Annual Report 2011

National Cancer Center

Hospital, Hospital East, Research Institute,
Research Center for Cancer Prevention and Screening,
Center for Cancer Control and Information Services,
Japan

CONTENTS

Hospital East

Center for Cancer Control and Information Services

Preface

From April 1, 2010, the National Cancer Center (NCC) changed its status to an Independent Administrative Institution (IAI) from an institution controlled directly by the Ministry of Health, Labour and Welfare, Japan. This status change was in line with the "Act on Independent Administrative Agencies Where Researches of Advanced Specialized Medical Service Are Conducted" enacted in December 2008. The purpose of an IAI is to pursue tasks decided by the Government, in the performance of which the Government itself has limitations.

I myself was a director of a national university hospital when the Act on transformation of national universities into independent administrative entities was passed by the National Diet. I was relaxed about reforms with this change in status because I was reforming the organization anyway. But I realized it DOES matter after reading three books about corporate organizations which had copied the British model. I became anxious regarding the loss of direct governmental control. Did this change in status mean that the country will no longer support us?

On the other hand, it is also true that any organization under direct governmental control can become tired and begin to stagnate - so I changed my way of thinking. Instead, I regarded it as a great opportunity to revitalize the national universities in line with the people's expectations.

There are many drawbacks to being an organization tied to the Government. For example, we encounter problems such as limitations regarding hiring government officers, and the single-year budget rule. Under these new changes, however, we will still receive operation subsidies from the nation's tax coffers for tasks that private companies cannot pursue, such as basic research and enlightenment activities. As an independent organization, the NCC will be able to cut out unnecessary expense.

After Japan started to fall behind in cancer research and treatment, the concept of building the National Cancer Center came from Dr. Takeo Tamiya, a former Dean of the Faculty of Medicine, the University of Tokyo, who realized that a research unit which would look exclusively at cancer, could not work within a faculty of medicine in a university hospital. Some two years in the creation, the NCC was built in 1962 where the Naval Hospital used to be.

Sometimes study is completed by a single researcher but most study comes from broad areas and it grows large, as history shows. In that context there were "Giants of Study" in the NCC who became pioneers later, such as Dr. Yoichiro Umegaki, who specialized in particle radiation therapy; Dr. Heizaburo Ichikawa, who developed the double contrast study for the gastrointestinal tract; Dr. Shichiro Ishikawa, a thoracic surgeon; Dr. Takashi Sugimura, who led internationally biochemical research projects; and Dr. Kiyoji Kimura, who poured energy into the development of pioneering chemotherapeutic regimens. They built the foundations of today's NCC. These pioneers attracted outstanding physicians and researchers from all parts of Japan, regardless of the universities they were from and they cut across networks. The NCC's accomplishments in the field of cancer led Japan and the rest of the world.

The work of the early Presidents' was notable: Dr. Takeo Tamiya (studied basic medicine, at Tokyo University), Dr. Yoshitatsu Hiki (basic medicine, Tokyo University), Dr. Masaru Kuru (clinical medicine, Tokyo University), Dr. Kenpo Tsukamoto (clinical medicine, Tokyo University), Dr. Waro Nakahara (basic medicine, Cornell University), Dr. Shichiro Ishikawa (clinical medicine, Keio University), and Dr. Takashi Sugimura (clinical medicine, Tokyo University). The subsequent Presidents, too, did a world-class job.

Unrecognized by those within the NCC, however, it faced institutional fatigue. For the past 10 years, from the viewpoint of outside specialists, the NCC's tasks tended to be standardized jobs, rather than the Center's own clinical work or research. Let us remember that the original mission of NCC was supposed to be something others cannot do. Perhaps past presidents should have noticed the institutional fatigue sooner and should have taken advanced actions, but it is easy to be wise after the event.

Now the NCC will be reborn from a National Center to gain the status of an Independent Administrative Institute. All of us in the NCC, physicians, nurses, researchers, and administrative workers, will start work under the new slogan, "All Activities for Cancer Patients"! Every single staff member is potently and highly motivated, I'm sure you'll be satisfied with our service. As from June 1st, 2010, the NCC's functions will

