2933, 2015

24. Katsuda T, Oki K, Ochiya T. Potential application of extracellular vesicles of human adipose tissue-derived mesenchymal stem cells in Alzheimer's disease therapeutics. Methods Mol Biol, 1212:171-181, 2015

25. Kawaharada K, Kawamata M, Ochiya T. Rat embryonic stem cells create new era in development of genetically manipulated rat models. World J Stem Cells, 7:1054-1063, 2015

26. Urata YN, Takeshita F, Tanaka H, Ochiya T, Takimoto M. Targeted knockdown of the kinetochore protein D40/Knl-1 inhibits human cancer in a p53 status-independent manner. Sci Rep, 5:13676, 2015

27. Kosaka T, Davydova J, Ono HA, Akiyama H, Hirai S, Ohno S, Takeshita F, Aoki K, Ochiya T, Yamamoto M, Kunisaki C, Endo I. Imaging and antitumoral effect of a cyclo-oxygenase 2-specific replicative adenovirus for small metastatic gastric cancer lesions. Anticancer Res, 35:5201-5210, 2015

28. Hagiwara K, Gailhouste L, Yasukawa K, Kosaka N, Ochiya T. A robust screening method for dietary agents that activate tumour-suppressor microRNAs. Sci Rep, 5:14697, 2015

29. Murakami Y, Kubo S, Tamori A, Itami S, Kawamura E, Iwaisako K, Ikeda K, Kawada N, Ochiya T, Taguchi YH. Comprehensive analysis of transcriptome and metabolome analysis in Intrahepatic Cholangiocarcinoma and Hepatocellular Carcinoma. Sci Rep, 5:16294, 2015

30. Yokoi A, Yoshioka Y, Ochiya T. Towards the realization of clinical extracellular vesicle diagnostics: challenges and opportunities. Expert Rev Mol Diagn, 15:1555-1566, 2015

31. Tominaga N, Yoshioka Y, Ochiya T. A novel platform for cancer therapy using extracellular vesicles. Adv Drug Deliv Rev, 95:50-55, 2015

32. Fujita Y, Araya J, Ito S, Kobayashi K, Kosaka N, Yoshioka Y, Kadota T, Hara H, Kuwano K, Ochiya T. Suppression of autophagy by extracellular vesicles promotes myofibroblast differentiation in COPD pathogenesis. J Extracell Vesicles, 4:28388, 2015

33. Katsuda T, Ochiya T. Molecular signatures of mesenchymal stem cell-derived extracellular vesicle-mediated tissue repair. Stem Cell Res Ther, 6:212, 2015

Book

1. Yoshioka Y, Katsuda T, Ochiya T. Circulating microRNAs as hormones: intercellular and inter-organ conveyors of epigenetic information? In: Igaz P (ed), Circulating microRNAs in disease diagnostics and their potential biological relevance, Switzerland, Springer Basel, pp 255-267, 2015

2. Fujiwara T, Fujita Y, Nezu Y, Kawai A, Ozaki T, Ochiya T. MicroRNAs in boen and soft tissue sarcoma and their values as biomarkers. In: García-Giménez JL (ed), Epigenetic Biomarkers and Diagnostics, 1st Edition, UK, USA, Academic Press, pp 613-635, 2015

Division of Molecular and Cellular Medicine (Aoki Group)

Kazunori Aoki, Chie Kudo, Kenta Narumi, Yoko Kobayashi, Yukihiro Mizoguchi , Ryousuke Ueda, Hisayoshi Hashimoto, Yuki Yamamoto, Yosei Rin, Masaki Nagasato, Chihiro Shibasaki, Marina Henmi

Introduction

Research programs in the Division of Molecular and Cellular Medicine (Aoki group) consist of development of novel therapeutic strategies for solid cancers based on the analysis of host-immune response against cancer cells and exploitation of cancer-targeting technologies. The specific activities in 2015 were as follows: 1) Clarification of immunological effects of myeloid-derived suppressor cells (MDSC) and type I neutrophils on antitumor immune reaction induced by immune therapies; and 2) Identification of cancer-targeting peptides using the peptide-display adenovirus library.

Research activities

Immunological effects of MDSC and neutrophils on antitumor immune reaction

We investigated the immunological effect of myeloid lineage cells such as MDSC and neutrophils in the tumor microenvironment on antitumor immune reaction induced by chemotherapy and hematopoietic stem cell transplantation.

1) Some anti-cancer drugs have been found to induce positive immune reactions against cancers, leading to the new concept of "chemo-immunotherapy". We found that the high frequency of MDSC in peripheral blood and tumor tissue was strongly associated with poor survival in patients with colorectal cancer who received the standard chemotherapy. Then, we examined whether the chemotherapy-induced tumor immunity is enhanced by the depletion of MDSC in murine colon cancer models. An Ly6G antibody was used to deplete MDSC. The tumor growth was retarded in treatment of 5-FU and Ly6G antibody alone, while a combination more strongly suppressed the growth (Figure. 1). In the spleens of 5-FU-treated mice, the number of AH-1 tetramer$^+$ cells was increased. The combination increased more the number of AH-1$^+$ cells in spleens and IFN-γ^+ CD8$^+$ T cells in tumors. In addition, the frequency of CD107a$^+$ NK cells/total NK cells was also increased by the combination. The results suggested that a combination of chemotherapy and inhibition of immune suppressive cells is a promising strategy in inducing strong tumor immunity.
2) It was reported that autologous hematopoietic stem cell transplantation (HSCT) also can induce a strong antitumor immunity following preconditioning-induced lymphopenia. However, the underlying mechanisms were fully understood. First, we showed that syngeneic HSCT-activated NK cells contributed to an antitumor effect using mouse colon cancer models. Then, we examined what factor influenced the activation of NK cells in tumors. We found that a large number of neutrophils accumulated in tumors especially in the early period after HSCT. The depletion of neutrophils significantly decreased the antitumor effect of HSCT. The fraction of IFN-γ^+ NK cells was clearly elevated in HSCT tumors compared with non-HSCT tumors, and the neutrophil depletion decreased the IFN-γ^+ fraction. The fraction of dead NK cells in the tumor was significantly increased by the neutrophil depletion (Figure. 2). The results indicated that neutrophils in tumors prevented NK cells from cell-death induction during homeostatic proliferation. This relationship between neutrophils and NK cells may reveal an important aspect of antitumor immunity.

Identification of cancer-targeting ligands using the peptide-display adenovirus library

The cancer-targeting ligands are useful to deliver

therapeutic reagents such as chemotherapeutic drugs, molecular targeted drugs, gene therapy vectors and oncolytic viruses to tumor regions in vivo. To identify the cancer-targeting ligands, we have constructed an adenovirus library displaying random peptides on the fiber, and have developed the screening procedures on cancer cell lines and murine cancer models. This year, we successfully isolated pancreatic and prostate cancer-targeting peptides and confirmed the specificity and effectiveness of targeting ligands on several cancer and normal cell lines. Furthermore, we began to develop the system to comprehensively explore the cognate receptors of identified targeting-ligands using the Human Proteome Expression Resource in collaboration with the National Institute of Advanced Industrial Science and Technology. The identification of cancer-targeting ligands and their cellular receptors are useful to develop novel diagnostic and therapeutic strategies for cancer.

Education

Two graduate students (doctoral course) linked with Keio University, three graduate students (doctoral course: one, master's course: two) linked with Tokyo Medical and Dental University and the undergraduate students in Tokyo University of Pharmacy and Life Sciences studied cancer immunology and cancer-targeted therapy in our laboratory.

Future prospects

We are investigating the molecular basis of an immune-suppressive microenvironment and the interaction between cancer cells, stromal cells and immune cells in a tumor microenvironment, which may open a new perspective on immune therapy for cancer. In addition, tumor-targeting ligands are also promising as a next-generation of molecular targeting therapy.

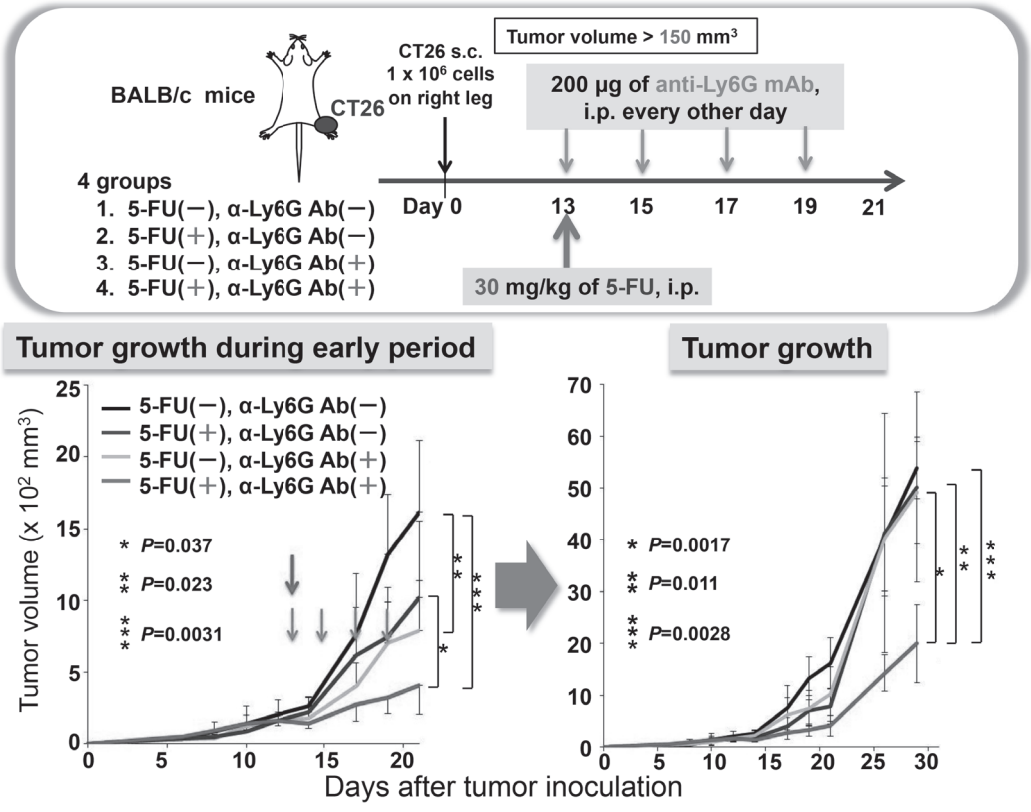


Figure 1. MDSC Depletion Enhanced 5-FU-mediated Antitumor Effect

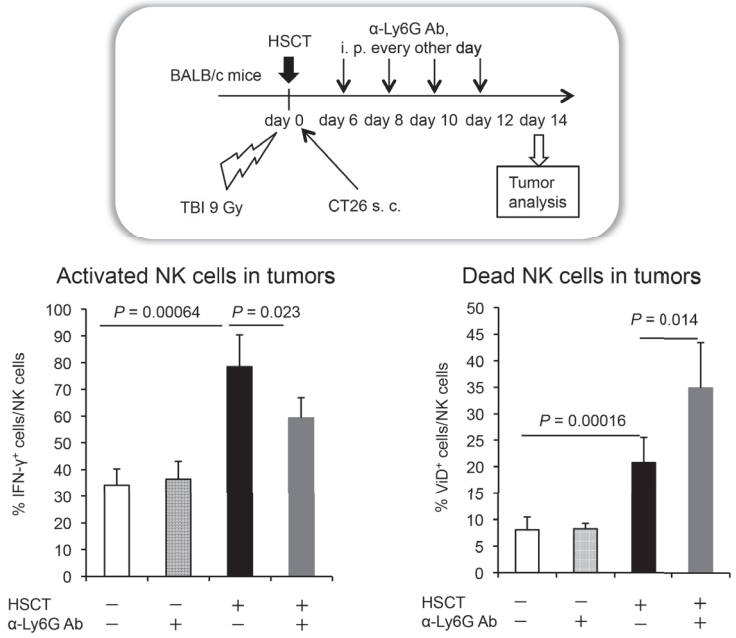


Figure 2. Neutrophils in tumors prevent NK cells from activation-induced cell death during HP

List of papers published in 2015

Journal

1. Narumi K, Miyakawa R, Ueda R, Hashimoto H, Yamamoto Y, Yoshida T, Aoki K. Proinflammatory Proteins S100A8/S100A9 Activate NK Cells via Interaction with RAGE. J Immunol, 194:5539-5548, 2015

2. Terracina KP, Aoyagi T, Huang WC, Nagahashi M, Yamada A, Aoki K, Takabe K. Development of a metastatic murine colon cancer model. J Surg Res, 199:106-114, 2015

3. Kudo-Saito C. Cancer-associated mesenchymal stem cells aggravate tumor progression. Front Cell Dev Biol, 3:23, 2015

4. Tanaka Y, Aoyagi K, Minashi K, Komatsuzaki R, Komatsu M, Chiwaki F, Tamaoki M, Nishimura T, Takahashi N, Oda I, Tachimori Y, Arao T, Nishio K, Kitano S, Narumi K, Aoki K, Fujii S, Ochiai A, Yoshida T, Muto M, Yamada Y, Sasaki H. Discovery of a Good Responder Subtype of Esophageal Squamous Cell Carcinoma with Cytotoxic T-Lymphocyte Signatures Activated by Chemoradiotherapy. PLoS One, 10:e0143804, 2015

5. Kosaka T, Davydova J, Ono HA, Akiyama H, Hirai S, Ohno S, Takeshita F, Aoki K, Ochiya T, Yamamoto M, Kunisaki C, Endo I. Imaging and antitumoral effect of a cyclo-oxygenase 2-specific replicative adenovirus for small metastatic gastric cancer lesions. Anticancer Res, 35:5201-5210, 2015

Book

1. Kawakami Y, Qian L, Kawamura N, Miyazaki J, Tsubota K, Kinoshita T, Nakaura K, Ohmura G, Satomi R, Sugiyama J, Nishio H, Hayakawa T, Popivanova B, Nuchsupha S, Liu TH, Kamijuku H, Kudo-Saito C, Tsukamoto N, Sakurai T, Fujita T, Yaguchi T. Cancer induced immunosuppression and its modulation by signal inhibitors. In: Bonavida B, Chouaib S (eds), Resistance of Cancer Cells to CTL-Mediated Immunotherapy, Switzerland, Springer International Publishing, pp 287-301, 2015

2. Kawakami Y, Qian L, Kawamura N, Miyazaki J, Nagumo H, Tsubota K, Kinoshita T, Nakamura K, Ohmura G, Satomi R, Sugiyama J, Nishio H, Hayakawa T, Popivanova B, Nuchsupha S, Liu TH, Kamijuku H, Kudo-Saito C, Tsukamoto N, Sakurai T, Fujita T, Yaguchi T. Development of personalized combination cancer immunotherapy based on the patients' immune status. In: Seya T, Matsumoto M, Udaka K, Sato N (eds), Inflammation and Immunity in Cancer, Japan, Springer Japan, pp 255-266, 2015

Division of Rare Cancer Research

Tadashi Kondo, Xiaoqing Pan, Rieko Ohki

Introduction

The research goal of the Division of Rare Cancer Research is to create the innovative seeds for better clinical outcomes for rare cancer patients. A rare cancer is defined as a cancer with prevalence of less than six. Rare cancer includes about 200 cancer types, and despite the rarity of each rare cancer, the rare cancers represent in total about 20% of all cancer cases in Japan. Thus, the rare cancer research deals with a wide-ranging subject. Although the research themes of rare cancer research are quite general ones such as those for prevention, diagnosis and treatment, as the clinical materials of rare cancers are limited, we need to make a special effort for rare cancer research. With this notion, the fundamental tools were created for rare cancer research. The establishment of the patient-derived cancer model, and the database for meta-analysis of genes are the efforts to solve the problems of the limited amount of clinical material. Re-localization of cancer drugs is a practical approach to rare cancer, and the experimental systems for re-localization of cancer drugs were created in our laboratory. Those include the high-throughput screening system and the application of Connectivity Map. Sarcomas are the major subjects of our rare cancer research, and the identification of candidates of therapeutic targets and biomarkers were undertaken. The predictive and prognostic biomarkers are the subjects of our research. Moreover, through the above-mentioned approach, we are discovering the novel utility of existing cancer drugs for rare cancers. Our experience and fundamental systems for rare cancer research will be applicable for major cancer research.

Research activities

1) Establishment of fundamental research system
   - Patient-derived cancer models were created from the clinical materials of sarcoma patients.
   - Screening system for the study of re-localization of cancer drugs was established and used for the cell panel.
   - Platform of bioinformatics such as the original Connectivity Map was created and applied to the study of re-localization of cancer drugs.
   - Database of gene status of rare cancer was created using bioinformatics approach.

2) Study of individual rare cancer

Sarcomas are presently major subjects of our rare cancer research. The identification of therapeutic targets and biomarkers was undertaken using clinical materials. The biomarker candidates to predict the resistance of molecular targeting drugs such as those used for sarcomas were identified by a multi-omics approach. Their molecular backgrounds and validation using additional cases are under consideration.

3) Reverse innovation

The research platforms were developed with the idea that they will be applicable to other malignancies.

Education

One PhD student and two post-doctorate researchers were educated.

Future prospects

Our research activities will benefit patients with rare cancers. The fundamental system for rare cancer research will be applicable to the research of all cancers.

List of papers published in 2015

Journal

1. Tajima T, Kito F, Ohta T, Kawai A, Kondo T. Interactome analysis reveals molecular mechanisms underlying the association between selenium binding protein 1 expression and the malignant features of tumor cells. J Electrophoresis, 59:1-6, 2015

2. Uemura N, Kondo T. Current advances in esophageal cancer proteomics. Biochim Biophys Acta, 1854:687-695, 2015

3. Fujita T, Yuno M, Okuzaki D, Ohki R, Fujii H. Identification of non-coding RNAs associated with telomeres using a combination of enChIP and RNA sequencing. PLoS One, 10:e0123387, 2015

4. Kikuta K, Morioka H, Kawai A, Kondo T. Global protein-expression profiling for reclassification of malignant fibrous histiocytoma. Biochim Biophys Acta, 1854:696-701, 2015

5. Ichikawa H, Yoshida A, Kanda T, Kosugi S, Ishikawa T, Hanyu T, Taguchi T, Sakumoto M, Katai H, Kawai A, Wakai T, Kondo T. Prognostic significance of promyelocytic leukemia expression in gastrointestinal stromal tumor; integrated proteomic and transcriptomic analysis. Cancer Sci, 106:115-124, 2015

Book

1. Kondo T. Novel prognostic biomarker, pfetin, in gastrointestinal stromal tumors: proteomics study. In: Victor RP, Vinood BP (eds), General methods in biomarker research and their applications 1st Edition, Netherlands, Springer Netherlands, pp 251-266, 2015

Division of Refractory and Advanced Cancer

Ryuichi Sakai, Hideki Yamaguchi, Masato Enari, Takuya Shirakihara, Katsuhiko Nakashima, Yumi Hasegawa, Ryo Otomo, Emi Saito, Yuko Hibiya

Introduction

The malignant characteristics of cancers causing invasion into surrounding tissue, metastasis to distant organs, and acquired resistance to therapeutics are serious threats to the clinical treatment of cancer. A number of receptor and non-receptor tyrosine kinases are involved in the acquisition of such malignant characteristics. Signals from activated tyrosine kinases are mediated through phosphorylation of substrate molecules to modulate cell characteristics during tumor proliferation and metastasis. The main object of our Division is to elucidate the roles of signaling molecules during cancer metastasis, invasion and drug resistance. One of the goals of our research is to establish models of novel therapy to overcome these malignant characteristics of progressed cancers by targeting critical proteins and signals involved in these procedures.

Routine activities

A weekly conference is held with the members of the Division of Refractory and Advanced Cancer. In addition, a monthly progress report is held with the members of the research institute.

Research activities

Molecules and Microenvironments regulating Metastasis and Invasion of Cancers

Scirrhous gastric carcinoma (SGC) show rapid expansion through progressive invasion, peritoneal dissemination and frequent metastasis to lymph nodes. Receptor tyrosine kinases such as fibroblast growth factor receptors (FGFRs) and Met are frequently activated in SGC and the contribution of signaling from these kinases to unique clinical aspects of SGC are suggested. We have recently identified numbers of phosphotyrosine-containing molecules under the regulation of these receptor tyrosine kinases by mass-spectrometry analysis. The function of these potent signal mediators involved in progression of SGC are being investigated.

It was revealed that the interaction of lung cancer with fibroblasts participates in the malignancy of lung cancer and that some factors secreted from cancer cells inactivate the p53 pathway in fibroblasts. Furthermore, we identified TSPAN12 as a factor that induced p53 inactivation in fibroblasts to promote cancer progression.

CDCP1 is a critical regulator of anoikis resistance, distant metastasis, and peritoneal dissemination of cancer cells. It was also shown that CDCP1 is required for the functional link between Ras and Src signaling during the multistage progression of human malignant tumors. Therapeutic antibodies and chemicals that block CDCP1-mediated signaling are being screened and several candidates were obtained.

In collaboration with Rome University, we found that clathrin heavy chain, which plays a role in endocytosis and p53 transactivation, interacts with the estrogen receptor, which leads to sustained signals from estrogen.

Regulation of Anaplastic Lymphoma Kinase (ALK) activity and drug resistance in cancers

ALK fusion-positive lung adenocarcinoma cell lines were successfully established from patients and it was revealed by utilizing these cells that the combination of the ALK inhibitor with the p53 activator can reduce the resistance of ALK fusion-positive lung cancer cells to the ALK inhibitor. In addition, the combination treatment of the ALK inhibitor with the p53 activator was also effective in the ALK-positive neuroblastoma.

Flotillin-1 (FLOT1), a plasma-membrane-localizing protein, and SHP2/PTPN11, a tyrosine

phosphatase, were identified as the ALK-binding tyrosine-phosphorylated proteins in neuroblastoma. It was revealed that FLOT1 negatively regulates ALK expression and signaling via endocytosis. It was shown that SHP2 is tyrosine-phosphorylated by ALK and appears to mediate the ALK-dependent oncogenic property of NB-39-nu cells, while SHP2 induces dephosphorylation of ALK protein. Our findings suggest that the loss of FLOT1-mediated regulation of ALK or enhanced expression of SHP2 contributes to malignancy of clinical neuroblastoma cases and those cases might be sensitive to ALK inhibitors even without the genetic alteration of ALK.

Education

We accept students or graduate students as trainees from various institutes including the University of Tokyo and educate future basic cancer researchers. We also make efforts in the education of young post-doctoral researchers.

Future prospects

In patients with advanced stages of cancers, the control of metastasis, invasion and drug resistance is crucial for maintaining quality of life (QOL) in addition to prolonged survival. Our approach to elucidate the underlying mechanism of these malignant characteristics of cancers will give us ways to develop novel therapeutic strategies for advanced cancers. Especially, identification of molecules and signals involved in drug resistance and cancer-stromal interaction will be intensively studied to find novel approaches to overcome refractory cancers.

List of papers published in 2015

Journal

1. Totta P, Pesiri V, Enari M, Marino M, Acconcia F. Clathrin heavy chain interacts with estrogen receptor α and modulates 17β-estradiol signaling. Mol Endocrinol, 29:739-755, 2015
2. Ueno H, Tomiyama A, Yamaguchi H, Uekita T, Shirakihara T, Nakashima K, Otani N, Wada K, Sakai R, Arai H, Mori K. Augmentation of invadopodia formation in temozolomide-resistant or adopted glioma is regulated by c-Jun terminal kinase-paxillin axis. Biochem Biophys Res Commun, 468:240-247, 2015
3. Yamaguchi H, Sakai R. Direct interaction between carcinoma cells and cancer associated fibroblasts for the regulation of cancer invasion. Cancers (Basel), 7:2054-2062, 2015

Division of Cancer Immunology

Hitoshi Nakagama, Yuka Maeda

Introduction

Our Division was established in April 2015. The recent success of cancer immunotherapy makes it an important strategy for cancer treatment, and a lot of clinical trials are ongoing to develop new reagents. However, not all subjects expect to derive therapeutic benefits; in some patients it does not work. Based on our previous work, we found that regulatory T cells rendered self-tumor-antigen-specific $CD8^+$ T cells anergic (that is, hypo-proliferative and cytokine hypo-producing upon antigen re-stimulation) to maintain self-tolerance (Maeda Y et al. *Science*, 346:1536-40, 2014).

Research activities

1) Clarify immune suppressive mechanism of Tregs at tumor sites with melanoma samples.
2) Analyze immunologically and pathologically BRAF mutated melanoma pre-and post-treated with a BRAF inhibitor.

Future prospects

As most tumor antigens are derived from self-antigens, immunological self-tolerance induced by natural occurring Tregs may hamper the induction of effective anti-tumor T-cell responses. When responder patients with non-small cell lung cancers treated with anti-PD-1 mAb were examined by whole-exome sequencing, $CD8^+$ T-cells mainly recognized antigens generated by tumor-specific mutations (neo-antigens) (Rizvi NA…Maeda Y.. et al. Science, 348:124-128, 2015). Therefore, Tregs-mediated anergy induction in tumor (self) antigen-specific $CD8^+$ T cells may inhibit their activation, and neo-antigens stemmed from tumor-specific gene mutations could become the main target of $CD8^+$ T cells that actually induce tumor regression. We reveal Treg suppressive mechanisms against anti-tumor responses in tumor local sites and offer new combination immunotherapy.

List of papers published in 2015

Journal

1. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN, Chan TA. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science, 348:124-128, 2015

Research Support Division

Teruhiko Yoshida, Tesshi Yamada, Toshio Imai, Issay Kitabayashi, Tatsuhiro Shibata, Hiromi Sakamoto, Fumie Hosoda, Yae Kanai, Hitoshi Ichikawa, Hiroki Sasaki, Yasuhito Arai, Masaya Ono, Tadashi Kondo, Mami Takahashi, Yoshinori Ikarashi, Takuo Katsumoto, Koji Okamoto, Tetsuya Ishikawa

Introduction

The concept of the Research Core Facility (CF) originated from the first lecture given by Dr. Hitoshi Nakagama on May 9, 2011 after his appointment as the Director of the National Cancer Center (NCC) Research Institute (RI). Along with the biobank, the CF has been positioned between the NCCRI and the NCC hospital to establish a bidirectional translational bridge. The combination of the rich collection of high-quality clinical samples and advanced, reliable analytical power should be a crucial asset of our Institute. However, the latest genome and other omics technologies demand heavy and stable investments both in hardware, its maintenance and human expertise, especially in the field of bioinformatics, which are increasingly difficult if not impossible to afford by individual laboratories, such as those led by young PIs and physician scientists. As a consequence, the CF has become an essential component integrated in many leading biomedical research institutes in the world. The current NCC CF is a virtual organization based on mutual support among research scientists and laboratories, each engaging in their own competitive research.

Figure 1 shows the original CF framework officially started on September 5, 2011 with four major arms: Genome & Epigenome, Proteome, Biology, and Common Equipment for self-service use of shared resource-demanding machines in terms of cost, space and other installation specifications.

In August 2014, the original CF system was incorporated into the newly established Fundamental Innovative Oncology Core Center (FIOC). The Research Support Division of the FIOC corresponds to the Genome, Epigenome and Proteome CF and is reported here. The biology CF function is being offered by the Central Animal Division and reported in its pages.

Research activities

The mission of the CF is not limited to mutual support and collaboration inside the NCCRI, but extends to other sectors of the NCC. For instance, the CF offers a genotyping service for population-based cohort studies in the Research Center for Cancer Prevention and Screening (RCCPS), and helping observation studies in the framework of clinical trials in the hospital (Figure 2). One important mission of the CF is its contribution to the genetic diagnosis of hereditary cancer syndromes at the outpatient genetic counseling clinic in the NCC hospital. Such services, however, are undoubtedly in the transitional zone between research and clinical practice and need special consideration and practice to assure its analytical validity.

Because the CF covers such diverse activities, its performance is difficult to quantify, but just as a simplified example, the numbers of individual research projects and samples submitted to the CF are summarized in Table 1.

Education

Although not always apparent, one of the most important contributions of the CF may be the discussion and consultation BEFORE offering the actual CF service.

Future prospects

CF should keep exploring the latest needs

among NCC researchers and revising its service menu accordingly. It is also crucial to evaluate the effort of the CF staff in an appropriate way and develop sound and effective incentives for active commitment to the CF service. At least a part of the CF financial fundamentals needs to continue to be supported by the NCC in-house budget, such as machine maintenance and basic human resource cost.

As a member of the FIOC, the Research Support Division will contribute to its mission in line with the grand strategy and directives of FIOC.

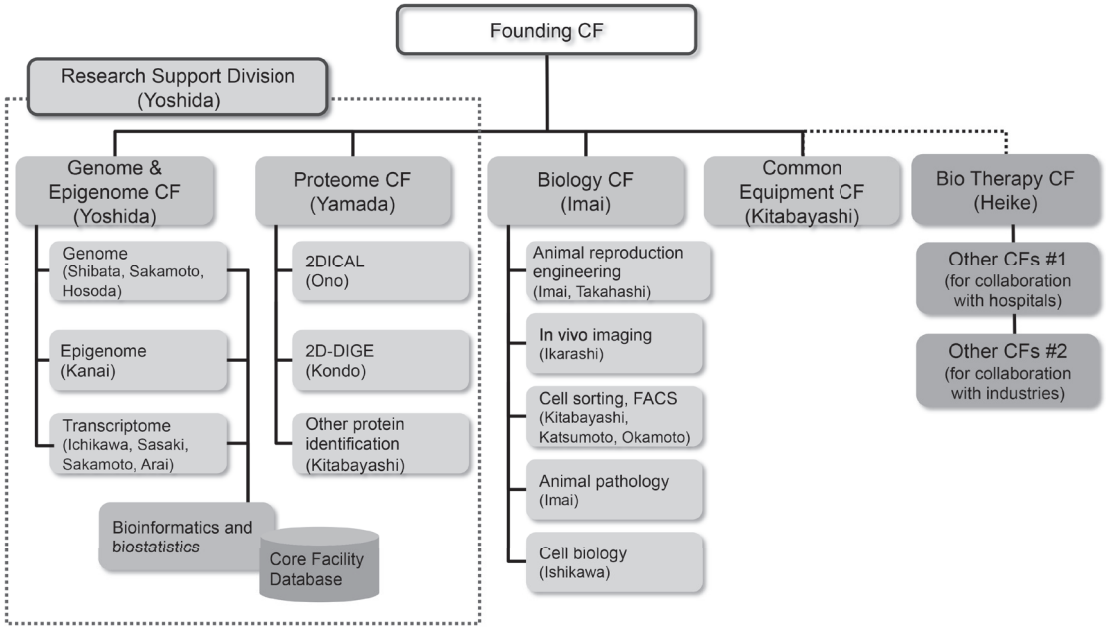


Figure 1. CF Organization (as of 2014)

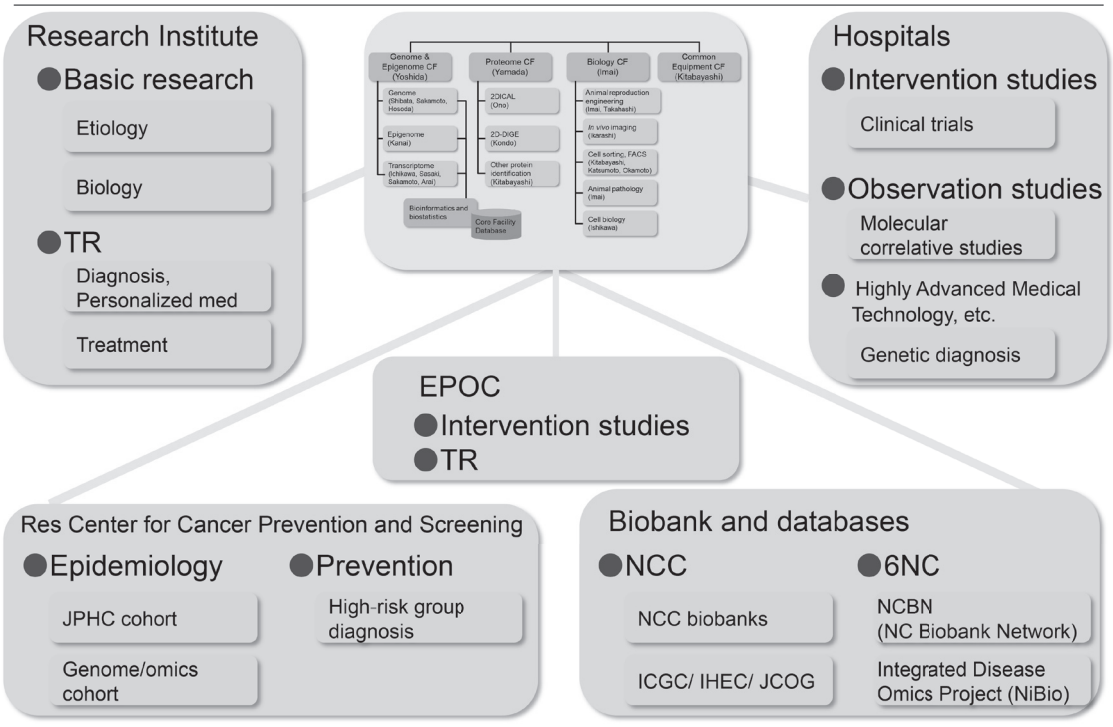


Figure 2. CF Interactions and Participations

Table 1. CF Activities in FY 2011-2015 (excluding the self-service type)

Omics	Applications	# samples				
		FY 2011	FY 2012	FY2013	FY2014	FY2015
Genome	Next Generation Sequencer	248	180	160	1,203	1,063
	SNP array/CGH array analyses	2,359	2,226	1,885	529	7,309
Epigenome	NGS	102	14	8	30	697
	Infinium array	1,646	569	801	705	63
Transcriptome	NGS	44	157	0	243	15
	Oligonucleotide microarray	155	132	178	232	403
Proteome	2DICAL	524	112	54	126	42
	2D-DIGE	0	308	83	199	24
	Protein identification	0	483	612	1,573	1,555
Total		5,078	4,181	3,781	4,840	11,171

List of papers published in 2015

Journal

1. Hashimoto T, Ogawa R, Matsubara A, Taniguchi H, Sugano K, Ushiama M, Yoshida T, Kanai Y, Sekine S. Familial adenomatous polyposis-associated and sporadic pyloric gland adenomas of the upper gastrointestinal tract share common genetic features. Histopathology, 67:689-698, 2015

2. Kumamoto K, Ishida H, Ohsawa T, Ishibashi K, Ushiama M, Yoshida T, Iwama T. Germline and somatic mutations of the APC gene in papillary thyroid carcinoma associated with familial adenomatous polyposis: Analysis of three cases and a review of the literature. Oncol Lett, 10:2239-2243, 2015

3. Saeki N, Ono H, Sakamoto H, Yoshida T. Down-regulation of Immune-related Genes by PSCA in Gallbladder Cancer Cells Implanted into Mice. Anticancer Res, 35:2619-2625, 2015

4. Tanaka Y, Aoyagi K, Minashi K, Komatsuzaki R, Komatsu M, Chiwaki F, Tamaoki M, Nishimura T, Takahashi N, Oda I, Tachimori Y, Arao T, Nishio K, Kitano S, Narumi K, Aoki K, Fujii S, Ochiai A, Yoshida T, Muto M, Yamada Y, Sasaki H. Discovery of a Good Responder Subtype of Esophageal Squamous Cell Carcinoma with Cytotoxic T-Lymphocyte Signatures Activated by Chemoradiotherapy. PLoS One, 10:e0143804, 2015

5. Saeki N, Ono H, Yanagihara K, Aoyagi K, Sasaki H, Sakamoto H, Yoshida T. rs2294008T, a risk allele for gastric and gallbladder cancers, suppresses the PSCA promoter by recruiting the transcription factor YY1. Genes Cells, 20:382-391, 2015

6. Yamanoi K, Arai E, Tian Y, Takahashi Y, Miyata S, Sasaki H, Chiwaki F, Ichikawa H, Sakamoto H, Kushima R, Katai H, Yoshida T, Sakamoto M, Kanai Y. Epigenetic clustering of gastric carcinomas based on DNA methylation profiles at the precancerous stage: its correlation with tumor aggressiveness and patient outcome. Carcinogenesis, 36:509-520, 2015

7. Suzuki M, Chiwaki F, Sawada Y, Ashikawa M, Aoyagi K, Fujita T, Yanagihara K, Komatsu M, Narita M, Suzuki T, Nagase H, Kushima R, Sakamoto H, Fukagawa T, Katai H, Nakagama H, Yoshida T, Uezono Y, Sasaki H. Peripheral opioid antagonist enhances the effect of anti-tumor drug by blocking a cell growth-suppressive pathway in vivo. PLoS One, 10:e0123407, 2015

8. Budhathoki S, Iwasaki M, Yamaji T, Sasazuki S, Takachi R, Sakamoto H, Yoshida T, Tsugane S. Dietary heterocyclic amine intake, NAT2 genetic polymorphism, and colorectal adenoma risk: the colorectal adenoma study in Tokyo. Cancer Epidemiol Biomarkers Prev, 24:613-620, 2015

9. Fujita T, Chiwaki F, Takahashi RU, Aoyagi K, Yanagihara K, Nishimura T, Tamaoki M, Komatsu M, Komatsuzaki R, Matsusaki K, Ichikawa H, Sakamoto H, Yamada Y, Fukagawa T, Katai H, Konno H, Ochiya T, Yoshida T, Sasaki H. Identification and Characterization of CXCR4-Positive Gastric Cancer Stem Cells. PLoS One, 10:e0130808, 2015

10. Iwakawa R, Kohno T, Totoki Y, Shibata T, Tsuchihara K, Mimaki S, Tsuta K, Narita Y, Nishikawa R, Noguchi M, Harris CC, Robles AI, Yamaguchi R, Imoto S, Miyano S, Totsuka H, Yoshida T, Yokota J. Expression and clinical significance of genes frequently mutated in small cell lung cancers defined by whole exome/RNA sequencing. Carcinogenesis, 36:616-621, 2015

Central Animal Division

Toshio Imai, Mami Takahashi, Tetsuya Ishikawa, Teruo Komatsu, Kotomi Otsubo, Yoshinori Ikarashi, Naoaki Uchiya, Rikako Ishigamori, Yukiko Nakamura, Masashi Yasuda, Manabu Tsuchida, Ayami Kawashima, Satoshi Ikeda, Junichi Zukeyama, Shiho Ozawa, Yudai Seki, Karin Miura, Junya Asahira

Routine activities

The important role of the Central Animal Division is health management of experimental animals and maintenance of the animal experimentation facility. Some researchers and technical staff also act for several support services, which are provided based on their biological skills, such as reproductive technologies for animal cleaning/embryo-sperm preservation, histopathological techniques for animal tissues and establishment of expandable cells/xenograft transplantable models from clinical cancer tissues (PDX models).

Research activities

The research activities of the Central Animal Division have focused on studies of chemical carcinogenesis using laboratory animals, genetically modified cancer-developing animal models and, occasionally, clinical samples.

1) Involvement of obesity/pancreatic fatty infiltration (FI) in pancreatic carcinogenesis

Epidemiologically, obesity and diabetes are risk factors for pancreatic cancer, but the underlying mechanisms are not clearly understood. Obesity and diabetes are also associated with the degree of FI in the pancreas. Our recent clinical studies have showed that there is a positive correlation between FI of the pancreas and pancreatic ductal adenocarcinomas, suggesting severe pancreatic FI could be a risk factor of pancreatic cancer. To clarify the role of obesity/pancreatic fatty infiltration (FI) in pancreatic carcinogenesis, we crossed pancreas-specific K-ras mutant mice with obesity model mice. A significant increase of tumor development was observed and the enhancing mechanisms are being investigated.

2) Mechanisms of promotion of mammary carcinogenesis associated with a high-fat diet

The effects of a high-fat diet (HFD) during prepubertal and pubertal stages were investigated in 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in female F344 rats. Recently, a BALB/c strain background heterozygous p53 deficient mouse model is also used. The results obtained indicated that HFD promoted carcinogenesis. Molecular mechanisms of the promotion as assessed with DNA microarray analysis for non-cancerous mammary tissues were suggested to be associated with the altered expression of a planar cell polarity-related gene, which was at least partly affected by DNA methylation.

3) Human-induced hepatic lineage-oriented stem cells (hiHSCs)

hiHSCs were generated and expanded as a new type of hiPSC under non-typical coculture with feeder cells in a chemically defined hiPSC medium at a very high density. Self-renewing hiHSCs expressed markers of both human embryonic stem cells and hepatocytes. Those cells were highly expandable, markedly enhancing gene expression of serum hepatic proteins and cytochrome P450 enzymes with the omission of FGF-2 from an undefined hiPSC medium. Approximately 90% of hiHSCs autonomously differentiated to hepatocyte-like cells, even in a defined minimum medium without any of the exogenous growth factors necessary for hepatic specification.

Future prospects

Research approaches using immune deficient/severely immune-deficient mice have become increasingly important over the past few years, and microbiological controls of the animal experimentation facility should become more

strictly controlled. For development of research fields to conquer rare cancers/refractory cancers, establishment of their PDX models should be systematically organized.

List of papers published in 2015

Journal

1. Kitahashi T, Takahashi M, Imai T. Biphasic alterations in expression and subcellular localization of MUC1 in pancreatic ductal carcinogenesis in Syrian hamsters. Pancreas, 44:76-86, 2015

2. Ishikawa T, Kobayashi M, Yanagi S, Kato C, Takashima R, Kobayashi E, Hagiwara K, Ochiya T. Human Induced Hepatic Lineage-Oriented Stem Cells: Autonomous Specification of Human iPS Cells toward Hepatocyte-Like Cells without Any Exogenous Differentiation Factors. PLoS One, 10:e0123193, 2015

RI Research Support Division

Yutaka Yamada, Mitsuko Masutani, Gen Fujii

Introduction

The RI Research Support Division provides advanced technical training and education for researchers in the fields of molecular genetics and radiology. This Division is equipped with separate laboratories where registered users can conduct experiments safely with various types of radioisotopes.

Routine activities

The important roles of the RI Research Support Division are exposure control of radiation workers and management of the radiation controlled area.

Research activities

The research activities of the RI Research Support Division have focused on studies of radiation effect. The mechanism of cell death induced by boron neutron capture reaction (BNCR) were investigated using human oral squamous carcinoma cell line, SAS cells. The cells were irradiated with a thermal neutron beam after incubation with or without boronophenylalanine (BPA). BNCR (irradiation with BPA) induced typical apoptosis in the cells 24 hours after irradiation. Proteins functioning in endoplasmic reticulum, DNA repair, and RNA processing showed dynamic changes at the early phase after BNCR, suggesting that the proteins could be involved in the regulation of cellular response to BNCR. In addition, BNCR induces fragments of endoplasmic reticulum-localized lymphoid-restricted protein (LRMP). The fragmentation of LRMP was also observed in the rat tumor graft model 20 hours after boron neutron capture therapy. These data suggest that dynamic changes of LRMP could be involved during cellular response to BNCR.

Future prospects

These changes will be available as biomarkers for evaluating the effects of boron neutron capture therapy (BNCT). For clinical application of BNCT, the identification of appropriate biomarkers is needed. Further analysis of different types of cancer cells will facilitate the identification of useful biomarkers for BNCT.

List of papers published in 2015

Journal

1. Sato A, Itoh T, Imamichi S, Kikuhara S, Fujimori H, Hirai T, Saito S, Sakurai Y, Tanaka H, Nakamura H, Suzuki M, Murakami Y, Baiseitov D, Berikkhanova K, Zhumadilov Z, Imahori Y, Itami J, Ono K, Masunaga S, Masutani M. Proteomic analysis of cellular response induced by boron neutron capture reaction in human squamous cell carcinoma SAS cells. Appl Radiat Isot, 106:213-219, 2015

Department of Biobank and Tissue Resources

Yae Kanai, Masumi Tanaka, Teiko Yamane, Nobuko Nangi

Activities of National Cancer Center Biobank

The Department of Biobank Tissue Resources operates National Cancer Center Biobank under the supervision of the National Cancer Center Biobank Administration Committee (Figure 1).

In 2015, 9,652 vials of tissue specimens obtained from surgically resected materials of 1,796 patients were newly deposited at the National Cancer Center Biobank and 1,786 vials of tissue specimens obtained from surgically resected materials of 1,370 patients were provided for research approved by the National Cancer Center Ethics Committee. The ratio of the number of patients from whom samples were provided for research to those of whom samples were newly deposited at the Biobank was about 76%. At the end of 2015, we reposited 81,314 vials of tissue specimens of 19,355 patients.

In 2015, 43,902 vials of plasma samples drawn from 9,831 patients were newly deposited at the National Cancer Center Biobank and 3,482 vials of plasma samples drawn from 3,340 patients were provided for research approved by the National Cancer Center Ethics Committee. At the end of 2015, we reposited 151,796 vials of blood samples of 37,570 patients who consented to give blood samples for research purposes.