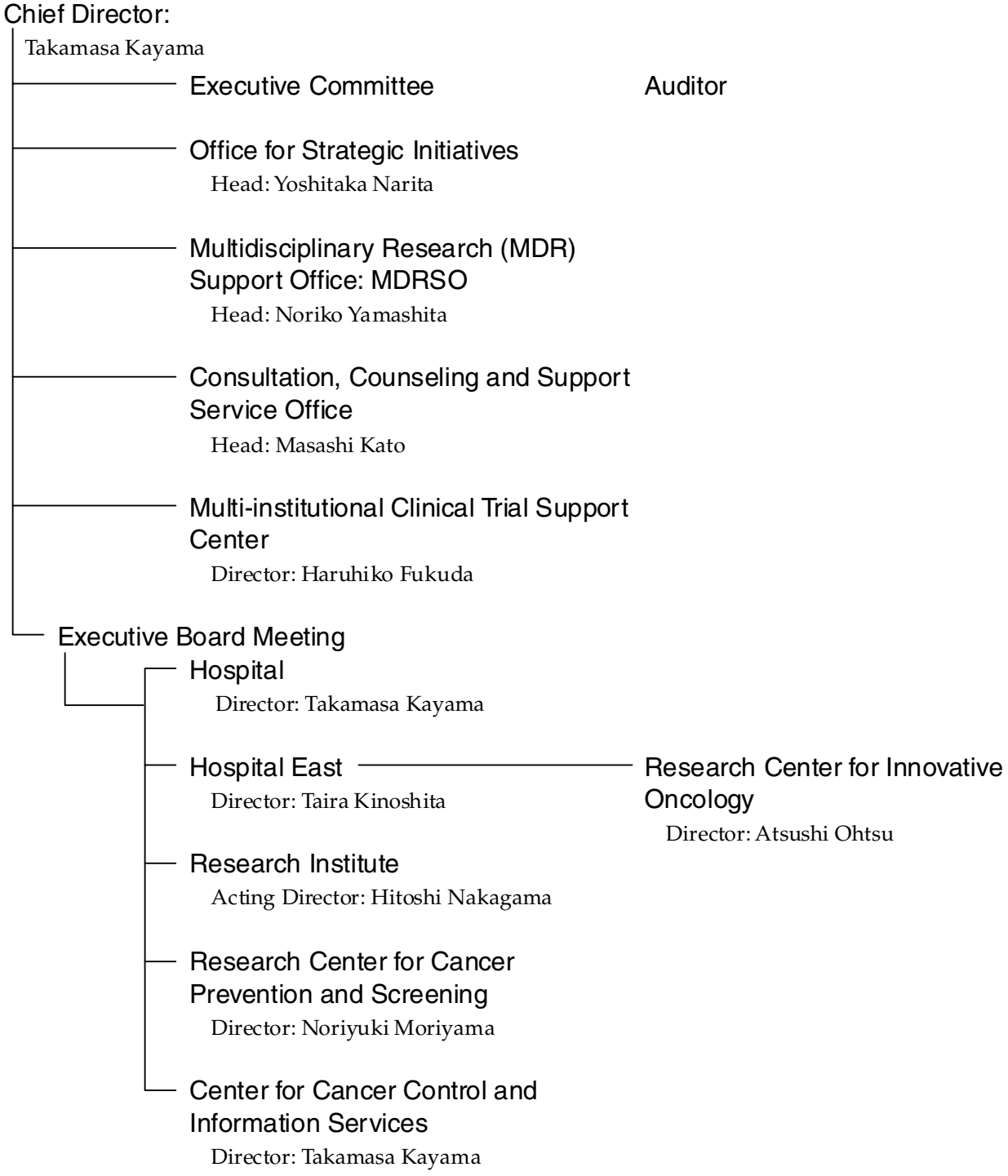
include clinic services, nursing, research, enlightenment activities, providing cancer information and policy making. You can review our course of action, which is posted on the NCC website, at “Vision and Mission”.

Finally, I would like to extend my thanks to everyone who contributed to this report, and I look forward to continuing to work at the head of this distinguished group of professionals.

Takamasa Kayama. M.D., Ph.D.
Chief Director of the National Cancer Center

Sections Directed by Chief Director

Organization of the National Cancer Center



MULTIDISCIPLINARY RESEARCH (MDR) SUPPORT OFFICE: MDRSO

Noriko Yamashita, Suga Yamagami, Mari Tomoda, Izumi Kobayashi

Introduction

The Multidisciplinary Research Support Office (MDRSO) was set up on August 12, 2010, under the direct control of the Chief Director of the National Cancer Center to promote clinical research, public health research, and basic research and to help the NCC departments work closely together. To be specific, the MDRSO works on the biobank and develops the infrastructure for research. The MDRSO also provides information that may be helpful to conduct research projects.

Routine Activities

1. Biobank related office work

1) Preparation for Biobank organization

The MDRSO is involved with setting up a "National Cancer Center Biobank Coordination Committee" that constantly oversees the correct and consistent working of the National Cancer Center Biobank. After its establishment on January 13, 2011, the MDRSO works as this Committee's secretariat. The MDRSO reviewed the current system of research partnership requests, then coordinated and distributed throughout the NCC in the shift to a new system. Specifically, the MDRSO organized five briefing sessions for the NCC staff. One thousand and six staff members in total participated, which contributed to improve the environment. The Tsukiji campus shifted to the new system on May 13, 2011, and Kashiwa campus did so on June 13, 2011. The MDRSO held one briefing session for newcomers to the Tsukiji campus on November 17, and 43 staff members participated in the session.

2) Research Concierge Desk

The MDRSO is in charge of asking hospital patients for their cooperation in research projects after giving them an adequate explanation. The MDRSO hired six "Research Concierges" and trained them to be able to handle the explanation to patients. Their duty started on May 13, 2011. By the final working day of the year, which was December 28, 3,845 new patients were approached, from whom 3,616 agreed, giving a consent rate of 94.0%. Also the Concierges support new patients with processes as explaining common preliminary diagnosis cards and infection tests. The MDRSO supported 5,650 new patients from May 13 through December 28.

3) National Cancer Center Biobank Coordination Committee Secretariat

The MDRSO works not only as a secretariat of the Committee, but also a supporter of working groups in many fields. The MDRSO organized 10 Coordination Committees in total and 9 WGs during the year.

2. Research infrastructure building and offering functions

1) Clinical research education

1)-1 Planning and coordinating for research ethics seminars

The MDRSO organized research ethics seminars three times for the NCC staff in cooperation with the Cancer Control Programs Administration Division. The total participants were 538 persons.

Date	Mar 24, 2011	Apr 27, 2011	Nov 17, 2011
Programs & Speakers	1. Research Ethics and Human Research Protection by Dr. Akihiro Sato 2. How to write a good Informed Consent Form by Ms. Yoko Kishimoto 3. Application procedure for a new protocol by IRB Office	1. Lecture on the ethical guideline for clinical Research by Dr. Yasuhiro Fujiwara 2. Research Ethics and Human Research Protection By Dr. Masashi Ando 3. Application procedure for a new protocol by IRB Office	1. Research Ethics and Human Research Protection By Dr. Masashi Ando 2. Application procedure for a new protocol by IRB Office
No. of Participants	180	217	180

1)-2 Management of the completion history of seminars by researchers

The MDRSO created a database which manages researchers' attendance history at research ethics seminars in a unified manner. Moreover, the MDRSO began issuing an attendance history from the seminar of April 27, which helps researchers to keep on track by themselves.

1)-3 Creation of clinical research teaching materials

The MDRSO constructed teaching materials on "Guidance on the Method of Clinical Trial Registration" and "How to write an informed consent form" then uploaded these to the NCC's internal server where researchers can easily access them.

2) Construction of quality control of, and the quality assurance system for, clinical research

2)-1 Arrangement of the acceptance procedure of the audit and monitoring from the outside

The MDRSO is now in the preparation of issuing a manual on accepting audits and monitoring of clinical studies.

2)-2 Construction and preparation of an internal audit system for clinical research

To enable self-checking whether clinical research is being properly done based on the ethics guidelines, the MDRSO is planning to establish an internal audit system and is now writing a manual to cover this.

3) Inquiry about clinical research for patients

The MDRSO started a system where receptionists primarily respond to inquiries, complaint s and so on from patients regaring clinical studies and related matters.

The MDRSO has now started to serve as the first contact for patients who have complaints, questions and inquires about clinical researches.

4) Planning for and coordinating of reseach conferences

To encourage joint research inside the NCC, the MDRSO planned and carried out 7 research conferences jointly with the Office for Strategic Initiatives (OSI), at which 21 researchers made presentations and led discussions. The speakers and the number of participants at each conference are as follows. The total participants were 1,190 persons.

5) Alliance / partnership activity support

The MDRSO held two meetings to support cooperative activities between the NCC researchers and companies that match alliance contracts, aiming for early development tests. (No. of participants: 57 on May 13, 83 on October 2)

6) Holding of various meetings

6)-1 An open forum on radioactive exposure

As a joint program with the OSI, the MDRSO held an open forum on radioactive exposure on June 22, 2011, aiming to understand the influence of radiation correctly and to minimize the influence of future exposure as much as possible. Three hundred and ninety-six attendees participated, including those affected by radiation, scientists, health professionals, and members of the media (62 from the public, 114 from Designated Hospitals, and 220 from the NCC) What was debated there was put into a book and published on December 22.