We have built up the catalog database, HosCanR Biobank Edition, by extracting appropriate information from the Interview Sheet Database in a common form among six National Centers in Japan and HosCanR, an application specialized for the National Program of Cancer Registries. Researchers and biobank users can find samples suitable for their own research plans using the search commands of this catalog database. In 2015, we adjusted the HosCanR Biobank Edition to correspond to the central database platform of the National Center Biobank Network (NCBN) and prepared a wide distribution of samples from NCBN, which are not based on collaborative research, for outside researchers including researchers employed by industry.

Researchers who received samples from the Biobank have published 354 scientific papers (total impact factor: 1,831.289, total citation index; 5,630). A total of 64% of the published papers were based on collaborative research between researchers of the National Cancer Center and outside researchers; in particular, 21% were based on collaborative research with industry.

Many founders and/or contact persons of bioresource repositories of other universities and hospitals and television crews visited the National Cancer Center Biobank to learn about the management knowhow of the biobank. We have been consulted by contact persons of bioresource repositories of other universities about the storage system for specimens.

Staff of the National Cancer Center Biobank participate in the General Ethics Support Sector, Sample Utilization Review Working Group, Sample Handling System Review Working Group and Medical Information System Review Working Group of NCBN.

Future prospects

The continuous collection of samples for various research needs and management of the biobank, including a high-quality clinicopathological information database, are considered to be a national mission. The National Cancer Center Biobank should be continued and become a more robust and permanent research base, it should also continuously support NCBN and connect the intentions of voluntary donors to next generation personalized medicine.

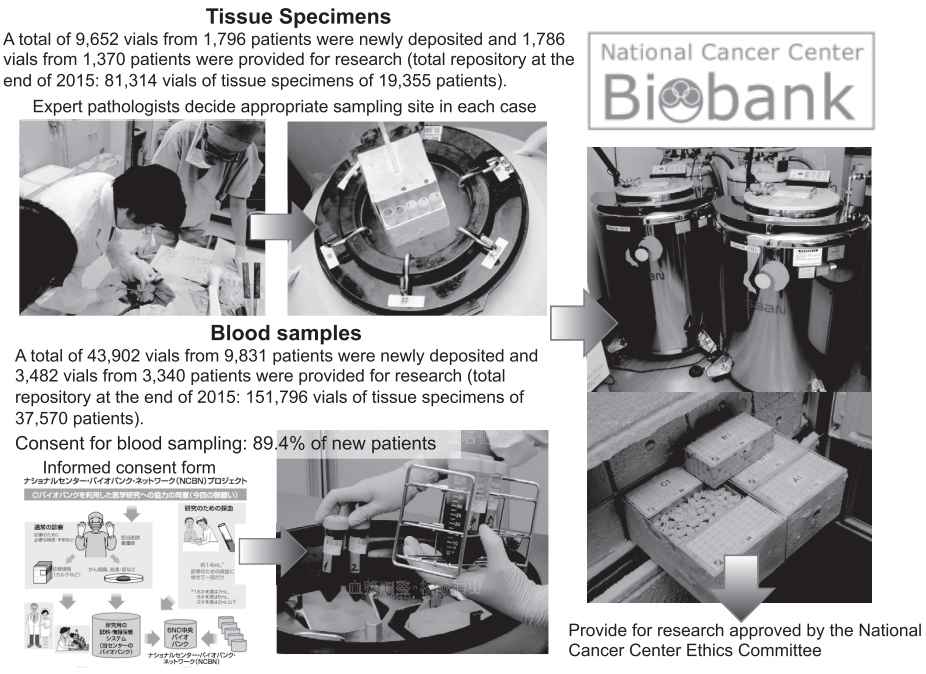


Figure 1. National Cancer Center Biobank

Department of Patient-Derived Cell Line and Xenograft

Tohru Kiyono, Farhana Ishrat Ghani, Chiho Kohno

Introduction

There are mainly two approaches to amplify cancer cells from patients: *in vitro* cell culture and patient-derived xenograft (PDX). Since HeLa cell line, the first human cancer cell line, has been established, human cancer cell lines have been essential for cancer research. Patient-derived xenografts (PDXs) generated from fresh tumor specimens generally reflect histopathology, tumor behavior, and the metastatic properties of the original tumor. Recently, both PDX models and cell line-derived xenograft (CDX) models are considered to be important preclinical tools. However, the success rate to establish new cell lines or PDX lines is not satisfactory.

Routine activities

This Department was founded in 2014 for the establishment of new cancer cell lines and PDX lines. With the help of the pathology division, we have systemically started to store valuable cancer specimens so that cancer tissues or cancer cells can be transplanted into immune-deficient mice or cultivated *in vitro* in the future.

Research activities

So far we have tried to cultivate ovarian cancer cells from more than 30 operative specimens. This year, we have succeeded to establish 14 novel ovarian cancer cell lines out of 15 operative specimens, including three clear cell carcinomas.

Future prospects

The number of cell lines derived from Asian patients is limited. Cell lines from some of the rare cancers remain to be established. Since we have developed a method to efficiently establish ovarian cancer cell lines, we will expand our method to other cancers. These cell lines are valuable resources with detailed clinical information. For example, the correlation between genomic mutations and drug sensitivity can be evaluated.

Department of Molecular imaging and Pharmacokinetics

Akinobu Hamada, Mitsuhiro Hayashi, Makiko Yamashita, Shoraku Ryu, Tomomi Nishijo, Mayu Ohuchi, Mariko Mizui

Introduction

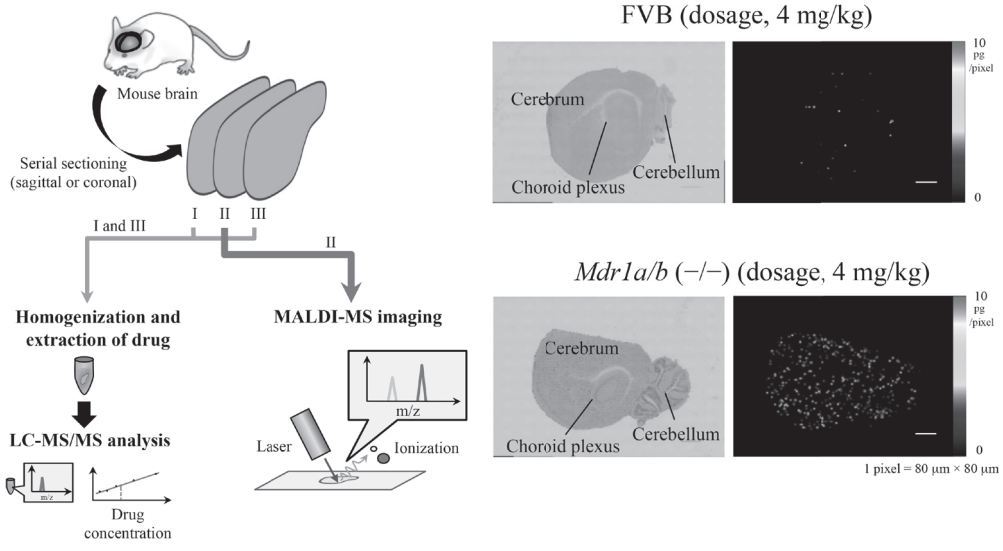
The Department of Clinical Pharmacology is focused on the development of a pharmacokinetics/pharmacodynamics (PK/PD) analyzing system. The system provides drug exposure in blood and tissues by using a high-sensitivity liquid chromatography tandem mass spectrometry (LC-MS/MS) and spatial drug distribution on tissue by using mass spectrometry imaging without labeling reagents. We are also focused on the development of an immunomonitoring system detecting patient's antibody-dependent cellular cytotoxicity (ADCC) activity.

Research activities

We established a quantitative mass spectrometry imaging system that provides both quantitative information and spatial distribution of target drugs. We used this system to visualize the amount and the distribution of anti-cancer drugs in several mouse models. To assess the efficacy and the behavior of target drugs in tumor tissues, we are now establishing not only a cell-derived xenotraft mouse model but also a patient-derived xenograft model. Moreover, we established an immunomonitoring system that can detect ADCC activity from patient's peripheral blood mononuclear cell (PBMC). Both research projects were submitted as papers to scientific journals.

Future prospects

The combination of PK/PD analysis, mass spectrometry imaging, measurement of ADCC activity, and establishment of a patient-derived xenograft (PDX) model can provide us with more accurate information about patients. These systems will help to actualize personalized medicine in the future.



P糖タンパク質(Mdr1)の基質薬剤の脳内組織移行性は、ノックアウトマウスで上昇

Figure 1. MALDI-MSI imaging analysis showed that the intra-brain transitivity of the drug was elevated on Mdr1(-/-) mouse brain.

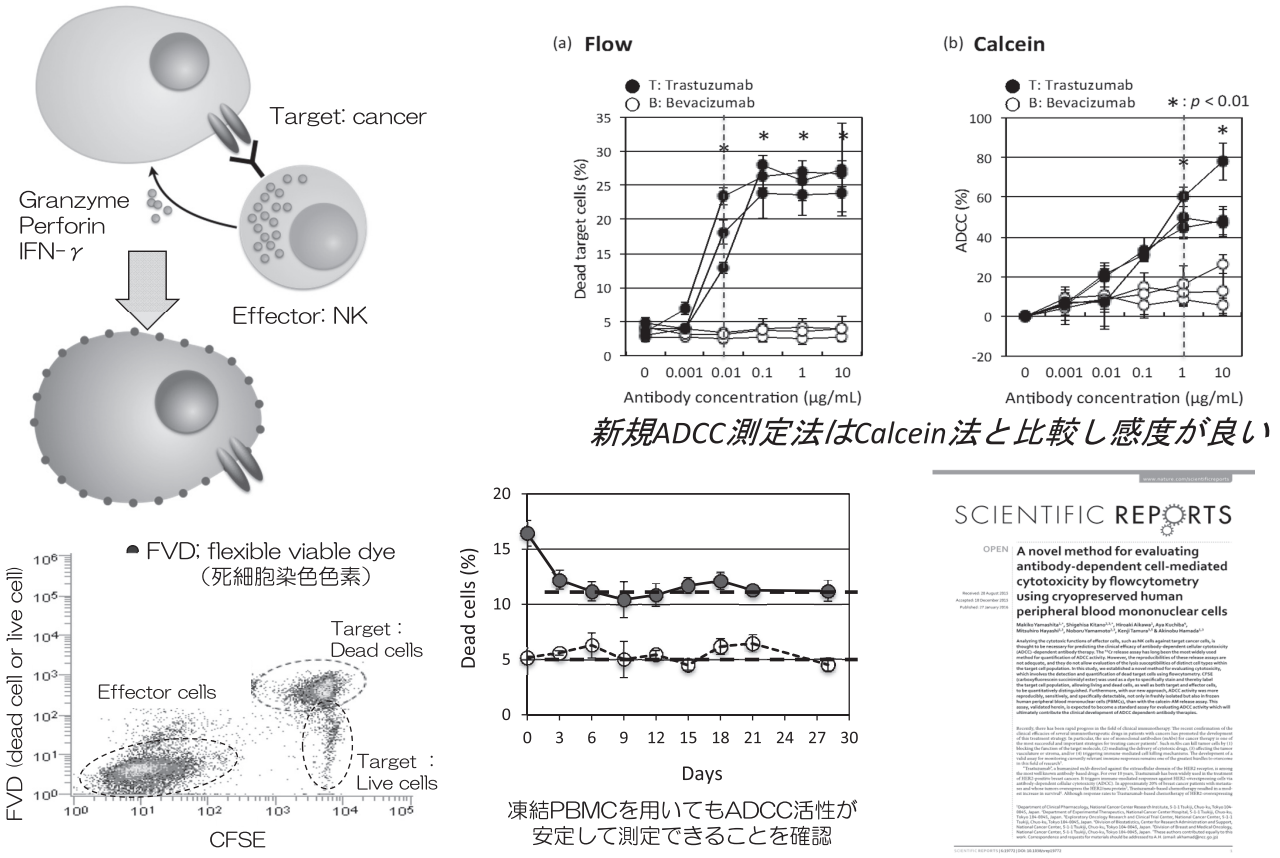


Figure 2. We developed a highly sensitive method for quantifying the ADCC activity of patient's blood.

List of papers published in 2015

Journal

1. Fujiwara Y, Kobayashi S, Nagano H, Kanai M, Hatano E, Toyoda M, Ajiki T, Takashima Y, Yoshimura K, Hamada A, Minami H, Ioka T. Pharmacokinetic Study of Adjuvant Gemcitabine Therapy for Biliary Tract Cancer following Major Hepatectomy (KHBO1101). PLoS One, 10:e0143072, 2015

2. Katsuya Y, Fujiwara Y, Sunami K, Utsumi H, Goto Y, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Takashima Y, Osawa S, Ohe Y, Tamura T, Hamada A. Comparison of the pharmacokinetics of erlotinib administered in complete fasting and 2 h after a meal in patients with lung cancer. Cancer Chemother Pharmacol, 76:125-132, 2015

3. Kurihara H, Hamada A, Yoshida M, Shimma S, Hashimoto J, Yonemori K, Tani H, Miyakita Y, Kanayama Y, Wada Y, Kodaira M, Yunokawa M, Yamamoto H, Shimizu C, Takahashi K, Watanabe Y, Fujiwara Y, Tamura K. ^{64}Cu-DOTA-trastuzumab PET imaging and HER2 specificity of brain metastases in HER2-positive breast cancer patients. EJNMMI Res, 5:8, 2015

4. Otani S, Hamada A, Sasaki J, Wada M, Yamamoto M, Ryuge S, Takakura A, Fukui T, Yokoba M, Mitsufuji H, Toyooka I, Maki S, Kimura M, Hayashi N, Ishihara M, Kasajima M, Hiyoshi Y, Katono K, Asakuma M, Igawa S, Kubota M, Katagiri M, Saito H, Masuda N. Phase I and pharmacokinetic study of erlotinib administered in combination with amrubicin in patients with previously treated, advanced non-small cell lung cancer. Am J Clin Oncol, 38:405-410, 2015

5. Sakata S, Sasaki J, Saeki S, Hamada A, Kishi H, Nakamura K, Tanaka H, Notsute D, Sato R, Saruwatari K, Iriki T, Akaike K, Fujii S, Hirosako S, Kohrogi H. Dose Escalation and Pharmacokinetic Study of Carboplatin plus Pemetrexed for Elderly Patients with Advanced Nonsquamous Non-Small-Cell Lung Cancer: Kumamoto Thoracic Oncology Study Group Trial 1002. Oncology, 88:201-207, 2015

6. Hayashi M, Yamamoto Y, Sueta A, Tomiguchi M, Yamamoto-Ibusuki M, Kawasoe T, Hamada A, Iwase H. Associations Between Elastography Findings and Clinicopathological Factors in Breast Cancer. Medicine (Baltimore), 94:e2290, 2015

7. Iwamoto N, Umino Y, Yamane N, Hamada A, Shimada T. The development of the validated LCMS bioanalysis of trastuzumab in human plasma using a selective detection method for complementarity-determining regions of monoclonal antibodies: nano-surface and molecular-orientation limited (nSMOL) proteolysis. Anal Methods, 7:9177-9183, 2015

8. Oguri T, Shimokata T, Ito I, Yasuda Y, Sassa N, Nishiyama M, Hamada A, Hasegawa Y, Ando Y. Extension of the Calvert formula to patients with severe renal insufficiency. Cancer Chemother Pharmacol, 76:53-59, 2015

9. Yoshitake Y, Fukuma D, Yuno A, Hirayama M, Nakayama H, Tanaka T, Nagata M, Takamune Y, Kawahara K, Nakagawa Y, Yoshida R, Hirosue A, Ogi H, Hiraki A, Jono H, Hamada A, Yoshida K, Nishimura Y, Nakamura Y, Shinohara M. Phase II clinical trial of multiple peptide vaccination for advanced head and neck cancer patients revealed induction of immune responses and improved OS. Clin Cancer Res, 21:312-321, 2015

Department of Innovative Seeds Evaluation

Tadashi Kondo, Tsutomu Ohta, Rieko Oyama, Yoko Takai, Fusako Kito, Marimu Sakumoto, Shoko Tanahashi

Introduction

The establishment of a patient-derived cancer model is our research activity. Although there are many patient-derived cancer models, those for rare cancers are rarely available. A rare cancer is defined as a cancer with prevalence of less than six. Rare cancer includes about 200 cancer types, and despite the rarity of each rare cancer, the rare cancers represent in total about 20% of all cancer cases in Japan. Thus, the rare cancers are quite important subjects. With this notion, the fundamental tools were created for rare cancer research. The establishment of patient-derived cancer models, especially those for sarcomas, has been conducted in our laboratory. The established models are currently used to evaluate the efficacy of novel cancer drugs.

Research activities

The clinical materials obtained in the National Cancer Center Hospital are used to develop the patient-derived cancer models. The development of methods for establishment of cancer models and the characterization of established cancer models are the major activities of our laboratory. The clinical materials are quite diverse depending on the original tissue samples, and the methods for individual histology are required to establish the cancer models. The molecular characterization is also important to use the cancer models in the research. It is quite important to know how the developed cancer models retain the original molecular backgrounds. For this sake, we employ the multi-omics approach. The DNA, RNA and proteins are comprehensively and intensively examined, comparing the original tissue samples and the established models. Our cancer models are included in the collaborative study with pharmaceutical companies. The research activity of our Department is linked to that of the Division of Rare Cancer Research. The ideas and the fundamental research tools are shared between two laboratories for novel innovative seeds development.

Future prospects

Our research activities will benefit the patients with rare cancers by contributing to the development of novel cancer drugs. We will establish more collaborative studies with pharmaceutical companies as well as academic research groups.

List of papers published in 2015

Journal

1. Tajima T, Kito F, Ohta T, Kawai A, Kondo T. Interactome analysis reveals molecular mechanisms underlying the association between selenium binding protein 1 expression and the malignant features of tumor cells. J Electrophoresis, 59:1-6, 2015

2. Uemura N, Kondo T. Current advances in esophageal cancer proteomics. Biochim Biophys Acta, 1854:687-695, 2015

3. Kikuta K, Morioka H, Kawai A, Kondo T. Global protein-expression profiling for reclassification of malignant fibrous histiocytoma. Biochim Biophys Acta, 1854:696-701, 2015

4. Ichikawa H, Yoshida A, Kanda T, Kosugi S, Ishikawa T, Hanyu T, Taguchi T, Sakumoto M, Katai H, Kawai A, Wakai T, Kondo T. Prognostic significance of promyelocytic leukemia expression in gastrointestinal stromal tumor; integrated proteomic and transcriptomic analysis. Cancer Sci, 106:115-124, 2015

Book

1. Kondo T. Novel prognostic biomarker, pfetin, in gastrointestinal stromal tumors: proteomics study. In: Victor RP, Vinood BP (eds), General methods in biomarker research and their applications 1st Edition, Netherlands, Springer Netherlands, pp 251-266, 2015

Department of Clinical Genomics

Hitoshi Ichikawa, Fumie Hosoda, Sachiyo Mitani, Shizuka Shinohara, Erika Arakawa, Ayano Doi

Introduction

The aim of our Department is to contribute to realize precision medicine for cancer patients based on the molecular profiles of their malignancies. To this end, we have developed a next-generation sequencing (NGS)-based genomic testing system using original gene panels. In addition, we are working on identification of novel diagnostic and therapeutic biomarkers for several types of malignancies by the use of NGS and microarray technologies.

Research activities

1) Development of an original NGS-based genomic testing system

We developed an NGS-based in-house genomic testing system, and have been continuously improving this system to become an accurate and clinically useful in vitro diagnostics (IVD) system. In this system, an original cancer gene panel (NCC oncopanel) was designed and used. With this gene panel, mutations and amplifications of ~100 genes and fusions of ~10 genes can be accurately identified from FFPE tumor tissue samples. In 2015, we renewed our gene panel (NCC oncopanel v3), and confirmed its performance in a prospective feasibility study to examine patients considering entry into an early-phase clinical trial. In addition, we supported the setting-up of SCI-Lab in the Hospital, in which our system was used as a clinical test with quality assurance to detect actionable genetic alterations for cancer patients.

2) Development of novel biomarkers

Through the use of NGS and microarray technologies, we are searching novel diagnostic and therapeutic biomarkers for sarcoma, gastric cancer and pediatric acute myeloid leukemia (AML). In 2015, from microarray-based gene expression profiling analysis of 130 Japanese pediatric AML patients, we found that the *EVI1* and *MEL1* genes were overexpressed in approximately 30% of patients, and that their high expression was significantly associated with inferior survival. High *EVI1* expression was detected mainly in myelomonocytic-lineage leukemia with *MLL* rearrangements and in megakaryocytic-lineage leukemia. On the other hand, high *MEL1* expression was detected in myelocytic-lineage and myelomonocytic-lineage leukemia without *MLL* rearrangements. Because of their subtype-dependent and mutually exclusive expression, a combined evaluation of their high expression enabled a clear distinction of patients with inferior survival. This association was confirmed by quantitative RT-PCR analysis of an independent cohort of 81 patients. We propose that the combined estimation of *EVI1* and *MEL1* expression will be an effective method to predict the prognosis of pediatric AML.

3) Target sequencing services

We provided target sequencing services using our original genomic testing system and commercially available cancer panel systems, upon requests from researchers in the Research Institute and Hospital. In 2015, about 600 samples from various types of cancers were analyzed.

List of papers published in 2015

Journal

1. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, Hama N, Hosoda F, Urushidate T, Ohashi S, Hiraoka N, Ojima H, Shimada K, Okusaka T, Kosuge T, Miyagawa S, Shibata T. Genomic spectra of biliary tract cancer. Nat Genet, 47:1003-1010, 2015

2. Gocho Y, Kiyokawa N, Ichikawa H, Nakabayashi K, Osumi T, Ishibashi T, Ueno H, Terada K, Oboki K, Sakamoto H, Shioda Y, Imai M, Noguchi Y, Arakawa Y, Kojima Y, Toyama D, Hata K, Yoshida T, Matsumoto K, Kato M, Fukushima T, Koh K, Manabe A, Ohara A, Tokyo Children's Cancer Study Group. A novel recurrent EP300-ZNF384 gene fusion in B-cell precursor acute lymphoblastic leukemia. Leukemia, 29:2445-2448, 2015

3. Jo A, Mitani S, Shiba N, Hayashi Y, Hara Y, Takahashi H, Tsukimoto I, Tawa A, Horibe K, Tomizawa D, Taga T, Adachi S, Yoshida T, Ichikawa H. High expression of EVI1 and MEL1 is a compelling poor prognostic marker of pediatric AML. Leukemia, 29:1076-1083, 2015

4. Nakaguro M, Kiyonari S, Kishida S, Cao D, Murakami-Tonami Y, Ichikawa H, Takeuchi I, Nakamura S, Kadomatsu K. Nucleolar protein PES1 is a marker of neuroblastoma outcome and is associated with neuroblastoma differentiation. Cancer Sci, 106:237-243, 2015

5. Yamanoi K, Arai E, Tian Y, Takahashi Y, Miyata S, Sasaki H, Chiwaki F, Ichikawa H, Sakamoto H, Kushima R, Katai H, Yoshida T, Sakamoto M, Kanai Y. Epigenetic clustering of gastric carcinomas based on DNA methylation profiles at the precancerous stage: its correlation with tumor aggressiveness and patient outcome. Carcinogenesis, 36:509-520, 2015

6. Takenaka M, Saito M, Iwakawa R, Yanaihara N, Saito M, Kato M, Ichikawa H, Shibata T, Yokota J, Okamoto A, Kohno T. Profiling of actionable gene alterations in ovarian cancer by targeted deep sequencing. Int J Oncol, 46:2389-2398, 2015

7. Fujita T, Chiwaki F, Takahashi RU, Aoyagi K, Yanagihara K, Nishimura T, Tamaoki M, Komatsu M, Komatsuzaki R, Matsusaki K, Ichikawa H, Sakamoto H, Yamada Y, Fukagawa T, Katai H, Konno H, Ochiya T, Yoshida T, Sasaki H. Identification and Characterization of CXCR4-Positive Gastric Cancer Stem Cells. PLoS One, 10:e0130808, 2015

8. Saito M, Shimada Y, Shiraishi K, Sakamoto H, Tsuta K, Totsuka H, Chiku S, Ichikawa H, Kato M, Watanabe S, Yoshida T, Yokota J, Kohno T. Development of lung adenocarcinomas with exclusive dependence on oncogene fusions. Cancer Res, 75:2264-2271, 2015

Department of Translational Oncology

Hiroki Sasaki, Masayuki Komatsu, Rie Komatsuzaki, Fumiko Chiwaki, Tomoko Hiroki, Akio Ashida, Kanako Nakamura, Daichi Inami

Introduction

In 2015, the two major research areas of the Department of Translational Oncology were 1) preclinical studies using newly established gastric, esophageal, pancreatic, and ovarian cancer cell lines for derivation of industrial and academia seeds/drugs to the Exploratory Oncology Research & Clinical Trial Center (EPOC), and 2) basic research and development of personalized cancer diagnosis and treatment for gastric and esophageal cancers.

Preclinical Studies Using Newly Established Cell Lines from Common Cancers in Asia

Genome-wide genetic information in about 1,000 cancer cell lines is available on COSMIC DB (Sanger Center, UK) and on recent NGS analyses (Klijin C et al, Nat Biotech 2015); however, among them, only 28 cell lines are derived from gastric cancer (GC). Almost all of the 28 GC cell lines were established many years ago, thereby, insufficient clinical and pathological information is attached. The wait is on for the establishment of new GC cell lines, especially from metastatic sites after therapy. Peritoneal metastasis is most frequent in GCs, especially diffuse-type GCs. Furthermore, since driver gene mutation frequency in a certain cancer is often less than 5%, establishment of cell lines from each patient to be analyzed is desired for functional selection of driver gene mutations. In collaboration with the Division of Genetics, we have newly established 59 diffuse-type GC-derived cell lines (NSC-1~49 series) from the cancer ascites of 34 patients. Now, we have 94 GC cell lines including 80 diffuse-type (new 59 and existing 21) and 14 intestinal-type, and also have 52 esophageal squamous cell carcinoma (ESCC) cell lines. In 2015, we successfully established six pancreatic and one ovarian cancer cell lines. We are conducting omics analyses for gene expression and copy number variation, and hot spot-and genome wide-gene alteration in these cell lines. Moreover, for in vivo preclinical study, their tumorigenicity and histopathological characteristics of PDXs, such as fibroblast rich-, hypovascular-, and dormant-state, were evaluated. Through collaboration with five pharmaceutical industries, in vitro and in vivo preclinical studies were conducted to derivate them to EPOC.

Basic Research and Development of Personalized Diagnosis and Treatment for GC and ESCC

Two major research projects, basic research and personalized medicine for GC and ESCC, are under way.

The study for GC: Diffuse-type solid tumors are often composed of a high proportion of rarely proliferating (that is, dormant) cancer cells, strongly indicating the involvement of cancer stem cells (CSCs). Although diffuse-type GC patients have a poor prognosis due to high-frequency development of peritoneal dissemination (PD), knowledge is limited about the PD-associated CSCs and efficacy of CSC-targeting therapy in diffuse-type GC. We established highly metastatic GC cell lines by in vivo selection designed for the enrichment of PD-associated GC cells. By microarray analysis, we found that C-X-C chemokine receptor type 4 (CXCR4) can be a novel marker for highly metastatic CSCs, since CXCR4-positive cells can grow anchorage-independently, initiate tumors in mice, be resistant to cytotoxic drugs, and produce differentiated daughter cells. In clinical samples, these CXCR4-positive cells were found from not only in the late metastasis stage (accumulated ascites) but also in the earlier stage (peritoneal washings). Moreover, treatment with transforming growth factor-β enhanced the anti-cancer effect of docetaxel via induction of cell differentiation/asymmetric cell division of the CXCR4-positive gastric CSCs even in a dormant state. Therefore,

differentiation inducers hold promise for obtaining the maximum therapeutic outcome from currently available anti-cancer drugs through re-cycling of CSCs (Fujita T et al, PLoS One 2015). Thus, the dormancy of tumor cells is a major problem in chemotherapy. One potential way to overcome chemo-resistance is to "wake up" these dormant cells. We showed that the opioid antagonist methylnaltrexone (MNTX) enhances the effect of docetaxel (Doc) by blocking a cell growth-suppressive pathway (Suzuki M et al, PLoS One 2015). PENK, which encodes opioid growth factor (OGF) and suppresses cell growth, was predominantly expressed in diffuse-type GCs. The blockade of OGF signaling by MNTX released cells from their arrest and boosted the effect of Doc. In comparison with the use of Doc alone, the combined use of Doc and MNTX significantly prolonged survival, alleviated abdominal pain, and diminished Doc-resistant spheroids on the peritoneal membrane in model mice. These results suggest that blockade of the pathways that suppress cell growth may enhance the effects of anti-tumor drugs.

In personalized medicine, we have developed mini DNA chips containing six marker and three control genes for predicting GC recurrence from peritoneal washings. Peritoneal cytology (CY) offers important prognostic information for GC after surgery; however, CY provides only a limited sensitivity and the task requires great skill. Our collaborating company continues to prepare a lot of supporting data for submitting the mini DNA chip to the Pharmaceuticals and Medical Devices Agency (PMDA) for marketing approval as an in vitro diagnostic (IVD).

The study for ESCC: Definitive chemoradiotherapy (CRT) is a less invasive therapy for esophageal squamous cell carcinoma (ESCC); however, the five-year survival rate of locally advanced ESCC patients was only 37%. Therefore, a prediction of CRT-responder is awaited. We have successfully identified 5 intrinsic subtypes of ESCCs by gene expression profile-based unsupervised clustering of 274 biopsy samples obtained before treatment. The 274 profiles were divided into a test set (107 cases containing 35 and 72 cases that received CRT or surgery, respectively) and a validation set (167 cases containing 90 and 77 cases, respectively). Five intrinsic subtypes (1a/M1, 2a/I, 3b, 5/M2, 7/E) including 2 new subtypes (2a/I, 3b) were identified in the test set, and these were reproducibly found in the validation set. For the cases treated with CRT, the 5-year survival rate was 24% in subtype M2, whereas it was 74% in subtype E. Furthermore, we found transcriptional pathways activated characteristically in each subtype; the subtype E showed a differentiation phenotype, while the non-E subtypes including M1 and M2 showed an epithelial-mesenchymal transition phenotype. We previously reported that tumor-specific cytotoxic T-lymphocyte (CTL) activation signatures were preferentially found in long-term survivors. However, it is unknown whether the tumor-specific cytotoxic T-lymphocyte (CTL) activation is actually driven by CRT. We compared gene expression profiles among pre- and post-treatment biopsy specimens of 30 ESCC patients and 121 pre-treatment ESCC biopsy specimens. In the complete response (CR) cases, 999 overexpressed genes including at least 234 tumor-specific CTL-activation associated genes such as IFNG, PRF1, and GZMB, were found in post-treatment biopsy specimens. Clustering analysis using expression profiles of these 234 genes allowed us to distinguish the immune-activated cases, designating them as I-type, from other cases. However, despite the better CR rate in the I-type, overall survival was not significantly better in both these 30 cases and another 121 cases. Further comparative study identified a series of epithelial to mesenchymal transition-related genes overexpressed in the early relapse cases. Importantly, the clinical outcome of CDH2-negative cases in the I-type was significantly better than that of the CDH2-positive cases in the I-type. Furthermore, NK cells, which were activated by neutrophils-producing S100A8/S100A9, and CTLs were suggested to cooperatively enhance the effect of CRT in the CDH2-negative I-type. These results suggested that CTL gene activation may provide a prognostic advantage in ESCCs with epithelial characteristics (Tanaka Y et al, PLoS One 2015). Our findings may contribute not only to the elucidation of CRT responsiveness but also for future therapeutic development. To develop an IVD, we are collaborating with a pharmaceutical company.

List of papers published in 2015

Journal

1. Tanaka Y, Aoyagi K, Minashi K, Komatsuzaki R, Komatsu M, Chiwaki F, Tamaoki M, Nishimura T, Takahashi N, Oda I, Tachimori Y, Arao T, Nishio K, Kitano S, Narumi K, Aoki K, Fujii S, Ochiai A, Yoshida T, Muto M, Yamada Y, Sasaki H. Discovery of a Good Responder Subtype of Esophageal Squamous Cell Carcinoma with Cytotoxic T-Lymphocyte Signatures Activated by Chemoradiotherapy. PLoS One, 10:e0143804, 2015

2. Tanabe S, Aoyagi K, Yokozaki H, Sasaki H. Regulated genes in mesenchymal stem cells and gastric cancer. World J Stem Cells, 7:208-222, 2015

3. Saeki N, Ono H, Yanagihara K, Aoyagi K, Sasaki H, Sakamoto H, Yoshida T. rs2294008T, a risk allele for gastric and gallbladder cancers, suppresses the PSCA promoter by recruiting the transcription factor YY1. Genes Cells, 20:382-391, 2015

4. Yamanoi K, Arai E, Tian Y, Takahashi Y, Miyata S, Sasaki H, Chiwaki F, Ichikawa H, Sakamoto H, Kushima R, Katai H, Yoshida T, Sakamoto M, Kanai Y. Epigenetic clustering of gastric carcinomas based on DNA methylation profiles at the precancerous stage: its correlation with tumor aggressiveness and patient outcome. Carcinogenesis, 36:509-520, 2015

5. Saeki N, Komatsuzaki R, Chiwaki F, Yanagihara K, Sasaki H. A GSDMB enhancer-driven HSV thymidine kinase-expressing vector for controlling occult peritoneal dissemination of gastric cancer cells. BMC Cancer, 15:439, 2015

6. Higuchi Y, Kojima M, Ishii G, Aoyagi K, Sasaki H, Ochiai A. Gastrointestinal Fibroblasts Have Specialized, Diverse Transcriptional Phenotypes: A Comprehensive Gene Expression Analysis of Human Fibroblasts. PLoS One, 10:e0129241, 2015

7. Tanabe S, Komatsu M, Aoyagi K, Yokozaki H, Sasaki H. Implications of epithelial-mesenchymal transition in gastric cancer. Transl Gastrointest Cancer, 4:258-264, 2015

8. Naito Y, Oue N, Pham TT, Yamamoto M, Fujihara M, Ishida T, Mukai S, Sentani K, Sakamoto N, Hida E, Sasaki H, Yasui W. Characteristic miR-24 Expression in Gastric Cancers among Atomic Bomb Survivors. Pathobiology, 82:68-75, 2015

9. Suzuki M, Chiwaki F, Sawada Y, Ashikawa M, Aoyagi K, Fujita T, Yanagihara K, Komatsu M, Narita M, Suzuki T, Nagase H, Kushima R, Sakamoto H, Fukagawa T, Katai H, Nakagama H, Yoshida T, Uezono Y, Sasaki H. Peripheral opioid antagonist enhances the effect of anti-tumor drug by blocking a cell growth-suppressive pathway *in vivo*. PLoS One, 10:e0123407, 2015

10. Fujita T, Chiwaki F, Takahashi RU, Aoyagi K, Yanagihara K, Nishimura T, Tamaoki M, Komatsu M, Komatsuzaki R, Matsusaki K, Ichikawa H, Sakamoto H, Yamada Y, Fukagawa T, Katai H, Konno H, Ochiya T, Yoshida T, Sasaki H. Identification and Characterization of CXCR4-Positive Gastric Cancer Stem Cells. PLoS One, 10:e0130808, 2015

Department of Analytical Pathology

Nobuyoshi Hiraoka, Yoshinori Ino-Ishikawa

Introduction

In the Department of Analytical Pathology, the pathobiological and clinicopathological characteristics of the target molecules are analyzed for evaluating their potential significance in applying diagnostic or treatment use in the future. Expression of the molecules or genes in human tissues is assessed by morphological techniques, immunohistochemistry, RT-PCR, in situ hybridization, and so forth, and the results are compared to clinicopathological information. We also try to develop new, more reliable, or more effective analytical methods and tools.

Research activities

Tertiary lymphoid organs (TLOs) are induced in various inflamed tissues. There were two different localizations of pancreatic ductal carcinoma (PDC)-associated TLOs: intratumoral and peritumoral. The presence of intratumoral TLOs represents a microenvironment that has an active immune reaction, and shows a relatively intact vascular network being retained.

Education

Teaching the analytical techniques to technicians and researchers in several departments of the National Cancer Center was performed.

Future prospects

We will answer requests from a selected project in various types of studies containing basic, preclinical, and clinical studies, and assess the clinicopathological or pathobiological significance of the target molecules. We will develop methods of quantitative analysis to evaluate morphological findings that are currently analyzed qualitatively.

List of papers published in 2015

Journal

1. Hiraoka N, Ino Y, Yamazaki-Itoh R, Kanai Y, Kosuge T, Shimada K. Intratumoral tertiary lymphoid organ is a favourable prognosticator in patients with pancreatic cancer. Br J Cancer, 112:1782-1790, 2015

2. Yoshida A, Yoshida H, Yoshida M, Mori T, Kobayashi E, Tanzawa Y, Yasugi T, Kawana K, Ishikawa M, Sugiura H, Maeda D, Fukayama M, Kawai A, Hiraoka N, Motoi T. Myoepithelioma-like Tumors of the Vulvar Region: A Distinctive Group of SMARCB1-deficient Neoplasms. Am J Surg Pathol, 39:1102-1113, 2015

3. Yoshida M, Ogawa R, Yoshida H, Maeshima A, Kanai Y, Kinoshita T, Hiraoka N, Sekine S. TERT promoter mutations are frequent and show association with MED12 mutations in phyllodes tumors of the breast. Br J Cancer, 113:1244-1248, 2015

4. Oguro S, Ino Y, Shimada K, Hatanaka Y, Matsuno Y, Esaki M, Nara S, Kishi Y, Kosuge T, Hiraoka N. Clinical significance of tumor-infiltrating immune cells focusing on BTLA and Cbl-b in patients with gallbladder cancer. Cancer Sci, 106:1750-1760, 2015

Department of Functional Analysis

Fumitaka Takeshita, Megumi Miyagi

Introduction

The Department of Functional Analysis carries out functional analysis for the development of scientific-based diagnosis and pre-clinical studies in corporation with other departments in the Fundamental Innovative Oncology Core Center (FIOC).

In 2015, we supported the following projects:

1) The project in FIOC for the establishment of xenografts and cell lines derived from cancer patients.
2) Investigator-initiated clinical trial for treatment-resistant breast cancer patients with novel siRNA against ribophorin II (RPN2) gene.
3) Development of Diagnostic Technology for Detection of miRNA in Body Fluids, grant from AMED.
4) Training and counseling for techniques for developing cancer models through experiments on animals and in vivo imaging for cancer model animals.

Research activities

In our laboratory, evaluation of treatments with cancer model studies and imaging for gene medicine molecules such as microRNA are undertaken by making good use of imaging devices that detect luminescence and fluorescence from living animals (Kosaka, Anticancer Res, Urata, Sci Rep, Takahashi, Nat Commun, Ono, Pathol Int, Fujita, Oncotarget, Fujita, Mol Ther).

Clinical trials

An investigator-initiated clinical trial (first-in-human phase I study) for treatment-resistant breast cancer patients with novel siRNA against ribophorin II (RPN2) gene was started from July 2015. This clinical trial is conducted by the Department of Breast and Medical Oncology in the National Cancer Center (NCC) Hospital. We have evaluated the POC of RPN2-siRNA using clinical samples.

List of papers published in 2015

Journal

1. Fujita Y, Yagishita S, Takeshita F, Yamamoto Y, Kuwano K, Ochiya T. Prognostic and therapeutic impact of RPN2-mediated tumor malignancy in non-small-cell lung cancer. Oncotarget, 6:3335-3345, 2015

2. Fujita Y, Yagishita S, Hagiwara K, Yoshioka Y, Kosaka N, Takeshita F, Fujiwara T, Tsuta K, Nokihara H, Tamura T, Asamura H, Kawaishi M, Kuwano K, Ochiya T. The clinical relevance of the miR-197/CKS1B/STAT3-mediated PD-L1 network in chemoresistant non-small-cell lung cancer. Mol Ther, 23:717-727, 2015

3. Takahashi RU, Miyazaki H, Takeshita F, Yamamoto Y, Minoura K, Ono M, Kodaira M, Tamura K, Mori M, Ochiya T. Loss of microRNA-27b contributes to breast cancer stem cell generation by activating ENPP1. Nat Commun, 6:7318, 2015

4. Ono M, Tsuda H, Kobayashi T, Takeshita F, Takahashi RU, Tamura K, Akashi-Tanaka S, Moriya T, Yamasaki T, Kinoshita T, Yamamoto J, Fujiwara Y, Ochiya T. The expression and clinical significance of ribophorin II (RPN2) in human breast cancer. Pathol Int, 65:301-308, 2015

5. Urata YN, Takeshita F, Tanaka H, Ochiya T, Takimoto M. Targeted knockdown of the kinetochore protein D40/Knl-1 inhibits human cancer in a p53 status-independent manner. Sci Rep, 5:13676, 2015

6. Kosaka T, Davydova J, Ono HA, Akiyama H, Hirai S, Ohno S, Takeshita F, Aoki K, Ochiya T, Yamamoto M, Kunisaki C, Endo I. Imaging and antitumoral effect of a cyclo-oxygenase 2-specific replicative adenovirus for small metastatic gastric cancer lesions. Anticancer Res, 35:5201-5210, 2015

Department of Animal Experimentation

Toshio Imai, Masako Ochiai, Yoshitaka Hippo, Tetsuya Matsuura, Takashi Nishizawa

Introduction

A pivotal role of this Department is the establishment of cancer animal models (human cancer tissue/cell-transplanted immune-deficient mice) used for exploration/screening of molecular target drugs. The goal is to set up flexible models that have greater accuracy than previous ones using cancer cell lines. In experiments using immune-deficient/severely immune-deficient mice, the microbiological environment of the animal experimentation facility should be strictly controlled and technical staff take great care of the facility.

Research activities

The research activities of the Department of Animal Experimentation are focused on studies of recapitulation of multi-step adenocarcinogenesis for diverse organs through an in vitro approach. Whereas both genetic and environmental factors cooperate for tumorigenesis in vivo, we demonstrated that the lentivirus-mediated introduction of genetic alterations in cultured murine primary epithelial cells, so called organoids, could lead to the development of adenocarcinoma in the dorsal skin of immunedeficient mice. Notably, tumor initiation and subsequent stepwise progression from normal cells via precancerous lesions to carcinoma could be accurately recapitulated for various vital organs in a cell-autonomous manner. By taking this approach, genetic and/or environmental interactions toward tumorigenesis could be conveniently investigated in vitro, which would likely accelerate elucidation of the molecular mechanisms underlying carcinogenesis. Large intestinal and pulmonary tissue-originated organoids have been newly established this year, and they are confirmed to lead to the development of adenocarcinoma by introduction of cancer-related genetic alterations.

Future prospects

The staff of the Department of Animal Experimentation are united in our resolve to establish a wide-ranging cancer animal model panel, which can be selected depending on the intended use.

List of papers published in 2015

Journal

1. Sakamaki A, Katsuragi Y, Otsuka K, Tomita M, Obata M, Iwasaki T, Abe M, Sato T, Ochiai M, Sakuraba Y, Aoyagi Y, Gondo Y, Sakimura K, Nakagama H, Mishima Y, Kominami R. Bcl11b SWI/SNF-complex subunit modulates intestinal adenoma and regeneration after γ-irradiation through Wnt/β-catenin pathway. Carcinogenesis, 36:622-631, 2015

Department of Cell Culture Technology

Tohru Kiyono, Farhana Ishrat Ghani, Chiho Kohno

Introduction

Human cells in culture have a limited lifespan and undergo a non-dividing state named senescence. The replicative senescence is caused by telomere shortening since most human somatic cells do not express telomerase to the level sufficient for maintenance of telomere length. Human epithelial cells also undergo a non-dividing state much earlier, not because of telomere shortening but because of accumulation of $p16^{INK4A}$ and activation of pRB. Stem or progenitor cells of human epithelia often express higher levels of TERT so that telomere shortening is delayed. In a certain culture condition that induces higher levels of TERT expression and inhibits $p16^{INK4A}$ induction, they could proliferate infinitely without any transgenes.

Routine activities

This Department was founded in 2014 for developing better methods to cultivate normal human cells as well as cancer cells derived from clinical specimens obtained by operation, biopsy and therapy.

Research activities

Recently, a culture condition with feeder layer cells and the ROCK inhibitor, Y-27632, has been developed for infinite proliferation of several epithelial cell types. Based on the improved method developed by the Division of Carcinogenesis and Prevention, we now can cultivate so far difficult-to-cultivate primary human cells, such as hepatocytes, pancreatic duct cells, gastric epithelial cells and colon epithelial cells without feeder cells. A method for a long-term culture of these cell types has been established, and also can be immortalized by transduction of CDK4, cyclin D1 and TERT so as to be cultivated in more general culture conditions.

Future prospects

Our goal is to establish a cell culture method that can easily amplify every cell type including normal, pre-neoplastic and cancer cells. Our trials include organoid culture as well as conventional two-dimensional culture. Once cells-of-origin of every cancer can be easily amplified *in vitro*, they can be used for normal control cells for each cancer. The causal relationship of a gene mutation found in cancer and a certain phenotype such as drug resistance can be directly evaluated by transducing the mutant gene into them. They might also be applied to development of cell transplantation therapy.