6)-2 A workshop for medical equipment development

In cooperation with the OSI, the MDRSO planned and held a workshop for medical equipment development with the Faculty of Technology, the University of Tokyo on Oct 31, 2011. Its objective was to connect medicine and engineering, technology (seeds) and problems (needs) in the medical field. In part I, the instructors and the students of the Faculty of Technology, the University of Tokyo, had a clinical field tour. In the following part II five lecturers gave presentations regarding proposals introducing cooperative research between medical engineering and the clinical field. The total number of participants was 182 persons (from the University of Tokyo, 79; from the NCC, 103).

Date	Presenter	No. of Participant
Feb 21, 2011	Yasuhiro Matsumura/Tetsuya Hamaguchi	167
Apr 13, 2011	Toshikazu Ushijima/Takeshi Nakajima	217
Jun 14, 2011	Yoshitaka Narita/Tesshi Yamada	168
Jul 5, 2011	Yae Kanai/Yuji Heike/Shoichiro Tsugane/Noriyuki Moriyama/Jun Itami	164
Aug 8, 2011	Toshikazu Ushijima/Hiroaki Onaya/Hirtoshi Tsuda/Yoshitaka Narita/Atsushi Ochiai	203
Aug 30, 2011	Tetsuya Nakatsura/Takuji Okusaka/Yuji Heike	130
Dec 22, 2011	Yukio Kobayashi/Issay Kitabayashi	141

CONSULTATION, COUNSELING AND SUPPORT SERVICE OFFICE

Masashi Kato, Yukiko Higuchi, Mariko Suda, Kayoko Miyata, Shogo Arihara, Ryuta Suyama, Maki Tanaka, Mieko Yamagata, Natsuko Moroi, Eri Hirayama, Yukari Nakagawa, Maiko Fujimori, Keiko Nozawa, Tomoko Takayama, Chikako Yamaki, Yuko Ogo

Introduction

Since its establishment in August 2010, Consultation, Counseling and Support Service Office (CCSSO) has been placed as an independent section under the direct control of the Chief Director of National Cancer Center. The staff members called "cancer counseling and support specialists" work mainly at Consultation, Counseling and Support Service Center of National Cancer Center Hospital (NCCH). The staff cope with various problems of cancer patients and their families with the ultimate aim to help patients feel relieved and receive medical treatment. By putting ourselves in the patients' position, we can make real efforts to solve the problems.

Routine Activities

1 Consultation, Counseling and Support Services
  (1) Consultation and counseling in person
  (2) Consultation and counseling on the telephone

On September 15, 2010, "Kanja-Hikkei Support Center", our so-called telephone counseling center, was established. Center for Cancer Control and Information Services (CIS) published booklets, with the idea that the booklets, "Kanja-Hikkei", should be a 'must-have' item for the patients. We counsel on the telephone in the hope that patients can see the benefit of the information in the booklets, and make use of this information by themselves.

From January to December, 2011, the CCSSO handled 12,755 cases in total (1,063 cases per month). 7,322 of those were new cases: 1,003 cases were from the NCCH inpatient unit.

One of the characteristics of this Center is that most advice seekers are other hospitals' patients and they contact us most of the time, by telephone.

2 Activities accompanying Consultation, Counseling and Support Services
  (1) Cooperation with other hospitals and institutions
  (2) Cooperation inside the hospital
  (3) Administration of group program for patients and their families

We cooperate with other hospitals and institutions so that cancer patients can live with as high a quality of life as possible. we rearranged community services were required and helped patients to change hospitals.

In the hospital, we discuss with the doctors and medical staff about patients. We are participating in the medical meetings of six specialties. We hold classes designed for outpatients after bone marrow transplantation named "GVHD and living a life". We also hold classes for patients with pancreatic cancer or biliary tract cancer named "The pancreatic cancer and biliary tract cancer classroom". Additionally, we developed and conducted a new class for families of brain tumor patients, and a body image class for women before receiving breast cancer surgery, in collaboration with other in-hospital experts.

3 Activities of cooperation with other regional hospitals and institutions
  (1) Support for holding information exchange meetings with regional hospitals and institutions
  (2) Administration of database on information about regional hospitals and institutions

4 Activities related to volunteers of NCCH
5 Activities related to committees of NCCH
6 Activities related to education of NCCH staff
7 Others
  (1) Administration of the patient library

Research Activities

We analyze information and opinions obtained by counseling. In addition, we develop effective procedures for counseling and support for cancer patients and their families.