Department of Bioinformatics

Mamoru Kato, Asmaa Elzawahry, Eisaku Furukawa, Joe Miyamoto, Momoko Nagai, Daichi Narushima

Introduction

The missions of our Department are 1) to develop new bioinformatics and data-analysis methods necessary for cancer studies, 2) to build new theories for understanding cancer through data analysis and computational approaches, and 3) bioinformatics analysis support for experimental groups in the Center as well as other research institutions.

Research activities

- We took charge of the bioinformatics part in the clinical sequencing project in the National Cancer Center (NCC). The bioinformatics part consists of 1) development of DNA-alteration calling programs, 2) development of medical information systems for clinical sequencing, and 3) construction of the computer network for clinical sequencing.

1) We improved our computer programs optimized for FFPE samples used in clinical sequencing. These programs detect SNV, indels, gene fusions, and copy number alterations from a large amount of data produced by the next generation sequencer (NGS). We compared our programs with other well-known programs (originally developed for cell-line and frozen samples for research purposes). We confirmed that our programs greatly outperformed the other programs. We also developed a special program that detects known alterations that were in principle hard to detect previously.
2) We developed a pipeline system for detection of somatic and germline alterations based on tumors and two types of normal tissue samples (matched and un-matched mixed normal). We also developed a program to output an Expert Panel report that integrates detected alterations with clinical information.
3) We set up a cluster machine and constructed a computer network for clinical sequencing in the NCC Central Hospital. We implemented the calling programs into the network to automatically run procedures from alteration detection to making a report.

- We performed big data analysis for trans-omics data of lung adenocarcinoma and hepatocellular carcinoma as a part of the Medical Big Data project, and found new prognosis markers.
- We provided bioinformatics support for studies such as those on liver cancer and bile duct cancer as a part of ICGC, pancreas cancer, tumor immunity, and cell-free DNA in the Division of Cancer Genomics; on DNA adductome, gene expression of cancer stem cells, and carcinogen DNA variants in the Division of Cancer Development System; and on germinoma in the Division of Brain Tumor Translational Research.
- We performed single-cell sequencing to reveal intra-tumor heterogeneity and cancer-cell evolution, collaborating with the Division of Cancer Genomics and Chiba Cancer Center. Using a mouse model for cancer development, we performed single-cell exome and transcriptome sequencing and developed pipeline programs to analyze the dynamics of cancer-cell subpopulations along the time-course.

Education

Our Department employed three technical staff members this year (two of them were staff-transferred) and educated them through on-the-job training. Our Department gave advice to bioinformatics technical staff in the Division of Cancer Genomics.

Future prospects

We will develop information technologies for clinical sequencing and promote technology transfer to implement precision medicine. We will also develop algorithms to find novel tumor molecular markers and cancer subtypes, using medical big data that will be accelerated by clinical sequencing. We will promote single-cell sequencing studies to reveal the dynamics of intra-tumor heterogeneity. We will keep continue to provide bioinformatics support for other groups in the Center.

List of papers published in 2015

Journal

1. Takai E, Totoki Y, Nakamura H, Morizane C, Nara S, Hama N, Suzuki M, Furukawa E, Kato M, Hayashi H, Kohno T, Ueno H, Shimada K, Okusaka T, Nakagama H, Shibata T, Yachida S. Clinical utility of circulating tumor DNA for molecular assessment in pancreatic cancer. Sci Rep, 5:18425, 2015

2. Ishino K, Kato T, Kato M, Shibata T, Watanabe M, Wakabayashi K, Nakagama H, Totsuka Y. Comprehensive DNA adduct analysis reveals pulmonary inflammatory response contributes to genotoxic action of magnetite nanoparticles. Int J Mol Sci, 16:3474-3492, 2015

3. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, Hama N, Hosoda F, Urushidate T, Ohashi S, Hiraoka N, Ojima H, Shimada K, Okusaka T, Kosuge T, Miyagawa S, Shibata T. Genomic spectra of biliary tract cancer. Nat Genet, 47:1003-1010, 2015

4. Takenaka M, Saito M, Iwakawa R, Yanaihara N, Saito M, Kato M, Ichikawa H, Shibata T, Yokota J, Okamoto A, Kohno T. Profiling of actionable gene alterations in ovarian cancer by targeted deep sequencing. Int J Oncol, 46:2389-2398, 2015

5. Saito M, Shimada Y, Shiraishi K, Sakamoto H, Tsuta K, Totsuka H, Chiku S, Ichikawa H, Kato M, Watanabe S, Yoshida T, Yokota J, Kohno T. Development of lung adenocarcinomas with exclusive dependence on oncogene fusions. Cancer Res, 75:2264-2271, 2015

Department of Omics Network

Masaru Katoh

Introduction

The Department of Omics Network, established in August 2014, is derived from Masaru Katoh's laboratory, which was also known as the Genetics and Cell Biology Section (from 1998 to 2009) and the Katoh's Unit (from 2009 to 2014). The Department is involved in innovation based on the balance between its main world-class projects and cutting-edge new projects. Masaru Katoh has been changing his field in medical and life sciences: he was engaged in clinical medicine from 1986 to 1990, basic medicine from 1990 to 2002 and information science from 2003 to 2011. Since 2012, Masaru Katoh has been engaged in the Knowledgebase Project with the slogan "Back to the Medicine".

The WNT (PMID: 17634527), FGF (PMID: 23696246), Notch (PMID: 17143535) and Hedgehog (PMID: 19860666) signaling cascades and the Forkhead-box (FOX) family of transcription factors (PMID: 23022474) are the main (fundamental) projects of the Department. Cell adhesion (PMID 25865774), epigenetics (PMID 26411517) and microRNA (miRNA) (PMID 25364765) are new (cutting-edge) projects of the Department. The fundamental projects and cutting-edge projects are the essential constituent parts of the Department (Figure 1).

Research activities

Genomics, transcriptomics, proteomics and metabolomics are representative "omics" disciplines of life science that deal with the entirety of genes, transcripts, proteins, and metabolites, respectively. Omics medicine is an emerging discipline of medical science that produces large amounts of omics data on genetics, genomics, epigenetics, transcriptomics, proteomics, and metabolomics. Omics medicine consists of three layers: the first layer corresponds to clinical medicine that involves patients' care and clinical sampling of blood and tissues (bio-banks); the second layer corresponds to basic medicine that produces high-throughput omics data using microarrays and next-generation sequencing technologies (databases); and the third layer corresponds to translational medicine that generates knowledge on mechanisms of pathogenesis, diagnostics, therapeutics, and so forth (knowledge base). The goal of the Department is the establishment of a knowledge base focused on the regulatory signaling network for the development of novel diagnostics and therapeutics. Integrative clinicopathological analyses have been carried out in the Department using the solid data on genomics, epigenomics, proteomics, exosome, and so forth.

ASXL1, ASXL2 and ASXL3 are epigenetic regulators associated with BAP1, EZH2 and nuclear hormone receptors. Germline mutations in the *ASXL* family genes cause Bohring-Opitz and related syndromes presented with intellectual disability, cranioskeletal features and feeding problems. Somatic alterations in the *ASXL* family genes occur in hematological malignancies, such as myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), acute myeloid leukaemia (AML) and chronic lymphocytic leukaemia (CLL), as well as solid tumors, such as colorectal cancer with microsatellite instability (MSI), breast cancer, prostate cancer and pancreatic cancer. ASXLs themselves are not appropriate drug targets, because ASXLs are adaptor molecules without their intrinsic enzymatic function. At present, there are no therapeutics for cases with ASXL mutations.

ALK, CSF1R (FMS), DDR2, EGFR, ERBB2, EFBB3, ERBB4, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, IGF1R, KIT, MET, PDGFRA, RET and

VEGFR2 (KDR) are receptor tyrosine kinases (RTKs) on the Oncomine Cancer Research Panel (OCP) for clinical sequencing. FGFR1, FGFR2, FGFR3 and FGFR4 are activated in breast cancer, gastric cancer, glioblastma, leukemia, lung cancer, prostate cancer, soft-tissue sarcomas, and so forth, owing to gene amplification, gene fusion or gain-of-function mutation. AZD4547, BGJ398 and dovitinib are representative FGFR inhibitors that are in clinical trials for cancer patients with FGFR alterations. The tumor microenvironment consists of cancer cells and stromal/immune cells, such as cancer-associated fibroblasts (CAFs), endothelial cells, myeloid-derived suppressor cells (MDSCs), tumor-associating macrophages of M2 type (M2-TAMs) and regulatory T (Treg) cells. Therapeutics targeting cancer cells, tumor angiogenesis and immune evasion are ongoing themes of the in-house study in the Department.

CD44 is a cell-adhesion molecule that functions as a hyaluronan receptor as well as a co-receptor of growth factors and is utilized as a functional biomarker of cancer stem cells. Exploration of drug targets and development of disease biomarkers related to CD44 and other cell-adhesion molecules are ongoing themes of the international collaboration study in the Department.

Contribution to the global scientific community

Masaru Katoh has been contributing to the global scientific community based on manuscript publication, reviewer activity and editor activity. Katoh carried out peer reviews of grant proposals or journal manuscripts written in English 64 times in 2015. Katoh is an Academic Editor of *PLoS ONE*, and carried out editorial decisions 102 times in 2015. Masaru Katoh is the Chief Editor of *Frontiers in Molecular Medicine* that aims to address the gap between cell and developmental biology and clinical medicine, together with 113 editorial board members.

The manuscript citation count in the Web of Science Database (Thomson Reuters) is a surrogate marker of the contribution to the global science community. Katoh's manuscripts were cited at least 640 times by others in 2015.

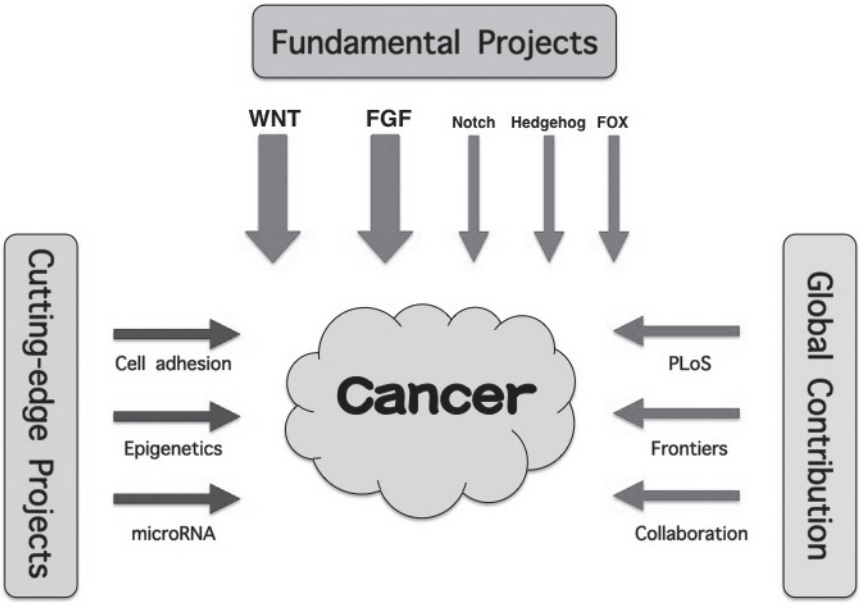


Figure 1. Fundamental Projects, Cutting-edge Projects and International Contribution in the Department of Omics Network

List of papers published in 2015

Journal

1. Jiang WG, Sanders AJ, Katoh M, Ungefroren H, Gieseler F, Prince M, Thompson SK, Zollo M, Spano D, Dhawan P, Sliva D, Subbarayan PR, Sarkar M, Honoki K, Fujii H, Georgakilas AG, Amedei A, Niccolai E, Amin A, Ashraf SS, Ye L, Helferich WG, Yang X, Boosani CS, Guha G, Ciriolo MR, Aquilano K, Chen S, Azmi AS, Keith WN, Bilsland A, Bhakta D, Halicka D, Nowsheen S, Pantano F, Santini D. Tissue invasion and metastasis: Molecular, biological and clinical perspectives. Semin Cancer Biol, 35:S244-S275, 2015
2. Katoh M. Functional proteomics of the epigenetic regulators ASXL1, ASXL2 and ASXL3: a convergence of proteomics and epigenetics for translational medicine. Expert Rev Proteomics, 12:317-328, 2015

Exploratory Oncology
Research & Clinical Trial Center

Preface

In 2011, the National Cancer Center was selected as one of the five designated centers for early/exploratory clinical trials. In 2012, with budget support from the Japanese Ministry of Health, Labour and Welfare (MHLW), we organized "the Exploratory Oncology Research and Clinical Trial Center" (NCC-EPOC) through the Kashiwa and Tsukiji campuses, which focus on early/exploratory clinical trials and translational research (TR). The NCC-EPOC was actually activated in April 2013 consisting of a phase I unit in each campus, a central/data center function unit for clinical trials, and a translational research (TR) unit. The TR unit additionally included the immunotherapy division in July 2013. As for drug developments from Japan, three missions are focused on in the NCC-EPOC: to conduct first-in-human (FIH) trials, investigator-initiated trials (IITs) with unapproved agents, and TRs during early clinical studies. In addition to drug development, EPOC was integrated with the Research Center for Innovative Oncology (RCIO) in 2015 and has started developing medical equipment and accelerating higher quality TR in the NCC. The activities in each unit in 2015 are described as follows:

1) Group for Clinical Research: The Department of Experimental Therapeutics consisting of several medical oncologists with backgrounds in each organ department was newly organized in both hospitals in order to conduct all-comer-type FIH/phase I studies. A regular weekly teleconference is held to collaborate with the two groups in each hospital. In 2015, several FIH trials including three IITs have been achieved in total at both hospitals. The number of phase I studies in the NCC means it is ranked as the largest academic center in Asia. New seed subjects from outside academic research organizations have been introduced.
2) Group for Innovative Center Treatment: We organized and co-developed several new seeds including newly developed antibodies, an antibody-drug-conjugate (ADC), a peptide vaccine, immune cell therapy and drugs for supportive care in both campuses. In 2015, two venture businesses, a new immune therapy business at the Tsukiji campus and a new antibody development business at the Kashiwa campus, have been launched to organize quick introduction to early clinical trials. With collaboration with the Seeds selection committee, we support early non-clinical seeds for quick introduction to early clinical development and follow them up.
3) Group for Translational Research: Nationwide genome screening network (SCRUM Japan). Several pharmaceutical companies, which conducted similar new agent development studies for tiny populations with driver gene alterations, joined this network under contract with the NCC. A similar screening system for some driver genes has also started in colorectal cancers using an originally developed screening panel, followed by an organization of nationwide genome screening academia-industry consortium (SCRUM-JAPAN) using a cutting-edge pan-cancer NGS panel. A total of 15 pharmaceutical companies are collaborating with the consortium for more than 2,500 new patients per year with lung and gastrointestinal cancer genome screening in association with more than 30 agent studies. This study will contribute to making a public database of genome profiling and the distribution of precision medicine in Japan. The TOP-GEAR study aiming to establish genome information-driven standard treatment has started in collaboration with the in-house genome sequencing laboratory (SCI Lab), in which QA/QC is regulated according to the CLIA law in the Department of Pathology and Clinical Laboratories, Hospital at Tsukiji campus
4) Group for Innovative Diagnostic an Therapeutic Device: Four fields concerning development of endoscopy, surgical equipment, functional imaging and proton therapy have innovated new medical equipment and introduced them to clinical trials for obtaining approval as medical equipment. We established "C-square" jointly with Chiba prefecture chambers of commerce and local manufacturing companies in the Tohkatsu area to establish industry-academia cooperation. We are aggressively developing new radiation therapies as intensity modulated radiation therapy and boron neutron capture therapy (BNCT) and are planning for clinical introduction in both campuses.

Atsushi Ochiai, M.D., Ph.D
Director, Exploratory Oncology Research & Clinical Trial Center

Organization

President:
Tomomitsu Hotta

Director:
Atsushi Ohtsu

- Group for Clinical Research
  - Division of Experimental Therapeutics
    Chief (Kashiwa): Toshihiko Doi
    Chief (Tsukiji): Noboru Yamamoto
- Group for Translational Research
  - Division of Pathology
    Chief: Atsushi Ochiai
  - Division of Translational Research
    Chief (Kashiwa): Katsuya Tsuchihara
    Chife (Tsukiji): Takashi Kohno
  - Division of Cancer Immunology
    Chief: Hiroyoshi Nishikawa
  - Division of Clinical Pharmacology and Translational Research
    Chief: Akinobu Hamada
- Group for Innovative Cancer Treatment
  - Division of Developmental Therapeutics
    Chief: Yasuhiro Matsumura
  - Division of Cancer Immunotherapy
    Chief (Kashiwa): Tetsuya Nakatsura
    Chief (Tsukiji): Kiyoshi Yoshimura
  - Division of Psycho-Oncology
    Chief: Asao Ogawa
- Group for Innovative Diagnostic and Therapeutic Device
  - Division of Radiation Oncology and Particle Therapy
    Chief: Tetsuo Akimoto
  - Division of Functional Imaging
    Chief: Hirofumi Fujii
  - Division of Science and Technology for Endoscopy
    Chief: Kazuhiro Kaneko
  - Division of Surgical Technology
    Chief: Masaaki Ito
- Section of Experimental Animals
  Chief: Yoshikatsu Koga

Activities of the Divisions

Division of Experimental Therapeutics

[Kashiwa Campus] Toshihiko Doi, Kiyotaka Yoh, Yoichi Naito, Takahiro Kogawa, Kohei Shitara, Hideaki Takahashi, Tomoko Yamazaki, Yasutoshi Kuboki
[Tsukiji Campus] Noboru Yamamoto, Kenji Tamura, Yutaka Fujiwara, Shigehisa Kitano, Shunsuke Kondo, Satoru Iwasa

Introduction

The Division of Experimental Therapeutics supports efforts toward the creation of new drugs and other products from breakthroughs originating from academic institutions by achieving results at the level of basic research. We evaluate and discover excellent research and development proposals, and provide integrated management of the program so that basic research outcomes are linked through to clinical research and clinical trial for approval. We have conducted several IITs as applications for approval and also have promoted research and development in the field of medicine.

Routine activities

Engaging in medical R&D and establishment/ maintenance of medical research environment

Research activities

We promote the following activities for appropriate conducting of research and trials.

- To plan the clinical trial as IIT for achieving POC of new academic seeds
- Explanation meetings for researchers and office employees on compliance of laws, ordinances and guidelines
- To consider development design to create a new with the goal of creating innovative drugs, medical devices, as well as ensuring that research projects on promising results proceed more rapidly and in greater depth

Clinical trials

We have conducted several IITs using unapproved drugs from academia and pharmaceutical companies (Table 1).

Table 1. Experimental Therapeutics 2015 Number of Investigator-Initiated Trials

Phase I	Phase I (FIH)	Phase Ib	Phase II	Phase IIa	EAP
1	3	2 (1)	9 (4)	1 (1)	3

* ( ) Pharmaceutical company grant

List of papers published in 2015

Journal

(Kashiwa Campus)

1. Watanabe N, Umemura S, Niho S, Kirita K, Matsumoto S, Yoh K, Ohmatsu H, Goto K. Docetaxel for platinum-refractory advanced thymic carcinoma. Jpn J Clin Oncol, 45:665-669, 2015
2. Fouad TM, Kogawa T, Liu DD, Shen Y, Masuda H, El-Zein R, Woodward WA, Chavez-MacGregor M, Alvarez RH, Arun B, Lucci A, Krishnamurthy S, Babiera G, Buchholz TA, Valero V, Ueno NT. Overall survival differences between patients with inflammatory and noninflammatory breast cancer presenting with distant metastasis at diagnosis. Breast Cancer Res Treat, 152:407-416, 2015

3. Fujii T, Le Du F, Xiao L, Kogawa T, Barcenas CH, Alvarez RH, Valero V, Shen Y, Ueno NT. Effectiveness of an Adjuvant Chemotherapy Regimen for Early-Stage Breast Cancer: A Systematic Review and Network Meta-analysis. JAMA Oncol, 1:1311-1318, 2015

4. Kai M, Kogawa T, Liu DD, Fouad TM, Kai K, Niikura N, Hsu L, Willey JS, Theriault RL, Valero V, Ueno NT. Clinical characteristics and outcome of bone-only metastasis in inflammatory and noninflammatory breast cancers. Clin Breast Cancer, 15:37-42, 2015

5. Hayashi N, Niikura N, Masuda N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M, Kondo N, Naito Y, Honda Y, Matsui A, Fujisawa T, Oshitanai R, Yasojima H, Yamauchi H, Saji S, Iwata H. Prognostic factors of HER2-positive breast cancer patients who develop brain metastasis: a multicenter retrospective analysis. Breast Cancer Res Treat, 149:277-284, 2015

6. Mukai H, Saeki T, Shimada K, Naito Y, Matsubara N, Nakanishi T, Obaishi H, Namiki M, Sasaki Y. Phase 1 combination study of eribulin mesylate with trastuzumab for advanced or recurrent human epidermal growth factor receptor 2 positive breast cancer. Invest New Drugs, 33:119-127, 2015

7. Yoshida T, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Ohe Y, Goto K. RECIST progression patterns during EGFR tyrosine kinase inhibitor treatment of advanced non-small cell lung cancer patients harboring an EGFR mutation. Lung Cancer, 90:477-483, 2015

8. Daga H, Takeda K, Okada H, Miyazaki M, Ueda S, Kaneda H, Okamoto I, Yoh K, Goto K, Konishi K, Sarashina A, Tanaka T, Kaiser R, Nakagawa K. Phase I study of nintedanib in combination with pemetrexed as second-line treatment of Japanese patients with advanced non-small cell lung cancer. Cancer Chemother Pharmacol, 76:1225-1233, 2015

9. Yoshida T, Ishii G, Goto K, Neri S, Hashimoto H, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Iida S, Niimi A, Nagai K, Ohe Y, Ochiai A. Podoplanin-positive cancer-associated fibroblasts in the tumor microenvironment induce primary resistance to EGFR-TKIs in lung adenocarcinoma with EGFR mutation. Clin Cancer Res, 21:642-651, 2015

10. Miura T, Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Takahashi H, Furuse J, Inagaki M, Higashi S, Kato H, Terao K, Ochiai A. Characterization of patients with advanced pancreatic cancer and high serum interleukin-6 levels. Pancreas, 44:756-763, 2015

11. Fujii S, Fujihara A, Natori K, Abe A, Kuboki Y, Higuchi Y, Aizawa M, Kuwata T, Kinoshita T, Yasui W, Ochiai A. TEM1 expression in cancer-associated fibroblasts is correlated with a poor prognosis in patients with gastric cancer. Cancer Med, 4:1667-1678, 2015

12. Komatsu Y, Doi T, Sawaki A, Kanda T, Yamada Y, Kuss I, Demetri GD, Nishida T. Regorafenib for advanced gastrointestinal stromal tumors following imatinib and sunitinib treatment: a subgroup analysis evaluating Japanese patients in the phase III GRID trial. Int J Clin Oncol, 20:905-912, 2015

13. Sugiyama E, Umemura S, Nomura S, Kirita K, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Ohe Y, Goto K. Impact of single nucleotide polymorphisms on severe hepatotoxicity induced by EGFR tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring EGFR mutations. Lung Cancer, 90:307-313, 2015

14. Hishida T, Tsuboi M, Shukuya T, Takamochi K, Sakurai H, Yoh K, Ohashi Y, Kunitoh H. Multicenter observational cohort study of post-operative treatment for completely resected non-small-cell lung cancer of pathological stage I (T1 >2 cm and T2 in TNM classification version 6). Jpn J Clin Oncol, 45:499-501, 2015

15. Udagawa H, Ishii G, Morise M, Umemura S, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A, Ohe Y. Comparison of the expression levels of molecular markers among the peripheral area and central area of primary tumor and metastatic lymph node tumor in patients with squamous cell carcinoma of the lung. J Cancer Res Clin Oncol, 141:1417-1425, 2015

16. Koriyama H, Ishii G, Yoh K, Neri S, Morise M, Umemura S, Matsumoto S, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A. Presence of podoplanin-positive cancer-associated fibroblasts in surgically resected primary lung adenocarcinoma predicts a shorter progression-free survival period in patients with recurrences who received platinum-based chemotherapy. J Cancer Res Clin Oncol, 141:1163-1170, 2015

17. Doi T, Tamura K, Tanabe Y, Yonemori K, Yoshino T, Fuse N, Kodaira M, Bando H, Noguchi K, Shimamoto T, Ohtsu A. Phase 1 pharmacokinetic study of the oral pan-AKT inhibitor MK-2206 in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:409-416, 2015

18. Asao T, Nokihara H, Yoh K, Niho S, Goto K, Ohmatsu H, Kubota K, Yamamoto N, Sekine I, Kunitoh H, Fujiwara Y, Ohe Y. Phase II study of amrubicin at a dose of 45 mg/m2 in patients with previously treated small-cell lung cancer. Jpn J Clin Oncol, 45:941-946, 2015

19. Doi T, Yoshino T, Shitara K, Matsubara N, Fuse N, Naito Y, Uenaka K, Nakamura T, Hynes SM, Lin AB. Phase I study of LY2603618, a CHK1 inhibitor, in combination with gemcitabine in Japanese patients with solid tumors. Anticancer Drugs, 26:1043-1053, 2015

20. Kawazoe A, Shitara K, Fukuoka S, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yamanaka T, Doi T, Ohtsu A, Yoshino T. A retrospective observational study of clinicopathological features of KRAS, NRAS, BRAF and PIK3CA mutations in Japanese patients with metastatic colorectal cancer. BMC Cancer, 15:258, 2015

21. Kawazoe A, Shitara K, Fukuoka S, Noguchi M, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yoshino T, Ohtsu A, Doi T. Clinical outcomes in 66 patients with advanced gastric cancer treated in phase I trials: the NCCHE experience. Invest New Drugs, 33:664-670, 2015

22. Kondoh C, Shitara K, Nomura M, Takahari D, Ura T, Tachibana H, Tomita N, Kodaira T, Muro K. Efficacy of palliative radiotherapy for gastric bleeding in patients with unresectable advanced gastric cancer: a retrospective cohort study. BMC Palliat Care, 14:37, 2015

23. Oh DY, Doi T, Shirao K, Lee KW, Park SR, Chen Y, Yang L, Valota O, Bang YJ. Phase I Study of Axitinib in Combination with Cisplatin and Capecitabine in Patients with Previously Untreated Advanced Gastric Cancer. Cancer Res Treat, 47:687-696, 2015

24. Saito T, Kondo C, Shitara K, Ito Y, Saito N, Ikehara Y, Yatabe Y, Yamamichi K, Tanaka H, Nakanishi H. Comparison of intratumoral heterogeneity of HER2 expression between primary tumor and multiple organ metastases in gastric cancer: Clinicopathological study of three autopsy cases and one resected case. Pathol Int, 65:309-317, 2015

25. Ikeda M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Kondo S, Morizane C, Ueno H, Okusaka T. Chemotherapy for advanced poorly differentiated pancreatic neuroendocrine carcinoma. J Hepatobiliary Pancreat Sci, 22:623-627, 2015

26. Takahashi H, Kaniwa N, Saito Y, Sai K, Hamaguchi T, Shirao K, Shimada Y, Matsumura Y, Ohtsu A, Yoshino T, Doi T, Takahashi A, Odaka Y, Okuyama M, Sawada J, Sakamoto H, Yoshida T. Construction of possible integrated predictive index based on EGFR and ANXA3 polymorphisms for chemotherapy response in fluoropyrimidine-treated Japanese gastric cancer patients using a bioinformatic method. BMC Cancer, 15:718, 2015

27. Ueda S, Satoh T, Gotoh M, Gao L, Doi T. A phase ib study of safety and pharmacokinetics of ramucirumab in combination with paclitaxel in patients with advanced gastric adenocarcinomas. Oncologist, 20:493-494, 2015

28. Kurose K, Ohue Y, Wada H, Iida S, Ishida T, Kojima T, Doi T, Suzuki S, Isobe M, Funakoshi T, Kakimi K, Nishikawa H, Udono H, Oka M, Ueda R, Nakayama E. Phase Ia Study of FoxP3+ CD4 Treg Depletion by Infusion of a Humanized Anti-CCR4 Antibody, KW-0761, in Cancer Patients. Clin Cancer Res, 21:4327-4336, 2015

29. Nishio M, Horiike A, Nokihara H, Horinouchi H, Nakamichi S, Wakui H, Ohyanagi F, Kudo K, Yanagitani N, Takahashi S, Kuboki Y, Yamamoto N, Yamada Y, Abe M, Tahata T, Tamura T. Phase I study of the anti-MET antibody onartuzumab in patients with solid tumors and MET-positive lung cancer. Invest New Drugs, 33:632-640, 2015

30. Okusaka T, Ueno H, Morizane C, Kondo S, Sakamoto Y, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Ikeda M. Cytotoxic chemotherapy for pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci, 22:628-633, 2015

31. Takahashi H, Ikeda M, Kumada T, Osaki Y, Kondo S, Kusumoto S, Ohkawa K, Nadano S, Furuse J, Kudo M, Ito K, Yokoyama M, Okusaka T, Shimoyama M, Mizokami M. Multicenter cooperative case survey of hepatitis B virus reactivation by chemotherapeutic agents. Hepatol Res, 45:1220-1227, 2015

32. Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, Goto K. Beyond *ALK-RET*, ROS1 and other oncogene fusions in lung cancer. Transl Lung Cancer Res, 4:156-164, 2015

33. Nagatsuma AK, Aizawa M, Kuwata T, Doi T, Ohtsu A, Fujii H, Ochiai A. Expression profiles of HER2, EGFR, MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma. Gastric Cancer, 18:227-238, 2015

34. Shinohara A, Ikeda M, Okuyama H, Kobayashi M, Funazaki H, Mitsunaga S, Shimizu S, Ohno I, Takahashi H, Ichida Y, Takahashi K, Okusaka T, Saitoh S. Efficacy of prophylactic minocycline treatment for skin toxicities induced by erlotinib plus gemcitabine in patients with advanced pancreatic cancer: a retrospective study. Am J Clin Dermatol, 16:221-229, 2015

35. Shitara K, Ohtsu A. Ramucirumab for gastric cancer. Expert Rev Gastroenterol Hepatol, 9:133-139, 2015

36. Sasaki T, Fuse N, Kuwata T, Nomura S, Kaneko K, Doi T, Yoshino T, Asano H, Ochiai A, Komatsu Y, Sakamoto N, Ohtsu A. Serum HER2 levels and HER2 status in tumor cells in advanced gastric cancer patients. Jpn J Clin Oncol, 45:43-48, 2015

37. Okuyama H, Ikeda M, Kuwahara A, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Senda S, Okusaka T. Prognostic factors in patients with hepatocellular carcinoma refractory or intolerant to sorafenib. Oncology, 88:241-246, 2015

38. Doi T, Yoshino T, Fuse N, Boku N, Yamazaki K, Koizumi W, Shimada K, Takinishi Y, Ohtsu A. Phase I study of TAS-102 and irinotecan combination therapy in Japanese patients with advanced colorectal cancer. Invest New Drugs, 33:1068-1077, 2015

39. Kataoka K, Tokunaga M, Mizusawa J, Machida N, Katayama H, Shitara K, Tomita T, Nakamura K, Boku N, Sano T, Terashima M, Sasako M, Stomach Cancer Study Group/Japan Clinical Oncology Group. A randomized Phase II trial of systemic chemotherapy with and without trastuzumab followed by surgery in HER2-positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1301 (Trigger Study). Jpn J Clin Oncol, 45:1082-1086, 2015

40. Kogawa T, Fouad TM, Wei C, Masuda H, Kai K, Fujii T, El-Zein R, Chavez-MacGregor M, Litton JK, Brewster A, Alvarez RH, Hortobagyi GN, Valero V, Theriault R, Ueno NT. Association of Body Mass Index Changes during Neoadjuvant Chemotherapy with Pathologic Complete Response and Clinical Outcomes in Patients with Locally Advanced Breast Cancer. J Cancer, 6:310-318, 2015

41. Enomoto Y, Kenmotsu H, Watanabe N, Baba T, Murakami H, Yoh K, Ogura T, Takahashi T, Goto K, Kato T. Efficacy and Safety of Combined Carboplatin, Paclitaxel, and Bevacizumab for Patients with Advanced Non-squamous Non-small Cell Lung Cancer with Pre-existing Interstitial Lung Disease: A Retrospective Multi-institutional Study. Anticancer Res, 35:4259-4263, 2015

42. Soria JC, Wu YL, Nakagawa K, Kim SW, Yang JJ, Ahn MJ, Wang J, Yang JC, Lu Y, Atagi S, Ponce S, Lee DH, Liu Y, Yoh K, Zhou JY, Shi X, Webster A, Jiang H, Mok TS. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol, 16:990-998, 2015

43. Takahashi A, Ishii G, Neri S, Yoshida T, Hashimoto H, Suzuki S, Umemura S, Matsumoto S, Yoh K, Niho S, Goto K, Ohmatsu H, Nagai K, Gemma A, Ohe Y, Ochiai A. Podoplanin-expressing cancer-associated fibroblasts inhibit small cell lung cancer growth. Oncotarget, 6:9531-9541, 2015

44. Watanabe N, Niho S, Kirita K, Umemura S, Matsumoto S, Yoh K, Ohmatsu H, Goto K. Second-line docetaxel for patients with platinum-refractory advanced non-small cell lung cancer and interstitial pneumonia. Cancer Chemother Pharmacol, 76:69-74, 2015

45. Watanabe N, Niho S, Kirita K, Umemura S, Matsumoto S, Yoh K, Ohmatsu H, Goto K. Vinorelbine and cisplatin in patients with advanced non-small cell lung cancer with interstitial pneumonia. Anticancer Res, 35:1697-1701, 2015

(Tsukiji Campus)

1. Ono M, Tsuda H, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Kinoshita T, Fujiwara Y. Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers. Breast Cancer, 22:141-152, 2015

2. Yamamoto H, Ando M, Aogi K, Iwata H, Tamura K, Yonemori K, Shimizu C, Hara F, Takabatake D, Hattori M, Asakawa T, Fujiwara Y. Phase I and pharmacokinetic study of trastuzumab emtansine in Japanese patients with HER2-positive metastatic breast cancer. Jpn J Clin Oncol, 45:12-18, 2015

3. Yagishita S, Horinouchi H, Katsui Taniyama T, Nakamichi S, Kitazono S, Mizugaki H, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. Int J Radiat Oncol Biol Phys, 91:140-148, 2015

4. Utsumi H, Honma Y, Nagashima K, Iwasa S, Takashima A, Kato K, Hamaguchi T, Yamada Y, Shimada Y, Kishi Y, Nara S, Esaki M, Shimada K. Bevacizumab and postoperative wound complications in patients with liver metastases of colorectal cancer. Anticancer Res, 35:2255-2261, 2015

5. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Fujiwara Y, Tamura Y, Wakui H, Honda K, Mizugaki H, Kitazono S, Tanabe Y, Asahina H, Yamazaki N, Suzuki S, Matsuoka M, Ogita Y, Tamura T. Phase I and pharmacokinetics/pharmacodynamics study of the MEK inhibitor RO4987655 in Japanese patients with advanced solid tumors. Invest New Drugs, 33:641-651, 2015

6. Abe S, Oda I, Nakajima T, Suzuki H, Nonaka S, Yoshinaga S, Sekine S, Taniguchi H, Kushima R, Iwasa S, Saito Y, Katai H. A case of local recurrence and distant metastasis following curative endoscopic submucosal dissection of early gastric cancer. Gastric Cancer, 18:188-192, 2015

7. Asao T, Nokihara H, Yoh K, Niho S, Goto K, Ohmatsu H, Kubota K, Yamamoto N, Sekine I, Kunitoh H, Fujiwara Y, Ohe Y. Phase II study of amrubicin at a dose of 45 mg/m2 in patients with previously treated small-cell lung cancer. Jpn J Clin Oncol, 45:941-946, 2015

8. Chua C, Tan IB, Yamada Y, Rha SY, Yong WP, Ong WS, Tham CK, Ng M, Tai DW, Iwasa S, Lim HY, Choo SP. Phase II study of trastuzumab in combination with S-1 and cisplatin in the first-line treatment of human epidermal growth factor receptor HER2-positive advanced gastric cancer. Cancer Chemother Pharmacol, 76:397-408, 2015

9. Davies BR, Guan N, Logie A, Crafter C, Hanson L, Jacobs V, James N, Dudley P, Jacques K, Ladd B, D'Cruz CM, Zinda M, Lindemann J, Kodaira M, Tamura K, Jenkins EL. Tumors with AKT1E17K Mutations Are Rational Targets for Single Agent or Combination Therapy with AKT Inhibitors. Mol Cancer Ther, 14:2441-2451, 2015

10. Fujiwara Y, Kobayashi S, Nagano H, Kanai M, Hatano E, Toyoda M, Ajiki T, Takashima Y, Yoshimura K, Hamada A, Minami H, Ioka T. Pharmacokinetic Study of Adjuvant Gemcitabine Therapy for Biliary Tract Cancer following Major Hepatectomy (KHBO1101). PLoS One, 10:e0143072, 2015

11. Fujiwara Y, Nokihara H, Yamada Y, Yamamoto N, Sunami K, Utsumi H, Asou H, Takahashl O, Ogasawara K, Gueorguieva I, Tamura T. Phase 1 study of galunisertib, a TGF-beta receptor I kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1143-1152, 2015

12. Guidance Development Review Committee, Working Group for Clinical Studies of Cancer Immunotherapy, Working Group for Effector Cell Therapy, Working Group for CMC/Non-clinical Studies, Working Group for Cancer Vaccines and Adjuvants, Working Group for Anti-immune Checkpoint Therapy and Comprehensive Cancer Immunotherapy, Biostatistics Subcommittee. 2015 Guidance on cancer immunotherapy development in early-phase clinical studies. Cancer Sci, 106:1761-1771, 2015

13. Hashimoto H, Kitano S, Ueda R, Ito A, Tada K, Fuji S, Kim SW, Yamashita T, Tomura D, Nukaya I, Mineno J, Fukuda T, Mori S, Takaue Y, Heike Y. Erratum to: Infusion of donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene for recurrent hematologic malignancies after allogeneic hematopoietic stem cell transplantation. Int J Hematol, 102:506, 2015

14. Hashimoto H, Kitano S, Ueda R, Ito A, Tada K, Fuji S, Yamashita T, Tomura D, Nukaya I, Mineno J, Fukuda T, Mori S, Takaue Y, Heike Y. Infusion of donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene for recurrent hematologic malignancies after allogeneic hematopoietic stem cell transplantation. Int J Hematol, 102:101-110, 2015

15. Hashimoto H, Kitano S, Yamagata S, Miyagi Maeshima A, Ueda R, Ito A, Tada K, Fuji S, Yamashita T, Tomura D, Nukaya I, Mineno J, Fukuda T, Mori S, Takaue Y, Heike Y. Donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene: detailed immunological function following add-back after haplo-identical transplantation. Cytotherapy, 17:1820-1830, 2015

16. Hojo T, Masuda N, Mizutani T, Shibata T, Kinoshita T, Tamura K, Hara F, Fujisawa T, Inoue K, Saji S, Nakamura K, Fukuda H, Iwata H. Intensive vs. Standard Post-Operative Surveillance in High-Risk Breast Cancer Patients (INSPIRE): Japan Clinical Oncology Group Study JCOG1204. Jpn J Clin Oncol, 45:983-986, 2015

17. Horinouchi H, Yamamoto N, Fujiwara Y, Sekine I, Nokihara H, Kubota K, Kanda S, Yagishita S, Wakui H, Kitazono S, Mizugaki H, Tokudome T, Tamura T. Phase I study of ipilimumab in phased combination with paclitaxel and carboplatin in Japanese patients with non-small-cell lung cancer. Invest New Drugs, 33:881-889, 2015

18. Ikeda M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Kondo S, Morizane C, Ueno H, Okusaka T. Chemotherapy for advanced poorly differentiated pancreatic neuroendocrine carcinoma. J Hepatobiliary Pancreat Sci, 22:623-627, 2015

19. Ito A, Kondo S, Tada K, Kitano S. Clinical Development of Immune Checkpoint Inhibitors. Biomed Res Int, 2015:605478, 2015

20. Iwasa S, Nagashima K, Yamaguchi T, Matsumoto H, Ichikawa Y, Goto A, Yasui H, Kato K, Okita NT, Shimada Y, Yamada Y. S-1 and irinotecan with or without bevacizumab versus 5-fluorouracil and leucovorin plus oxaliplatin with or without bevacizumab in metastatic colorectal cancer: a pooled analysis of four phase II studies. Cancer Chemother Pharmacol, 76:605-614, 2015

21. Iwasa S, Souda H, Yamazaki K, Takahari D, Miyamoto Y, Takii Y, Ikeda S, Hamaguchi T, Kanemitsu Y, Shimada Y. Safety and efficacy of adjuvant therapy with oxaliplatin, leucovorin and 5-fluorouracil after mesorectal excision with lateral pelvic lymph node dissection for stage iii lower rectal cancer. Anticancer Res, 35:1815-1819, 2015

22. Kanai M, Hatano E, Kobayashi S, Fujiwara Y, Marubashi S, Miyamoto A, Shiomi H, Kubo S, Ikuta S, Yanagimoto H, Terajima H, Ikoma H, Sakai D, Kodama Y, Seo S, Morita S, Ajiki T, Nagano H, Ioka T. A multi-institution phase II study of gemcitabine/cisplatin/S-1 (GCS) combination chemotherapy for patients with advanced biliary tract cancer (KHBO 1002). Cancer Chemother Pharmacol, 75:293-300, 2015

23. Kanda S, Horinouchi H, Fujiwara Y, Nokihara H, Yamamoto N, Sekine I, Kunitoh H, Kubota K, Tamura T, Ohe Y. Cytotoxic chemotherapy may overcome the development of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) therapy. Lung Cancer, 89:287-293, 2015

24. Katsuya Y, Fujiwara Y, Sunami K, Utsumi H, Goto Y, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Takashima Y, Osawa S, Ohe Y, Tamura T, Hamada A. Comparison of the pharmacokinetics of erlotinib administered in complete fasting and 2 h after a meal in patients with lung cancer. Cancer Chemother Pharmacol, 76:125-132, 2015

25. Kitazono S, Fujiwara Y, Nakamichi S, Mizugaki H, Nokihara H, Yamamoto N, Yamada Y, Inukai E, Nakamura O, Tamura T. A phase I study of resminostat in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 75:1155-1161, 2015

26. Kitazono S, Fujiwara Y, Tsuta K, Utsumi H, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Sasada S, Watanabe S, Asamura H, Tamura T, Ohe Y. Reliability of Small Biopsy Samples Compared With Resected Specimens for the Determination of Programmed Death-Ligand 1 Expression in Non-Small-Cell Lung Cancer. Clin Lung Cancer, 16:385-390, 2015

27. Kondo S, Shiba S, Udagawa R, Ryushima Y, Yano M, Uehara T, Asanabe M, Tamura K, Hashimoto J. Assessment of adverse events via a telephone consultation service for cancer patients receiving ambulatory chemotherapy. BMC Res Notes, 8:315, 2015

28. Kurihara H, Hamada A, Yoshida M, Shimma S, Hashimoto J, Yonemori K, Tani H, Miyakita Y, Kanayama Y, Wada Y, Kodaira M, Yunokawa M, Yamamoto H, Shimizu C, Takahashi K, Watanabe Y, Fujiwara Y, Tamura K. ^{64}Cu-DOTA-trastuzumab PET imaging and HER2 specificity of brain metastases in HER2-positive breast cancer patients. EJNMMI Res, 5:8, 2015

29. Hattori Y, Yoshida A, Sasaki N, Shibuki Y, Tamura K, Tsuta K. Desmoplastic small round cell tumor with sphere-like clusters mimicking adenocarcinoma. Diagn Cytopathol, 43:214-217, 2015

30. Mizugaki H, Yamamoto N, Fujiwara Y, Nokihara H, Yamada Y, Tamura T. Current Status of Single-Agent Phase I Trials in Japan: Toward Globalization. J Clin Oncol, 33:2051-2061, 2015

31. Mizugaki H, Yamamoto N, Nokihara H, Fujiwara Y, Horinouchi H, Kanda S, Kitazono S, Yagishita S, Xiong H, Qian J, Hashiba H, Shepherd SP, Giranda V, Tamura T. A phase 1 study evaluating the pharmacokinetics and preliminary efficacy of veliparib (ABT-888) in combination with carboplatin/paclitaxel in Japanese subjects with non-small cell lung cancer (NSCLC). Cancer Chemother Pharmacol, 76:1063-1072, 2015

32. Motonaga M, Yamamoto N, Makino Y, Ando-Makihara R, Ohe Y, Takano M, Hayashi Y. Phase I dose-finding and pharmacokinetic study of docetaxel and gefitinib in patients with advanced or metastatic non-small-cell lung cancer: evaluation of drug-drug interaction. Cancer Chemother Pharmacol, 76:713-721, 2015