MULTI-INSTITUTIONAL CLINICAL TRIAL SUPPORT CENTER

Haruhiko Fukuda, Taro Shibata, Kenichi Nakamura, Atsuo Takashima, Harumi Kaba, Noriko Yamashita

Introduction

The Multi-institutional Clinical Trial Support Center was organized as a direct sector to the Chief Director of the National Cancer Center by transferring the Clinical Trials Support Division from the Center for Cancer Control and Information Services in September 2011. The Center supports multi-institutional clinical trials conducted by the Japan Clinical Oncology Group (JCOG) aiming to improve the standard treatment for cancer patients. The JCOG is a nationwide, multi-institutional, multi-disease, multi-modality cooperative study group supported by the National Cancer Center Research and Development Fund and Health Sciences Research Grants from the Ministry of Health, Labour and Welfare. The JCOG has 15 disease-oriented or modality-oriented subgroups covering most cancer types except leukemia and pediatric cancer, and approximately 3,000 physicians from 180 hospitals participate in the JCOG.

The Clinical Investigations Section, Biostatistics and Epidemiology Section, Regulatory Science Section, Data Management Section, and Project Management Section of the Center are jointly managing JCOG headquarters, the JCOG Data Center and the JCOG Operations Office, in collaboration with the non-profit organization named the Clinical Oncology Research and Education (CORE). The Center and the CORE support all JCOG trials for study design, protocol development, patient registration and randomization, data management, interim central monitoring, statistical analysis, adverse event reporting, quality assurance site visit audits, quality control of radiotherapy, central review of imaging and pathology, publication, and various kind of peer-review based committee activities.

Routine Activities

At the end of 2011, the Center had supported 34 open trials, 19 trials on follow-up, 14 trials in preparation, and the yearly patient accrual was 2,743, which increased by 20% compared to 2010. As for safety management, 52 adverse event reports for serious and/or unexpected adverse events were submitted to and reviewed by the Data and Safety Monitoring Committee (DSMC). The DSMC also reviewed 9 interim analysis reports, and 31 protocol amendment/revisions. The Audit Committee made site visits for 30 sites in 6 hospitals, and a total of 87 cases were audited. A central pathology review is on-going in 5 trials (2 lymphoma, 1 osteosarcoma, 1 glioblastoma, 1 gastric cancer). The quality control program for radiotherapy continued in 13 trials. A web-based 24-hour online patient registration system is available in 20 trials among 34 open trials.

As for activity other than support of the JCOG, the Center also acts as the secretariat of the Clinical Trial Working Group (CTWG) under the Liaison Council of Prefectural Designated Cancer Care Hospitals. The CTWG aims to enhance the resources for investigator-initiated cancer clinical trials in the Designated Cancer Care Hospitals and to promote the efficiency of investigator-initiated cancer therapeutic development nationwide.

Research Activities

The Center is conducting intramural studies related to clinical trial methodology including statistical methods and data management, such as a timing analysis for streamlining clinical trial protocol development, a timing analysis of local Institutional Review Board approval, a timing analysis of publication after the final analysis report, exploration of factors associated with serious adverse events, an association analysis between timeliness of case report form submission and protocol deviation, a validity analysis of clinical tumor response and pathological tumor response by chemotherapy, and a validity analysis of surrogate time-to-event endpoints.