33. Nagashima K, Iwasa S, Yanai T, Hashimoto H, Suzuki K, Ohyanagi F, Shimada Y, Yamamoto N. A double-blind randomized Phase II study of olanzapine 10 mg versus 5 mg for emesis induced by highly emetogenic chemotherapy. Jpn J Clin Oncol, 45:229-231, 2015

34. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Honda K, Tamura Y, Wakui H, Sasaki T, Yusa W, Fujino K, Tamura T. A phase 1 study of lenvatinib, multiple receptor tyrosine kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:1153-1161, 2015

35. Nishio M, Horiike A, Murakami H, Yamamoto N, Kaneda H, Nakagawa K, Horinouchi H, Nagashima M, Sekiguchi M, Tamura T. Phase I study of the HER3-targeted antibody patritumab (U3-1287) combined with erlotinib in Japanese patients with non-small cell lung cancer. Lung Cancer, 88:275-281, 2015

36. Nishio M, Horiike A, Nokihara H, Horinouchi H, Nakamichi S, Wakui H, Ohyanagi F, Kudo K, Yanagitani N, Takahashi S, Kuboki Y, Yamamoto N, Yamada Y, Abe M, Tahata T, Tamura T. Phase I study of the anti-MET antibody onartuzumab in patients with solid tumors and MET-positive lung cancer. Invest New Drugs, 33:632-640, 2015

37. Okusaka T, Ueno H, Morizane C, Kondo S, Sakamoto Y, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Ikeda M. Cytotoxic chemotherapy for pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci, 22:628-633, 2015

38. Shiba S, Morizane C, Hiraoka N, Sasaki M, Koga F, Sakamoto Y, Kondo S, Ueno H, Ikeda M, Yamada T, Shimada K, Kosuge T, Okusaka T. Pancreatic neuroendocrine tumors: A single-center 20-year experience with 100 patients. Pancreatology, 16:99-105, 2015

39. Shoji H, Yamada Y, Okita N, Takashima A, Honma Y, Iwasa S, Kato K, Hamaguchi T, Shimada Y. Amplification of FGFR2 Gene in Patients with Advanced Gastric Cancer Receiving Chemotherapy: Prevalence and Prognostic Significance. Anticancer Res, 35:5055-5061, 2015

40. Takahashi H, Ikeda M, Kumada T, Osaki Y, Kondo S, Kusumoto S, Ohkawa K, Nadano S, Furuse J, Kudo M, Ito K, Yokoyama M, Okusaka T, Shimoyama M, Mizokami M. Multicenter cooperative case survey of hepatitis B virus reactivation by chemotherapeutic agents. Hepatol Res, 45:1220-1227, 2015

41. Takahashi N, Yamada Y, Furuta K, Nagashima K, Kubo A, Sasaki Y, Shoji H, Honma Y, Iwasa S, Okita N, Takashima A, Kato K, Hamaguchi T, Shimada Y. Association between serum ligands and the skin toxicity of anti-epidermal growth factor receptor antibody in metastatic colorectal cancer. Cancer Sci, 106:604-610, 2015

42. Eba J, Shimokawa T, Nakamura K, Shibata T, Misumi Y, Okamoto H, Yamamoto N, Ohe Y, Lung Cancer Study Group of the Japan Clinical Oncology Group. A Phase II/III study comparing carboplatin and irinotecan with carboplatin and etoposide for the treatment of elderly patients with extensive-disease small-cell lung cancer (JCOG1201). Jpn J Clin Oncol, 45:115-118, 2015

43. Tamura Y, Fujiwara Y, Yamamoto N, Nokihara H, Horinouchi H, Kanda S, Goto Y, Kubo E, Kitahara S, Tsuruoka K, Tsuta K, Ohe Y. Retrospective analysis of the efficacy of chemotherapy and molecular targeted therapy for advanced pulmonary pleomorphic carcinoma. BMC Res Notes, 8:800, 2015

44. Tanaka Y, Aoyagi K, Minashi K, Komatsuzaki R, Komatsu M, Chiwaki F, Tamaoki M, Nishimura T, Takahashi N, Oda I, Tachimori Y, Arao T, Nishio K, Kitano S, Narumi K, Aoki K, Fujii S, Ochiai A, Yoshida T, Muto M, Yamada Y, Sasaki H. Discovery of a Good Responder Subtype of Esophageal Squamous Cell Carcinoma with Cytotoxic T-Lymphocyte Signatures Activated by Chemoradiotherapy. PLoS One, 10:e0143804, 2015

45. Yagishita S, Horinouchi H, Sunami KS, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Sumi M, Shiraishi K, Kohno T, Furuta K, Tsuta K, Tamura T, Ohe Y. Impact of KRAS mutation on response and outcome of patients with stage III non-squamous non-small cell lung cancer. Cancer Sci, 106:1402-1407, 2015

46. Yunokawa M, Tsuta K, Tanaka T, Nara E, Koizumi F, Ito J, Sekine S, Fujiwara Y, Tamura K. Back with a vengeance: microvascular tumor embolism. Am J Med, 128:834-836, 2015

47. Takahashi RU, Miyazaki H, Takeshita F, Yamamoto Y, Minoura K, Ono M, Kodaira M, Tamura K, Mori M, Ochiya T. Loss of microRNA-27b contributes to breast cancer stem cell generation by activating ENPP1. Nat Commun, 6:7318, 2015

48. Ono M, Tsuda H, Kobayashi T, Takeshita F, Takahashi RU, Tamura K, Akashi-Tanaka S, Moriya T, Yamasaki T, Kinoshita T, Yamamoto J, Fujiwara Y, Ochiya T. The expression and clinical significance of ribophorin II (RPN2) in human breast cancer. Pathol Int, 65:301-308, 2015

49. Okita K, Izumi N, Ikeda K, Osaki Y, Numata K, Ikeda M, Kokudo N, Imanaka K, Nishiguchi S, Kondo S, Nishigaki Y, Shiomi S, Ueshima K, Isoda N, Karino Y, Kudo M, Tanaka K, Kaneko S, Moriwaki H, Makuuchi M, Okusaka T, Hayashi N, Ohashi Y, Kumada H, Peretinoin Study Group. Survey of survival among patients with hepatitis C virus-related hepatocellular carcinoma treated with peretinoin, an acyclic retinoid, after the completion of a randomized, placebo-controlled trial. J Gastroenterol, 50:667-674, 2015

Division of Pathology

Atsushi Ochiai, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Takeshi Kuwata, Masato Sugano, Chisako Yamauchi, Syuichi Mitsunaga, Akiko Nagatsuma, Kazuyoshi Yanagihara, Yuka Nakamura, Tomofumi Miura, Ken Hatogai, Naoki Sakuyama, Masayuki Ishibashi, Hiroko Hashimoto, Sachiko Fukuda, Tamae Hanai, Ayumi Iwaya, Aya Endo, Natsuko Maruyama, Yuki Iino, Teruo Komatsu, Motoko Suzaki, Yoshiko Onuma, Youichi Higuchi, Anna Abe, Yoshitaka Suda, Tomoyuki Miyashita, Yusuke Asai, Syota Yamazaki

Introduction

The major contribution of the Division of Pathology to both the Research Center for Innovative Oncology (RCIO) and the National Cancer Center Hospital (East) [NCCH-E] includes four major activities: 1) Basic and translational research in the cancer field; 2) Pathological diagnoses in the NCCH-E; 3) Clinical resident training for diagnosis and translational research (TR); and 4) Establishment and maintenance of the NCCH-E tissue bank (Bio-bank) system.

Routine activities

The staff members of the Division of Pathology are responsible for basic and translational research in the cancer biology and cancer treatment fields. Members are also involved in all routine pathological and cytological diagnosis in the NCCH-E with the collaboration of staff pathologists of the Department of Pathology and Clinical Laboratories of the NCCH-E. The Division participates in the training of clinical residents in pathological diagnosis and translational research using clinical samples from NCCH-E, in addition to participating in clinicopathological conferences and research meetings between the NCCH-E and the RCIO.

Research activities

The goal of the research at the Division of Pathology is to explore the cause of the cancer and to develop novel diagnostic and therapeutic methods for cancer patients. The research activities of the Division of Pathology start with the detection of cancer-specific pathological conditions closely associated with clinical outcomes. The appropriate in vitro and *in vivo* models are required to solve the molecular mechanism of the relevant issues. Research is further confirmed in final validation studies using human samples. The following are the major research results of this year.

1) Podoplanin-positive cancer-associated fibroblasts play an important role in promoting cancer cell invasion (16, 22). Moreover, these fibroblasts can cause primary resistance to chemotherapy in lung adenocarcinoma patients (20, 28).
2) In the head and neck carcinomas, carcinomas with neuroendocrine features were found to have an aggressive clinical course, which corresponded with the Ki-67 index and mitotic count (35). Genes involved in cancer-related pathways were frequently affected not only by genetic but also by epigenetic alterations in HER2-positive breast cancer (36).
3) Peritoneal invasion in colon cancer is an important prognostic factor and the cancer microenvironment formed by both cancer cells and subperitoneal fibroblasts is involved in the promotion of tumor growth and metastasis (4, 5, 17).
4) Approximately two-thirds of patients with gastric adenocarcinoma exhibited the expression of at least one tyrosine kinase receptor and would be candidates for targeted therapies. Moreover, one-third of at least one RTK over-expressing cases showed multiple RTKs expression, which may be useful for selecting the most suitable patients for each targeted therapy (21, 25, 26).
5) High serum IL-6 was related to advanced age, the presence of hepatic metastasis, a large tumor burden in the liver, severe fatigue, high

carcinoembryonic antigen, high C-reactive protein, and anemia in patients with treatment-naive advanced pancreatic cancer (9).

Prognostic factors and clinicopathological characteristics of various cancers have also been investigated in collaboration with the NCCH-E Diagnostic Pathology Section and other institutions.

These include lung cancers (7, 10, 18, 27, 29, 30, 31), colon cancers (8, 12, 13, 14), gastric cancers (2, 24, 38), pancreatic cancers (15, 19, 39), breast cancers (11, 16), esophageal cancers (1, 34) and head and neck cancer (32).

Clinical trials

Central pathological diagnosis in a global trial (gastric cancer).

Education

The Division participates in the pathological training of clinical residents in NCCH-E. Moreover, staff members give professional guidance for doctoral students of Juntendo University, Keio University, Tokyo Medical and Dental University and the Graduate School of Frontier Sciences, University of Tokyo.

Future prospects

We are strengthening particularly in 1) promotion of basic research of cancer biology and cancer treatment, 2) promotion of translational research and 3) collecting fundamental pathological information for cancer diagnosis and treatment.

List of papers published in 2015

Journal

1. Sugimoto M, Takahashi S, Kobayashi T, Kojima M, Gotohda N, Satake M, Ochiai A, Konishi M. Pancreatic perfusion data and post-pancreaticoduodenectomy outcomes. J Surg Res, 194:441-449, 2015

2. Kitaguchi K, Kato Y, Kojima M, Okubo S, Takahashi D, Okada R, Nakayama Y, Nishida Y, Gotohda N, Takahashi S, Konishi M. A resected case of intraductal tubulopapillary neoplasm of the pancreas: report of a case. Int Surg, 100:281-286, 2015

3. Kojima M, Puppa G, Kirsch R, Basturk O, Frankel WL, Vieth M, Lugli A, Sheahan K, Yeh M, Lauwers GY, Risio M, Shimazaki H, Iwaya K, Kage M, Akiba J, Ohkura Y, Horiguchi S, Shomori K, Kushima R, Nomura S, Ajioka Y, Adsay V, Ochiai A. Blood and lymphatic vessel invasion in pT1 colorectal cancer: an international concordance study. J Clin Pathol, 68:628-632, 2015

4. Yoshida T, Ishii G, Goto K, Neri S, Hashimoto H, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Iida S, Niimi A, Nagai K, Ohe Y, Ochiai A. Podoplanin-positive cancer-associated fibroblasts in the tumor microenvironment induce primary resistance to EGFR-TKIs in lung adenocarcinoma with EGFR mutation. Clin Cancer Res, 21:642-651, 2015

5. Miura T, Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Takahashi H, Furuse J, Inagaki M, Higashi S, Kato H, Terao K, Ochiai A. Characterization of patients with advanced pancreatic cancer and high serum interleukin-6 levels. Pancreas, 44:756-763, 2015

6. Fujii S, Fujihara A, Natori K, Abe A, Kuboki Y, Higuchi Y, Aizawa M, Kuwata T, Kinoshita T, Yasui W, Ochiai A. TEM1 expression in cancer-associated fibroblasts is correlated with a poor prognosis in patients with gastric cancer. Cancer Med, 4:1667-1678, 2015

7. Matsumoto T, Sasako M, Mizusawa J, Hirota S, Ochiai A, Kushima R, Katai H, Tanaka Y, Fukushima N, Nashimoto A, Tsuburaya A, Stomach Cancer Study Group of the Japan Clinical Oncology Group. HER2 expression in locally advanced gastric cancer with extensive lymph node (bulky N2 or paraaortic) metastasis (JCOG1005-A trial). Gastric Cancer, 18:467-475, 2015

8. Yoshida M, Sekine S, Ogawa R, Yoshida H, Maeshima A, Kanai Y, Kinoshita T, Ochiai A. Frequent MED12 mutations in phyllodes tumours of the breast. Br J Cancer, 112:1703-1708, 2015

9. Ishikawa T, Takahashi J, Kasai M, Shiina T, Iijima Y, Takemura H, Mizoguchi H, Kuwata T. Support system for pathologists and researchers. J Pathol Inform, 6:34, 2015

10. Neri S, Ishii G, Hashimoto H, Kuwata T, Nagai K, Date H, Ochiai A. Podoplanin-expressing cancer-associated fibroblasts lead and enhance the local invasion of cancer cells in lung adenocarcinoma. Int J Cancer, 137:784-796, 2015

11. Nishida Y, Kuwata T, Nitta H, Dennis E, Aizawa M, Kinoshita T, Ohtsu A, Ochiai A. A novel gene-protein assay for evaluating HER2 status in gastric cancer: simultaneous analyses of HER2 protein overexpression and gene amplification reveal intratumoral heterogeneity. Gastric Cancer, 18:458-466, 2015

12. Haruki T, Aokage K, Miyoshi T, Hishida T, Ishii G, Yoshida J, Tsuboi M, Nakamura H, Nagai K. Mediastinal nodal involvement in patients with clinical stage I non-small-cell lung cancer: possibility of rational lymph node dissection. J Thorac Oncol, 10:930-936, 2015

13. Yoshida J, Ishii G, Hishida T, Aokage K, Tsuboi M, Ito H, Yokose T, Nakayama H, Yamada K, Nagai K. Limited resection trial for pulmonary ground-glass opacity nodules: case selection based on high-resolution computed tomography-interim results. Jpn J Clin Oncol, 45:677-681, 2015

14. Udagawa H, Ishii G, Morise M, Umemura S, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A, Ohe Y. Comparison of the expression levels of molecular markers among the peripheral area and central area of primary tumor and metastatic lymph node tumor in patients with squamous cell carcinoma of the lung. J Cancer Res Clin Oncol, 141:1417-1425, 2015

15. Koriyama H, Ishii G, Yoh K, Neri S, Morise M, Umemura S, Matsumoto S, Niho S, Ohmatsu H, Tsuboi M, Goto K, Ochiai A. Presence of podoplanin-positive cancer-associated fibroblasts in surgically resected primary lung adenocarcinoma predicts a shorter progression-free survival period in patients with recurrences who received platinum-based chemotherapy. J Cancer Res Clin Oncol, 141:1163-1170, 2015

16. Matsumura Y, Umemura S, Ishii G, Tsuta K, Matsumoto S, Aokage K, Hishida T, Yoshida J, Ohe Y, Suzuki H, Ochiai A, Goto K, Nagai K, Tsuchihara K. Expression profiling of receptor tyrosine kinases in high-grade neuroendocrine carcinoma of the lung: a comparative analysis with adenocarcinoma and squamous cell carcinoma. J Cancer Res Clin Oncol, 141:2159-2170, 2015

17. Morise M, Hishida T, Takahashi A, Yoshida J, Ohe Y, Nagai K, Ishii G. Clinicopathological significance of cancer stem-like cell markers in high-grade neuroendocrine carcinoma of the lung. J Cancer Res Clin Oncol, 141:2121-2130, 2015

18. Suzuki S, Ishii G, Matsuwaki R, Neri S, Hashimoto H, Yamauchi C, Aokage K, Hishida T, Yoshida J, Kohno M, Nagai K, Ochiai A. Ezrin-expressing lung adenocarcinoma cells and podoplanin-positive fibroblasts form a malignant microenvironment. J Cancer Res Clin Oncol, 141:475-484, 2015

19. Kinoshita T, Yoshida J, Ishii G, Hishida T, Wada M, Aokage K, Nagai K. The availability of pre- and intraoperative evaluation of a solitary pulmonary nodule in breast cancer patients. Ann Thorac Cardiovasc Surg, 21:31-36, 2015

20. Kawano S, Kojima M, Higuchi Y, Sugimoto M, Ikeda K, Sakuyama N, Takahashi S, Hayashi R, Ochiai A, Saito N. Assessment of elasticity of colorectal cancer tissue, clinical utility, pathological and phenotypical relevance. Cancer Sci, 106:1232-1239, 2015

21. Makinoshima H, Takita M, Saruwatari K, Umemura S, Obata Y, Ishii G, Matsumoto S, Sugiyama E, Ochiai A, Abe R, Goto K, Esumi H, Tsuchihara K. Signaling through the Phosphatidylinositol 3-Kinase (PI3K)/Mammalian Target of Rapamycin (mTOR) Axis Is Responsible for Aerobic Glycolysis mediated by Glucose Transporter in Epidermal Growth Factor Receptor (EGFR)-mutated Lung Adenocarcinoma. J Biol Chem, 290:17495-17504, 2015

22. Kawachi H, Eishi Y, Ueno H, Nemoto T, Fujimori T, Iwashita A, Ajioka Y, Ochiai A, Ishiguro S, Shimoda T, Mochizuki H, Kato Y, Watanabe H, Koike M, Sugihara K. A three-tier classification system based on the depth of submucosal invasion and budding/sprouting can improve the treatment strategy for T1 colorectal cancer: a retrospective multicenter study. Mod Pathol, 28:872-879, 2015

23. Kojima M, Sudo H, Kawauchi J, Takizawa S, Kondou S, Nobumasa H, Ochiai A. MicroRNA markers for the diagnosis of pancreatic and biliary-tract cancers. PLoS One, 10:e0118220, 2015

24. Fujii S, Srivastava V, Hegde A, Kondo Y, Shen L, Hoshino K, Gonzalez Y, Wang J, Sasai K, Ma X, Katayama H, Estecio MR, Hamilton SR, Wistuba I, Issa JP, Sen S. Regulation of AURKC expression by CpG island methylation in human cancer cells. Tumour Biol, 36:8147-8158, 2015

25. Daiko H, Fujita T, Ohgara T, Yamazaki N, Fujii S, Ohno Y, Yano T. Minimally invasive hybrid surgery combined with endoscopic and thoracoscopic approaches for submucosal tumor originating from thoracic esophagus. World J Surg Oncol, 13:40, 2015

26. Satake H, Yano T, Muto M, Minashi K, Yoda Y, Kojima T, Oono Y, Ikematsu H, Aoyama I, Morita S, Miyamoto S, Fujii S, Yoshizawa A, Ochiai A, Hayashi R, Kaneko K. Clinical outcome after endoscopic resection for superficial pharyngeal squamous cell carcinoma invading the subepithelial layer. Endoscopy, 47:11-18, 2015

27. Taniguchi H, Yamazaki K, Yoshino T, Muro K, Yatabe Y, Watanabe T, Ebi H, Ochiai A, Baba E, Tsuchihara K, Japanese Society of Medical Oncology. Japanese Society of Medical Oncology Clinical Guidelines: RAS (KRAS/NRAS) mutation testing in colorectal cancer patients. Cancer Sci, 106:324-327, 2015

28. Hamamoto T, Fujii S, Miyazaki M, Shinozaki T, Tomioka T, Hayashi R. Nine cases of carcinoma with neuroendocrine features in the head and neck: clinicopathological characteristics and clinical outcomes. Jpn J Clin Oncol, 45:328-335, 2015

29. Tanaka Y, Aoyagi K, Minashi K, Komatsuzaki R, Komatsu M, Chiwaki F, Tamaoki M, Nishimura T, Takahashi N, Oda I, Tachimori Y, Arao T, Nishio K, Kitano S, Narumi K, Aoki K, Fujii S, Ochiai A, Yoshida T, Muto M, Yamada Y, Sasaki H. Discovery of a Good Responder Subtype of Esophageal Squamous Cell Carcinoma with Cytotoxic T-Lymphocyte Signatures Activated by Chemoradiotherapy. PLoS One, 10:e0143804, 2015

30. Higuchi Y, Kojima M, Ishii G, Aoyagi K, Sasaki H, Ochiai A. Gastrointestinal Fibroblasts Have Specialized, Diverse Transcriptional Phenotypes: A Comprehensive Gene Expression Analysis of Human Fibroblasts. PLoS One, 10:e0129241, 2015

31. Yokota M, Kojima M, Higuchi Y, Nishizawa Y, Kobayashi A, Ito M, Saito N, Ochiai A. Spread of tumor microenvironment contributes to colonic obstruction through subperitoneal fibroblast activation in colon cancer. Cancer Sci, 106:466-474, 2015

32. Yamaguchi T, Mukai H, Yamashita S, Fujii S, Ushijima T. Comprehensive DNA methylation and extensive mutation analyses of HER2-positive breast cancer. Oncology, 88:377-384, 2015

33. Nagatsuma AK, Aizawa M, Kuwata T, Doi T, Ohtsu A, Fujii H, Ochiai A. Expression profiles of HER2, EGFR, MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma. Gastric Cancer, 18:227-238, 2015

34. Sasaki T, Fuse N, Kuwata T, Nomura S, Kaneko K, Doi T, Yoshino T, Asano H, Ochiai A, Komatsu Y, Sakamoto N, Ohtsu A. Serum HER2 levels and HER2 status in tumor cells in advanced gastric cancer patients. Jpn J Clin Oncol, 45:43-48, 2015

35. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishihara S, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Boku N, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K, Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol, 20:207-239, 2015

36. Takahashi A, Ishii G, Neri S, Yoshida T, Hashimoto H, Suzuki S, Umemura S, Matsumoto S, Yoh K, Niho S, Goto K, Ohmatsu H, Nagai K, Gemma A, Ohe Y, Ochiai A. Podoplanin-expressing cancer-associated fibroblasts inhibit small cell lung cancer growth. Oncotarget, 6:9531-9541, 2015

37. Nakamura K, Kuwata T, Shimoda T, Mizusawa J, Katayama H, Kushima R, Taniguchi H, Sano T, Sasako M, Fukuda H. Determination of the optimal cutoff percentage of residual tumors to define the pathological response rate for gastric cancer treated with preoperative therapy (JCOG1004-A). Gastric Cancer, 18:597-604, 2015

Division of Translational Research (Kashiwa Campus)

Katsuya Tsuchihara, Sachiyo Mimaki, Hideki Makinoshima, Shingo Matsumoto, Wataru Okamoto, Ayako Suzuki, Atsushi Yagishita, Rumi Fujioka, Hiroko Kumakura, Megumi Iwakura, Koutatsu Matsushima, Masahiro Takita, Motoki Kasahara, Sayuri Todoroki, Tomohiro Sakamoto, Hiroyasu Esumi, Satoshi Owada, Tatsunosuke Ikemura, Satoshi Tada, Takanori Kawashima, Kenta Murata, Chikako Nakai

Introduction

This Division closely collaborates with intramural and extramural basic and clinical researchers to develop novel anti-cancer therapeutics as well as to prove their concepts. The Division has been developing genome biomarker diagnostics based on next generation DNA sequencing technologies, exploring rational molecular targets for anti-cancer therapies, and elucidating molecular mechanisms of oncogenesis, tumor progression and therapeutic responses. The Division also managed a data center that handles clinical and genome information of advanced lung and gastrointestinal cancer cases that were enrolled in a nationwide cancer genome screening program, SCRUM-Japan.

Routine activities

Weekly conferences for the whole division and individual research groups are held. A monthly tele-conference is held with the Group of Translational Research at Tsukiji Campus.

Research activities

1) Developing a multiplex mutation detection kit for KRAS and NRAS genes for selecting anti-EGFR antibody treatment for advanced colorectal cancer. The kit was approved and reimbursed in Japan in April 2015.
2) Developing a prototype of a multiplex gene alteration detection kit for choosing appropriate drugs for advanced lung cancer.
3) Establishing a datacenter and an interactive database program for SCRUM-Japan (Figures 1 and 2).
4) Identifying that EGFR inhibitors affect glycolysis of lung adenocarcinoma cells via the PI3K pathway and induced anti-tumor effect.

Clinical trials

1) Screening Project for Individualized Medicine in Japan (SCRUM-Japan): Data center
2) Biomarker Research for Anti-EGFR Monoclonal Antibodies by Comprehensive Cancer Genomics (BREAC Study): Secretariat, data center, genome analysis

Education

This Division accepted and trained the following trainees: Graduate students from the University of Tokyo (four), Tokyo Medical and Dental University (one), Keio University (one) and Juntendo University (one), staff physician of National Cancer Center Hospital East (one) and Tottori University (one), senior resident (one) and junior resident (two), visiting scientists (six)

Future prospects

Integrating the multi-omics analysis and precise clinical information is necessary to develop novel anti-cancer therapeutics. Education of specialists with a background of medical oncology, biology and bioinformatics is most important.

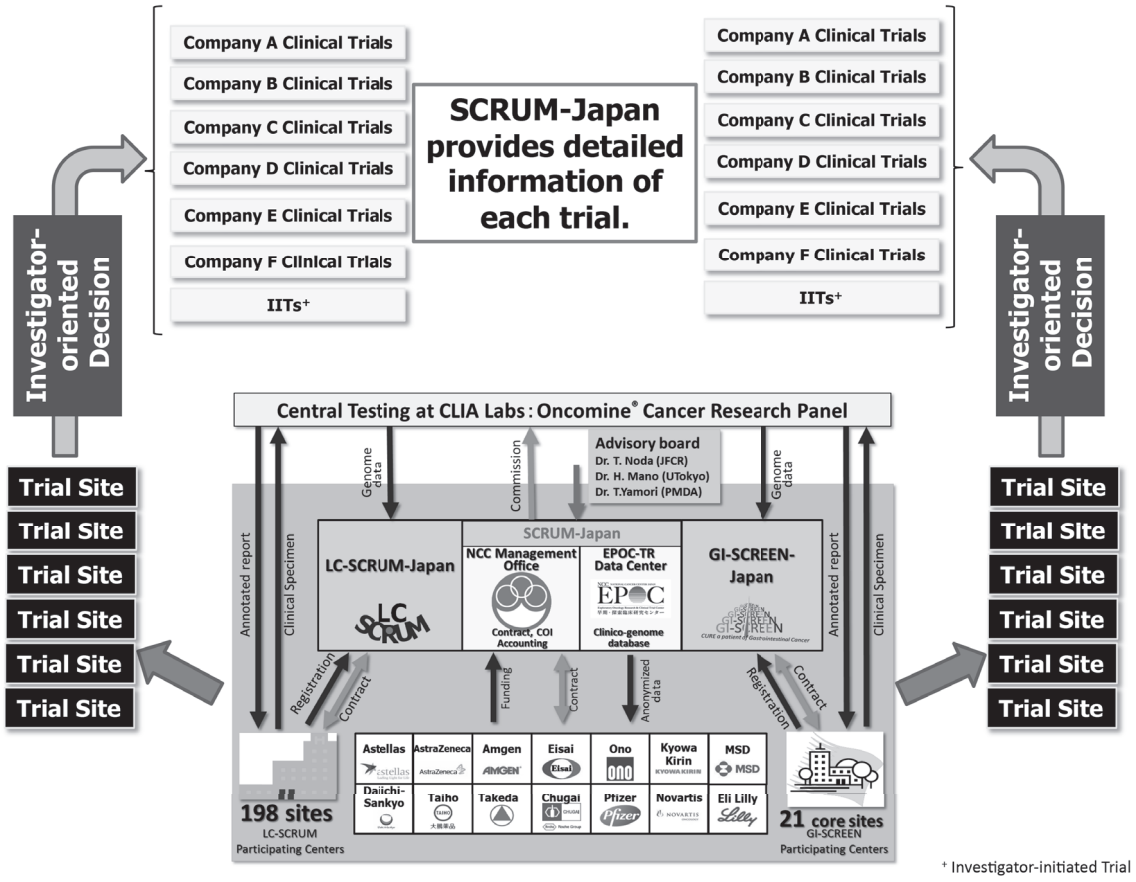


Figure 1. Nationwide cancer genome screening program, SCRUM-Japan

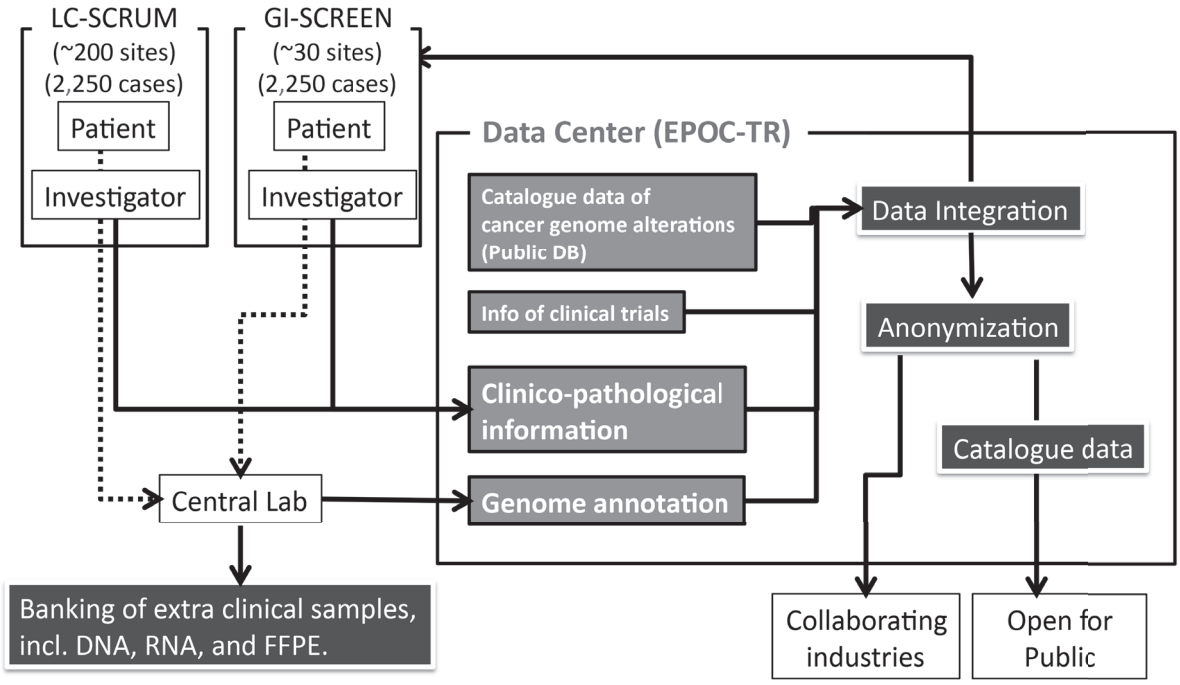


Figure 2. Flow of the clinical and genomic information in SCRUM-Japan

List of papers published in 2015

Journal

1. Matsumura Y, Umemura S, Ishii G, Tsuta K, Matsumoto S, Aokage K, Hishida T, Yoshida J, Ohe Y, Suzuki H, Ochiai A, Goto K, Nagai K, Tsuchihara K. Expression profiling of receptor tyrosine kinases in high-grade neuroendocrine carcinoma of the lung: a comparative analysis with adenocarcinoma and squamous cell carcinoma. J Cancer Res Clin Oncol, 141:2159-2170, 2015

2. Suzuki A, Matsushima K, Makinoshima H, Sugano S, Kohno T, Tsuchihara K, Suzuki Y. Single-cell analysis of lung adenocarcinoma cell lines reveals diverse expression patterns of individual cells invoked by a molecular target drug treatment. Genome Biol, 16:66, 2015

3. Makinoshima H, Takita M, Saruwatari K, Umemura S, Obata Y, Ishii G, Matsumoto S, Sugiyama E, Ochiai A, Abe R, Goto K, Esumi H, Tsuchihara K. Signaling through the Phosphatidylinositol 3-Kinase (PI3K)/Mammalian Target of Rapamycin (mTOR) Axis Is Responsible for Aerobic Glycolysis mediated by Glucose Transporter in Epidermal Growth Factor Receptor (EGFR)-mutated Lung Adenocarcinoma. J Biol Chem, 290:17495-17504, 2015

4. Taniguchi H, Yamazaki K, Yoshino T, Muro K, Yatabe Y, Watanabe T, Ebi H, Ochiai A, Baba E, Tsuchihara K, Japanese Society of Medical Oncology. Japanese Society of Medical Oncology Clinical Guidelines: RAS (KRAS/NRAS) mutation testing in colorectal cancer patients. Cancer Sci, 106:324-327, 2015

5. Suzuki A, Wakaguri H, Yamashita R, Kawano S, Tsuchihara K, Sugano S, Suzuki Y, Nakai K. DBTSS as an integrative platform for transcriptome, epigenome and genome sequence variation data. Nucleic Acids Res, 43:D87-D91, 2015

6. Umemura S, Tsuchihara K, Goto K. Genomic profiling of small-cell lung cancer: the era of targeted therapies. Jpn J Clin Oncol, 45:513-519, 2015

7. Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, Goto K. Beyond *ALK-RET, ROS1* and other oncogene fusions in lung cancer. Transl Lung Cancer Res, 4:156-164, 2015

8. Iwakawa R, Kohno T, Totoki Y, Shibata T, Tsuchihara K, Mimaki S, Tsuta K, Narita Y, Nishikawa R, Noguchi M, Harris CC, Robles AI, Yamaguchi R, Imoto S, Miyano S, Totsuka H, Yoshida T, Yokota J. Expression and clinical significance of genes frequently mutated in small cell lung cancers defined by whole exome/RNA sequencing. Carcinogenesis, 36:616-621, 2015

Division of Translational Research (Tsukiji Campus)

Takashi Kohno, Hitoshi Ichikawa, Hiroki Sasaki, Takashi Kubo

Introduction

This Division facilitates early phase clinical trials by conducting translational research (TR) focusing on the development of therapeutic and in vitro diagnostic seeds and the discovery of biomarkers.

Research activities

Establishment of NGS-based genomic testing system for precision cancer medicine

We developed a next-generation sequencing (NGS)-based in-house genomic testing system in which an original cancer gene panel (NCC oncopanel) was used to guide cancer treatments, and are continuously improving this system to construct an accurate and clinically useful in vitro diagnostics (IVD) system. In 2015, we renewed our original gene panel (NCC oncopanel v3) and confirmed its performance in a prospective feasibility study, which tested patients considering entry into an early phase clinical trial in a sequencing laboratory located in the Research Institute. Fifty-four patients were successfully examined, and actionable genetic alterations were identified in 24 patients (Figure). In addition, we set up the SCI-Lab, a laboratory for clinical sequencing with international standard quality assurance, in the Department of Clinical Laboratories of the Hospital through the technology transfer of our genomic testing system.

Preclinical studies using newly established cell lines of common cancers in Asia

In collaboration with the Division of Genetics, we have newly established 59 diffuse-type gastric cancer (GC)-derived cell lines (NSC-1~49 series) from the cancer ascites of 34 patients. Now, we possess 94 GC cell lines including 80 diffuse-type (new 59 and existing 21) and 14 intestinal-type, and also have 52 esophageal squamous cell carcinoma (ESCC) cell lines. In 2015, we successfully established six pancreatic and one ovarian cancer cell lines. We are conducting omics analyses for gene expression and copy number variation, and hot spot- and genome wide-gene alteration in these cell lines. Moreover, for an in vivo preclinical study, their tumorigenicity and histopathological characteristics of PDXs, such as fibroblast rich-, hypovascular-, and dormant-state, were evaluated. Through collaboration with five pharmaceutical companies, in vitro and in vivo preclinical studies are being conducted to translate "therapeutic and diagnostic seeds" to the cancer clinic.

Clinical trials

TOP-GEAR: Trial of Onco-Panel for Gene-profiling to Estimate both Adverse events and Response by cancer treatment (UMIN000011141)

Education

Graduate students, post-doctoral fellows, and chief residents in the National Cancer Center (NCC) were educated through the "on-the-job training" in several translational research projects.

Future prospects

The feasibility and clinical utility of our clinical sequencing system with international standard quality assurance will be shown. Early-phase clinical trials will further progress through utilization of original cancer cell lines.

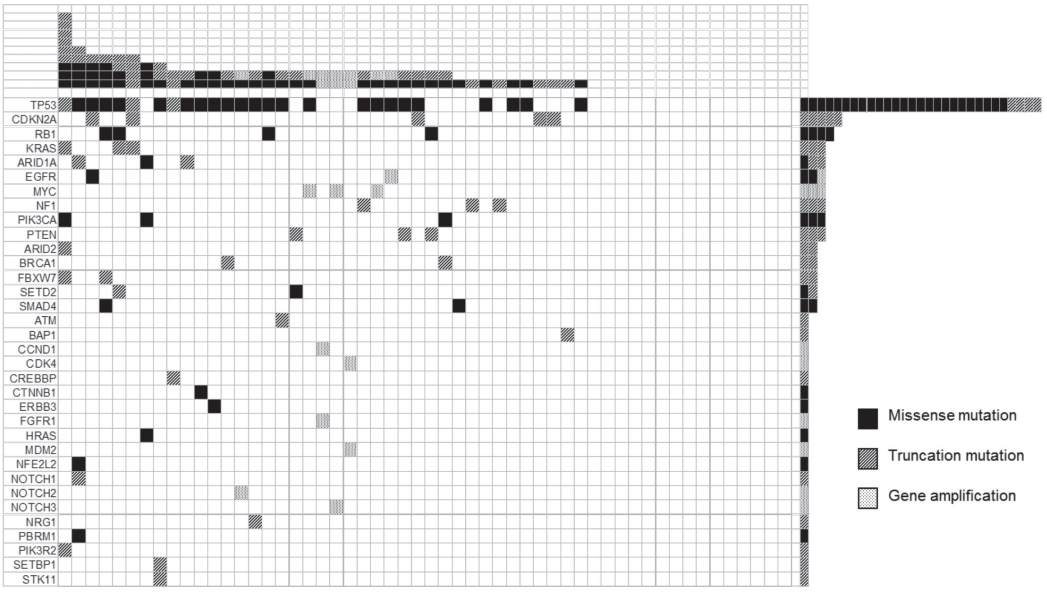


Figure 1. Gene alterations detected by clinical sequencing using NCC oncopanel ver. 3

List of papers published in 2015

Journal

1. Suzuki M, Shiraishi K, Yoshida A, Shimada Y, Suzuki K, Asamura H, Furuta K, Kohno T, Tsuta K. *HER2* gene mutations in non-small cell lung carcinomas: concurrence with *Her2* gene amplification and her2 protein expression and phosphorylation. Lung Cancer, 87:14-22, 2015

2. Suzuki A, Matsushima K, Makinoshima H, Sugano S, Kohno T, Tsuchihara K, Suzuki Y. Single-cell analysis of lung adenocarcinoma cell lines reveals diverse expression patterns of individual cells invoked by a molecular target drug treatment. Genome Biol, 16:66, 2015

3. Tanaka Y, Aoyagi K, Minashi K, Komatsuzaki R, Komatsu M, Chiwaki F, Tamaoki M, Nishimura T, Takahashi N, Oda I, Tachimori Y, Arao T, Nishio K, Kitano S, Narumi K, Aoki K, Fujii S, Ochiai A, Yoshida T, Muto M, Yamada Y, Sasaki H. Discovery of a Good Responder Subtype of Esophageal Squamous Cell Carcinoma with Cytotoxic T-Lymphocyte Signatures Activated by Chemoradiotherapy. PLoS One, 10:e0143804, 2015

4. Tanabe S, Aoyagi K, Yokozaki H, Sasaki H. Regulated genes in mesenchymal stem cells and gastric cancer. World J Stem Cells, 7:208-222, 2015

5. Saeki N, Ono H, Yanagihara K, Aoyagi K, Sasaki H, Sakamoto H, Yoshida T. rs2294008T, a risk allele for gastric and gallbladder cancers, suppresses the PSCA promoter by recruiting the transcription factor YY1. Genes Cells, 20:382-391, 2015

6. Yamanoi K, Arai E, Tian Y, Takahashi Y, Miyata S, Sasaki H, Chiwaki F, Ichikawa H, Sakamoto H, Kushima R, Katai H, Yoshida T, Sakamoto M, Kanai Y. Epigenetic clustering of gastric carcinomas based on DNA methylation profiles at the precancerous stage: its correlation with tumor aggressiveness and patient outcome. Carcinogenesis, 36:509-520, 2015

7. Saeki N, Komatsuzaki R, Chiwaki F, Yanagihara K, Sasaki H. A GSDMB enhancer-driven HSV thymidine kinase-expressing vector for controlling occult peritoneal dissemination of gastric cancer cells. BMC Cancer, 15:439, 2015

8. Higuchi Y, Kojima M, Ishii G, Aoyagi K, Sasaki H, Ochiai A. Gastrointestinal Fibroblasts Have Specialized, Diverse Transcriptional Phenotypes: A Comprehensive Gene Expression Analysis of Human Fibroblasts. PLoS One, 10:e0129241, 2015

9. Tanabe S, Komatsu M, Aoyagi K, Yokozaki H, Sasaki H. Implications of epithelial-mesenchymal transition in gastric cancer. Transl Gastrointest Cancer, 4:258-264, 2015

10. Naito Y, Oue N, Pham TT, Yamamoto M, Fujihara M, Ishida T, Mukai S, Sentani K, Sakamoto N, Hida E, Sasaki H, Yasui W. Characteristic miR-24 Expression in Gastric Cancers among Atomic Bomb Survivors. Pathobiology, 82:68-75, 2015

11. Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, Goto K. Beyond *ALK-RET, ROS1* and other oncogene fusions in lung cancer. Transl Lung Cancer Res, 4:156-164, 2015

12. Suzuki M, Chiwaki F, Sawada Y, Ashikawa M, Aoyagi K, Fujita T, Yanagihara K, Komatsu M, Narita M, Suzuki T, Nagase H, Kushima R, Sakamoto H, Fukagawa T, Katai H, Nakagama H, Yoshida T, Uezono Y, Sasaki H. Peripheral opioid antagonist enhances the effect of anti-tumor drug by blocking a cell growth-suppressive pathway *in vivo*. PLoS One, 10:e0123407, 2015

13. Sakata S, Sasaki J, Saeki S, Hamada A, Kishi H, Nakamura K, Tanaka H, Notsute D, Sato R, Saruwatari K, Iriki T, Akaike K, Fujii S, Hirosako S, Kohrogi H. Dose Escalation and Pharmacokinetic Study of Carboplatin plus Pemetrexed for Elderly Patients with Advanced Nonsquamous Non-Small-Cell Lung Cancer: Kumamoto Thoracic Oncology Study Group Trial 1002. Oncology, 88:201-207, 2015

14. Fujita T, Chiwaki F, Takahashi RU, Aoyagi K, Yanagihara K, Nishimura T, Tamaoki M, Komatsu M, Komatsuzaki R, Matsusaki K, Ichikawa H, Sakamoto H, Yamada Y, Fukagawa T, Katai H, Konno H, Ochiya T, Yoshida T, Sasaki H. Identification and Characterization of CXCR4-Positive Gastric Cancer Stem Cells. PLoS One, 10:e0130808, 2015

15. Saito M, Shimada Y, Shiraishi K, Sakamoto H, Tsuta K, Totsuka H, Chiku S, Ichikawa H, Kato M, Watanabe S, Yoshida T, Yokota J, Kohno T. Development of lung adenocarcinomas with exclusive dependence on oncogene fusions. Cancer Res, 75:2264-2271, 2015

Division of Cancer Immunology

Hiroyoshi Nishikawa, Daisuke Sugiyama, Chika Sakai, Yasuko Tada, Miyuki Nakai, Tomoka Takaku, Sayuri Yoshimatsu, Yoshiko Takeuchi, Yuki Fujioka, Danbee Ha, Motoya Mie, Masahiro Tokunaga, Shigeyuki Mori, Sho Isoyama, Hiroki Fukutomi

Introduction

The Division of Cancer Immunology aims at identifying novel strategies that can tip the balance to augmenting anti-tumor immune responses by focusing on anti-tumor immune responses and their suppressive mechanisms in a tumor microenvironment. Regulatory T (Treg) cells, actively engaged in the maintenance of immunological self-tolerance and homeostasis, are present in tumor tissues with higher frequencies compared with the periphery and inhibit the development of effective anti-tumor immune responses. We are now investigating the detailed mechanisms of Treg-cell infiltration/proliferation in tumor tissues to control them for a novel target of cancer immunotherapy.