Published Papers

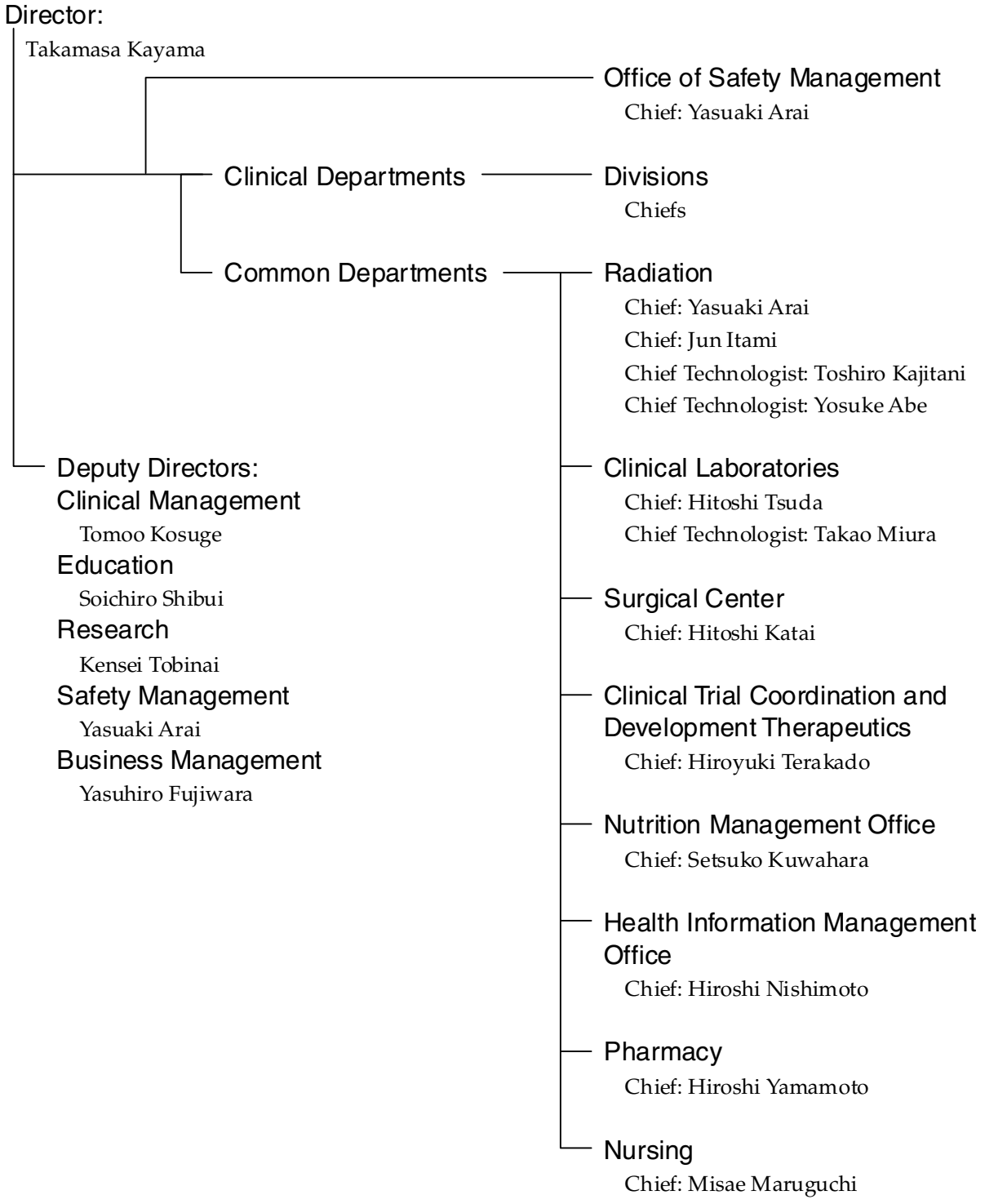
1. Kurokawa Y, Sasako M, Sano T, Shibata T, Ito S, Nashimoto A, Kurita A, Kinoshita T. Functional outcomes after extended surgery for gastric cancer. Br J Surg, 98:239-245, 2011

2. Takashima A, Shimada Y, Hamaguchi T, Ito Y, Nakano A, Nakamura K, Shibata T, Fukuda H, Moriya Y. A Phase I/II trial of chemoradiotherapy concurrent with S-1 plus mitomycin C in patients with clinical Stage II/III squamous cell carcinoma of anal canal (JCOG0903: SMART-AC). Jpn J Clin Oncol, 41:713-717, 2011

3. Takeda K, Negoro S, Tanaka M, Fukuda H, Nakagawa K, Kawahara M, Semba H, Kudoh S, Sawa T, Saijo N, Fukuoka M. A phase II study of cisplatin and irinotecan as induction chemotherapy followed by concomitant thoracic radiotherapy with weekly low-dose irinotecan in unresectable, stage III, non-small cell lung cancer: JCOG 9706. Jpn J Clin Oncol, 41:25-31, 2011

Hospital

Organization



Clinical Departments

Director:
Takamasa Kayama

- Department of Neurosurgery and Neuro-Oncology
  - Chief: Soichiro Shibui
  - Chief: Yoshitaka Narita
- Department of Ophthalmic Oncology
  - Chief: Shigenobu Suzuki
- Department of Head and Neck Oncology and Plastic and Reconstructive Surgery
  - Chief: Masao Asai
  - Chief: Shimpei Miyamoto
  - Head and Neck Surgery Division
  - Plastic and Reconstructive Surgery Division
- Department of Breast Oncology and Medical Oncology
  - Chief: Yasuhiro Fujiwara
  - Chief: Takayuki Kinoshita
  - Breast Surgery Division
  - Breast and Medical Oncology Division
- Department of Thoracic Oncology
  - Chief: Hisao Asamura
  - Chief: Tomohide Tamura
  - Chief: Masahiro Kaneko
  - Thoracic Surgery Division
  - Thoracic Oncology Division
  - Respiratory Endoscopy Division
- Department of Gastrointestinal Oncology
  - Chief: Hitoshi Katai
  - Chief: Yoshihiro Moriya
  - Chief: Yasuhiro Shimada
  - Chief: Yuji Tachimori
  - Chief: Yutaka Saito
  - Esophageal Surgery Division
  - Gastric Surgery Division
  - Colorectal Surgery Division
  - Gastrointestinal Medical Oncology Division
  - Gastrointestinal Endoscopy Division
- Department of Hepatobiliary and Pancreatic Oncology
  - Chief: Tomoo Kosuge
  - Chief: Takuji Okusaka
  - Hepatobiliary and Pancreatic Surgery Division
  - Hepatobiliary and Pancreatic Oncology Division
- Department of Urology
  - Chief: Hiroyuki Fujimoto
- Department of Gynecology
  - Chief: Takahiro Kasamatsu
- Department of Orthopedic Surgery
  - Chief: Hirokazu Chuman
- Department of Dermatologic Oncology
  - Chief: Naoya Yamazaki
- Department of Hematology and Hematopoietic Stem Cell Transplantation
  - Chief: Kensei Tobinai
  - Chief: Takahiro Fukuda
  - Hematology Division
  - Hematopoietic Stem Cell Transplantation Division
- Department of Pediatric Oncology
  - Chief: Atsushi Makimoto
  - Sarcoma Outpatient
- Department of Internal Medicine
  - Chief: Ken Ohashi
  - Diabetology, Cardiology, General Internal Medicine, Genetic Counseling, Dental
- Department of Anesthesiology and Intensive Care Unit
  - Chief: Tetsufumi Sato
  - Chief: Daisuke Yamaguchi
  - Anesthesiology Division
  - Intensive Care Unit
- Department of Palliative Care and Psycho-Oncology
  - Chief: Motohiro Matoba
  - Chief: Ken Shimizu
  - Palliative Care Division
  - Psycho-Oncology Division
- Department of Diagnostic Radiology
  - Chief: Yasuaki Arai
  - Chief: Masahiko Kusumoto
- Department of Radiation Oncology
  - Chief: Jun Itami
- Department of Pathology and Clinical Laboratories
  - Chief: Hitoshi Tsuda
  - Chief: Ryuji Tanosaki

Activities of the Departments

DEPARTMENT OF NEUROSURGERY AND NEURO-ONCOLOGY

Soichiro Shibui, Yoshitaka Narita, Yasuji Miyakita, Makoto Ohno, Yoshiko Okita

Introduction

Patients with primary and metastatic brain tumors are treated by five neurosurgeons in the Neurosurgery Division. Three hundred and thirteen patients were admitted and 92 craniotomies for tumor removal were carried out in 2011 including 35 gliomas, 39 metastatic brain tumors, 6 primary CNS lymphomas, and 5 meningiomas (Table 1). Ten ventriculo-peritoneal shunts and 7 neuroendoscopic surgeries for the IIIrd ventriculostomy or biopsy were also carried out for patients with hydrocephalus. Every craniotomy was carried out with the aid of a surgical navigation system (Stealth station). The site of the craniotomy and the extent of tumor removal were visualized on the CRT of this system 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 MR tractography were also used to preserve patient neurological function. Nine awake surgeries were also performed, particularly for removal of gliomas near the speech center. Postoperative radiotherapy and chemotherapy using high-dose methotrexate were carried out for malignant tumors. 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 is held with doctors of the Department of Radiation Oncology on diagnosis and treatment of the patients with brain tumors. Usually 20 patients are hospitalized and two or three of them undergo surgical treatment every week. The Stealth navigation system is used for surgical planning during every craniotomy. 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 the 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 2 years. The 1-year and 5-year survival rates of the patients with anaplastic astrocytomas were 86.7% and 34.3%, respectively, which were better than those recorded in the Brain Tumor Registry of Japan. But the 1-year and 5-year survival rates of patients with glioblastomas has remained at 58.3% and 11.9%, respectively (Table 2). 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 Brain Tumor Registry of Japan (BTRJ) since 1969. More than 100,000 patients have been registered and followed up. The Department of Neurosurgery and Neuro-Oncology, 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.