Research activities

1) We have established a sample collection system of cancer tissues and peripheral blood from cancer patients such as gastrointestinal and lung cancers in the National Cancer Center Hospital East. Tumor infiltrating lymphocytes and peripheral blood lymphocytes are prepared and stocked in a cell bank with a barcode system. This system provides a chance to analyze kinetics of immune responses pre- and post-therapy including immunotherapy. Furthermore, somatic mutations and gene expression were also examined together to define the cellular immune response to neo antigens derived from somatic mutations and shared antigens derived from aberrantly or highly expressing self-antigens (Figure 1).
2) In collaboration with Osaka University, we addressed the role of FOXP3$^+$ T cells in colorectal cancers. While abundant Treg-cell infiltration into tumors is significantly associated with poor clinical outcomes in various types of cancer, the role of Treg cells is controversial in colorectal cancers, in which FOXP3$^+$ T-cell infiltration indicated better prognosis in some studies. FOXP3$^+$ T cells infiltrating into colorectal cancers were divided into subpopulations including FOXP3$^+$ suppressive Treg cells and non-suppressive inflammatory FOXP3$^+$ T cells, and showed that colorectal cancers were classified into two types, one with predominant infiltration of immune-suppressive FOXP3-high Treg cells and the other with inflammatory non-suppressive FOXP3-low T cells in addition to FOXP3-high Treg cells. The two types showed opposite prognosis: the former type is poor, the latter better. In addition, the possible contribution of tissue cytokines (IL-12, TGF-β and TNF-α) and colonic microbiota (*Fusobacterium nucleatum*) to the development of the two different types was detected. Therefore, in addition to depletion of FOXP3^{hi} Treg cells from tumor tissues to augment tumor immunity, strategies to locally increase FOXP3^{lo} non-Treg cells, for example, by the use of specific microbes could be tumor-suppressive and -preventive.

Education

Post-doctoral fellows and graduate school students from Osaka University and Akita University are trained in our Division.

Future prospects

Samples from peripheral blood and tumor tissues have been collected more rapidly than expected. In addition to immune assays, we also analyze environmental factors such as

microbiota in colon cancers. Base on this, we will comprehensively investigate immune cells such as $CD4^+$, $CD8^+$ T cells and macrophages, cancer cells and environmental factors to clarify the molecular mechanisms that control immune balances in a tumor microenvironment.

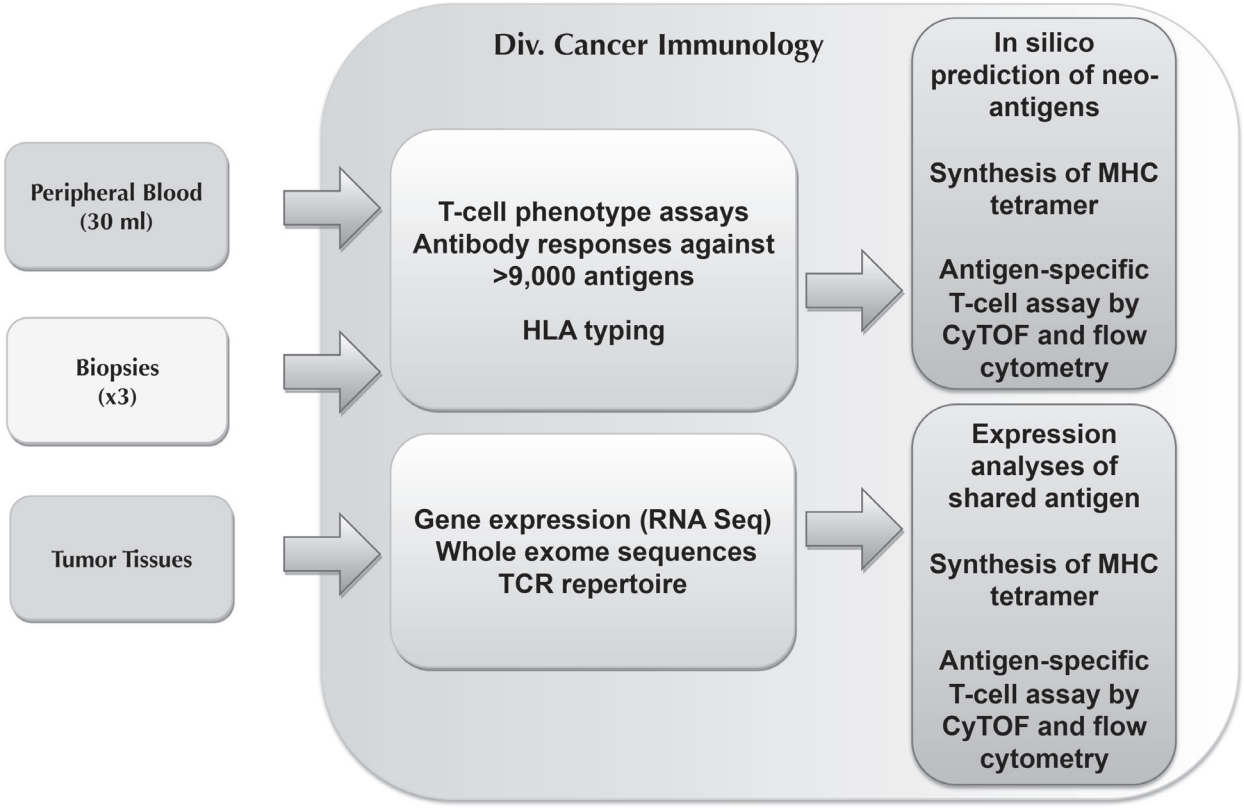


Figure 1. Immunological assay in the NCC

List of papers published in 2015

Journal

1. Nishikawa H. Overview: New Modality for Cancer Treatment. Oncology, 891:33-35, 2015

2. Adeegbe DO, Nishikawa H. Regulatory T cells in cancer; can they be controlled? Immunotherapy, 7:843-846, 2015

3. Miyara M, Chader D, Sage E, Sugiyama D, Nishikawa H, Bouvry D, Claër L, Hingorani R, Balderas R, Rohrer J, Warner N, Chapelier A, Valeyre D, Kannagi R, Sakaguchi S, Amoura Z, Gorochov G. Sialyl Lewis x (CD15s) identifies highly differentiated and most suppressive FOXP3high regulatory T cells in humans. Proc Natl Acad Sci U S A, 112:7225-7230, 2015

4. Kurose K, Ohue Y, Wada H, Iida S, Ishida T, Kojima T, Doi T, Suzuki S, Isobe M, Funakoshi T, Kakimi K, Nishikawa H, Udono H, Oka M, Ueda R, Nakayama E. Phase Ia Study of FoxP3+ CD4 Treg Depletion by Infusion of a Humanized Anti-CCR4 Antibody, KW-0761, in Cancer Patients. Clin Cancer Res, 21:4327-4336, 2015

Division of Clinical Pharmacology and Translational Research

Akinobu Hamada, Mitsuhiro Hayashi, Hiroaki Aikawa, Miyuki Momma

Introduction

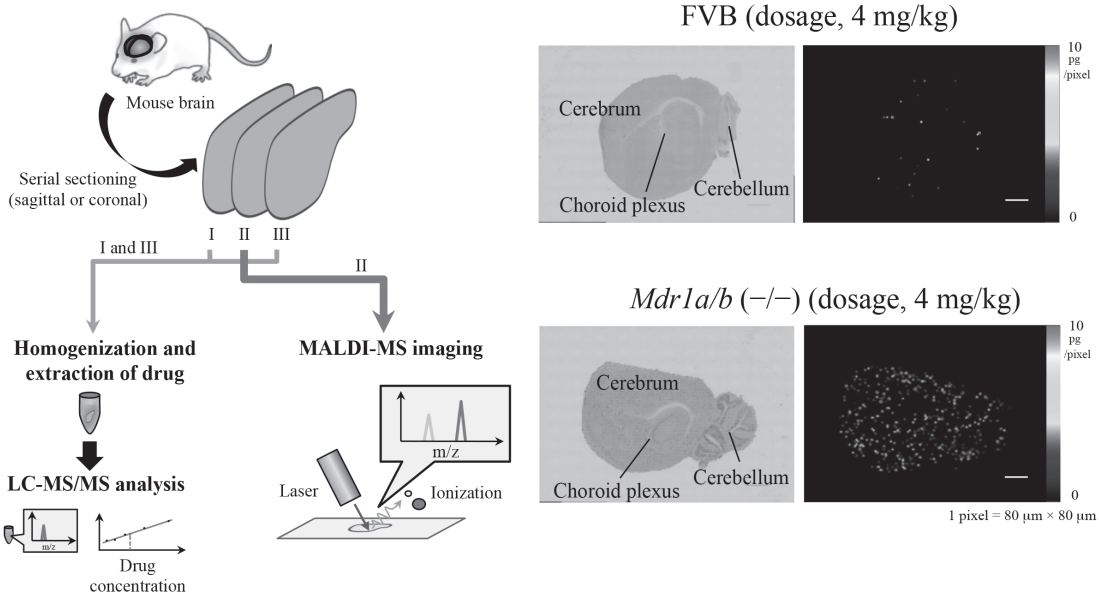
The Division of Clinical Pharmacology and Translational Research Group is focused on the development of a pharmacokinetics/pharmacodynamics (PK/PD) analyzing system. The system provides drug exposure in blood and tissues by using high-sensitivity liquid chromatography tandem mass spectrometry (LC-MS/MS) and spatial drug distribution on tissue by using mass spectrometry imaging without labeling reagents. We are also focused on the development of an immunomonitoring system detecting patient's ADCC activity.

Research activities

We established a quantitative mass spectrometry imaging system that provides both quantitative information and spatial distribution of target drugs. We used this system to visualize the amount and the distribution of anti-cancer drugs in several mouse models. To assess the efficacy and the behavior of target drugs in tumor tissue, we are now establishing not only a cell-derived xenotraft mouse model but also a patient-derived xenograft model. Moreover, we established an immunomonitoring system that can detect ADCC activity from patient's PBMC. Both research projects were submitted as papers to scientific journals.

Future prospects

The combination of PK/PD analysis, mass spectrometry imaging, measurement of ADCC activity and establishment of a PDX model can provide us with more accurate information about patients. These systems will help to actualize personalized medicine in the future.



P糖タンパク質(Mdr1)の基質薬剤の脳内組織移行性は、ノックアウトマウスで上昇

Figure 1. MALDI-MSI imaging analysis showed that the intra-brain transitivity of the drug was elevated on Mdr1(-/-) mouse brain.

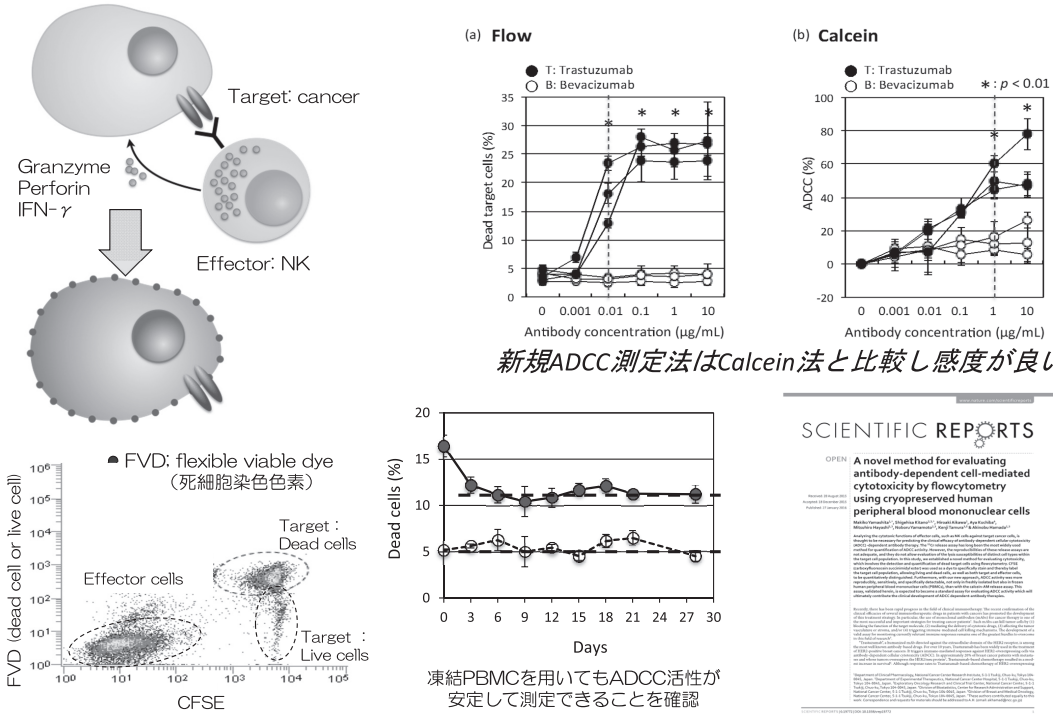


Figure 2. We developed a highly sensitive method for quantifying the ADCC activity of patient's blood.

List of papers published in 2015

Journal

1. Fujiwara Y, Kobayashi S, Nagano H, Kanai M, Hatano E, Toyoda M, Ajiki T, Takashima Y, Yoshimura K, Hamada A, Minami H, Ioka T. Pharmacokinetic Study of Adjuvant Gemcitabine Therapy for Biliary Tract Cancer following Major Hepatectomy (KHBO1101). PLoS One, 10:e0143072, 2015

2. Katsuya Y, Fujiwara Y, Sunami K, Utsumi H, Goto Y, Kanda S, Horinouchi H, Nokihara H, Yamamoto N, Takashima Y, Osawa S, Ohe Y, Tamura T, Hamada A. Comparison of the pharmacokinetics of erlotinib administered in complete fasting and 2 h after a meal in patients with lung cancer. Cancer Chemother Pharmacol, 76:125-132, 2015

3. Kurihara H, Hamada A, Yoshida M, Shimma S, Hashimoto J, Yonemori K, Tani H, Miyakita Y, Kanayama Y, Wada Y, Kodaira M, Yunokawa M, Yamamoto H, Shimizu C, Takahashi K, Watanabe Y, Fujiwara Y, Tamura K. ^{64}Cu-DOTA-trastuzumab PET imaging and HER2 specificity of brain metastases in HER2-positive breast cancer patients. EJNMMI Res, 5:8, 2015

4. Otani S, Hamada A, Sasaki J, Wada M, Yamamoto M, Ryuge S, Takakura A, Fukui T, Yokoba M, Mitsufuji H, Toyooka I, Maki S, Kimura M, Hayashi N, Ishihara M, Kasajima M, Hiyoshi Y, Katono K, Asakuma M, Igawa S, Kubota M, Katagiri M, Saito H, Masuda N. Phase I and pharmacokinetic study of erlotinib administered in combination with amrubicin in patients with previously treated, advanced non-small cell lung cancer. Am J Clin Oncol, 38:405-410, 2015

5. Sakata S, Sasaki J, Saeki S, Hamada A, Kishi H, Nakamura K, Tanaka H, Notsute D, Sato R, Saruwatari K, Iriki T, Akaike K, Fujii S, Hirosako S, Kohrogi H. Dose Escalation and Pharmacokinetic Study of Carboplatin plus Pemetrexed for Elderly Patients with Advanced Nonsquamous Non-Small-Cell Lung Cancer: Kumamoto Thoracic Oncology Study Group Trial 1002. Oncology, 88:201-207, 2015

6. Hayashi M, Yamamoto Y, Sueta A, Tomiguchi M, Yamamoto-Ibusuki M, Kawasoe T, Hamada A, Iwase H. Associations Between Elastography Findings and Clinicopathological Factors in Breast Cancer. Medicine (Baltimore), 94:e2290, 2015

7. Iwamoto N, Umino Y, Yamane N, Hamada A, Shimada T. The development of the validated LCMS bioanalysis of trastuzumab in human plasma using a selective detection method for complementarity-determining regions of monoclonal antibodies: nano-surface and molecular-orientation limited (nSMOL) proteolysis. Anal Methods, 7:9177-9183, 2015

8. Oguri T, Shimokata T, Ito I, Yasuda Y, Sassa N, Nishiyama M, Hamada A, Hasegawa Y, Ando Y. Extension of the Calvert formula to patients with severe renal insufficiency. Cancer Chemother Pharmacol, 76:53-59, 2015

9. Yoshitake Y, Fukuma D, Yuno A, Hirayama M, Nakayama H, Tanaka T, Nagata M, Takamune Y, Kawahara K, Nakagawa Y, Yoshida R, Hirosue A, Ogi H, Hiraki A, Jono H, Hamada A, Yoshida K, Nishimura Y, Nakamura Y, Shinohara M. Phase II clinical trial of multiple peptide vaccination for advanced head and neck cancer patients revealed induction of immune responses and improved OS. Clin Cancer Res, 21:312-321, 2015

Division of Developmental Therapeutics

Yasuhiro Matsumura, Masahiro Yasunaga, Yoshikatsu Koga

Introduction

Our Division has been involved in basic research on drug delivery systems (DDS) and antibody therapeutics including an anticancer agent incorporating a micelle system, monoclonal antibody development (mAb), and antibody drug conjugate. We also investigate the mechanism of cancer-induced blood coagulation and are developing a new cancer diagnosis based on the cancer-specific mAb. In addition to the research work, we are operating the Japan Clinical Oncology Group Tumor Repository.

Routine activities

- Examination of clinical trials as an IRB member
- Operation of the JCOG Tumor Repository
- Management of personal information protection in the National Cancer Center (NCC) East Hospital

Research activities

1) DDS in Cancer Chemotherapy

Tumor-targeted delivery of therapeutic agents is a longstanding pharmacological goal to improve the treatment selectivity and therapeutic index. Most scientists have sought to use 'active' receptor-mediated tumor-targeting systems. However, the 'passive' targeting afforded by the "Enhanced Permeability and Retention (EPR) effect" provides a versatile and non-saturable approach for tumor-selective delivery. Polymeric micelles are ideally suited to exploit the EPR effect, and have been used for the delivery of a range of anticancer drugs in preclinical and clinical studies.

We showed the stronger antitumor effect and lower toxicity of the combination of the epirubicin-incorporating polymeric micelle and DACHP (oxaliplatin parent complex)-incorporating polymeric micelle in a human gastric cancer model than that of epirubicin and oxaliplatin.

2) Cancer Stromal Targeting Therapy

In spite of the recent success of antibody drug conjugate (ADC) therapy in patients with hypervascular and special tumors recognized by a particular mAb, there are several issues to be solved for ADC to be counted as a universal therapy for any types of cancer. Especially, most human solid tumors possess abundant stroma that hinders the distribution of ADC. To overcome these drawbacks, we developed a unique strategy that the cancer-stromal targeting (CAST) therapy by cytotoxic immunoconjugate bound to the collagen 4, tissue factor (TF), or fibrin network in the tumor stroma from which the payload is released gradually and distributed throughout the tumor, resulting in the arrest of tumor growth due to induced damage to tumor cells and tumor vessels. We successfully developed a mAb (102-10 clone) that reacted only with human fibrin, not with human fibrinogen and cross-reacted with mouse fibrin but not with mouse fibrinogen. The specificity of our 102-10 differs from existing anti-fibrin mAbs. Namely, 102-10 reacts only with a fibrin clot, but not with fibrinogen, soluble fibrin, or D-dimer. The anti-fibrin antibody therefore did not make an immune complex in the bloodstream and circulated in the blood for a long time. We then prepared the antibody drug conjugate (ADC) that is MMAE conjugated anti-fibrin mAb. The ADC may selectively extravasate from leaky tumor vessels, bind to the fibrin network in the stroma and create a scaffold from which effective sustained release of the free MMAE occurs. This free MMAE may easily reach the cancer cells by diffusion through the stroma barrier. Another benefit is that MMAE released from the ADC may also attack the vascular endothelial cells.

3) Infrastructure for the mAb development

We have established an infrastructure for antibody development including antigen production, animal immunization, hybridoma production, antibody expansion and purification, SPR characterization, and ELISA development. Simultaneously, we have found various cell surface molecules specific to colorectal cancer and succeeded in developing one of those molecules.

4) Noninvasive Diagnostic Test for Colorectal Cancer

Regarding colorectal cancer (CRC), we investigated the applicability of the fecal miRNA test (FmiRT) to fecal samples used for a previous fecal occult blood test (FOBT) stored under various conditions.

Education

1) Doctoral student

Graduate School of Frontier Science, The University of Tokyo: four students

Juntendo University Graduate School of Medicine: two students

Department of Gastroenterology and Hepatology, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba: one student

Department of Neurosurgery, Kumamoto University Graduate School of Medical Science: one student

2) Master course student

Graduate School of Frontier Science, The University of Tokyo: two students

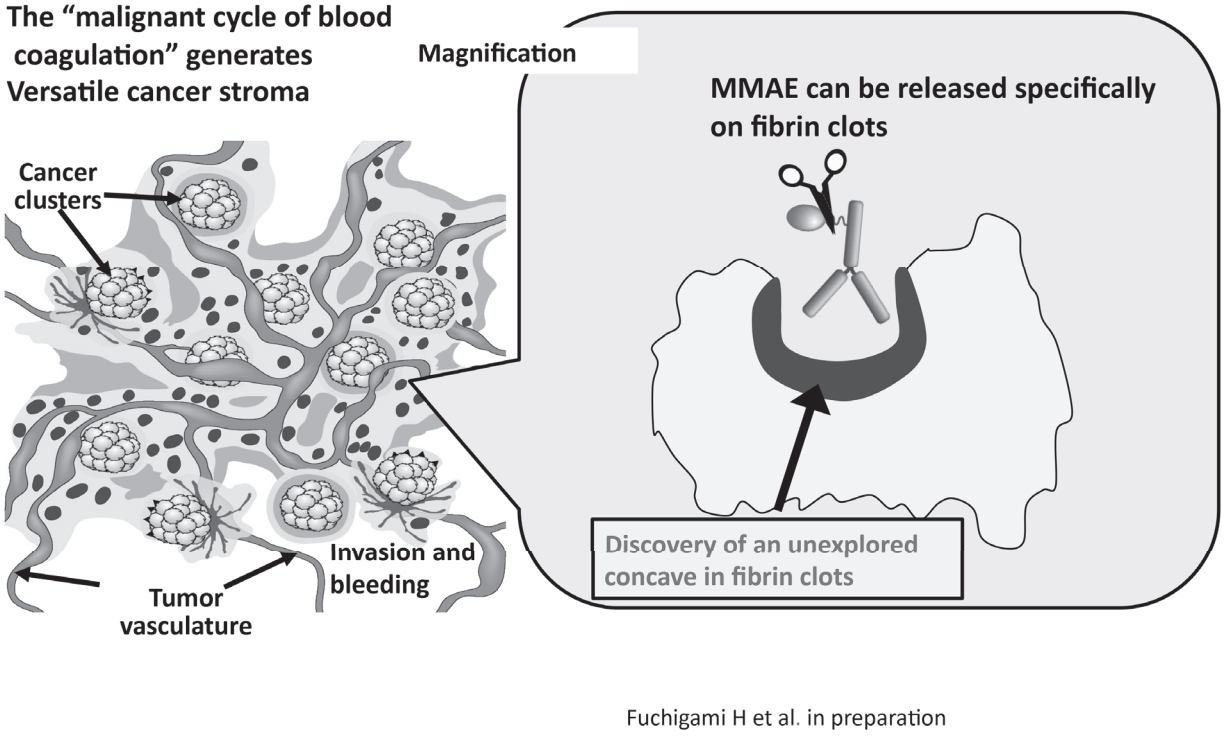


Figure 1. CAST therapy using anti-insoluble fibrin antibody - MMAE conjugate

List of papers published in 2015

Journal

1. Ahn J, Miura Y, Yamada N, Chida T, Liu X, Kim A, Sato R, Tsumura R, Koga Y, Yasunaga M, Nishiyama N, Matsumura Y, Cabral H, Kataoka K. Antibody fragment-conjugated polymeric micelles incorporating platinum drugs for targeted therapy of pancreatic cancer. Biomaterials, 39:23-30, 2015

2. Koga Y, Manabe S, Aihara Y, Sato R, Tsumura R, Iwafuji H, Furuya F, Fuchigami H, Fujiwara Y, Hisada Y, Yamamoto Y, Yasunaga M, Matsumura Y. Antitumor effect of antitissue factor antibody-MMAE conjugate in human pancreatic tumor xenografts. Int J Cancer, 137:1457-1466, 2015

3. Yamamoto Y, Hyodo I, Koga Y, Tsumura R, Sato R, Obonai T, Fuchigami H, Furuya F, Yasunaga M, Harada M, Kato Y, Ohtsu A, Matsumura Y. Enhanced antitumor effect of anti-tissue factor antibody-conjugated epirubicin-incorporating micelles in xenograft models. Cancer Sci, 106:627-634, 2015

4. Tsumura R, Sato R, Furuya F, Koga Y, Yamamoto Y, Fujiwara Y, Yasunaga M, Matsumura Y. Feasibility study of the Fab fragment of a monoclonal antibody against tissue factor as a diagnostic tool. Int J Oncol, 47:2107-2114, 2015

5. Sakai-Kato K, Nishiyama N, Kozaki M, Nakanishi T, Matsuda Y, Hirano M, Hanada H, Hisada S, Onodera H, Harashima H, Matsumura Y, Kataoka K, Goda Y, Okuda H, Kawanishi T. General considerations regarding the in vitro and in vivo properties of block copolymer micelle products and their evaluation. J Control Release, 210:76-83, 2015

Division of Cancer Immunotherapy (Kashiwa Campus)

Tetsuya Nakatsura, Yasushi Uemura, Toshiaki Yoshikawa, Keigo Saito, Manami Shimomura, Rong Zhang, Nobuhiro Tsuchiya, Yoshitaka Tada, Tatsuaki Iwama, Shoichi Mizuno, Yumi Tokumitsu, Kayoko Shoda, Yukiko Kozaki, Norihiro Fujinami, Shiori Sugai, Megumi Ozaki

Introduction

Our Division aims to investigate evidenced-based cancer immunotherapy, repeating basic research and translational research. This Division is focused on developing not only more effective immunotherapies but also an immunological method for suppression of recurrence or for cancer prevention.

Research activities

Three-dimensional (3D) cell culture is beneficial for physiological studies of tumor cells, due to its potential to deliver a high quantity of cell culture information that is representative of the cancer microenvironment and predictive of drug responses in vivo. Currently, gel-associated or matrix-associated 3D cell culture is comprised of intricate procedures that often result in experimental complexity. Therefore, we developed an innovative anti-cancer drug sensitivity screening technique for 3D cell culture on NanoCulture Plates (NCP) by employing the imaging device BioStation CT. Here, we showed that the human breast cancer cell lines BT474 and T47D form multicellular spheroids on NCP plates and compared their sensitivity to the anti-cancer drugs trastuzumab and paclitaxel using the BioStation CT. The anticancer drugs reduced spheroid migration velocity and suppressed spheroid fusion. In addition, primary cells derived from the human breast cancer tissues B58 and B61 grown on NCP plates also exhibited similar drug sensitivity. These results were in good agreement with the conventional assay method using ATP quantification. We confirmed the antitumor effects of the drugs on cells seeded in 96-well plates using the BioStation CT imaging technique. We expect this method to be useful in research for new antitumor agents and for drug sensitivity tests in individually tailored cancer treatments (3).

Novel treatment modalities are required urgently in patients with Hepatocellular carcinoma (HCC). A vaccine that induces cytotoxic T lymphocytes (CTLs) is an ideal strategy for cancer, and glypican-3 (GPC3) is a potential option for HCC. Blocking the programmed death-1 (PD-1)/PD-L1 pathway is a rational strategy to overcome tumor escape and tolerance toward CTLs. In the present study, we investigated whether anti-PD-1 blocking antibodies (α PD-1 Ab) enhanced the number of vaccine-induced peptide-specific CTLs in peripheral blood mononuclear cells (PBMCs) following the administration of GPC3 peptide vaccine to both patients and in a mouse model. The inhibitory receptor PD-1 was highly expressed in ex vivo GPC3-specific CTLs isolated from the PBMCs of vaccinated HCC patients. In vitro, interferon- γ induced PD-L1 expression in liver cancer cell lines. In addition, PD-1 blockade increased the number of GPC3-specific CTLs, which degranulate against liver cancer cell lines. In vivo experiments using tumor-bearing mouse models showed that the combination therapy of peptide vaccine and α PD-1 Ab suppressed tumor growth synergistically. PD-1 blockade increased the number of peptide-specific tumor-infiltrating T cells (TILs) and decreased the expression of inhibitory receptors on TILs. This study demonstrated that PD-1/PD-L1 blockade augmented the antitumor effects of a peptide vaccine by increasing the immune response of vaccine-induced CTLs, and provided a foundation for the clinical development of a combination therapy using a GPC3 peptide vaccine and α PD-1 Ab (7).

The use of dendritic cells (DC) to prime tumor-associated antigen-specific T-cell responses provides a promising approach to cancer

immunotherapy. Embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC) can differentiate into functional DCs, thus providing an unlimited source of DCs. However, the previously established methods of generating practical volumes of DCs from pluripotent stem cells (PSC) require a large number of PSCs at the start of the differentiation culture. In this study, we generated mouse proliferating myeloid cells (pMC) as a source of antigen-presenting cells (APC) using lentivirus-mediated transduction of the c-Myc gene into mouse PSC-derived myeloid cells. The pMCs could propagate almost indefinitely in a cytokine-dependent manner, while retaining their potential to differentiate into functional APCs. After treatment with IL4 plus GM-CSF, the pMCs showed impaired proliferation and differentiated into immature DC-like cells (pMC-DC) expressing low levels of major histocompatibility complex (MHC)-I, MHC-II, CD40, CD80, and CD86. In addition, exposure to maturation stimuli induced the production of TNF α and IL12p70, and enhanced the expression of MHC-II, CD40, and CD86, which is thus suggestive of typical DC maturation. Similar to bone marrow-derived DCs, they stimulated a primary mixed lymphocyte reaction. Furthermore, the in vivo transfer of pMC-DCs pulsed with H-2K(b)-restricted OVA257-264 peptide primed OVA-specific cytotoxic T cells and elicited protection in mice against challenge with OVA-expressing melanoma. Overall, myeloid cells exhibiting cytokine-dependent proliferation and DC-like differentiation may be used to address issues associated with the preparation of DCs (8).

Clinical trials

We are performing a phase I study of HSP105 peptide vaccine for patients with esophageal cancer and colorectal cancer.

List of papers published in 2015

Journal

1. Tsuchiya N, Sawada Y, Endo I, Uemura Y, Nakatsura T. Potentiality of immunotherapy against hepatocellular carcinoma. World J Gastroenterol, 21:10314-10326, 2015
2. Tsuchiya N, Sawada Y, Endo I, Saito K, Uemura Y, Nakatsura T. Biomarkers for the early diagnosis of hepatocellular carcinoma. World J Gastroenterol, 21:10573-10583, 2015
3. Sakamoto R, Rahman MM, Shimomura M, Itoh M, Nakatsura T. Time-lapse imaging assay using the BioStation CT: a sensitive drug-screening method for three-dimensional cell culture. Cancer Sci, 106:757-765, 2015
4. Imamura Y, Mukohara T, Shimono Y, Funakoshi Y, Chayahara N, Toyoda M, Kiyota N, Takao S, Kono S, Nakatsura T, Minami H. Comparison of 2D- and 3D-culture models as drug-testing platforms in breast cancer. Oncol Rep, 33:1837-1843, 2015
5. Ofuji K, Tada Y, Yoshikawa T, Shimomura M, Yoshimura M, Saito K, Nakamoto Y, Nakatsura T. A peptide antigen derived from EGFR T790M is immunogenic in non-small cell lung cancer. Int J Oncol, 46:497-504, 2015
6. Kinoshita Y, Tanaka S, Souzaki R, Miyoshi K, Kohashi K, Oda Y, Nakatsura T, Taguchi T. Glypican 3 expression in pediatric malignant solid tumors. Eur J Pediatr Surg, 25:138-144, 2015
7. Sawada Y, Yoshikawa T, Shimomura M, Iwama T, Endo I, Nakatsura T. Programmed death-1 blockade enhances the antitumor effects of peptide vaccine-induced peptide-specific cytotoxic T lymphocytes. Int J Oncol, 46:28-36, 2015
8. Zhang R, Liu TY, Senju S, Haruta M, Hirosawa N, Suzuki M, Tatsumi M, Ueda N, Maki H, Nakatsuka R, Matsuoka Y, Sasaki Y, Tsuzuki S, Nakanishi H, Araki R, Abe M, Akatsuka Y, Sakamoto Y, Sonoda Y, Nishimura Y, Kuzushima K, Uemura Y. Generation of mouse pluripotent stem cell-derived proliferating myeloid cells as an unlimited source of functional antigen-presenting cells. Cancer Immunol Res, 3:668-677, 2015
9. Nakatsuka R, Matsuoka Y, Uemura Y, Sumide K, Iwaki R, Takahashi M, Fujioka T, Sasaki Y, Sonoda Y. Mouse dental pulp stem cells support human umbilical cord blood-derived hematopoietic stem/progenitor cells in vitro. Cell Transplant, 24:97-113, 2015

Book

1. Sawada Y, Yoshikawa T, Ofuji K, Sakai M, Nakatsura T. Cancer vaccines: current status and future perspectives. In: Song J (ed), Cancer immunotherapy: mechanisms of cancer immunity, engineering immune-based therapies and developing clinical trials - book series: Frontiers in Cancer Immunology Volume 1, pp 236-258, 2015
2. Yoshikawa T, Sawada Y, Sakai M, Ofuji K, Nakatsura T. Development of glypican-3-targeted cancer immunotherapy. In: Seya T, Matsumoto M, Udaka K, Sato N (eds), Inflammation and immunity in cancer, Japan, Springer Japan, pp 133-143, 2015

Division of Cancer Immunotherapy (Tsukiji Campus)

Kiyoshi Yoshimura, Shigehisa Kitano, Tetsuhiko Asao, Ayumu Ito, Yonju Kim, Moeko Inoue, Masanori Fuse, Rie Ishibashi, Miki Kojima

Introduction

The Division of Cancer Immunotherapy aims to develop novel cancer immunotherapies as well as an immune monitoring system for finding biomarkers to predict the efficacy or side effects resulting from the application in clinical trials.

Routine activities

Maintenance of laboratory on 12F of the NCC Hospital and biotherapy core facility on 6F of the NCC institute: The maintenance includes an annual checkup and repair of research instruments, the deep freezer, the freezer, the tank for liquid nitrogen and the refrigerator.

Research activities

- Development of cancer immunotherapy via chimeric antigen receptor T cell (CAR-T) therapy for targeting Molecular L against disseminated gastric cancer
- Development of CAR-T therapy for Molecular N against advanced pancreatic cancer
- Development of CAR-T therapy for Molecular G against lung cancer
- Development of CAR-T therapy for acute myeloid lymphoma
- Development of immunotherapy for solid cancers by genetically activated and invasive T cells to maximize the effect of immune checkpoint inhibitors. Elucidation of mechanism of T cell infiltration to find predictive marker for immune checkpoint inhibitors
- Pre-clinical basic research for the first-in-human (FIH) clinical trial using novel CAR-T therapy
- Research on fundamental system for cancer immune cellular therapy in clinical practice
- Development of cancer immunotherapy against malignant pleural mesothelioma using antibodies for cancer-specific antigen and CAR-T
- Establishment of novel recognition system against cancer stem cell-like cells utilizing DNA or RNA aptamer
- Phase II clinical trial for adjuvant therapy against hepatocellular carcinoma using peptide vaccine (completed)
- Doctor-led clinical trial of multiple peptides mixed vaccine targeting pediatric cancer (completed)
- Pre-clinical research for FIH clinical trial of anti-CD4 antibody therapy
- Basic research on FIH clinical trial for induced pluripotent stem cell-based T cell therapy
- Development of predictive diagnostic method for recurrent hepatocellular carcinoma using blood samples
- Study of fundamental system for new immunotherapy in clinical practice (completed)

Findings

1) Molecule L expressed on the cell surface membrane expressed in gastric cancer and cancer stem cell-like cells is identified. Cytotoxic activation of CAR-T cells against the Molecule L is also confirmed.
2) Molecule N expressed on the cell surface membrane expressed in pancreatic cancer and cancer stem cell-like cells is identified. The Molecule N has the possibility to influence tumor micro environment based on the proliferation tumor cells and chemokine production by the downstream of signal transaction of Molecule N. In addition, it is possibly related to a mechanism of infiltration of T cells into solid cancer.
3) Molecule Y is expressed on T cell which is

infiltrated into solid cancers and influences T cell activation. The Molecule Y is under study because it seems to have a direct influence on the T cell infiltration unlike regular activation of T cell which produces interferon gamma.

4) Basic development of modified CAR-T cells forming activated and invasive T cells is in progress. The modified T cells will infiltrate into solid cancers and increase their number inside the cancer cell.
5) Immuno-monitoring for anti GD2 antibody therapy in combination with IL-2 and CSF against refractory neuroblastoma phase I has been completed and phase II is under preparation.
6) Clinical application of FITC-CAR-T therapy which was proposed by Dr. Tamada from Yamaguchi University is in progress. Our target is to apply the therapy against malignant pleural mesothelioma in two years.
7) Cell processing for CD19-CAR-T therapy (phase I) was executed. The operation of the therapy was set up based on the result of the investigation on cell processing. Investigation was done by US and Australian institutions.

Clinical trials

- Cell processing after leukapheresis, preservation and immunological analysis for CD19-CAR-T therapy
- Immune-monitoring phase I for anti GD2 antibody therapy in combination with IL-2 and CSF against refractory neuroblastoma

Education

- Training a doctor on a Ph.D. course
- Training a resident physician from respiratory medicine
- Working in close coordination with other branches at the NCC hospital and having junior doctors develop a deeper understanding of immunotherapy.

Future prospects

With NCC staff support, our research has been moving ahead after the initial setting up of our laboratory in May 2015 despite the fact that we went through a rough time in the first few months due to medical device problems, failures during take over and establishment of new projects. We will continue to act as an intermediary between basic research and clinical applications, aiming to develop novel immunotherapies. We are planning to publish papers and apply for patents in 2016.

List of papers published in 2015

Journal

1. Maeda Y, Yoshimura K, Matsui H, Shindo Y, Tamesa T, Tokumitsu Y, Hashimoto N, Tokuhisa Y, Sakamoto K, Sakai K, Suehiro Y, Hinoda Y, Tamada K, Yoshino S, Hazama S, Oka M. Dendritic cells transfected with heat-shock protein 70 messenger RNA for patients with hepatitis C virus-related hepatocellular carcinoma: a phase 1 dose escalation clinical trial. Cancer Immunol Immunother, 64:1047-1056, 2015

2. Ishiguro S, Yoshimura K, Tsunedomi R, Oka M, Takao S, Inui M, Kawabata A, Wall T, Magafa V, Cordopatis P, Tzakos AG, Tamura M. Involvement of angiotensin II type 2 receptor (AT2R) signaling in human pancreatic ductal adenocarcinoma (PDAC): a novel AT2R agonist effectively attenuates growth of PDAC grafts in mice. Cancer Biol Ther, 16:307-316, 2015

3. Tokumitsu Y, Yoshino S, Iida M, Yoshimura K, Ueno T, Hazama S, Oka M. Intraoperative dissemination during gastrectomy for gastric cancer associated with serosal invasion. Surg Today, 45:746-751, 2015

4. Shindo Y, Yoshimura K, Kuramasu A, Watanabe Y, Ito H, Kondo T, Oga A, Ito H, Yoshino S, Hazama S, Tamada K, Yagita H, Oka M. Combination immunotherapy with 4-1BB activation and PD-1 blockade enhances antitumor efficacy in a mouse model of subcutaneous tumor. Anticancer Res, 35:129-136, 2015

Division of Psycho-Oncology

Asao Ogawa, Hiroya Kinoshita, Ken Shimizu

Introduction

The aim of the Division is to develop mind-centered interventions to restore, maintain, and improve the quality of life of patients and their families throughout cancer treatment, and for end-of-life care. The Division has focused on developing effective interventions for delirium, dementia, and depression in cancer patients as well as on determining the mechanism underlying the relationship between cancer and the mind through a combination of neuropsychiatric, psychosocial, and behavioral sciences.

Research activities

1) Development of the Japanese Version of the Edmonton Symptom Assessment System – Revised

A revised version of the Edmonton Symptom Assessment System (ESAS-r) is a self-report symptom measurement tool, which includes nine common symptom-related items of advanced cancer: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. We administered the tool to validate and investigate optimal cutoff points for the Japanese version of the ESAS-r in 292 Japanese adult patients with cancer. As for results of the study, the Japanese version of the ESAS-r is a reliable (intraclass correlation coefficient: 0.90) and valid (Cronbach's alpha: 0.87) tool for measuring symptoms, and can accurately represent the severity of many symptoms in Japanese adult patients with cancer *(Yokomichi N, et al. J Pain Symptom Manage. 2015; Yamaguchi T, et al. J Pain Symptom Manage. 2015).*

2) Effect of continuous deep sedation on survival in patients with advanced cancer (J-Proval): a propensity score-weighted analysis of a prospective cohort study.

We aimed to examine whether CDS shortens patient survival using the propensity score-weighting method, and to explore the effect of artificial hydration during CDS on survival. After propensity-score weighting, median survival was 22 days (95% CI 21-24) and 26 days (24-27), respectively (median difference -1 day [95% CI -6 to 4]; HR 1.01 [95% CI 0.87-1.17]; log-rank p=0.91). Age (pinteraction=0.67), sex (pinteraction=0.26), performance status (pinteraction=0.90), and volume of artificial hydration (pinteraction=0.14) did not have an effect modification on the association between sedation and survival, although care setting did have a significant effect modification (pinteraction=0.021). CDS does not seem to be associated with a measurable shortening of life in patients with advanced cancer cared for by specialized palliative care services, and could be considered a viable option for palliative care in this setting *(Maeda I, et al. Lancet Oncol. 2016).*

List of papers published in 2015

Journal

1. Baba M, Maeda I, Morita T, Inoue S, Ikenaga M, Matsumoto Y, Sekine R, Yamaguchi T, Hirohashi T, Tajima T, Tatara R, Watanabe H, Otani H, Takigawa C, Matsuda Y, Nagaoka H, Mori M, Tei Y, Hiramoto S, Suga A, Kinoshita H. Survival prediction for advanced cancer patients in the real world: A comparison of the Palliative Prognostic Score, Delirium-Palliative Prognostic Score, Palliative Prognostic Index and modified Prognosis in Palliative Care Study predictor model. Eur J Cancer, 51:1618-1629, 2015

2. Hamano J, Morita T, Inoue S, Ikenaga M, Matsumoto Y, Sekine R, Yamaguchi T, Hirohashi T, Tajima T, Tatara R, Watanabe H, Otani H, Takigawa C, Matsuda Y, Nagaoka H, Mori M, Yamamoto N, Shimizu M, Sasara T, Kinoshita H. Surprise Questions for Survival Prediction in Patients With Advanced Cancer: A Multicenter Prospective Cohort Study. Oncologist, 20:839-844, 2015

3. Hamano J, Morita T, Ozawa T, Shishido H, Kawahara M, Aoki S, Demizu A, Goshima M, Goto K, Gyoda Y, Hashimoto K, Otomo S, Sekimoto M, Shibata T, Sugimoto Y, Matsunaga M, Takeda Y, Nagayama J, Kinoshita H. Validation of the Simplified Palliative Prognostic Index Using a Single Item From the Communication Capacity Scale. J Pain Symptom Manage, 50:542-547.e4, 2015

4. Maeda I, Morita T, Kinoshita H. Reply to H. Nakayama et al. J Clin Oncol, 33:2228-2229, 2015

5. Wada S, Shimizu K, Inoguchi H, Shimoda H, Yoshiuchi K, Akechi T, Uchida M, Ogawa A, Fujisawa D, Inoue S, Uchitomi Y, Matsushima E. The Association Between Depressive Symptoms and Age in Cancer Patients: A Multicenter Cross-Sectional Study. J Pain Symptom Manage, 50:768-777, 2015

6. Kizawa Y, Morita T, Miyashita M, Shinjo T, Yamagishi A, Suzuki S, Kinoshita H, Shirahige Y, Yamaguchi T, Eguchi K. Improvements in Physicians' Knowledge, Difficulties, and Self-Reported Practice After a Regional Palliative Care Program. J Pain Symptom Manage, 50:232-240, 2015

7. Miura T, Matsumoto Y, Hama T, Amano K, Tei Y, Kikuchi A, Suga A, Hisanaga T, Ishihara T, Abe M, Kaneishi K, Kawagoe S, Kuriyama T, Maeda T, Mori I, Nakajima N, Nishi T, Sakurai H, Morita T, Kinoshita H. Glasgow prognostic score predicts prognosis for cancer patients in palliative settings: a subanalysis of the Japan-prognostic assessment tools validation (J-ProVal) study. Support Care Cancer, 23:3149-3156, 2015

8. Umezawa S, Fujimori M, Matsushima E, Kinoshita H, Uchitomi Y. Preferences of advanced cancer patients for communication on anticancer treatment cessation and the transition to palliative care. Cancer, 121:4240-4249, 2015

9. Igarashi T, Abe K, Miura T, Tagami K, Motonaga S, Ichida Y, Hasuo H, Matsumoto Y, Saito S, Kinoshita H. Oxycodone frequently induced nausea and vomiting in oxycodone-naïve patients with hepatic dysfunction. J Palliat Med, 18:399, 2015

10. Mori M, Shimizu C, Ogawa A, Okusaka T, Yoshida S, Morita T. A National Survey to Systematically Identify Factors Associated With Oncologists' Attitudes Toward End-of-Life Discussions: What Determines Timing of End-of-Life Discussions? Oncologist, 20:1304-1311, 2015

11. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Ogawa A, Fujisawa D, Sone T, Yoshiuchi K, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Personality traits and coping styles explain anxiety in lung cancer patients to a greater extent than other factors. Jpn J Clin Oncol, 45:456-463, 2015

12. Umezawa S, Fujisawa D, Fujimori M, Ogawa A, Matsushima E, Miyashita M. Prevalence, associated factors and source of support concerning supportive care needs among Japanese cancer survivors. Psychooncology, 24:635-642, 2015

13. Yokomichi N, Morita T, Nitto A, Takahashi N, Miyamoto S, Nishie H, Matsuoka J, Sakurai H, Ishihara T, Mori M, Tarumi Y, Ogawa A. Validation of the Japanese Version of the Edmonton Symptom Assessment System-Revised. J Pain Symptom Manage, 50:718-723, 2015

14. Kinoshita H, Maeda I, Morita T, Miyashita M, Yamagishi A, Shirahige Y, Takebayashi T, Yamaguchi T, Igarashi A, Eguchi K. Place of death and the differences in patient quality of death and dying and caregiver burden. J Clin Oncol, 33:357-363, 2015

Book

1. Ogawa A. Long-term cognitive function. In: Bruera E, Higginson IJ, von Gunten CF, Morita T (eds), Textbook of Palliative Medicine and Supportive Care, Second Edition, USA, CRC Press, pp 1269-1275, 2015

Division of Radiation Oncology and Particle Therapy

Tetsuo Akimoto, Sadatomo Zenda, Hidenobu Tachibana, Ryosuke Kohno, Kenji Hotta, Hiromi Baba

Introduction

The aim of research in the Division of Radiation Oncology and Particle Therapy at the National Cancer Center Hospital East is to study and develop innovative treatment techniques and pilot a clinical trial for proton beam therapy (PBT). Medical physicists mainly perform development and verification of the systems for beam irradiation, a dose calculation system, dose measurement and imaging of PBT. Radiation oncologists mainly perform studies on the clinical trials, efficacy and side-effects of PBT.

Routine activities

At present, the staff of the Radiation Oncology and Particle Therapy Division consists of seven consultant physicians (radiation oncologists), six radiation technologists, four medical physicists, one nurse, and one clerk. We have more than 300 new patients for PBT every year, and quality assurances of PBT are performed by medical physicists and radiation technologists, and the conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. PBT are routinely based on three-dimensional radiation therapy planning and PBT using RT-dedicated multi-detector-row helical computed tomography (CT) scanning in order to confirm a precise radiation dose to the targeted tumors. Respiratory-gating has been applied especially in radiotherapeutic management for patients with lung, esophagus and liver cancers. The section is responsible for PBT that is composed of seven operating staff members and one technician for fabricating the compensator and aperture; they are sent from manufacturing companies and work in collaboration with the other staff members of the Division. PBT consists of two treatment rooms, both of which are routinely used for rotational gantry treatment. The Division ensures quality assurance and regular maintenance of the PBT machines for precise dose delivery and safe treatment.

Research activities

1) PBT as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study.
2) Phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.
3) Phase I/II study of dose escalated PBT combined with chemotherapy for esophageal cancer.
4) Establishment of feasibility and effectiveness of line scanning for localized prostate cancer.
5) Proton dose distribution measurements using a MOSFET detector with a simple dose-weighted correction method for LET effects.
6) Radiobiological evaluation of cellular response to PBT.
7) Radiobiological evaluation of combined effect of chemotherapeutic agents on enhancement of PBT.
8) Standardization of methods of PBT and quality assurance of PBT among Japanese proton beam facilities.
9) Establishment of infrastructure for multi-institutional study of PBT for various cancers.
10) Technical development of intensity modulated proton beam therapy (IMPT).

Clinical trials

The following in-house and multi-institutional clinical trials are under way.

1) Phase II study of PBT for malignant melanoma of nasal cavity.
2) Phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.

3) Phase I/II study of dose escalated study of PBT combined with chemotherapy for esophageal cancer
4) Phase I/II study of line scanning for localized prostate cancer

Education

We established an education and training system for residents and junior radiation oncologists through clinical conferences and lectures on radiation oncology, physics and radiation biology. In addition, a training course regarding quality assurance of radiation therapy including proton beam therapy has been regularly held for medical physicists and radiological technologists.

Future prospects

We are now aiming at the establishment of the system that can provide high-quality and safe proton beam therapy. In addition, we would like to promote research and development of innovative technologies regarding proton beam therapy, radiation biology and medical physics.

Table 1. Number of patients treated with PBT during 2011-2015

	2011	2012	2013	2014	2015
New patients	200	245	378	331	310
Head and neck cancers	49	45	35	33	38
Lung and mediastinal cancers	24	76	101	82	80
Hepatocellular carcinoma	27	35	38	21	23
Prostate cancer	93	79	143	111	85
Others	7	17	45	54	84

Table: The changes in the number of patients treated with PBT

List of papers published in 2015

Journal

1. Tahara M, Kiyota N, Mizusawa J, Nakamura K, Hayashi R, Akimoto T, Hasegawa Y, Iwae S, Monden N, Matsuura K, Fujii H, Onozawa Y, Homma A, Kubota A, Fukuda H, Fujii M. Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). Cancer Sci, 106:726-733, 2015

2. Hotta K, Kohno R, Nagafuchi K, Yamaguchi H, Tansho R, Takada Y, Akimoto T. Evaluation of monitor unit calculation based on measurement and calculation with a simplified Monte Carlo method for passive beam delivery system in proton beam therapy. J Appl Clin Med Phys, 16:228-238, 2015

3. Mizowaki T, Aoki M, Nakamura K, Yorozu A, Kokubo M, Karasawa K, Kozuka T, Nakajima N, Sasai K, Akimoto T. Current status and outcomes of patients developing PSA recurrence after prostatectomy who were treated with salvage radiotherapy: a JROSG surveillance study. J Radiat Res, 56:750-756, 2015

4. Hashimoto Y, Akimoto T, Iizuka J, Tanabe K, Mitsuhashi N. Correlation between the changes in the EPIC QOL scores and the dose-volume histogram parameters in high-dose-rate brachytherapy combined with hypofractionated external beam radiation therapy for prostate cancer. Jpn J Clin Oncol, 45:81-87, 2015

5. Motegi A, Kawashima M, Arahira S, Zenda S, Toshima M, Onozawa M, Hayashi R, Akimoto T. Accelerated radiotherapy for T1 to T2 glottic cancer. Head Neck, 37:579-584, 2015

6. Zenda S, Ishi S, Akimoto T, Arahira S, Motegi A, Tahara M, Hayashi R, Asanuma C. DeCoP, a Dermatitis Control Program using a moderately absorbent surgical pad for head and neck cancer patients receiving radiotherapy: a retrospective analysis. Jpn J Clin Oncol, 45:433-438, 2015

7. Hatanaka S, Miyabe Y, Tohyama N, Kumazaki Y, Kurooka M, Okamoto H, Tachibana H, Kito S, Wakita A, Ohotomo Y, Ikagawa H, Ishikura S, Nozaki M, Kagami Y, Hiraoka M, Nishio T. Dose calculation accuracies in whole breast radiotherapy treatment planning: a multi-institutional study. Radiol Phys Technol, 8:200-208, 2015

8. Zenda S, Kawashima M, Arahira S, Kohno R, Nishio T, Tahara M, Hayashi R, Akimoto T. Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up. Int J Clin Oncol, 20:447-454, 2015

Division of Functional Imaging

Hirofumi Fujii, Izumi O. Umeda, Masayuki Yamaguchi, Mitsuyoshi Yoshimoto

Introduction

The Division of Functional Imaging actively investigates three kinds of imaging modalities, namely, radionuclide imaging, optical imaging and magnetic resonance (MR) imaging, to establish therapeutic strategies for minimally invasive and personalized cancer treatments. For radionuclide and optical imaging, some experimental studies were performed to develop unique applications of imaging probes and the usefulness of new methods was evaluated by *in vivo* imaging. For MR imaging, some experimental and clinical studies were done using two kinds of scanners: a 9.4 T scanner dedicated to small animal imaging and a 3.0 T whole-body scanner.

Research activities

In the field of nuclear medicine, we studied the prediction of the therapeutic efficacy of liposomal anti-cancer agents, such as Doxil®, by using SPECT imaging with radiolabeled liposomes. We found a good correlation between tumor accumulation of radiolabeled liposomes and the therapeutic efficacy of Doxil. This result suggested that radiolabeled liposomes would be useful to predict the sensitivity of liposomal drugs to the patients, and this method will contribute to the development of personalized medicine.

Radiolabeled liposomes are also promising for tumor theranostics because of their high affinity to tumors. However, conventional liposomes also accumulate in normal tissues such as liver and spleen. This has hindered their clinical application. We have already developed a certain system that accelerated the clearance from normal tissues using a unique chelating ligand, EC (ethylenedicysteine). However, our concept did not work on mouse xenograft models bearing human cancer. We decreased the liposomal dosage according to the hepatic clearance rate of the mouse and modified liposomes with PEG. As a result, we could overcome this problem due to the difference of mouse strain and we made progress in clinical application of this concept.

In boron neutron capture therapy (BNCT), 4-borono-L-phenylalanine (BPA) is a representative ^{10}B carrier and PET using ^{18}F-FBPA, which is an analogue of BPA, has been performed to estimate BPA uptake in tumors. We compared the transport mechanism of ^{18}F-FBPA with that of ^{14}C-BPA in in vitro studies. In a cell uptake experiment, the uptake of ^{18}F-FBPA and ^{14}C-BPA was drastically inhibited by 2-aminobicyclo-(2.2.1)-heptane-2-carboxylic acid (BCH), indicating that these are transported through a system L transporter. Western blotting revealed that A-253 and FaDu that showed the high FBPA uptake highly express L-type amino acid transporter 1. In addition, ^{18}F-FBPA uptake significantly correlated with ^{14}C-BPA uptake. We investigated the correlation between ^{18}F-FBPA uptake and BPA uptake in tumor-bearing mice models. A biodistribution study and microPET study indicated that the tumor uptake of ^{18}F-FBPA correlated with a boron concentration derived from BPA. These results suggest that ^{18}F-FBPA PET is useful to estimate the sensitivity to BNCT using BPA.

In the field of magnetic resonance (MR) imaging, superparamagnetic iron oxide (SPIO)-enhanced MR imaging was investigated to precisely visualize the margins of treated areas of hepatic tumors after radiofrequency ablation (RFA) as well as radiation therapies. Our experimental studies using rats revealed that SPIO particles remained for a long time in damaged liver tissues due to RFA or radiotherapy, and visualized the damaged liver tissues as dark areas in contrast to tumors as bright areas on MR images. Therefore, it was suggested that SPIO-enhanced MR imaging was utilized to delineate the margin of RFA- or radio-

treated areas. In addition, our recent experiments have demonstrated that the visualization of the margins of irradiated liver tissue helps to evaluate the response of liver cancer lesions to radiotherapy. Collectively, we contend that this imaging technique helps clinicians to evaluate the risk of recurrence and enhance the curability of liver tumors.

Clinical trials

We carried out a prospective cohort study to investigate metabolite levels in the brain after cancer chemotherapy in 68 Japanese breast cancer patients by using MR spectroscopy (MRS). This was a cooperative study with the Division of Psycho-Oncology, National Cancer Center. A 3.0-tesla MR scanner and MRS methods called PRESS and MEGA-PRESS detected various brain metabolites including glutamate and γ-aminobutyric acid (GABA), which are principal neurotransmitters. Importantly, these MRS methods allowed longitudinal observation of brain metabolite levels during the prospective study (average duration, 54 weeks; standard deviation, 19 weeks). Thus we contend that MR spectroscopy by using a 3.0-tesla MR scanner is a valuable approach to longitudinally monitor brain metabolite levels in chemotherapy-treated breast cancer patients. This approach will hopefully provide important information with regard to chemotherapy-related cognitive impairment (so called "chemo-brain") in breast cancer survivors.

Education

Some graduate school students took part in our studies and received doctor or master degrees in the field of medicine and related sciences.

Future prospects

We will develop our research projects to translate our research products into clinical practice.

List of papers published in 2015

Journal

1. Yoshimoto M, Kurihara H, Fujii H. Theragnostic imaging using radiolabeled antibodies and tyrosine kinase inhibitors. ScientificWorldJournal, 2015:842101, 2015

2. Nagai M, Yamaguchi M, Mori K, Furuta T, Ashino H, Kurosawa H, Kasahara H, Minami M, Fujii H. Magnetic resonance-based visualization of thermal ablative margins around hepatic tumors by means of systemic ferucarbotran administration before radiofrequency ablation: animal study to reveal the connection between excess iron deposition and T2*-weighted hypointensity in ablative margins. Invest Radiol, 50:376-383, 2015

3. Okamoto M, Naka K, Kitagawa Y, Ishiwata K, Yoshimoto M, Shimizu I, Toyohara J. Synthesis and evaluation of 7α-(3-[(18)F] fluoropropyl) estradiol. Nucl Med Biol, 42:590-597, 2015

4. Fujii H, Iimoto T, Tsuzuki T, Iizumi S, Someya S, Hamamichi S, Kessler MM. Collaboration of local governments and experts responding to the increase of the environmental radiation level secondary to the nuclear accident: a unique activity to relieve residents' anxiety. Radiat Prot Dosimetry, 167:370-375, 2015

5. Iimoto T, Nunokawa J, Fujii H, Takashima R, Hashimoto M, Fukuhara T, Yajima T, Matsuzawa H, Kurosawa K, Yanagawa Y, Someya S. Collaboration of local government and experts responding to increase in environmental radiation level due to the nuclear disaster: focusing on their activities and latest radiological discussion. Radiat Prot Dosimetry, 167:358-364, 2015

Division of Science and Technology for Endoscopy

Kazuhiro Kaneko, Tomonori Yano, Mari Takahashi, Atsushi Yagishita

Introduction

Approximately 50 years have passed since the gastrofiberscope came into existence, and diagnostic techniques have progressed rapidly. Now, endoscopy is widely used for screening, diagnosis, and treatment of early cancer in aero-digestive tracts including the pharynx, esophagus, stomach, and colorectum. With conventional endoscopy, observations are made using white light to illuminate the mucosal surface with special attention paid to the appearance of reddish and irregular portions compared to adjacent areas. Thus, detection of suspicious early cancerous lesions has been largely based on macroscopic characteristics of the lesions.

One of the characteristics of early cancer is the growth of blood vessels (neovascularity). Using two narrow wave bands of light (blue: 390-445nm; green: 530-550nm) that can be absorbed by circulating hemoglobin, Narrow band imaging (NBI) endoscopy may provide better images of the capillaries in the mucosal surface.

Another characteristic of a tumor is hypoxia. As a tumor grows, it rapidly outgrows its blood supply, leaving portions of the tumor with regions where the oxygen concentration is significantly lower than in healthy tissues. Thus, there have been attempts to visualize spatial distribution of tumor hypoxia, such as fluorescent labeling techniques or hemoglobin absorption-based techniques. However, these methods are limited because of low spatiotemporal resolution. We developed an imaging technology that can derive oxygen saturation (StO_2) images from small numbers of wavelength measurements. Thus, next-generation novel endoscopy will be required to make visible specific functions in cancerous tissues. To advance the technology, laser light and near-infrared light will be necessary.

Routine activities

The present research activities mainly focus on the development of new instruments for endoscopic diagnosis and new endoscopic treatment modalities. In the present situation, because questions still need to be raised in development research regarding endoscopy, our Division collaborates with the Endoscopy Division. Therefore, endoscopic diagnosis is routinely performed for cancer patients and endoscopic treatment, such as EMR or ESD, is performed in patients with early GI tract cancers. We give lectures to resident doctors regarding individual projects. Furthermore, meetings are constantly conducted with faculties including of technology and science students of the university.

Research activities

Research studies have been conducted in various fields: endoscopic diagnosis and treatment, and prevention of cancer in the GI tract and head and neck. In addition, the present research is to develop new devices or procedures in innovative less-invasive laparoscopic surgery for gastrointestinal malignancies. These projects are conducted as prospective clinical studies and preclinical studies in collaboration with not only commercial companies but also the faculties of Technology and Science of the university.

Developing research into novel endoscopy systems is being performed. Hypoxia imaging is detected for neoplastic lesions of the head and neck and alimentary tracts, with two types of visualized images: a pseudocolor StO_2 image and a StO_2 overlay image. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm with various spectrums. This system is capable of penetrating through the gastrointestinal wall and obtaining images. Furthermore, a preclinical study of molecular

imaging endoscopy using small molecules, peptides and antibodies was planned this year. With a low-temperature atmospheric pressure plasma system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnosis system using photosensitizing agents, such as hypericin, has been constructed. A novel tattooing system under endoscopy has been developed. Now, a patent is being sought for this system. Ongoing projects are to develop needle graspers, needle ultrasonic coagulators in the surgical field. A clinical trial regarding confocal laser endocytoscopy using fluorescein is planned. This type of endocytoscopy is classified into a new category.

Clinical trials

A first-in-human clinical trial of hypoxia imaging was incorporated into the endoscopic diagnosis of early and advanced cancers of the esophagus, stomach, and colorectum. We conducted a proof-of-concept trial for 40 patients with neoplastic lesions in the esophagus including the pharynx, stomach and colorectum. In this first-in-human trial (UMIN 000004983), two types of StO_2 images were used. One was a pseudocolor StO_2 image that showed StO_2 levels as different hues, and the other was a StO_2 overlay image that overlapped StO_2 levels in blue on a white light illumination image to detect background mucosa. In a system of near-infrared light with nanoparticles, nanoparticles of rare earth act as fluorescent agents. Nanoparticles attached probe excite due to emission of near-infrared light, when probes attach to the surface of cancer cells. Now, molecular imaging endoscopy for the use of this system with InGaAs CCD has been developed in collaboration with the Technology Department of the University. Preclinical studies, such as a low-temperature atmospheric pressure plasma system, and photodynamic diagnosis of hypericin, are performed using animal models. Furthermore, a clinical trial for biodegradable (BD) stent implantation for benign esophageal stricture after curative treatment and a clinical trial for photodynamic diagnosis using 5ALA are ongoing. A treatment of a new concept for a precursor or early cancer of the duodenum was planned in collaboration with Norway University of Science and Technology.

Education

The aim is the cultivation of human resources who specialize in endoscopic diagnosis and treatment for alimentary tract cancer. Staff supervise individual residents. The importance of positiveness is highlighted in periodic case conferences and joint conferences among internal medicine, surgery and radiology. Staff supervise in congress presentations and writing manuscripts after deciding upon individual themes, and a lot of discussion is undertaken in department conferences. For residents interested in development research, the opportunity to study is supported after graduation. Personal exchanges were performed with PMDA.

Future prospects

Existing endoscopic diagnosis for neoplasia of the alimentary tract is performed on the basis of the morphological features of tumors. Molecular imaging endoscopy is a novel system to visualize cancer using a specific laser source under phosphor combined with cancer-specific agents. We can obtain new imaging, since functions or the metabolic state in cancer cells is visualized. In additional modalities, there are photodynamic diagnosis, endomicroscopy, and hypoxia imaging endoscopy. We endeavor to perform first-in-human clinical trials. These modalities will be expected as next-generation endoscopy, and we try innovative approaches to produce all-new endoscopy in collaboration with academia and companies.

List of papers published in 2015

Journal

1. Osera S, Ikematsu H, Odagaki T, Oono Y, Yano T, Kobayashi A, Ito M, Saito N, Kaneko K. Efficacy and safety of endoscopic radial incision and cutting for benign severe anastomotic stricture after surgery for lower rectal cancer (with video). Gastrointest Endosc, 81:770-773, 2015

2. Zako T, Yoshimoto M, Hyodo H, Kishimoto H, Ito M, Kaneko K, Soga K, Maeda M. Cancer-targeted near infrared imaging using rare earth ion-doped ceramic nanoparticles. Biomater Sci, 3:59-64, 2015

3. Satake H, Yano T, Yoda Y, Fujii S, Zenda S, Tomioka T, Shinozaki T, Miyazaki M, Kaneko K, Hayashi R. Feasibility of salvage endoscopic resection for patients with locoregional failure after definitive radiotherapy for pharyngeal cancer. Endosc Int Open, 3:E274-E280, 2015

4. Zako T, Ito M, Hyodo H, Yoshimoto M, Watanabe M, Takemura H, Kishimoto H, Kaneko K, Soga K, Maeda M. Extra-luminal detection of assumed colonic tumor site by near-infrared laparoscopy. Surg Endosc, 2015

5. Ikematsu H, Matsuda T, Osera S, Imajoh M, Kadota T, Morimoto H, Sakamoto T, Oono Y, Kaneko K, Saito Y. Usefulness of narrow-band imaging with dual-focus magnification for differential diagnosis of small colorectal polyps. Surg Endosc, 29:844-850, 2015

6. Kanesaka T, Uedo N, Yao K, Ezoe Y, Doyama H, Oda I, Kaneko K, Kawahara Y, Yokoi C, Sugiura Y, Ishikawa H, Kato M, Takeuchi Y, Muto M, Saito Y. A significant feature of microvessels in magnifying narrow-band imaging for diagnosis of early gastric cancer. Endosc Int Open, 3:E590-E596, 2015

7. Mochizuki S, Uedo N, Oda I, Kaneko K, Yamamoto Y, Yamashina T, Suzuki H, Kodashima S, Yano T, Yamamichi N, Goto O, Shimamoto T, Fujishiro M, Koike K, SAFE Trial Study Group. Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. Gut, 64:397-405, 2015

8. Satake H, Yano T, Muto M, Minashi K, Yoda Y, Kojima T, Oono Y, Ikematsu H, Aoyama I, Morita S, Miyamoto S, Fujii S, Yoshizawa A, Ochiai A, Hayashi R, Kaneko K. Clinical outcome after endoscopic resection for superficial pharyngeal squamous cell carcinoma invading the subepithelial layer. Endoscopy, 47:11-18, 2015

9. Osera S, Yano T, Odagaki T, Oono Y, Ikematsu H, Ohtsu A, Kaneko K. Peritonitis related to percutaneous endoscopic gastrostomy using the direct method for cancer patients. Surg Endosc, 29:2941-2946, 2015

Division of Surgical Technology

Masaaki Ito, Takahiro Kinoshita

Activities/Research activities

Our research activity in the Department of Surgical Innovation started in 2013. The main purpose of this Department is to develop surgical devices that are truly necessary, to deliver them to clinical fields, and to prove their efficacy and safety through clinical trials.

The three main elements of our innovation are creating devices reflecting true needs in the medical field, practicing with the devices in clinical trials and connecting our innovations to a wider world.

We have collaborated between clinical surgeons and engineers in the NEXT Innovating Group. We have continued to clarify problem points in previously developed Japanese medical devices and focused on innovation plans and formed partnerships with various companies.

Contents of innovation

Establishment of NEXT Conference

We started discussions to make innovative surgical devices in the NEXT Conference, which was jointly held by professionals consisting of surgeons and coordinators of surgical innovation, intellectual property and pharmaceutical affairs. Specific devices started to be created through discussion in the NEXT Conference.

Innovation schemes were divided into two groups according to the risk level: Level I and Level II.

The devices made were as follows:

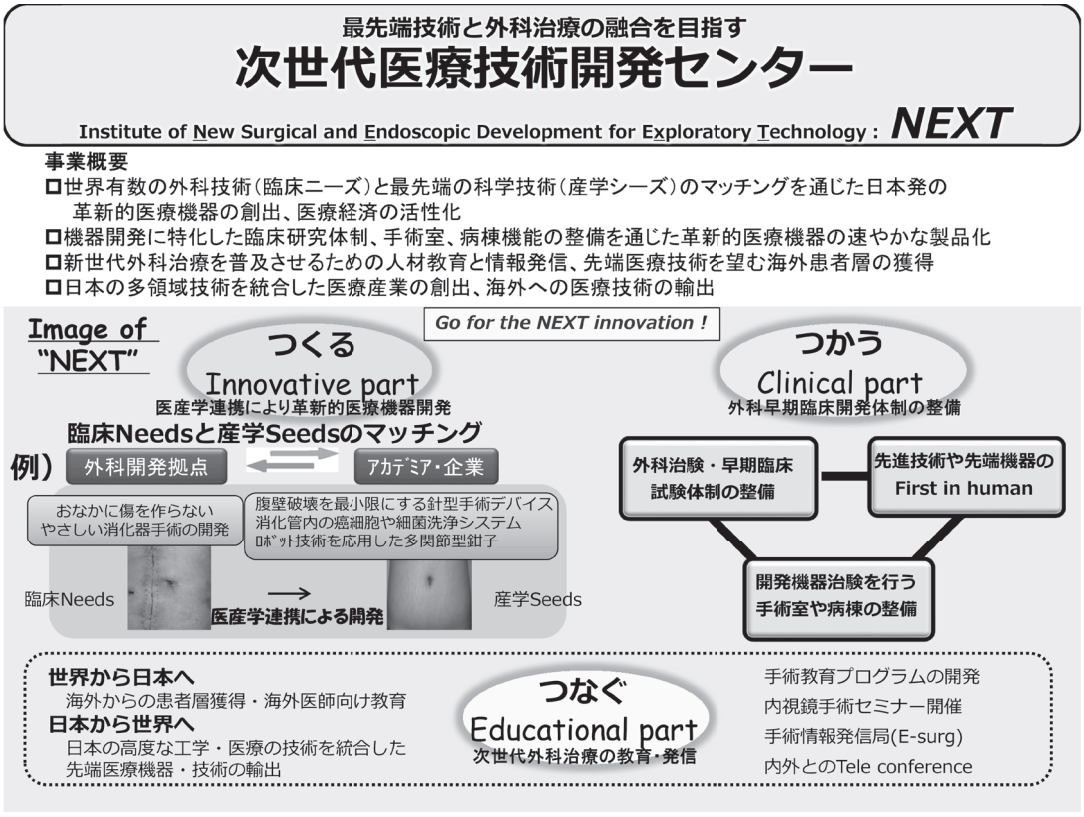


Figure 1.

Level I Devices

1) Device assisting standing position during long-time surgery
2) Suture thread for training
3) Endoscopic simulator

Level II Devices

1) Surgical robot undertaking endoscopy
2) Anal drain reducing anastomotic pressure
3) New puncture therapy

Surgical robotic system innovated by the National Cancer Center (NCC)-certified venture company, A-Traction

A-Traction Company was established in August 2015 to innovate new surgical robotic systems.

This venture company received a major investment from Medventure Partners Company and was certified as a collaborative company with the National Cancer Center.

Create supportive infrastructure for surgical innovation

We are aiming to establish a clinical trials infrastructure for surgical innovation in the National Cancer Center Hospital East. Two surgical clinical trials were completed this year and reinforced the infrastractures through these trials. Clinical trials concerning robotic surgery for gastric cancer and rectal cancer are on-going.

Activity of regional cooperation group for surgical innovation, C-Square

Last year, we established a regional cooperation group for surgical innovation with a framework that consisted of Chiba Prefecture, Chiba Industry Advancement Center, Chiba University and the National Cancer Center Hospital. The aim of the activities of C-Square is to realize surgical innovation based on clinical needs through use of regional industrial technology. Development of certain new surgical devices began through two symposiums held in C-square.

Education

We held regular in-house seminars to teach about surgical innovations for the development of human resources.

Future prospect

We are going to establish a clinical support team for early-phase surgical innovations and aim to make a road-map for surgical innovation.

List of papers published in 2015

Journal

1. Shiomi A, Ito M, Maeda K, Kinugasa Y, Ota M, Yamaue H, Shiozawa M, Horie H, Kuriu Y, Saito N. Effects of a diverting stoma on symptomatic anastomotic leakage after low anterior resection for rectal cancer: a propensity score matching analysis of 1,014 consecutive patients. J Am Coll Surg, 220:186-194, 2015
2. Kawai T, Shin M, Nishizawa Y, Horise Y, Nishikawa A, Nakamura T. Mobile locally operated detachable end-effector manipulator for endoscopic surgery. Int J Comput Assist Radiol Surg, 10:161-169, 2015
3. Ohue M, Hamaguchi T, Ito Y, Sakai D, Noura S, Kinugasa Y, Fujita S, Shimada Y, Saito N, Moriya Y. A phase I trial of preoperative S-1 in combination with oxaliplatin and pelvic radiation for lower rectal cancer with T4 and lateral pelvic lymph node metastasis. Int J Clin Oncol, 20:338-344, 2015
4. Kobayashi S, Ito M, Yamamoto S, Kinugasa Y, Kotake M, Saida Y, Kobatake T, Yamanaka T, Saito N, Moriya Y. Randomized clinical trial of skin closure by subcuticular suture or skin stapling after elective colorectal cancer surgery. Br J Surg, 102:495-500, 2015
5. Yokota M, Kojima M, Higuchi Y, Nishizawa Y, Kobayashi A, Ito M, Saito N, Ochiai A. Spread of tumor microenvironment contributes to colonic obstruction through subperitoneal fibroblast activation in colon cancer. Cancer Sci, 106:466-474, 2015
6. Yokota M, Kobayashi A, Nomura S, Nishizawa Y, Ito M, Nagai K, Saito N. Patterns and treatment of recurrence following pulmonary resection for colorectal metastases. World J Surg, 39:1758-1766, 2015
7. Kondo A, Nishizawa Y, Akamoto S, Fujiwara M, Okano K, Suzuki Y. Internal inguinal hernia on the transplant side after kidney transplantation: a case report. Surg Case Rep, 1:108, 2015

Section of Experimental Animals

Yoshikatsu Koga, Kimie Iijima, Taeko Aruga, Aki Kawaida

Introduction

The basic and translational research undertaken in the Exploratory Oncology Research & Clinical Trial Center (EPOC) is aimed toward future clinical use. To develop anti-cancer drugs based on a novel concept or a novel imaging technology, animal experiments are necessary. The Section of Experimental Animals supports the animal experiments conducted in EPOC.

Routine activities

- Health management of the experimental animals and maintenance of the animal laboratories.
  -Animal-breeding rooms: specific pathogen-free (SPF) rooms (eight rooms for mice and one room for rats), conventional rooms (one room for mice, one room for rats, hamsters, and rabbits, and one room for pigs), and P2 animal laboratory.
- Approval of animal experiments and gene recombinant experiments in accordance with regulations.
  -In 2015, 58 studies involving animal experiments and 35 studies with gene recombinant experiments were approved by the Committee of Experimental Animals and Gene Recombination.

List of papers published in 2015

Journal

1. Ahn J, Miura Y, Yamada N, Chida T, Liu X, Kim A, Sato R, Tsumura R, Koga Y, Yasunaga M, Nishiyama N, Matsumura Y, Cabral H, Kataoka K. Antibody fragment-conjugated polymeric micelles incorporating platinum drugs for targeted therapy of pancreatic cancer. Biomaterials, 39:23-30, 2015
2. Koga Y, Manabe S, Aihara Y, Sato R, Tsumura R, Iwafuji H, Furuya F, Fuchigami H, Fujiwara Y, Hisada Y, Yamamoto Y, Yasunaga M, Matsumura Y. Antitumor effect of antitissue factor antibody-MMAE conjugate in human pancreatic tumor xenografts. Int J Cancer, 137:1457-1466, 2015
3. Yamamoto Y, Hyodo I, Koga Y, Tsumura R, Sato R, Obonai T, Fuchigami H, Furuya F, Yasunaga M, Harada M, Kato Y, Ohtsu A, Matsumura Y. Enhanced antitumor effect of anti-tissue factor antibody-conjugated epirubicin-incorporating micelles in xenograft models. Cancer Sci, 106:627-634, 2015
4. Tsumura R, Sato R, Furuya F, Koga Y, Yamamoto Y, Fujiwara Y, Yasunaga M, Matsumura Y. Feasibility study of the Fab fragment of a monoclonal antibody against tissue factor as a diagnostic tool. Int J Oncol, 47:2107-2114, 2015

Research Center for Cancer Prevention and Screening

Preface

The Research Center for Cancer Prevention and Screening (RCCPS) was established in February 2004 to research effective cancer prevention and screening methods, and create a scientific basis for the efficient dissemination of these methods to the public. As of 2015, the organization consisted of the following: the Epidemiology and Prevention Group (Division of Epidemiology and Division of Prevention), the Screening Research Group (Division of Screening Assessment and Management and Division of Screening Technology and System Development), the Common Research Group (Division of Public Health Policy Research), and the Division of Screening Practice, which is responsible for carrying out cancer screenings. Our mission is to advance cancer prevention and screening research in order to provide correct information and the most appropriate methods for preventing cancer cases and fatalities to the greatest degree possible.

The Epidemiology and Prevention Group consists of the Division of Epidemiology, which mainly conducts evidence building that contributes to the investigation of cancer causes and the clarification of pathologic conditions, and the Division of Prevention, which conducts the development of evidence-based prevention methods; both Divisions mutually cooperate to fulfill the group's mission. In 2015, the Division of Epidemiology pursued continuous, long-term epidemiological studies of various sizes such as the Japan Public Health Center-based Prospective Study (JPHC Study) and the JPHC Study for the Next Generation (JPHC-NEXT), and published analyses of the accumulated data sets and biological samples. On the other hand, the Division of Prevention played a central role in systematically collecting research results especially at the national level and evaluating anti-cancer effects and carcinogens, ultimately recommending (updating) prevention guidelines for the Japanese public. In addition, based on the results of the cohort studies, the Division developed and released the "Cancer Risk Check by 5 Healthy Lifestyles," a series of diagnostic tools available online that determine cancer risks. The Division also has been coordinating the Japanese and Asian Cohort Consortium.

With the aim of reducing cancer mortality rates, the Screening Research Group (Division of Screening Assessment and Management) promotes cancer screening assessments, cancer screening implementation management, and screening as a countermeasure to cancer. While the Division has been conducting continuous research like randomized controlled trials on cancer screening and investigations into the effectiveness of various cancer screenings, the Division also started the publication of updated cervical cancer screening guidelines. Using checklists, the Division conducted investigations into municipal public screenings, evaluations and training workshops for the standardization of cancer screening accuracy control. The Division also updated its website contents for relevant government personnel.

The Common Research Group (Division of Public Health Policy Research) conducts research for the dissemination of scientific evidence concerning the public health field (cancer prevention, screening, and survivorship). To establish a research infrastructure, the Division also conducts methodological research on behavioral science, epidemiology, and statistics, supports and accumulates know-how from large-scale interventional studies, and teaches medical research methodologies.

The Division supports municipalities (16 prefectures and 96 local governments), and develops and provides tools for further cancer screening and consultation awareness. Furthermore, in this fiscal year, the Division released its children's cancer education comics as e-books to promote their use, and conducted intervention trials to evaluate their effectiveness. In addition, the Division also registered 4,900 patients (cumulative total) in a breast cancer patient cohort study.

The Division of Screening Practice conducts cancer screenings with the primary goal of research based on the comprehensive consent of screening participants. In 2015, the total number of screening participants were 3,140 (40% were new and 75% were comprehensive screening participants). As part of its research, the Division has published several scientific papers in evaluating screening modalities such as CT screenings for lung cancer and PET for colorectal cancer screening.

Research results are returned to the public through paper publications, information on the Cancer Information Service by the Center for Cancer Control and Information Services, and other websites, leaflets and pamphlets, and so forth. To achieve our mission, all members of the RCCPS share a strong will to keep moving forward steadily and diligently.

Shoichiro Tsugane, M.D., D.M.Sc.
Director, Research Center for Cancer Prevention and Screening

Organization

President:
Tomomitsu Hotta

Director:
Shoichiro Tsugane

- Prevention Research (Chief: Shoichiro Tsugane)
  - Division of Epidemiology (Chief: Motoki Iwasaki)
  - Division of Prevention (Chief: Shizuka Sasazuki)
- Screening Research (Chief: Hiroshi Saito)
  - Division of Screening Assessment and Management (Chief: Hiroshi Saito)
  - Division of Screening Technology and System Development (Chief: Hiroshi Saito)
- Common Research (Chief: Shoichiro Tsugane)
  - Division of Public Health Policy Research (Chief: Seiichiro Yamamoto)
- Deputy Director (Chief: Yasuaki Arai)
  - Division of Screening Practice (Chief: Takahisa Matsuda)

Activities of the Divisions

Division of Epidemiology

Motoki Iwasaki, Norie Sawada, Taiki Yamaji, Izumi Mishiro, Akihisa Hidaka, Sanjeev Budhathoki, Masanori Goto, Kayo Ohashi, Jun Umesawa, Ari Nakamura, Tsuyuka Ohtsuki

Introduction

Research is conducted aimed at constructing evidence connected to the development of cancer prevention by clarifying the causes of cancer in humans by using a study base of large-scale cohort study and others of local residents.

Research activities

1) Japan Public Health Center-based prospective study (JPHC study)/JPHC study for the NEXT generation (JPHC-NEXT)

Follow-up surveys and data analysis of the Japan Public Health Center-based prospective study (JPHC study) with 140,000 local residents as subjects have been conducted continuously since 1990.

We investigated gene-environment interaction based on nested case-control studies within the JPHC study. In this study, we hypothesized that genetic polymorphisms related to alcohol and acetaldehyde dehydrogenase may modify association between alcohol consumption and the risk of gastric cancer. Alcohol consumption was significantly associated with an increased risk of gastric cancer among subjects with G allele of ADH1C gene, whose enzyme activity is lower than those with A allele or subjects with A allele of ALDH2 gene whose enzyme activity is lower than those with G allele only.

The JPHC study participates in several international consortium studies and one of them investigated the association between alcohol consumption and the risk of breast cancer subtypes defined by an estrogen receptor based on 20 cohort studies including about one million women. It reported a significant positive association between alcohol consumption and the risk of breast cancer regardless of subtypes by estrogen receptor.

Structuring of the cohort for the JPHC study for the NEXT generation (JPHC-NEXT) is proceeding according to schedule with the recruitment of participants currently under way by obtaining questionnaire information from 95,671 participants, and by obtaining biological samples and information from 48,431 participants (see Table 1 below).

2) Molecular epidemiologic studies to investigate the cause of cancer through means such as omics data analysis

In order to develop a risk prediction model for cancer among Japanese using information on genetic factors and plasma biomarkers in addition to lifestyle factors, we conducted a case-cohort study of total cancer within the baseline survey of the JPHC study and have performed data analysis for identifying risk factors that contribute to personalized prevention.

Education

Supervised the research of three research resident fellowships and one senior resident in the hospital. Supervised the education of one medical student short-term trainee.

Future prospects

While focusing on the cohort structure of the JPHC study for the next generation (JPHC-NEXT) that becomes the study base, we hope to contribute to the development of cancer prevention through the analysis of information and samples of existing epidemiologic studies by identifying new risk

factors and the continued evaluation of risks in Japanese people.

Table 1. Progress of the JPHC for the NEXT generation (JPHC-NEXT)

Area	Total number of questionnaires	Total number of questionnaires and biospecimens	Status of data collection
Akita, Yokote	26,769	14,831	Ongoing
Nagano, Saku	31,395	13,333	Completed
Ibaraki, Chikusei	13,130	9,309	Ongoing
Kochi, Konan	3.872	1,594	Completed
Kochi, Aki	5,017	2,049	Completed
Nagasaki (2014 ～)	6,225	1,743	Ongoing
Ehime, Ohzu (2014 ～)	3,131	2,831	Ongoing
Iwate, Ninohe (2015 ～)	2,959	2,741	Ongoing
Total	95,671	48,431	

List of papers published in 2015

Journal

1. Wang H, Iwasaki M, Haiman CA, Kono S, Wilkens LR, Keku TO, Berndt SI, Tsugane S, Le Marchand L. Interaction between Red Meat Intake and NAT2 Genotype in Increasing the Risk of Colorectal Cancer in Japanese and African Americans. PLoS One, 10:e0144955, 2015

2. Kikuchi H, Inoue S, Odagiri Y, Inoue M, Sawada N, Tsugane S, Japan Public Health Centre (JPHC) study group. Occupational sitting time and risk of all-cause mortality among Japanese workers. Scand J Work Environ Health, 41:519-528, 2015

3. Hidaka A, Shimazu T, Sawada N, Yamaji T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S, Japan Public Health Center–based Prospective Study Group. Fish, n-3 PUFA consumption, and pancreatic cancer risk in Japanese: a large, population-based, prospective cohort study. Am J Clin Nutr, 102:1490-1497, 2015

4. Schumacher FR, Schmit SL, Jiao S, Edlund CK, Wang H, Zhang B, Hsu L, Huang SC, Fischer CP, Harju JF, Idos GE, Lejbkowicz F, Manion FJ, McDonnell K, McNeil CE, Melas M, Rennert HS, Shi W, Thomas DC, Van Den Berg DJ, Hutter CM, Aragaki AK, Butterbach K, Caan BJ, Carlson CS, Chanock SJ, Curtis KR, Fuchs CS, Gala M, Giovannucci EL, Gogarten SM, Hayes RB, Henderson B, Hunter DJ, Jackson RD, Kolonel LN, Kooperberg C, Küry S, LaCroix A, Laurie CC, Laurie CA, Lemire M, Levine D, Ma J, Makar KW, Qu C, Taverna D, Ulrich CM, Wu K, Kono S, West DW, Berndt SI, Bezieau S, Brenner H, Campbell PT, Chan AT, Chang-Claude J, Coetzee GA, Conti DV, Duggan D, Figueiredo JC, Fortini BK, Gallinger SJ, Gauderman WJ, Giles G, Green R, Haile R, Harrison TA, Hoffmeister M, Hopper JL, Hudson TJ, Jacobs E, Iwasaki M, Jee SH, Jenkins M, Jia WH, Joshi A, Li L, Lindor NM, Matsuo K, Moreno V, Mukherjee B, Newcomb PA, Potter JD, Raskin L, Rennert G, Rosse S, Severi G, Schoen RE, Seminara D, Shu XO, Slattery ML, Tsugane S, White E, Xiang YB, Zanke BW, Zheng W, Le Marchand L, Casey G, Gruber SB, Peters U. Corrigendum: genome-wide association study of colorectal cancer identifies six new susceptibility loci. Nat Commun, 6:8739, 2015

5. Kawabata-Shoda E, Charvat H, Ikeda A, Inoue M, Sawada N, Iwasaki M, Sasazuki S, Shimazu T, Yamaji T, Kimura H, Masuda S, Tsugane S. Trends in cancer prognosis in a population-based cohort survey: can recent advances in cancer therapy affect the prognosis? Cancer Epidemiol, 39:97-103, 2015

6. Fowke JH, McLerran DF, Gupta PC, He J, Shu XO, Ramadas K, Tsugane S, Inoue M, Tamakoshi A, Koh WP, Nishino Y, Tsuji I, Ozasa K, Yuan JM, Tanaka H, Ahn YO, Chen CJ, Sugawara Y, Yoo KY, Ahsan H, Pan WH, Pednekar M, Gu D, Xiang YB, Sauvaget C, Sawada N, Wang R, Kakizaki M, Tomata Y, Ohishi W, Butler LM, Oze I, Kim DH, You SL, Park SK, Parvez F, Chuang SY, Chen Y, Lee JE, Grant E, Rolland B, Thornquist M, Feng Z, Zheng W, Boffetta P, Sinha R, Kang D, Potter JD. Associations of body mass index, smoking, and alcohol consumption with prostate cancer mortality in the Asia Cohort Consortium. Am J Epidemiol, 182:381-389, 2015

7. Ueno M, Ohara S, Sawada N, Inoue M, Tsugane S, Kawaguchi Y. The association of active and secondhand smoking with oral health in adults: Japan public health center-based study. Tob Induc Dis, 13:19, 2015

8. Schumacher FR, Schmit SL, Jiao S, Edlund CK, Wang H, Zhang B, Hsu L, Huang SC, Fischer CP, Harju JF, Idos GE, Lejbkowicz F, Manion FJ, McDonnell K, McNeil CE, Melas M, Rennert HS, Shi W, Thomas DC, Van Den Berg DJ, Hutter CM, Aragaki AK, Butterbach K, Caan BJ, Carlson CS, Chanock SJ, Curtis KR, Fuchs CS, Gala M, Giovannucc EL, Giocannucci EL, Gogarten SM, Hayes RB, Henderson B, Hunter DJ, Jackson RD, Kolonel LN, Kooperberg C, Küry S, Kury S, LaCroix A, Laurie CC, Laurie CA, Lemire M, Lemire M, Levine D, Ma J, Makar KW, Qu C, Taverna D, Ulrich CM, Wu K, Kono S, West DW, Berndt SI, Bezieau S, Brenner H, Campbell PT, Chan AT, Chang-Claude J, Coetzee GA, Conti DV, Duggan D, Figueiredo JC, Fortini BK, Gallinger SJ, Gauderman WJ, Giles G, Green R, Haile R, Harrison TA, Hoffmeister M, Hopper JL, Hudson TJ, Jacobs E, Iwasaki M, Jee SH, Jenkins M, Jia WH, Joshi A, Li L, Lindor NM, Matsuo K, Moreno V, Mukherjee B, Newcomb PA, Potter JD, Raskin L, Rennert G, Rosse S, Severi G, Schoen RE, Seminara D, Shu XO, Slattery ML, Tsugane S, White E, Xiang YB, Zanke BW, Zheng W, Le Marchand L, Casey G, Gruber SB, Peters U. Genome-wide association study of colorectal cancer identifies six new susceptibility loci. Nat Commun, 6:7138, 2015

9. Abe SK, Inoue M, Sawada N, Iwasaki M, Shimazu T, Yamaji T, Sasazuki S, Tanaka Y, Mizokami M, Tsugane S, JPHC Study Group. Hepatitis B and C virus infection and risk of lymphoid malignancies: A population-based cohort study (JPHC Study). Cancer Epidemiol, 39:562-566, 2015

10. Kiyabu GY, Inoue M, Saito E, Abe SK, Sawada N, Ishihara J, Iwasaki M, Yamaji T, Shimazu T, Sasazuki S, Shibuya K, Tsugane S, JPHC Study Group. Fish, n-3 polyunsaturated fatty acids and n-6 polyunsaturated fatty acids intake and breast cancer risk: The Japan Public Health Center-based prospective study. Int J Cancer, 137:2915-2926, 2015

11. Kato M, Noda M, Mizoue T, Goto A, Takahashi Y, Matsushita Y, Nanri A, Iso H, Inoue M, Sawada N, Tsugane S, JPHC Study Group. Diagnosed diabetes and premature death among middle-aged Japanese: results from a large-scale population-based cohort study in Japan (JPHC study). BMJ Open, 5:e007736, 2015

12. Goto A, Noda M, Matsushita Y, Goto M, Kato M, Isogawa A, Takahashi Y, Kurotani K, Oba S, Nanri A, Mizoue T, Yamagishi K, Yatsuya H, Saito I, Kokubo Y, Sawada N, Inoue M, Iso H, Kadowaki T, Tsugane S, JPHC Study Group. Hemoglobin a1c levels and the risk of cardiovascular disease in people without known diabetes: a population-based cohort study in Japan. Medicine (Baltimore), 94:e785, 2015

13. Saito E, Inoue M, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Sasazuki S, Noda M, Iso H, Tsugane S, JPHC Study Group. Association of green tea consumption with mortality due to all causes and major causes of death in a Japanese population: the Japan Public Health Center-based Prospective Study (JPHC Study). Ann Epidemiol, 25:512-518.e3, 2015

14. Ma E, Sasazuki S, Shimazu T, Sawada N, Yamaji T, Iwasaki M, Inoue M, Tsugane S. Reactive oxygen species and gastric cancer risk: a large nested case-control study in Japan. Eur J Epidemiol, 30:589-594, 2015

15. Saito E, Inoue M, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Sasazuki S, Noda M, Iso H, Tsugane S. Association of coffee intake with total and cause-specific mortality in a Japanese population: the Japan Public Health Center-based Prospective Study. Am J Clin Nutr, 101:1029-1037, 2015

16. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Ogawa A, Fujisawa D, Sone T, Yoshiuchi K, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Personality traits and coping styles explain anxiety in lung cancer patients to a greater extent than other factors. Jpn J Clin Oncol, 45:456-463, 2015

17. Honjo K, Iso H, Nakaya T, Hanibuchi T, Ikeda A, Inoue M, Sawada N, Tsugane S, Japan Public Health Center-based Prospective Study Group. Impact of neighborhood socioeconomic conditions on the risk of stroke in Japan. J Epidemiol, 25:254-260, 2015

18. Nanri A, Mizoue T, Kurotani K, Goto A, Oba S, Noda M, Sawada N, Tsugane S, Japan Public Health Center-Based Prospective Study Group. Low-carbohydrate diet and type 2 diabetes risk in Japanese men and women: the Japan Public Health Center-Based Prospective Study. PLoS One, 10:e0118377, 2015

19. Iwasaki M, Franke AA, Hamada GS, Miyajima NT, Sharma S, Ishihara J, Takachi R, Tsugane S, Le Marchand L. Comparison of plasma levels of nutrient-related biomarkers among Japanese populations in Tokyo, Japan, São Paulo, Brazil, and Hawaii, USA. Eur J Cancer Prev, 24:155-161, 2015

20. Budhathoki S, Iwasaki M, Yamaji T, Sasazuki S, Takachi R, Sakamoto H, Yoshida T, Tsugane S. Dietary heterocyclic amine intake, NAT2 genetic polymorphism, and colorectal adenoma risk: the colorectal adenoma study in Tokyo. Cancer Epidemiol Biomarkers Prev, 24:613-620, 2015

21. Michikawa T, Inoue M, Sawada N, Tanaka Y, Yamaji T, Iwasaki M, Shimazu T, Sasazuki S, Mizokami M, Tsugane S, , for the Japan Public Health Center-based Prospective Study Group. Plasma isoflavones and risk of primary liver cancer in Japanese women and men with hepatitis virus infection: a nested case-control study. Cancer Epidemiol Biomarkers Prev, 24:532-537, 2015

22. Sawada N, Iwasaki M, Yamaji T, Shimazu T, Sasazuki S, Inoue M, Tsugane S, Japan Public Health Center–based Prospective Study Group. Fiber intake and risk of subsequent prostate cancer in Japanese men. Am J Clin Nutr, 101:118-125, 2015

23. Hidaka A, Sasazuki S, Matsuo K, Ito H, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Inoue M, Tsugane S, JPHC Study Group. Genetic polymorphisms of ADH1B, ADH1C and ALDH2, alcohol consumption, and the risk of gastric cancer: the Japan Public Health Center-based prospective study. Carcinogenesis, 36:223-231, 2015

24. Svensson T, Inoue M, Sawada N, Iwasaki M, Sasazuki S, Shimazu T, Yamaji T, Ikeda A, Kawamura N, Mimura M, Tsugane S, Japan Public Health Centre-based prospective Study Group. The association between complete and partial non-response to psychosocial questions and suicide: the JPHC Study. Eur J Public Health, 25:424-430, 2015

25. Budhathoki S, Iwasaki M, Yamaji T, Sasazuki S, Tsugane S. Coffee intake and the risk of colorectal adenoma: The colorectal adenoma study in Tokyo. Int J Cancer, 137:463-470, 2015

26. Hanibuchi T, Nakaya T, Honjo K, Ikeda A, Iso H, Inoue M, Sawada N, Tsugane S, Japan Public Health Center-based Prospective Study Group. Neighborhood contextual factors for smoking among middle-aged Japanese: a multilevel analysis. Health Place, 31:17-23, 2015

27. Budhathoki S, Iwasaki M, Sawada N, Yamaji T, Shimazu T, Sasazuki S, Inoue M, Tsugane S, JPHC Study Group. Soy food and isoflavone intake and endometrial cancer risk: the Japan Public Health Center-based prospective study. BJOG, 122:304-311, 2015

28. Hidaka A, Sasazuki S, Goto A, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Inoue M, Noda M, Tajiri H, Tsugane S, JPHC Study Group. Plasma insulin, C-peptide and blood glucose and the risk of gastric cancer: the Japan Public Health Center-based prospective study. Int J Cancer, 136:1402-1410, 2015

Division of Prevention

Shizuka Sasazuki, Taichi Shimazu, Michihiro Mutoh, Charvat Hadrien, Shingo Miyamoto, Yoshitaka Tsubono, Masayuki Tatemichi, Junko Ishihara, Minatsu Kobayashi, Ribeka Takachi, Azusa Hara, Manami Inoue, Yingyan Gong, Eiko Saito, Issei Ezawa, Ruri Nakanishi, Masami Komiya

Introduction

The Division of Prevention focuses on prevention research to investigate and develop prevention methods (lifestyle, chemoprevention, molecular marker, etc.), risk prediction, risk stratification models, and evidence-based cancer prevention guidelines.

Research activities

1) Evaluation of cancer prevention strategies in Japan and cancer prevention guidelines

To develop an evidence-based cancer prevention strategy in Japan, a systematic review of epidemiological research was conducted. The strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report, in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. Through this method, cigarette smoking was evaluated to have a 'convincing' effect on increasing the risk of head and neck cancer and bladder cancer. A web-based tool to predict the 10-year risk of developing cancer based on adhesion to 5 healthy lifestyle factors was constructed and released to the press to be more widely used. A pooled analysis of Japanese cohort studies was conducted and we found that a moderate intake of fruit decreases the risk of lung cancer in men. The Asia Cohort Consortium (ACC) is a collaborative effort seeking to understand the relationship between genetics, environmental exposure, and the etiology of disease through the establishment of a cohort of at least one million healthy people throughout Asian countries. The ACC Coordinating Center was established at the Fred Hutchinson Cancer Research Center and moved to the Prevention Division in 2014. The data analysis system on-site and via remote access is now established and several projects are ongoing.

2) Development of prevention measures based on interventional research

We started a double-blind, randomized clinical trial of aspirin and mesalazine to see if these drugs suppress the occurrence of new adenomas in patients with a history of multiple colorectal adenomas. Another clinical research project aiming to develop colorectal cancer chemopreventive drugs is in progress.

3) Population-based Prospective Study (the JPHC study and the JPHC-NEXT Study) (primarily the development of preventive measures such as risk prediction; searching for chemoprevention candidates)

Based on a nested case-control study of the Japan Public Health Center-based prospective (JPHC) Study, the interaction of ADH1C, ALDH2 and alcohol consumption on the development of gastric cancer was shown. We also developed a risk prediction model for gastric cancer based on clinical and lifestyle-related characteristics in combination with biological variables (ABC method) that allows the estimation of the 10-year probability of gastric cancer occurrence. These results suggest the importance of risk stratification as a tool of gastric cancer prevention. In addition, we started research on collecting stomach cancer tissue in order to consider subtypes of tumors by molecular biomarkers.

Education

Supervised the research of one research resident fellowship and one senior resident in a hospital.

Future prospects

We focus on research for the development of effective cancer prevention strategies. In addition to current established evidence, new perspectives such as biomarkers from blood and tumor tissues will be incorporated. This approach may lead to more accurate cancer prevention strategies by risk stratification.

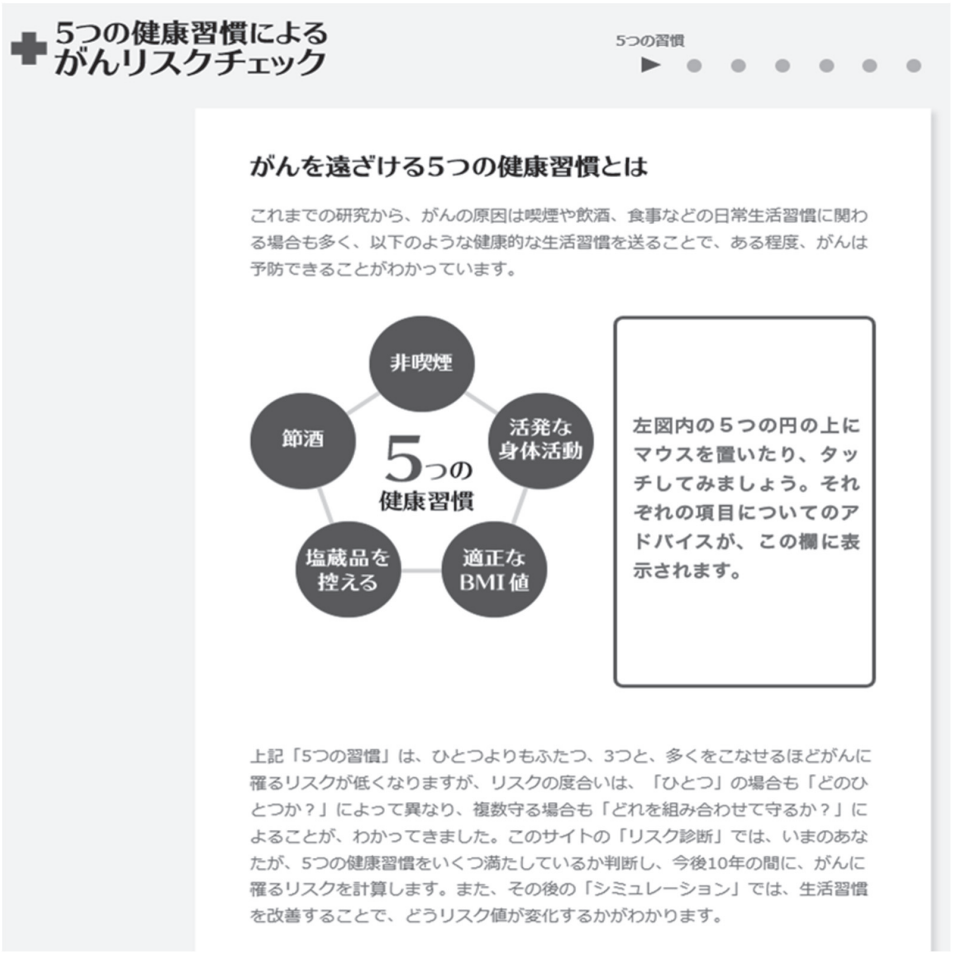


Figure 1. Web-based tool 'Five healthy lifestyle factors and cancer risk'.

List of papers published in 2015

Journal

1. Asada K, Nakajima T, Shimazu T, Yamamichi N, Maekita T, Yokoi C, Oda I, Ando T, Yoshida T, Nanjo S, Fujishiro M, Gotoda T, Ichinose M, Ushijima T. Demonstration of the usefulness of epigenetic cancer risk prediction by a multicentre prospective cohort study. Gut, 64:388-396, 2015

2. Yoneoka D, Henmi M, Sawada N, Inoue M. Synthesis of clinical prediction models under different sets of covariates with one individual patient data. BMC Med Res Methodol, 15:101, 2015

3. Kikuchi H, Inoue S, Odagiri Y, Inoue M, Sawada N, Tsugane S, Japan Public Health Centre (JPHC) study group. Occupational sitting time and risk of all-cause mortality among Japanese workers. Scand J Work Environ Health, 41:519-528, 2015

4. Hidaka A, Shimazu T, Sawada N, Yamaji T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S, Japan Public Health Center–based Prospective Study Group. Fish, n-3 PUFA consumption, and pancreatic cancer risk in Japanese: a large, population-based, prospective cohort study. Am J Clin Nutr, 102:1490-1497, 2015

5. Kashino I, Mizoue T, Tanaka K, Tsuji I, Tamakoshi A, Matsuo K, Wakai K, Nagata C, Inoue M, Tsugane S, Sasazuki S, Research Group for Development and Evaluation of Cancer Prevention Strategies in Japan. Vegetable consumption and colorectal cancer risk: an evaluation based on a systematic review and meta-analysis among the Japanese population. Jpn J Clin Oncol, 45:973-979, 2015

6. Charvat H, Goto A, Goto M, Inoue M, Heianza Y, Arase Y, Sone H, Nakagami T, Song X, Qiao Q, Tuomilehto J, Tsugane S, Noda M, Inoue M. Impact of population aging on trends in diabetes prevalence: A meta-regression analysis of 160,000 Japanese adults. J Diabetes Investig, 6:533-542, 2015

7. Micha R, Khatibzadeh S, Shi P, Andrews KG, Engell RE, Mozaffarian D, Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Global, regional and national consumption of major food groups in 1990 and 2010: a systematic analysis including 266 country-specific nutrition surveys worldwide. BMJ Open, 5:e008705, 2015

8. Kawabata-Shoda E, Charvat H, Ikeda A, Inoue M, Sawada N, Iwasaki M, Sasazuki S, Shimazu T, Yamaji T, Kimura H, Masuda S, Tsugane S. Trends in cancer prognosis in a population-based cohort survey: can recent advances in cancer therapy affect the prognosis? Cancer Epidemiol, 39:97-103, 2015

9. Fowke JH, McLerran DF, Gupta PC, He J, Shu XO, Ramadas K, Tsugane S, Inoue M, Tamakoshi A, Koh WP, Nishino Y, Tsuji I, Ozasa K, Yuan JM, Tanaka H, Ahn YO, Chen CJ, Sugawara Y, Yoo KY, Ahsan H, Pan WH, Pednekar M, Gu D, Xiang YB, Sauvaget C, Sawada N, Wang R, Kakizaki M, Tomata Y, Ohishi W, Butler LM, Oze I, Kim DH, You SL, Park SK, Parvez F, Chuang SY, Chen Y, Lee JE, Grant E, Rolland B, Thornquist M, Feng Z, Zheng W, Boffetta P, Sinha R, Kang D, Potter JD. Associations of body mass index, smoking, and alcohol consumption with prostate cancer mortality in the Asia Cohort Consortium. Am J Epidemiol, 182:381-389, 2015

10. Ueno M, Ohara S, Sawada N, Inoue M, Tsugane S, Kawaguchi Y. The association of active and secondhand smoking with oral health in adults: Japan public health center-based study. Tob Induc Dis, 13:19, 2015

11. Abe SK, Inoue M, Sawada N, Iwasaki M, Shimazu T, Yamaji T, Sasazuki S, Tanaka Y, Mizokami M, Tsugane S, JPHC Study Group. Hepatitis B and C virus infection and risk of lymphoid malignancies: A population-based cohort study (JPHC Study). Cancer Epidemiol, 39:562-566, 2015

12. Kiyabu GY, Inoue M, Saito E, Abe SK, Sawada N, Ishihara J, Iwasaki M, Yamaji T, Shimazu T, Sasazuki S, Shibuya K, Tsugane S, JPHC Study Group. Fish, n-3 polyunsaturated fatty acids and n-6 polyunsaturated fatty acids intake and breast cancer risk: The Japan Public Health Center-based prospective study. Int J Cancer, 137:2915-2926, 2015

13. Singh GM, Micha R, Khatibzadeh S, Lim S, Ezzati M, Mozaffarian D, Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Estimated Global, Regional, and National Disease Burdens Related to Sugar-Sweetened Beverage Consumption in 2010. Circulation, 132:639-666, 2015

14. Wakai K, Sugawara Y, Tsuji I, Tamakoshi A, Shimazu T, Matsuo K, Nagata C, Mizoue T, Tanaka K, Inoue M, Tsugane S, Sasazuki S, Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Risk of lung cancer and consumption of vegetables and fruit in Japanese: A pooled analysis of cohort studies in Japan. Cancer Sci, 106:1057-1065, 2015

15. Kato M, Noda M, Mizoue T, Goto A, Takahashi Y, Matsushita Y, Nanri A, Iso H, Inoue M, Sawada N, Tsugane S, JPHC Study Group. Diagnosed diabetes and premature death among middle-aged Japanese: results from a large-scale population-based cohort study in Japan (JPHC study). BMJ Open, 5:e007736, 2015

16. Goto A, Noda M, Matsushita Y, Goto M, Kato M, Isogawa A, Takahashi Y, Kurotani K, Oba S, Nanri A, Mizoue T, Yamagishi K, Yatsuya H, Saito I, Kokubo Y, Sawada N, Inoue M, Iso H, Kadowaki T, Tsugane S, JPHC Study Group. Hemoglobin a1c levels and the risk of cardiovascular disease in people without known diabetes: a population-based cohort study in Japan. Medicine (Baltimore), 94:e785, 2015

17. Saito E, Inoue M, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Sasazuki S, Noda M, Iso H, Tsugane S, JPHC Study Group. Association of green tea consumption with mortality due to all causes and major causes of death in a Japanese population: the Japan Public Health Center-based Prospective Study (JPHC Study). Ann Epidemiol, 25:512-518.e3, 2015

18. Ma E, Sasazuki S, Shimazu T, Sawada N, Yamaji T, Iwasaki M, Inoue M, Tsugane S. Reactive oxygen species and gastric cancer risk: a large nested case-control study in Japan. Eur J Epidemiol, 30:589-594, 2015

19. Saito E, Inoue M, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Sasazuki S, Noda M, Iso H, Tsugane S. Association of coffee intake with total and cause-specific mortality in a Japanese population: the Japan Public Health Center-based Prospective Study. Am J Clin Nutr, 101:1029-1037, 2015

20. Honjo K, Iso H, Nakaya T, Hanibuchi T, Ikeda A, Inoue M, Sawada N, Tsugane S, Japan Public Health Center-based Prospective Study Group. Impact of neighborhood socioeconomic conditions on the risk of stroke in Japan. J Epidemiol, 25:254-260, 2015

21. Fujimoto K, Fujii G, Taguchi K, Yasuda K, Matsuo Y, Hashiyama A, Mutoh M, Tanaka H, Wada M. Involvement of trefoil factor family 2 in the enlargement of intestinal tumors in *Apc*$^{Min/+}$ mice. Biochem Biophys Res Commun, 463:859-863, 2015

22. Iwasaki M, Franke AA, Hamada GS, Miyajima NT, Sharma S, Ishihara J, Takachi R, Tsugane S, Le Marchand L. Comparison of plasma levels of nutrient-related biomarkers among Japanese populations in Tokyo, Japan, São Paulo, Brazil, and Hawaii, USA. Eur J Cancer Prev, 24:155-161, 2015

23. Fujimoto K, Fujii G, Sakurai H, Yoshitome H, Mutoh M, Wada M. Intestinal Peyer's patches prevent tumorigenesis in *Apc*$^{Min/+}$mice. J Clin Biochem Nutr, 56:43-48, 2015

24. Budhathoki S, Iwasaki M, Yamaji T, Sasazuki S, Takachi R, Sakamoto H, Yoshida T, Tsugane S. Dietary heterocyclic amine intake, NAT2 genetic polymorphism, and colorectal adenoma risk: the colorectal adenoma study in Tokyo. Cancer Epidemiol Biomarkers Prev, 24:613-620, 2015

25. Nakamura K, Kitamura K, Takachi R, Saito T, Kobayashi R, Oshiki R, Watanabe Y, Tsugane S, Sasaki A, Yamazaki O. Impact of demographic, environmental, and lifestyle factors on vitamin D sufficiency in 9084 Japanese adults. Bone, 74:10-17, 2015

26. Michikawa T, Inoue M, Sawada N, Tanaka Y, Yamaji T, Iwasaki M, Shimazu T, Sasazuki S, Mizokami M, Tsugane S, , for the Japan Public Health Center-based Prospective Study Group. Plasma isoflavones and risk of primary liver cancer in Japanese women and men with hepatitis virus infection: a nested case-control study. Cancer Epidemiol Biomarkers Prev, 24:532-537, 2015

27. Sawada N, Iwasaki M, Yamaji T, Shimazu T, Sasazuki S, Inoue M, Tsugane S, Japan Public Health Center–based Prospective Study Group. Fiber intake and risk of subsequent prostate cancer in Japanese men. Am J Clin Nutr, 101:118-125, 2015

28. Hidaka A, Sasazuki S, Matsuo K, Ito H, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Inoue M, Tsugane S, JPHC Study Group. Genetic polymorphisms of ADH1B, ADH1C and ALDH2, alcohol consumption, and the risk of gastric cancer: the Japan Public Health Center-based prospective study. Carcinogenesis, 36:223-231, 2015

29. Svensson T, Inoue M, Sawada N, Iwasaki M, Sasazuki S, Shimazu T, Yamaji T, Ikeda A, Kawamura N, Mimura M, Tsugane S, Japan Public Health Centre-based prospective Study Group. The association between complete and partial non-response to psychosocial questions and suicide: the JPHC Study. Eur J Public Health, 25:424-430, 2015

30. Budhathoki S, Iwasaki M, Yamaji T, Sasazuki S, Tsugane S. Coffee intake and the risk of colorectal adenoma: The colorectal adenoma study in Tokyo. Int J Cancer, 137:463-470, 2015

31. Hanibuchi T, Nakaya T, Honjo K, Ikeda A, Iso H, Inoue M, Sawada N, Tsugane S, Japan Public Health Center-based Prospective Study Group. Neighborhood contextual factors for smoking among middle-aged Japanese: a multilevel analysis. Health Place, 31:17-23, 2015

32. Budhathoki S, Iwasaki M, Sawada N, Yamaji T, Shimazu T, Sasazuki S, Inoue M, Tsugane S, JPHC Study Group. Soy food and isoflavone intake and endometrial cancer risk: the Japan Public Health Center-based prospective study. BJOG, 122:304-311, 2015

33. Mutoh M, Ishikawa H. Metformin Use and Lung Cancer Risk--Letter. Cancer Prev Res (Phila), 8:760, 2015

34. Shiotani A, Ishikawa H, Mutoh M, Takeshita T, Nakamura T, Morimoto K, Sakai T, Wakabayashi K, Sakai T, Matuura N. Genetic polymorphisms in *ADH1B* and *ALDH2* are associated with colorectal tumors in Japan: a case-control study. J Cancer Ther, 6:1054-1062, 2015

35. Hidaka A, Sasazuki S, Goto A, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Inoue M, Noda M, Tajiri H, Tsugane S, JPHC Study Group. Plasma insulin, C-peptide and blood glucose and the risk of gastric cancer: the Japan Public Health Center-based prospective study. Int J Cancer, 136:1402-1410, 2015

36. Shimazu T, Asada K, Charvat H, Kusano C, Otake Y, Kakugawa Y, Watanabe H, Gotoda T, Ushijima T, Tsugane S. Association of gastric cancer risk factors with DNA methylation levels in gastric mucosa of healthy Japanese: a cross-sectional study. Carcinogenesis, 36:1291-1298, 2015

Book

1. Miyamoto S, Fujii G, Komiya M, Terasaki M, Mutoh M. Potential for sesame seed-derived factors to prevent colorectal cancer. In: Ullah MF, Ahmad A (eds), Critical Dietary Factors in Cancer Chemoprevention, Switzerland, Springer International Publishing, pp 183-197, 2015

Division of Screening Assessment and Management

Hiroshi Saito, Chisato Hamashima, Koichi Nagata, Kumiko Saika, Ryoko Machii, Kanako Kono, Ayako Aoki, Yoshiki Ishikawa, Sayuri Amanuma, Junko Asai, Kanoko Matsushima, Kazuko Matsuda, Akiko Totake, Taeko Aiko, Asako Kowada, Ikuko Tominaga, Masae Omaru

Introduction

The Division has conducted studies on the assessment and management of screening programs, particularly nationwide programs, and on other issues relevant to cancer screening.

In addition, the most important mission of the Research Center for Cancer Prevention and Screening in terms of screening is the central activity of assessing and managing cancer screening at the national level, which is closely related to the pillars in the Individual Targets for Cancer Screening in the Basic Cancer Control Plan issued in 2007 and revised in 2012. Thus, the Division has developed and updated screening guidelines (Cancer Screening Assessment) and constructed quality assurance systems for the screening programs (Cancer Screening Management).

Routine activities

・Development of cancer screening guidelines

Guidelines on screening for gastric cancer were published in 2015. Evidence report for cervical cancer will be published in 2016.

・Revision of Cancer Screening Checklists (CLs)

The screening programs performed as the Health Promotion Services by the Ministry of Health, Labour and Welfare consist of screening programs provided through large screening facilities and those via primary physicians. CLs were primarily developed targeting the former type of programs but could not cover the latter programs. The Division developed new structure indicators that cover all of the screening programs by revising the original CLs. The appropriateness of the new CLs was confirmed through preliminary use in six areas. The new CLs were proposed as the substitute for the present CLs for use after 2016 and adoption as the new ones was decided by the council of the Ministry of Health, Labour and Welfare.

・Quality Assurance (QA) in cancer screening at municipalities and prefectures

The Division collected the information related to implementation of cancer screening and its management situation using the Cancer Screening Checklists (CLs) as a structure indicator in quality assurance at municipalities. The Division set up the website in 2013 that allows support for municipalities such as provision of their QA data archives and information relevant to cancer screening. CLs data were collected from municipalities and evaluation results were fed back on the website. In this year, 1,592 municipalities (91%) utilized the website by registering as members of the site. Analysis of the results in 2015 will be available early in 2016. The Division evaluated QA activity in each of the 47 prefectures and published the results. For those prefectures whose performance level was below the defined level, instructions were sent to ask them to improve the status.

The Division also investigated the method to calculate the participation rate in screening programs provided at worksites as well as the construction of the QA system of those programs.

・Workshop on cancer screening management

The Division held one-day educational workshops for the members of prefectural committees for cancer screening management, aiming at activating quality assurance activities in each of the 47 prefectures. The themes this year were the breast and cervix. The main contents of the workshops were the methods of quality assurance

of the screening programs within each prefecture. Other basic issues required to conduct organized cancer screening programs such as those issues for screening assessment were also included in the contents. The Division also held a similar workshop targeting the new members of the cancer control section at each prefectural government.

There were 63 participants in the workshops from 34 prefectures, who consisted of administrative officers (51%) and members of the committee (49%). This activity was performed as a project for the Center for Cancer Control and Information Services and will be continued on an annual basis.

According to the survey on the activity of the prefectural committees, 37 to 39 prefectures held meetings to discuss cancer screening management and 20 to 22 (15 to 18 in the previous year) released the evaluation results of municipalities using CLs for each of the 5 cancers. These figures have been increasing after starting the workshop, suggesting there was an effect of the previously held workshop on the activity of the committees.

Research activities

- **A randomized controlled trial (RCT) of colonoscopic screening and other RCTs**

A randomized controlled trial evaluating one-time colonoscopic screening for colorectal cancer was started in 2009. The division has been responsible for designing and managing the study as the head office of the study. The cumulative number of subjects who gave informed consent, and who were thus enrolled in the study, was 8,576 at December 2015, corresponding to 86% of the planned number. Data monitoring results showed randomization has been performed successfully. No serious adverse effect was reported on screening colonoscopy. The Division has also participated in other RCTs (breast cancer and lung cancer screening) as a member of the headquarters of the research and supported those studies.

- **A cohort study to evaluate the efficacy of cervical cancer screening using human papilloma virus in conjunction with pap smear cytology.**

The Division has supported the management of the study as the head office. A total of 20,459 subjects have participated in the study as of the end of 2015 in 36 municipalities.

- **Evaluation and accuracy studies on gastric cancer screening**

A community-based, cohort study was conducted to evaluate the effectiveness of endoscopic screening in Niigata city. The 57% mortality reduction from gastric cancer was suggested by endoscopic screening for gastric cancer.

List of papers published in 2015

Journal

1. Tanaka S, Saitoh Y, Matsuda T, Igarashi M, Matsumoto T, Iwao Y, Suzuki Y, Nishida H, Watanabe T, Sugai T, Sugihara K, Tsuruta O, Hirata I, Hiwatashi N, Saito H, Watanabe M, Sugano K, Shimosegawa T, Japanese Society of Gastroenterology. Evidence-based clinical practice guidelines for management of colorectal polyps. J Gastroenterol, 50:252-260, 2015
2. Taniguchia T, Hiraib K, Haradac K, Ishikawad Y, Nagatsukae M, Fukuyoshif J, Araig H, Mizotah Y, Yamamotoi S, Saitoj H, Shibuyak D. The relationship between obtaining fecal occult blood test and beliefs regarding testing among Japanese. Health Psychol Behav Med, 3:251-262, 2015
3. Goto R, Hamashima C, Mun S, Lee WC. Why screening rates vary between Korea and Japan--differences between two national healthcare systems. Asian Pac J Cancer Prev, 16:395-400, 2015
4. Hamashima C, Ogoshi K, Narisawa R, Kishi T, Kato T, Fujita K, Sano M, Tsukioka S. Impact of endoscopic screening on mortality reduction from gastric cancer. World J Gastroenterol, 21:2460-2466, 2015
5. Hamashima C, Shabana M, Okamoto M, Osaki Y, Kishimoto T. Survival analysis of patients with interval cancer undergoing gastric cancer screening by endoscopy. PLoS One, 10:e0126796, 2015
6. Hamashima C, Ohta K, Kasahara Y, Katayama T, Nakayama T, Honjo S, Ohnuki K. A meta-analysis of mammographic screening with and without clinical breast examination. Cancer Sci, 106:812-818, 2015

7. Hamashima C, Shabana M, Okada K, Okamoto M, Osaki Y. Mortality reduction from gastric cancer by endoscopic and radiographic screening. Cancer Sci, 106:1744-1749, 2015

8. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, Straif K, International Agency for Research on Cancer Handbook Working Group. Breast-cancer screening--viewpoint of the IARC Working Group. N Engl J Med, 372:2353-2358, 2015

9. Hamashima C. Have we Comprehensively Evaluated the Effectiveness of Endoscopic Screening for Gastric Cancer? Asian Pac J Cancer Prev, 16:3591-3592, 2015

10. Saika K, Machii R. Five-year relative survival rate of brain and other nervous system cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 45:313-314, 2015

11. Machii R, Saika K. Morphological distribution of esophageal cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:506-507, 2015

12. Saika K, Matsuda T. Morphological distribution of ovarian cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:793, 2015

13. Matsuda T, Machii R. Morphological distribution of lung cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:404, 2015

14. Nagata K, Fujiwara M, Shimamoto T, Iida N, Mogi T, Mitsushima T. Colonic distention at CT colonography: randomized evaluation of both IV hyoscine butylbromide and automated carbon dioxide insufflation. AJR Am J Roentgenol, 204:76-82, 2015

15. Nagata K, Fujiwara M, Kanazawa H, Mogi T, Iida N, Mitsushima T, Lefor AT, Sugimoto H. Evaluation of dose reduction and image quality in CT colonography: comparison of low-dose CT with iterative reconstruction and routine-dose CT with filtered back projection. Eur Radiol, 25:221-229, 2015

Division of Public Health Policy Research

Seiichiro Yamamoto, Yuri Mizota, Michiyo Tada, Hiromi Koitabashi, Yoko Takahashi, Kumiko Toyoshima, Rika Nakamura

Introduction

The Division of Public Health Policy Research was established in June 2013. The Division investigates the methods of distribution and dissemination of scientific evidence concerning cancer prevention, screening, and survivorship. The aim of the research is to fill the gap between the scientific evidence and the behavior of the people for cancer prevention and screening by supporting local governments and directly approaching the public. In addition, because of the lack of evidence, we try to establish scientific evidence for cancer survivorship.

As for the activities to establish a research infrastructure, we conduct methodological research and education concerning behavioral science, epidemiology and biostatistics and support large-scale interventional studies.

Research concerning promotion of cancer prevention and screening using social marketing method

In order to increase participation rates for cancer screening, we developed several client reminders of cancer screening such as leaflets and supported local municipalities by conducting workshops and disseminating information through the website. As a result, a total of 96 municipalities in 16 prefectures used our materials. We evaluated the participation rates of cancer screening for the municipalities that used our materials last year and most of them obtained increased participation rates. To promote cancer education for kids, we developed "Gan no Himitsu (Secret of Cancer)" two years ago as comic-style education material. It is available from the website (http://kids.gakken.co.jp/) and also by downloading an application for smartphones free of charge. We conducted an evaluation study of the book this year. We are also developing materials for the promotion of participation in HCV testing and smoking cessation using a social marketing approach.

Research for cancer survivorship

A large cohort is being established for breast cancer patients to investigate the effect of lifestyle and psychosocial factors on their QOL and prognosis. The cohort consists of several sub-cohorts including collaborative cohorts of clinical trials, a cohort in the National Cancer Center, and a collaborative cohort with Setouchi cancer registry. As of February 2016, we had recruited more than 700 breast cancer patients this fiscal year and 4,945 patients in total. The cohort became one of the largest patient cohorts in the world. We also started a patient cohort with the same objectives for colon and rectal cancer in December. We have already recruited 80 patients in three months.

Education of staff involved in clinical research

We developed an e-learning website, ICRweb (http://icrweb.jp/), for the education of staff involved in clinical research such as researchers, data managers, clinical research coordinators, and members of institutional review boards. As of February 2016, more than 12,000 new users were registered this fiscal year and more than 49,900 users were registered in total. ICRweb provided 22 new content items this year and more than 160 content items are available in total. In order to improve convenience for the users, we developed an Android application in addition to the iPhone application, which provides off-line lectures, research ethics guidelines, and statistical tools such as a sample size calculator.

List of papers published in 2015

Journal

1. Taira N, Arai M, Ikeda M, Iwasaki M, Okamura H, Takamatsu K, Yamamoto S, Ohsumi S, Mukai H, Japanese Breast Cancer Society. The Japanese Breast Cancer Society clinical practice guideline for epidemiology and prevention of breast cancer. Breast Cancer, 22:16-27, 2015

2. Taniguchia T, Hiraib K, Haradac K, Ishikawad Y, Nagatsukae M, Fukuyoshif J, Araig H, Mizotah Y, Yamamotoi S, Saitoj H, Shibuyak D. The relationship between obtaining fecal occult blood test and beliefs regarding testing among Japanese. Health Psychol Behav Med, 3:251-262, 2015

3. Taira N, Akiyama I, Ishihara S, Ishibe Y, Kawasaki K, Saito M, Shien T, Nomura T, Hara F, Mizoo T, Mizota Y, Yamamoto S, Ohsumi S, Doihara H, Executive Committee for the Setouchi Breast Cancer Cohort Study. Impact of modifiable lifestyle factors on outcomes after breast cancer diagnosis: the Setouchi Breast Cancer Cohort Study. Jpn J Clin Oncol, 45:600-602, 2015

4. Shimizu C, Kato T, Tamura N, Bando H, Asada Y, Mizota Y, Yamamoto S, Fujiwara Y. Perception and needs of reproductive specialists with regard to fertility preservation of young breast cancer patients. Int J Clin Oncol, 20:82-89, 2015

Division of Screening Practice

Takahisa Matsuda*, Yukio Muramatsu, Gen Iinuma*, Miyuki Sone*, Nachiko Uchiyama, Hiroaki Kurihara*, Hirokazu Watanabe*, Ryutaro Kakinuma*, Takashi Terauchi*, Minoru Machida*, Mari Kikuchi*, Tomoko Manabe*, Mototaka Miyake*, Shunsuke Sugawara*, Hideaki Kobayashi*, Koji Tomita*, Seiko Kuroki*, Yasuo Kakugawa*, Minori Matsumoto*, Yosuke Otake*, Masayoshi Yamada*, Masau Sekiguchi*, Takaaki Tsuchida*, Takehiro Izumo*, Tomoyasu Kato*, Shunichi Ikeda*, Mitsuya Ishikawa*, Takashi Uehara*, Hanako Shimizu*, Yasuaki Arai* (*NCCH)

Introduction

In the Division of Screening Practice, since 2004, we have provided a wide range of opportunistic cancer screenings by using newly developed modalities. Most of the staff doctors hold two posts concurrently in both NCCH and the Research Center for Cancer Prevention and Screening (RCCPS). Our screening practice division consists of 13 radiologists, six gastroenterologists, two bronchoscopists, five gynecologists, seven radiologic technologists, four ultrasonographic technologists, two medical laboratory technologists, and four nurses. Our Division is in charge of multiphasic cancer screening using several imaging modalities to develop new cancer screening systems and to assess new screening tests. All medical images are digitalized and all imaging diagnosis can be made from CRT monitors.

Routine activities

1) Course of cancer screening

The basic plan for males consists of screening for cancer of the lung, esophagus, stomach, colorectum, liver, gall bladder, pancreas, kidney, and prostate. In the basic plan for females, the screening for cancer of the breast, uterus, and ovary are added to the plan for males, excluding the prostate. In addition, PET is provided as an option. Other than multiphasic programs, an independent cancer screening program has been prepared for lung and female genital cancers, including cancer of the uterus and ovary, breast cancer and gastrointestinal cancer. Blood samples are also obtained for biochemistry and tumor markers such as CA19-9, CEA, CA125, PSA, and genetic analysis.

2) Eligibility criteria for participants

The cancer screening program at the Research Center for Cancer Prevention and Screening (RCCPS) carried out before 2013 has been planned for applicants 40 years or older who give written informed consent for the screening, including blood samples for genetic analysis, and who take the questionnaire survey concerning lifestyles. These study protocols have been approved by the Institutional Review Board (IRB). Applicants who have been diagnosed as having cancer, and/or have a history of cancer treatment, such as surgery or endoscopic mucosal resection or chemotherapy within the previous one year, are excluded. In contrast, there are no conditions set to receive cancer screening programs for new participants after May 2014. But an inclusion agreement about the study is optionally demanded.

3) Cancer screening methods

In the multiphasic cancer screening programs, CT for lung cancer, abdominal US for cancer of the liver, gall bladder, pancreas, and kidney, gynecological examinations with pap-smear and HPV test for uterus cancer, and MMG and US for breast cancer are performed on the first day. On the following day, gastroscopy for cancer of the esophagus and stomach, and total colonoscopy for cancer of the colon and rectum are conducted. If a barium enema is chosen, the examination is carried out on the third day. Moreover, from the beginning of December 2010, CT-colonography (CTC) has been provided as an optional method for cancer screening. FDG-PET is offered on the first day as an option if the participants wish to undergo the examination. In addition, the one-day

cancer screening programs with the combination of gastrointestinal endoscopic examinations and other methods except PET or the combination of PET and other methods except for total colonoscopy were newly started in May 2014. Furthermore, methionin PET-CT/MRI has been provided as an optional examination from this year.

4) Number of participants of cancer screening

Recent accurate data of cancers have not been obtained due to the lack of adequate follow-up data from this year's participants. Therefore, we present the number of participants of cancer screening between January and December 2015 in this report (Table 1). A total of 3,140 people including 1,261 initial cases received cancer screening at the RCCPS in 2015. Most of the participants (76%; n=2,390) chose the comprehensive cancer screening course. Regarding the cancer detection rate data in each modality, we will report them in the next number.

Research activities

1) The follow-up system of pulmonary solitary solid nodules for evaluation of growth is being developed and published.
2) A large-scale analysis of diagnostic sensitivity of PET-CT for colorectal advanced neoplasm has been published.
3) In order to establish guidelines for the management of pulmonary nodules detected with low-dose chest CT screening, patients with pulmonary nodules between 5 mm and 10 mm in size are being examined in the follow-up clinic.

Future prospects

Based on cancer screening data such as examination results, medical institution findings, follow-up findings, and the questionnaire survey concerning lifestyles for 10 years, we started to assess them supported by the National Cancer Center Research and Development Fund (27-A-5).

Table 1. Number of participants of cancer screening

Comprehensive Cancer Screening Course

Jan-Dec 2015	Initial			5-year Follow-up			Repeater			Total
	M	F	Total	M	F	Total	M	F	Total	
Total	542	373	915	343	203	546	618	311	929	2,390

Independent Cancer Screening Course*

Jan-Dec 2015	Initial			5-year Follow-up			Repeater			Total
	M	F	Total	M	F	Total	M	F	Total	
Total	140	206	346	20	19	39	107	143	250	635

Chest CT Follow-up Course

Jan-Dec 2015	Initial			5-year Follow-up			Repeater			Total
	M	F	Total	M	F	Total	M	F	Total	
Total	0	0	0	0	0	0	81	34	115	115

Independent Cancer Screening Course*
Lung cancer screening course, Breast cancer screening course, Gastrointestinal (GI) cancer screening course, Colorectal cancer screening course using CT-colonography, Cervical cancer screening course, PET-CT course

List of papers published in 2015

Journal

1. Kamiyama Y, Kobayashi Y, Fukuhara S, Morikawa N, Munakata W, Miyagi Maeshima A, Maruyama D, Kim SW, Watanabe T, Terauchi T, Muramatsu Y, Tobinai K. Incidental detection of malignant lymphoma in subjects in a cancer surveillance programme. Br J Haematol, 169:138-142, 2015
2. Tateishi U, Tatsumi M, Terauchi T, Ando K, Niitsu N, Kim WS, Suh C, Ogura M, Tobinai K. Prognostic significance of metabolic tumor burden by positron emission tomography/computed tomography in patients with relapsed/refractory diffuse large B-cell lymphoma. Cancer Sci, 106:186-193, 2015

3. Sato C, Abe S, Saito Y, So Tsuruki E, Takamaru H, Makazu M, Sato Y, Sasaki H, Tanaka H, Ikezawa N, Yamada M, Sakamoto T, Nakajima T, Matsuda T, Kushima R, Kamiya M, Maeda S, Urano Y. A pilot study of fluorescent imaging of colorectal tumors using a γ-glutamyl-transpeptidase-activatable fluorescent probe. Digestion, 91:70-76, 2015

4. Toyoshima N, Sakamoto T, Makazu M, Nakajima T, Matsuda T, Kushima R, Shimoda T, Fujii T, Inoue H, Kudo SE, Saito Y. Prevalence of serrated polyposis syndrome and its association with synchronous advanced adenoma and lifestyle. Mol Clin Oncol, 3:69-72, 2015

5. Nakamura F, Saito Y, Sakamoto T, Otake Y, Nakajima T, Yamamoto S, Murakami Y, Ishikawa H, Matsuda T. Potential perioperative advantage of colorectal endoscopic submucosal dissection versus laparoscopy-assisted colectomy. Surg Endosc, 29:596-606, 2015

6. Nonaka S, Oda I, Tada K, Mori G, Sato Y, Abe S, Suzuki H, Yoshinaga S, Nakajima T, Matsuda T, Taniguchi H, Saito Y, Maetani I. Clinical outcome of endoscopic resection for nonampullary duodenal tumors. Endoscopy, 47:129-135, 2015

7. Ikehara H, Saito Y, Uraoka T, Matsuda T, Miwa H. Specimen retrieval method using a sliding overtube for large colorectal neoplasm following endoscopic submucosal dissection. Endoscopy, 471:E168-E169, 2015

8. Ikematsu H, Matsuda T, Osera S, Imajoh M, Kadota T, Morimoto H, Sakamoto T, Oono Y, Kaneko K, Saito Y. Usefulness of narrow-band imaging with dual-focus magnification for differential diagnosis of small colorectal polyps. Surg Endosc, 29:844-850, 2015

9. Uraoka T, Tanaka S, Oka S, Matsuda T, Saito Y, Moriyama T, Higashi R, Matsumoto T. Feasibility of a novel colonoscope with extra-wide angle of view: a clinical study. Endoscopy, 47:444-448, 2015

10. Saito Y, Nakajima T, Sakamoto T, Yamada M, Matsuda T, Mönkemüller K. Clinical pathway to discharge three days after colorectal endoscopic submucosal dissection: For whom and for what purpose? Dig Endosc, 27:662-664, 2015

11. Iacopini F, Saito Y, Yamada M, Grossi C, Rigato P, Costamagna G, Gotoda T, Matsuda T, Scozzarro A. Curative endoscopic submucosal dissection of large nonpolypoid superficial neoplasms in ulcerative colitis (with videos). Gastrointest Endosc, 82:734-738, 2015

12. Saito Y, Saito S, Oka S, Kakugawa Y, Matsumoto M, Aihara H, Watari I, Aoyama T, Nouda S, Kuramoto T, Watanabe K, Ohmiya N, Higuchi K, Goto H, Arakawa T, Tanaka S, Tajiri H. Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesions of the colon: prospective, multicenter, open study. Gastrointest Endosc, 82:861-869, 2015

13. Matsuda T, Ono A, Kakugawa Y, Matsumoto M, Saito Y. Impact of screening colonoscopy on outcomes in colorectal cancer. Jpn J Clin Oncol, 45:900-905, 2015

14. Makazu M, Sakamoto T, So E, Otake Y, Nakajima T, Matsuda T, Kushima R, Saito Y. Relationship between indeterminate or positive lateral margin and local recurrence after endoscopic resection of colorectal polyps. Endosc Int Open, 3:E252-E257, 2015

15. Sakamoto T, Abe S, Nakajima T, Matsuda T, Nakamura F, Kowazaki H, Saito Y. Complete removal of a colonic neoplasm extending into a diverticulum with hybrid endoscopic submucosal dissection-mucosal resection and endoscopic band ligation. Endoscopy, 471:E295-E296, 2015

16. Sekiguchi M, Sekine S, Sakamoto T, Otake Y, Nakajima T, Matsuda T, Taniguchi H, Kushima R, Ohe Y, Saito Y. Excellent prognosis following endoscopic resection of patients with rectal neuroendocrine tumors despite the frequent presence of lymphovascular invasion. J Gastroenterol, 50:1184-1189, 2015

17. Yamada M, Sakamoto T, Otake Y, Nakajima T, Kuchiba A, Taniguchi H, Sekine S, Kushima R, Ramberan H, Parra-Blanco A, Fujii T, Matsuda T, Saito Y. Investigating endoscopic features of sessile serrated adenomas/polyps by using narrow-band imaging with optical magnification. Gastrointest Endosc, 82:108-117, 2015

18. Tanaka S, Saitoh Y, Matsuda T, Igarashi M, Matsumoto T, Iwao Y, Suzuki Y, Nishida H, Watanabe T, Sugai T, Sugihara K, Tsuruta O, Hirata I, Hiwatashi N, Saito H, Watanabe M, Sugano K, Shimosegawa T, Japanese Society of Gastroenterology. Evidence-based clinical practice guidelines for management of colorectal polyps. J Gastroenterol, 50:252-260, 2015

19. Kakinuma R, Moriyama N, Muramatsu Y, Gomi S, Suzuki M, Nagasawa H, Kusumoto M, Aso T, Muramatsu Y, Tsuchida T, Tsuta K, Maeshima AM, Tochigi N, Watanabe S, Sugihara N, Tsukagoshi S, Saito Y, Kazama M, Ashizawa K, Awai K, Honda O, Ishikawa H, Koizumi N, Komoto D, Moriya H, Oda S, Oshiro Y, Yanagawa M, Tomiyama N, Asamura H. Ultra-high-resolution computed tomography of the lung: image quality of a prototype scanner. PLoS One, 10:e0137165, 2015

20. Kakinuma R, Muramatsu Y, Kusumoto M, Tsuchida T, Tsuta K, Maeshima AM, Asamura H, Moriyama N. Solitary pure ground-glass nodules 5 mm or smaller: frequency of growth. Radiology, 276:873-882, 2015

21. Matsuda T, Kawano H, Chiu HM. Screening colonoscopy: what is the most reliable modality for the detection and characterization of colorectal lesions? Dig Endosc, 271:25-29, 2015

22. Sung JJ, Ng SC, Chan FK, Chiu HM, Kim HS, Matsuda T, Ng SS, Lau JY, Zheng S, Adler S, Reddy N, Yeoh KG, Tsoi KK, Ching JY, Kuipers EJ, Rabeneck L, Young GP, Steele RJ, Lieberman D, Goh KL, Asia Pacific Working Group. An updated Asia Pacific Consensus Recommendations on colorectal cancer screening. Gut, 64:121-132, 2015

23. Kawamura T, Ikematsu H, Matsuda T. New-generation narrow band imaging system for detection of a laterally spreading tumor in the colon. Dig Endosc, 271:45, 2015

24. Oka S, Tamai N, Ikematsu H, Kawamura T, Sawaya M, Takeuchi Y, Uraoka T, Moriyama T, Kawano H, Matsuda T. Improved visibility of colorectal flat tumors using image-enhanced endoscopy. Dig Endosc, 271:35-39, 2015

25. Uchiyama N, Machida M, Kikuchi M, Tani H, Otsuka K, Ito T, Arai Y. Preliminary experience of multimodality reference system for breast cancer utilizing 4K large high-resolution color display. Int J Comput Assist Radiol Surg, 10:193-194, 2015

26. Shimazu T, Asada K, Charvat H, Kusano C, Otake Y, Kakugawa Y, Watanabe H, Gotoda T, Ushijima T, Tsugane S. Association of gastric cancer risk factors with DNA methylation levels in gastric mucosa of healthy Japanese: a cross-sectional study. Carcinogenesis, 36:1291-1298, 2015

Center for Cancer Control
and Information Services

Preface

The Center for Cancer Control and Information Services (CIS) is a nationally funded program established in 2006 as an essential part of NCC's extramural activities. The Task Force for the National Cancer Registry was newly established in January 2015. Then the CIS consisted of six Divisions and one Task Force.

The mission statement of the CIS is as follows: "The Center for Cancer Control and Information Services provides information needed to promote a comprehensive and systematic cancer control program in Japan." In collaboration with designated cancer care hospitals, the Ministry of Health, Labour and Welfare and other relevant ministries, the Center plays a central role to plan, manage and evaluate nationwide cancer control programs, through promotion of specialized, multidisciplinary and comprehensive cancer research, coordination of training and information dissemination, and support of prevention, diagnosis, treatment of cancer, rehabilitation from cancer and the continuing care of cancer patients and their families.

One of our key mandates is to provide all patients and their loved ones the means to access comprehensive cancer-related information at the point of need, and with appropriate context including websites such as "ganjoho.jp". An important step in this direction followed with publications for patients with cancer diagnosis, revision of a cancer information handbook for patients with cancer named "Guidebook for cancer patients", and a publication for workers named "Prescription for cancer survivors."

The CIS promotes the standardization of hospital-based cancer registries in designated cancer care hospitals and population-based cancer registries in prefectures. The data are collected from both hospital-based and population-based cancer registries, analyzed to calculate accurate cancer statistics and disseminated throughout Japan. In addition, the CIS has continuously made efforts to develop a reliable cancer surveillance system in Japan, which is stated as a key element in the Cancer Control Act. In 2015, the Act on Promotion of Cancer Registries was also implemented.

The CIS is also building partnerships with Designated Cancer Care Hospitals to support all health-allied professionals concerned with cancer control in Japan in a pathology consultation service, a radiology consultation service, a cancer image reference database, a radiotherapy case service and the promotion of medical education programs for cancer control.

The CIS aims to research activities and advocacies based on four pillars: Monitoring and Evaluation, Development and Research of Practical Programs, Public Education and Information Services, and Promoting Policy and Networking.

Fumihiko Wakao, M.D.,
Director, Center for Cancer Control and Information Services

Organization

President:
Tomomitsu Hotta

Director:
Fumihiko Wakao

- Division of Cancer Information Service
  Chief: Tomoko Takayama
- Division of Surveillance
  Chief: Hiroshi Nishimoto
- Division of Medical Support and Partnership
  Chief: Masashi Kato
- Division of Cansor Survivorship Research
  Chief: Miyako Takahashi
- Division of Health Services Research
  Chief: Takahiro Higashi
- Division of Tobacco Policy Research
  Chief: Yumiko Mochizuki
- Task Force for National Cancer Registry
  Chief: Hiroshi Nishimoto

Activities of the Divisions

Division of Cancer Information Service (DCIS)

Tomoko Takayama, Masayo Hayakawa, Haruto Ikeyama, Chikako Yamaki, Ayako Ishikawa, Akiko Urakubo, Satoko Matsumoto, Yuki Nakatani, Yuko Ogo, Yoshimi Ishibashi, Tomoko Ono, Masayo Sakurai, Eimi Sawai, Tomoko Matsuzawa, Yukako Urata, Sachiko Kawaguchi, Ayumi Kishimoto, Satoru Takizawa, Sanae Nemoto, Hitomi Yamashita, Kaori Shioda, Jun Nakamachi

Lines of service

We have continued to enhance and update "Ganjoho.jp", the nation's trusted source of cancer information with 1,500 new pages (159,601 pages as of the end of CY2015), and annual usage is now at 31.9 million PV. Our library of patient education publications has added two new titles, and 6 of the existing 87 titles in circulation have now been updated. Contents by cancer type and regional cancer information resources have also been updated extensively. All of our patient education publications, in either booklet or pamphlet formats, are available for free downloads online and hard copies are disseminated via a bulk order printing scheme, which has made it more cost effective for cancer care facilities and related healthcare providers of all sizes. These publications are now available via 795 facilities nationwide, with over 1 million copies distributed nationwide in the course of CY2015 alone, an 11% increase over the previous year.

Division of Cancer Information Service (DCIS) continues to act as a hub that brings together the over 2,000 specialists that man the 424 Cancer Information & Support Centers (CISCs) deployed nationwide, with a bi-annual conference for prefectural CISC leadership, where we seek not only to allow the practitioners to share the latest set of best practices but also, starting in 2015, we have belatedly begun the process of better assessing our effectiveness on a more systematic basis.

The DCIS Contact Center, now in its 5th year of operation, has accommodated 2,870 calls during the calendar year, with monthly call volumes that have experienced a 46% increase over the last CY, and are fielding an increasing number of calls from patients with rare forms of cancer.

Research activities

As part of our efforts to reduce the disparity of cancer information access, pilot research programs are on-going in the following areas: 1) Assessing the nature of cancer information access for patients with visual impairments and hearing disabilities, 2) Multi-modal cancer information delivery models for patients with visual impairments, 3) Use of radio broadcast dramas to encourage patients and families with lower net literacy to make use of manned cancer information resources. Further research will aim to determine both efficacy and cost effectiveness of such delivery and dissemination models, as an integral part of the broader efforts to reduce cancer disparity.

Nurturing professionals

The specialist cancer counselors who staff the nationwide network of CISC's undergo both online training (eLearning curriculums delivered via a site we operate) and on-site group training sessions. A newly introduced certification scheme has now made it possible for cancer counselors in hospitals outside the fold of the MHW-Designation (nationally orchestrated regional cancer center designation) schemes to undergo the same set of fundamental training, and to receive certifications. This potentially opens an avenue for cancer information counselors to be deployed at upwards of 300 prefecture-designated cancer care hospitals, above and beyond and 440 nationally designated locations.

DCIS has spearheaded efforts to encourage regional networking of CISC professionals, so that a more frequent and more pertinent mix of skill enhancing opportunities are made available to a broader set of professionals in this still nascent

field. During 2015, various workshops and public education forums were conducted in cities as far afield as Nagasaki, Shimane, Mie and Fukuoka.

Our media education initiatives are now in their eighth year, with four theme conferences held during 2015, and we have stepped up our initiatives to raise public awareness of the ongoing challenges of cancer survivorship, by focusing on "Working with Cancer" in conjunction with related national initiatives to ensure more cancer patients can return to their workplace.

Future prospects

DCIS remains committed to our stated aims of bringing more accurate and reliable information to patients, families, caregivers, as well as healthcare practitioners, in a context-sensitive manner. Towards this goal, our initiatives will focus not only on enhancing the set of information disseminated via our various channels, but also on enhancing delivery channels to cater to the needs of those patients and families for whom self-service channels are either inaccessible, or do not adequately meet their unique set of needs and circumstances. Raising awareness of the services provided at CISCs, and making them more accessible, particularly in regions were cancer stigma still runs high, are among our priorities in ensuring that cancer information dissemination helps drive reduction of cancer health disparities.

List of papers published in 2015

Journal

1. Seki Y, Takayama T, Yamaki C. Evaluating the Cancer Information Service - a qualitative study of evaluation criteria for the telephone service in Japan. Journal of Saitama University. Faculty of Education, 64:145-154, 2015

Division of Surveillance

Hiroshi Nishimoto, Koichi B. Ishikawa, Akiko Shibata, Kota Katanoda, Tomohiro Matsuda, Kumiko Saika, Megumi Hori, Ayako Okuyama, Yoshiko Emori, Kaori Nakano, Mariko Niino, Masako Sato

Introduction

The Division of Surveillance is in charge of providing credible cancer statistics to patients and their families, the public, healthcare professionals, policy makers and researchers. The Division also collects accurate and useful information on cancer statistics at the national level. We promote the standardization of hospital-based cancer registries in designated cancer care hospitals and population-based cancer registries in prefectures. The data are collected from both hospital-based and population-based cancer registries, analyzed to calculate accurate cancer statistics and disseminated throughout Japan. The newly incorporated economics section will augment epidemiologic data with economic information crucial for formulation of future policy.

Routine activities

1) Population-based Cancer Registries

The Division has continuously exerted efforts to develop a reliable cancer surveillance system in Japan, which is stated as a key element in the Cancer Control Act. The Division supports all these 47 registries, by disseminating up-to-date information through websites and mailing lists; by setting up a Q&A service; by holding 2-day educational workshops for cancer registrars and administrative officers in charge of cancer control who were new to their post in May; and organizing 2-day advanced educational workshops, attended by over 120 participants, in December. The Division also provided site visiting as part of the training for the Standard Database System (SDS), for promoting the protection of personal information, and for cancer registry start-up preparation. This activity supported a total of 17 prefectures this year. Forty-two registries had introduced the SDS as of January 2015. The self-check software on security control in cancer registration and security educational materials for new workers were updated and provided by the division. According to the Act on Promotion of Cancer Registry enacted in 2013, the division participated in preparations for establishment of the National Cancer Registry Data Center. Specifically, the preparation activities included advice for the Ministry of Health, Labour and Welfare, forming the materials and data for discussion, development of the National Cancer Registry System, checking the data of the current regional cancer registries, and visiting prefectures for giving explanations about the act.

2) Hospital-based Cancer Registries

Since a hospital-based cancer registry (HCR) is essential to evaluate cancer care in each hospital and also to achieve high completeness of population-based cancer registries, it should be established urgently for cancer control. The Division plays an important role as a driving force for the standardization and quality improvement of HCRs, which were performed at 409 designated cancer care hospitals (DCCHs) and over 300 other hospitals in 2014. In collaboration with other relevant parties, the division develops data standards for HCR, modifies datasets, and distributes the standardized software "Hos-CanR PLUS", which is used in about 800 hospitals. In 2015, individual records for 656,272 cancer cases diagnosed in 2013 were collected from 409 DCCHs. To improve the data quality, the Division devised an education program for cancer registrars through holding four one-week-long workshops for experts in Tokyo per year, and conducted the primary cancer registrar examination for certifying over 800 registrars.

3) Cancer Statistics

The Division is in charge of providing information

on cancer statistics. The updated data of cancer mortality, incidence, survival, and prevalence, the secular trends of cancer mortality and incidence, and the framework of cancer control in Japan have been published both on the website and in the book titled "Cancer Statistics in Japan".

Research activities

1) Population-based Cancer Registries

The national cancer incidences in 2012 were estimated based on the data from 47 cancer registries, covering all prefectures. The prefectures that meet the data quality standards increased since last year. The incidence data were then analyzed in detail by the cancer site. The study results were published in an international journal. The cancer incidence data have been used in a couple of research analyses; the results are presented at conferences both in Japan and abroad.

2) Cancer Statistics

International comparisons of cancer burden and survival rate were conducted based on the WHO mortality, GLOBOCAN, and cancer registry database. Updated trend analysis of cancer incidence and mortality in Japan was conducted. Descriptive analysis was also conducted for myelodysplastic syndrome in Japan. Tobacco control situations were analyzed in three East Asian countries: Japan, China and the Republic of Korea, and the association between environmental tobacco smoke and strokes was examined.

3) Economic studies on cancer care

A nationwide database of inpatient and outpatient clinical practice was constructed with DPC-survey-compliant data from over 1,000 hospitals. Using this data, we published a data book on the use of pharmaceuticals related to chemotherapy. Findings from this database and other information related to utilization of services are linked with population estimates to form future forecasts of supply and demand in cancer care.

Education

Our activities of extramural education were executed as mentioned above.

Future prospects

We will start the National Cancer Registry (NCR) in the National Cancer Center (NCC), which will be implemented in January 2016, based on the activities of the project team.

Table 1. Population-based Cancer Registries from Prefectural Registries

Year of Diagnosis	Prefectures	Number of New Cancer Cases
2011	40 (14 for estimation and 39 for inter-regional comparison)	851,537
2012	47 (28 for estimation and 47 for inter-regional comparison)	865,238

Table 2. Cancer Patients Data from Hospital-based Cancer Registries at Designated Cancer Care Hospitals

Year of Diagnosis	Applied Hospitals	Number of New Cancer Cases
2010	387	548,979
2011	395	584,120
2012	397	613,377
2013	409	656,272

List of papers published in 2015

Journal

1. Saika K, Machii R. Five-year relative survival rate of brain and other nervous system cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 45:313-314, 2015

2. Machii R, Saika K. Morphological distribution of esophageal cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:506-507, 2015

3. Saika K, Matsuda T. Morphological distribution of ovarian cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:793, 2015

4. Matsuda T, Machii R. Morphological distribution of lung cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:404, 2015

5. Tanaka H, Matsuda T. Arrival of a new era in Japan with the establishment of the Cancer Registration Promotion Act. Eur J Cancer Prev, 24:542-543, 2015

6. Niino M, Matsuda T. Morphological distribution of bladder cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:999, 2015

7. Matsuda T, Sobue T. Recent trends in population-based cancer registries in Japan: the Act on Promotion of Cancer Registries and drastic changes in the historical registry. Int J Clin Oncol, 20:11-20, 2015

8. Matsuda T, Niino M. Morphological distribution of testis cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:894, 2015

9. Matsuda T, Hori M. Five-year relative survival rate of kidney and renal pelvis cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 45:136, 2015

10. Katanoda K, Hori M, Matsuda T, Shibata A, Nishino Y, Hattori M, Soda M, Ioka A, Sobue T, Nishimoto H. An updated report on the trends in cancer incidence and mortality in Japan, 1958-2013. Jpn J Clin Oncol, 45:390-401, 2015

11. Hori M, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H, Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol, 45:884-891, 2015

12. Chihara D, Ito H, Izutsu K, Hattori M, Nishino Y, Ioka A, Matsuda T, Ito Y. Advance and stagnation in the treatment of patients with lymphoma and myeloma: Analysis using population-based cancer registry data in Japan from 1993 to 2006. Int J Cancer, 137:1217-1223, 2015

13. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen WQ, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP, CONCORD Working Group. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet, 385:977-1010, 2015

14. Nagai K, Hayashi K, Yasui T, Katanoda K, Iso H, Kiyohara Y, Wakatsuki A, Kubota T, Mizunuma H. Disease history and risk of comorbidity in women's life course: a comprehensive analysis of the Japan Nurses' Health Study baseline survey. BMJ Open, 5:e006360, 2015

15. Katanoda K, Hori M. Morphological distribution for cancer of the central nervous system from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:1096, 2015

16. Katanoda K, Hori M. Morphological distribution of liver cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:607, 2015

17. Hori M, Katanoda K. Morphological distribution of thyroid cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:1182, 2015

18. Hori M, Katanoda K. Morphological distribution of cervical and corpus uteri cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol, 45:697, 2015

19. Hori M, Katanoda K. Five-year relative survival rate of lymphoma in the USA, Europe and Japan. Jpn J Clin Oncol, 45:233-234, 2015

20. Nojiri T, Hosoda H, Tokudome T, Miura K, Ishikane S, Otani K, Kishimoto I, Shintani Y, Inoue M, Kimura T, Sawabata N, Minami M, Nakagiri T, Funaki S, Takeuchi Y, Maeda H, Kidoya H, Kiyonari H, Shioi G, Arai Y, Hasegawa T, Takakura N, Hori M, Ohno Y, Miyazato M, Mochizuki N, Okumura M, Kangawa K. Atrial natriuretic peptide prevents cancer metastasis through vascular endothelial cells. Proc Natl Acad Sci U S A, 112:4086-4091, 2015

21. Tanaka N, Ohno Y, Hori M, Utada M, Ito K, Suzuki T, Furukawa F. Predicting Preoperative Hemodynamic Changes Using the Visual Analog Scale. J Perianesth Nurs, 30:460-467, 2015

Division of Medical Support and Partnership

Masashi Kato, Yasuaki Arai, Jun Itami, Nobuyoshi Hiraoka, Hironobu Hashimoto, Miki Hosoya, Toshiyuki Minemura, Yoko Nakazawa, Hiroaki Onaya, Takashi Hanada, Yuichi Matsuyama, Saran Yoshida, Hideaki Kobayashi, Naotoshi Atoda, Chieko Nagashima, Ryoji Kushima, Risa Hiranuma, Yoshiko Yamaya, Hiroyo Ohchi, Hiromi Nakamura, Shiho Hirai, Ritsuko Chinda, Mayumi Kobayashi

Introduction

The Division builds partnerships with Designated Cancer Care Hospitals to support all health-allied professionals concerned with cancer control in Japan. The Medical Support and Partnership Section (MSPS) plays a unique role in supporting Designated Cancer Care Hospitals in Japan. The Pathology Consultation Section (PCS) makes efforts to perform human pathology research based on the histology of tumor cells and tumor-stromal cells to improve diagnostic pathology of the tumors. The Radiology Consultation Section (RCS) provides a consultation service and a cancer image reference database (NCC-CIR). A radiology consultation service aims at the improvement of the quality of diagnosis based on medical images. The NCC-CIR is a web-based reference database system of images of neoplasms for physicians, radiologists, and pathologists, providing medical diagnostic images and information together with pathology. The Outreach Radiation Oncology and Physics Section (ORPS) provides the following support programs for designated regional cancer centers and institutions participating in clinical trials. The Cancer Control Education and Training Section (CCET) plays a central role in the planning, management and evaluation of specialized and multidisciplinary training programs for physicians and other health professionals as trainers of each designated cancer care hospital, to promote a comprehensive and systematic cancer control program in Japan.

Routine activities

1) Networking among Designated Cancer Care Hospitals

The MSPS held the Designated Cancer Care Hospitals Liaison-council and the Palliative Care Committee (a subsidiary organization) to enhance partnerships for cancer control, and the PDCA cycle Forum to improve the quality of cancer care in Japan. The designated cancer care hospitals are important partners with the National Cancer Center (NCC) to promote comprehensive cancer control in Japan.

2) Pathology consultation service

The PCS received 466 cases requesting a specialist's second opinion regarding histopathological diagnosis in 2015. There are 86 consultants registered, many of them highly recognized experts in specialty disciplines. One of them assigned as a consultant examines the slides and quickly sends back their opinion report to each client. Most of the clients expressed satisfaction with the contents of the report and this consultation system. We also selected typical or educational cases from accumulated archives and constructed a referential database.

3) Radiology consultation service

Twenty-nine consultation reports have been put together for requests mainly from the Kanto and Kyushu regions. Hepato-biliary-pancreatic and musculoskeletal lesions were the common subjects. Consultation with a specialist was the most frequent reason (37.9%) for consultation. The client radiologists have evaluated 451 (91.1%) of the 570 consultation reports as being useful for the presence of a clinical impact on the final radiological diagnoses.

4) NCC-CIR

The average number of effective accesses to this site was almost the same as that in 2014, about 100,000 per month. Cases with cancers who underwent urological malignancies (n=1) have been published, resulting in the total provision of 301 cases.

5) Radiotherapy case service

Mailed dosimetry and on-site dosimetry were performed in 116 institutions and 17 institutions, respectively, at the ORPS. All data of the institutions were within the permissible limit.

Research activities

1) Develop a method to implement a PDCA cycle among the Designated Cancer Care Hospitals

The MSPS developed a method for carrying out a peer review about palliative care and examined how to implement the PDCA cycle continuously.

2) Develop the IMRT quality control support program

The ORPS were developing enforcement of the mailed dosimetry regarding the output dose of Intensity Modulated Radiotherapy (IMRT) in two institutions (designated regional cancer centers).

Clinical trials

1) The on-site dosimetry regarding the output dose of IMRT

In the Japan Clinical Oncology Group (JCOG1008, JCOG1208, JCOG1303) and the Japanese Radiation Oncology Study Group (JROSG12-1), the ORPS performed on-site dosimetry regarding the output dose of IMRT in 14 institutions.

2) Support for clinical trials

To support a central radiological review in clinical trials, we have provided a system for receiving and sending DICOM imaging data between participating multi-centers and the review board since September 2014. It has been already used by some clinical trials.

Education

The CCET provides and evaluates various oncology professional training programs about up-to-date information on early detection, diagnosis, treatment, nursing care, clinical trials and cancer statistics for physicians, nurses, pharmacists, cancer information (CI) specialists and cancer registrars. The CCET provides multidisciplinary training programs for Palliative Care Teams and Chemotherapy Teams. In order to develop leaders in each prefecture, CCET holds leadership training programs for skilled physicians, nurses, pharmacists and CI specialists. (Table 1, 2)

Future prospects

The MSPS searches a support system to meet the needs of the Designated Cancer Care hospitals. All sections will continue to be involved in our routine activities and education.

Table 1. Training programs conducted during April 2014 - March 2015

Category of Education and Training Program	Titles of Education and Training Program	Number of participants		
		Leaders in prefecture	Leaders in institute	Other
Oncology nursing education	Continuing education and development of oncology nursing workshop for trainers		54	
	Continuing education and development of oncology nursing workshop for trainers - Follow-up		60	
	Continuing education and development of oncology nursing workshop for trainers in prefecture	20		
	Oncology nursing seminar for trainers		422	
	Certified Nurse Follow-up Program		51	
	End-of-life nursing education workshop for trainers		84	
CI specialist education	CI Specialist Education Program - Basic course 1			624
	CI Specialist Education Program - Basic course 2			635
	CI Specialist Education Program - Basic course 3			338
	CI Specialist Education Program for trainers	188		
	CI Specialist Education Program for trainers - Follow-up	30		
	CI Specialist Education Program - Skill-up course			92
Hospital-based cancer registrar training	Training program for instructors of hospital-based cancer registrars	20		
	Continuous training program for instructors of hospital-based cancer registrars	6		
	Supplementary training program for instructors of hospital-based cancer registrars	96		
	Basic training program for hospital-based cancer registrars			1,582
	Supplementary training program for hospital-based cancer registrars of basic course completion			1,079
	Advanced training program for hospital-based cancer registrars			156
	Introduction program for implementation of hospital-based cancer registry			72
Training for population-based cancer registrars and administrative officers in charge of cancer control	Basic training programs on population-based cancer registry for population-based cancer registrars and administrative officers in charge of cancer control			191
Pharmacist education	Seminar for pharmacists of dispensing neoplastic agents to be trainers		58	
	On-the-job training for pharmacists of dispensing neoplastic agents to be trainers		24	
Palliative care physicians education	Palliative care education meeting for trainers	62		
Psycho-oncologists education	Psycho-oncology education meeting for trainers	27		
Palliative care team education	Palliative care team workshops for consultation - Basic course		46	
	Palliative care team workshops for trainers	38		
Chemotherapy team education	Chemotherapy team workshops to introduce new drug safety		32	
	Chemotherapy care team workshops for trainers	24		
Training for administrative officers in charge of cancer control				77
Total		511	831	4,846

Table 2. Training programs conducted during April 2015 - March 2016

Category of Education and Training Program	Titles of Education and Training Program	Number of participants		
		Leaders in prefecture	Leaders in institute	Other
Oncology nursing education	Continuing education and development of oncology nursing workshop for trainers		40	
	Continuing education and development of oncology nursing workshop for trainers - Follow-up		47	
	Continuing education and development of oncology nursing workshop for trainers in prefecture	23		
	Continuing education and development of oncology nursing workshop for trainers in prefecture - Follow-up	13		
	Oncology nursing seminar for trainers		376	
	Certified Nurse Follow-up Program		34	
CI specialist education	CI Specialist Education Program - Basic course 1 & 2			1,086
	CI Specialist Education Program - Basic course 3			557
	CI Specialist Education Program - Continuous course			191
	CI Specialist Education Program for trainers	93		
	CI Specialist Education Program for trainers - Follow-up	81		
	CI Specialist Education Program - Skill-up course		180	8
Hospital-based cancer registrar training	Training program for instructors of hospital-based cancer registrars	6		
	Continuous training program for instructors of hospital-based cancer registrars	6		
	Supplementary training program for instructors of hospital-based cancer registrars	101		
	Certification for primary cancer registrars			854
	Supplementary training program for certified primary cancer registrars			1,110
	Advanced training program and certification for intermediate cancer registrars			150
	Supplementary training program for certified intermediate cancer registrars			401
	Introduction program for implementation of hospital-based cancer registry			111
	Supplementary education program for the new datasets and rules of hospital-based cancer registries			568
Training for population-based cancer registrars and administrative officers in charge of cancer control	Basic training programs on population-based cancer registry for population-based cancer registrars and administrative officers in charge of cancer control			211
Pharmacist education	Oncology pharmacist workshops for trainers	32		
Palliative care team education	Palliative care team workshops for trainers	45		
Chemotherapy team education	Chemotherapy team workshops to introduce new drug safety		28	
	Chemotherapy care team workshops for trainers	28		
Surgical pathology education	Seminar for diagnostic tumor surgical pathology			107
Training for administrative officers in charge of cancer control				93
Total		428	705	5,447

List of papers published in 2015

Journal

1. Mori M, Shimizu C, Ogawa A, Okusaka T, Yoshida S, Morita T. A National Survey to Systematically Identify Factors Associated With Oncologists' Attitudes Toward End-of-Life Discussions: What Determines Timing of End-of-Life Discussions? Oncologist, 20:1304-1311, 2015

Division of Cancer Survivorship Research

Miyako Takahashi, Miyako Tsuchiya, Makiko Tomita, Makiko Tazaki, Kyoko Onozawa, Kayoko Horikawa

Introduction

The Division of Cancer Survivorship Research was established in April 2013. Our mission is to enhance the quality of life of people with cancer and their caregivers, and to promote social awareness in Japan about cancer survivorship issues.

Routine activities

As for academic research, we mainly deal with various psychosocial issues experienced by cancer survivors and their caregivers during and after treatment such as employment, interpersonal relationships, sexuality and fertility, prejudice against cancer, life-style modifications, and unmet needs. In particular, we examine the influence of the Japanese socio-cultural background on living with, through, and beyond cancer, and try to propose countermeasures based on the research findings.

As for activities to promote social awareness toward cancer survivorship, we plan and implement educational programs listed in the education section for the general public as well as healthcare providers.

In addition to the above-mentioned activities, Dr. Miyako Takahashi, Division Chief, served as a member of the "Coexistence of Treatment and Work" council organized by the Ministry of Health, Labour and Welfare, and contributed in creating guidelines for business people.

Research activities

The research projects we conducted in 2015 include "cancer and work", "psychosocial impact of appearance change among male cancer survivors", "pediatric cancer survivors' sexual development", "father-child communication when mother has cancer", "the effect of providing written, personalized information", and so on.

As for research on cancer and work, we revealed that about 40% of patients who stopped working decided to do so before initial treatment began, and that information and support needs among patients change across the passage of time since diagnosis. Also, we developed an intervention program for business people to promote their awareness in supporting employees with cancer.

This year, we conducted six keynote lectures, seven symposium presentations, and eight oral presentations in academic meetings. Also, we published three articles in English, six articles, and four chapters in a co-authored book in Japanese.

Education

As for education for healthcare providers and citizens in 2015, we delivered 22 lectures in answer to requests from universities, academic organizations, national and local governments, and medical institutions nationwide.

As for promoting social awareness of cancer survivorship, we planned and implemented three lecture series, "Community Center Café", "Gotochi (Local) Café", and "Cancer Survivorship Open Seminar", which were open to the public. These café and seminar programs were held in a relaxed atmosphere with refreshments, and consisted of a lecture that takes up various cancer survivorship topics followed by a small group discussion by participants. It provided participants with an opportunity to learn about cancer survivorship issues as well as exchange views with each other. In 2015, we held The Community Center Café 2 times with 100 participants in total in the Tsukishima Community Center in Chuo Ward, where the National Cancer Center is located. The Gotochi (Local) Café, the other café program, has the same structure as the Community Center Café, but was co-sponsored by our division and healthcare providers in prefectures outside of Tokyo, and

focused on high-priority survivorship issues within the local community. In 2015, we held the Gotochi Café twice in Kanazawa and Nagoya, and 100 people participated. The "Cancer Survivorship Open Seminar", held in the National Cancer Center Tsukiji campus, was newly started in 2015. It is a lecture series by researchers and focuses more on academic aspects of survivorship research. In 2015, we held the seminar three times on "dental-medical collaboration", "employment issues after cancer", and "cancer information". About 300 people participated.

Future prospects

Cancer survivorship research and care practice is indispensable in creating a society in which we can live in peace after having cancer. Our Division will conduct research on various cancer survivorship issues and propose countermeasures for them. As the center of information dispatch and the personnel exchange of survivorship research and care in Japan, we plan to develop activities in cooperation with domestic and international researchers and practitioners.

List of papers published in 2015

Journal

1. Miyashita M, Ohno S, Kataoka A, Tokunaga E, Masuda N, Shien T, Kawabata K, Takahashi M. Unmet Information Needs and Quality of Life in Young Breast Cancer Survivors in Japan. Cancer Nurs, 38:E1-E11, 2015
2. Okada H, Maru M, Maeda R, Iwasaki F, Nagasawa M, Takahashi M. Impact of childhood cancer on maternal employment in Japan. Cancer Nurs, 38:23-30, 2015

Division of Health Services Research

Takahiro Higashi, Momoko Iwamoto, Izumi Inoue, Fumiaki Nakamura, Yoichiro Tsukada, Naoki Sakakibara, Rei Goto, Kaoru Konno, Kazumi Shimamura

Research activities

The Division of Health Services Research conducts research that contributes to the improvement of the quality of cancer care in Japan through meaningful evaluation of health systems and health policy performance.

1) Cancer registry-linked DPC database

As part of our ongoing initiative to monitor the quality of cancer care in Japan using a database of cancer registry-linked diagnosis procedure combination (DPC) data, we continued building the database for cancer patients diagnosed in 2013. The Division distributed free encryption software designed to support different file formats used by various hospitals, which allowed multiple data sources to be synthesized smoothly into a single database. The database contains de-identified information on all procedures, tests, and prescriptions given to patients. We used the database to calculate 12 quality indicators (QIs) among 206 QIs that were previously developed by an expert panel led by Dr. Tomotaka Sobue, professor of Medicine at Osaka University, which ask if certain types of tests, procedures, or prescriptions were given to a specified set of patients, such as the proportion of stage III colorectal cancer patients that received adjuvant chemotherapy within eight weeks of surgery. Results of the QI scores were fed back to participating hospitals through an interactive website that allowed hospitals to compare its performance to other hospitals. A total of 182 hospitals participated in the first year we launched the program in 2013. This expanded to 232 hospitals in the following year and 297 hospitals in 2015.

2) Monitoring and Evaluation of National Cancer Control Programs

The Division conducted a national patient experience survey and mailed out roughly 15,000 surveys to cancer patients throughout the country. The purpose of the survey was to measure the performance of the nation's Cancer Control Program through patient evaluations. Results of the survey along with measured outcomes of other performance indicators were put together into a 300–page final report describing the significance of the indicators and the methods used to measure them in detail. The reports were printed and distributed to various stakeholders and prefectural policymakers.

3) Rare Cancer Policy

We conducted various analyses using cancer registry data and the cancer registry-linked DPC database to describe the distribution and patterns of care of rare cancer patients in Japan. We also surveyed clinicians concerning their opinions about the definition of "rare cancer" using epidemiological data, in order to create an agreeable and meaningful definition of the term. Findings from the analyses and survey were reported to the Ministry of Health, Labour, and Welfare's Commission Expert Group on Rare Cancer, and was used to further define rare cancer and discuss priority issues in Cancer Control Policy. The Division also hosted a symposium aiming to foster open discussion on the centralization of care for bone and soft-tissue tumors among clinicians who are daily engaged in the treatment of rare cancer patients. The Division has been assigned the administrative task of facilitating the Working Group for Rare Cancer Policy by the Ministry of Health, Labour, and Welfare in 2016.

Research training and Education

The Division received a continuous flow of physicians and graduate students for research training in 2015. We mentored two graduate

students: one pursuing a clinical doctorate and another from a nursing-related doctorate program. We accepted four medical students from The University of Tokyo for a clerkship in Public Health. The Division also established an Affiliate Graduate Program with The University of Tokyo's Department of Public Health/Health Policy, opening the doors to graduate school students who are interested in gaining hands-on public health training.

Future prospects

The Division supports evidence-based policymaking and strives to improve the care of cancer patients by monitoring the performance of cancer policy and quality of care among cancer treatment centers across the country. In addition to the current activities, the Division is working to provide an information exchange platform for specialists and various stakeholders, designed to foster smooth communication and active exchange of ideas for cancer policy planning at the local government level. The Division will continue to endeavor to make clinically relevant and evidence-based policy recommendations in order to help implement meaningful cancer control programs in Japan.

List of papers published in 2015

Journal

1. Inoue I, Higashi T, Iwamoto M, Heiney SP, Tamaki T, Osawa K, Inoue M, Shiraishi K, Kojima R, Matoba M. A national profile of the impact of parental cancer on their children in Japan. Cancer Epidemiol, 39:838-841, 2015

2. Iwamoto M, Higashi T, Miura H, Kawaguchi T, Tanaka S, Yamashita I, Yoshimoto T, Yoshida S, Matoba M. Accuracy of using Diagnosis Procedure Combination administrative claims data for estimating the amount of opioid consumption among cancer patients in Japan. Jpn J Clin Oncol, 45:1036-1041, 2015

3. Tsukada Y, Nakamura F, Iwamoto M, Nishimoto H, Emori Y, Terahara A, Higashi T. Are hospitals in Japan with larger patient volume treating younger and earlier-stage cancer patients? An analysis of hospital-based cancer registry data in Japan. Jpn J Clin Oncol, 45:719-726, 2015

Division of Tobacco Policy Research

Yumiko Mochizuki-Kobayashi, Tomoyasu Hirano, Yuriko Nishikawa

Introduction

The death toll attributable to tobacco use is a manmade disaster worldwide; however, many countries have successfully shown that such death toll is avoidable with effective tobacco control regulations. Thus, to achieve a global standard for tobacco policies, our missions are research activities and advocacies based on the following four pillars: Monitoring and Evaluation, Development and Research of Practical Programs, Public Education and Information Services, and Promoting Policies and Networking.

Routine and research activities

- Through government commissioned projects, we collected information about the implementation status of FCTC (Framework Convention on Tobacco Control) Parties. Analysis and evaluation were carried out by providing a study panel.

- We conducted participatory workshops with elementary school children on tobacco with respect to cancer education. Based on the results, we considered ways to continue helping to promote the "Tobacco Free Kids Japan" program. In 2015, we carried out test programs in Hakodate, Tokyo, and Kumamoto and reported the results in the 9th Annual Meeting of the Japan Society for Tobacco Control.

- We carried out a test trial of the quitline service program, which was considered appropriate to Japan's situation. The results are based on the efficient dissemination of quitline, which prepares the activities of semi-autonomous scheme-building intended for the workplace by private sectors. We registered the trademark of quitline (Figure 1) and started a scheme that combined supervision for private companies with permission to use the trademark.

- Through providing information and planning assistance to various societies, non-governmental organizations, and prefectural government departments related to tobacco, and so forth, we carried out networking and capacity development. This year, we contributed to reports on policy proposals, such as those by the Science Council of Japan and the Tobacco Control Medical-Dental Research Network.

Figure 1. Quitline Logo, registered trademark of the National Cancer Center

Task Force for National Cancer Registry

Hiroshi Nishimoto, Naoyuki Sato, Tomohiro Matsuda, Akiko Shibata, Mariko Niino, Masako Sato (-March 2015), Rika Nabata (April 2015-), Yumi Nishikawa, Seiya Kondo

Introduction

The Project team was in charge of development of the National Cancer Registry (NCR) in the National Cancer Center (NCC), which will be implemented in January 2016, according to the Act on Promotion of Cancer Registry enacted in December 2013, enacted by the Ministry of Health, Labour and Welfare (MHLW).

Routine activities

1) Development of the National Cancer Registry database system (NCR-DBS) and the network linking the NCC and 47 prefectures

In collaboration with Fujitsu Ltd., the team developed the NCR-DBS at NCC. The 47 prefectures and the NCC, through the NCR-DBS server, were linked by a secured network (VPN), and the prefectures were equipped with client PCs. The electronic system for automated coding of causes of death (Iris) was introduced in the NCC as a sub-system of the NCR-DBS.

2) Development of the Prefectural Cancer Registry Database System (Pref-DBS) and data migration from the Standard Database System (SDS)

In order to maintain the consistency of cancer statistics, the team developed the Pref-DBS replacing the SDS, and had a contract of use with the prefectures. Forty-two prefectures had introduced the Pref-DBS, and data migration is in progress. Ahead of the data migration, for an efficient procedure, the team verified the quality of cancer death data in seven prefectures.

3) Development of the Electronic Cancer Reporting System (ECRS)

The team has developed the ECRS, by using an auto-encrypting PDF format, and released it on the website (ganjoho.jp) mainly for the clinics that do not conduct a hospital-based cancer registration.

4) Plan for the online data submission network

The team discussed the future plans for the online data submission network with the MHLW, for online data submission by the hospitals with the highest security.

5) Discussion on the government ordinance and the manuals

The team discussed the settlement of the government ordinance on the NCR. The team developed several manuals for cancer reporting, data security and data use. These manuals were uploaded on the website.

6) Provision Information on the NCR

The team was in charge of development of the website, creation of a cancer registry PR movie, infographics, posters and a pamphlet on cancer registration for the public. In July, the team organized an educational workshop on the NCR for cancer registrars and administrative officers. The team supports all the 47 registries, by disseminating up-to-date information through websites and mailing lists, by setting up a Q&A service.

Future prospects

We will start the National Cancer Registry (NCR) in the National Cancer Center (NCC), which will be implemented in January 2016, based on the activities of the project team.

Annual Report 2015

Published by National Cancer Center

National Cancer Center Hospital
National Cancer Center Hospital East
National Cancer Center Research Institute
Exploratory Oncology Research & Clinical Trial Center
Research Center for Cancer Prevention and Screening
Center for Cancer Control and Information Services

5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
phone: +81-3-3542-2511 fax: +81-3-3542-2545

Editor

Hitoshi Nakagama, M.D, Ph.D

Compiled by

Kobunsha co., Ltd.
1-9-7 Sekiguchi,
Bunkyo-ku, Tokyo 112-0014, Japan

Date of Publication

December 2016

Annual Report 2015

National Cancer Center Japan