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 Genetics Division of the National Cancer Center Research Institute. Tumor samples of malignant gliomas were collected and were analyzed with a DNA microarray. FISH analysis using 1p/19q/EGFR/PTEN probes and the determination of the methylation status of O^6-methylguanine-DNA methyltransferase (MGMT) are also carried out to predict the prognosis of the patients with malignant gliomas.

Clinical Trials

The Japan Clinical Oncology Group (JCOG)-Brain

Table 1. Number of surgeries by year, 2009-2011

	2011	2010	2009
Glioma	35	51	46
Metastatic brain tumor	39	42	27
Meningioma	5	9	5
Primary CNS lymphoma	6	4	3
Other brain tumor	7	6	7
Others	31	33	25
Total	123	145	113

Table 2. Survival rates

Diagnosis	No	MST (mo)	5-yr (%)
Pilocytic astrocytoma	7	n.v.	100
Diffuse astrocytoma	47	n.v.	70.7
Oligoastrocytoma	21	n.v.	95.2
Anaplastic oligoastrocytoma	22	n.v.	65.8
Anaplastic astrocytoma	47	28.2	34.3
Glioblastoma	104	13.9	11.9

Op. year, 1995.1-2005.12; MST, median survival time; n.v., not verified

Tumor Study Group was organized in 2002 and a multi-institutional randomized controlled trial entitled "A randomized controlled phase II/III study of chemoradiotherapy using ACNU versus procarbazine and ACNU for astrocytoma grade 3 and 4" was carried out. The overall survival of both arms was longer than that of a Temozolomide (TMZ) study conducted by EORTC, but adverse events such as granulocytopenia and thrombocytopenia were observed more frequently. In April 2010 a randomized study was started entitled "A multicenter randomized phase II trial of Interferon-beta and Temozolomide combination chemoradiotherapy for newly diagnosed glioblastomas (JCOG 0911)". A clinical trial for metastatic brain tumors is also still ongoing: "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)". The efficacy of the gamma knife will be compared to that of whole brain irradiation. A new clinical trial for primary CNS lymphoma and grade 3 glioma will start in 2012. 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.

Published Papers

1. Terasaki M, Shibui S, Narita Y, Fujimaki T, Aoki T, Kajiwara K, Sawamura Y, Kurisu K, Mineta T, Yamada A, Itoh K. Phase I trial of a personalized peptide vaccine for patients positive for human leukocyte antigen--A24 with recurrent or progressive glioblastoma multiforme. J Clin Oncol, 29:337-344, 2011
2. Sunayama J, Sato A, Matsuda K, Tachibana K, Watanabe E, Seino S, Suzuki K, Narita Y, Shibui S, Sakurada K, Kayama T, Tomiyama A, Kitanaka C. FoxO3a functions as a key integrator of cellular signals that control glioblastoma stem-like cell differentiation and tumorigenicity. Stem Cells, 29:1327-1337, 2011
3. Ohno M, Narita Y, Miyakita Y, Ueno H, Kayama T, Shibui S. Reactivation of hepatitis B virus after glioblastoma treatment with temozolomide--case report. Neurol Med Chir, 51:728-731, 2011
4. Hashimoto K, Narita Y, Miyakita Y, Ohno M, Sumi M, Mayahara H, Kayama T, Shibui S. Comparison of clinical outcomes of surgery followed by local brain radiotherapy and surgery followed by whole brain radiotherapy in patients with single brain metastasis: single-center retrospective analysis. Int J Radiat Oncol Biol Phys, 81:e475-480, 2011

DEPARTMENT OF OPHTHALMIC ONCOLOGY

Shigenobu Suzuki

Introduction

Our Department is one of the rare groups specializing in ocular tumors, especially intraocular tumors. Recently, more than 60% of patients nationwide with retinoblastoma, which is the most frequent intraocular malignancy in childhood, and more than 50% of patients with uveal melanoma, which is the most frequent primary intraocular malignancy in adults, have been referred to the department.

Routine Activities

Our outpatient service is open for three days a week. Every week, six operations under general anesthesia and minor surgeries under local anesthesia are performed in our department. Our treatment strategies for ocular tumors are as follows:

1) Retinoblastoma

Unless the patient's family has anxiety about preserving the affected eye, if the eye has already suffered from complication such as uveitis or secondary glaucoma, 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 brachytherapy radiation 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 systemic chemotherapy are treated with dedicated support from the Department of Pediatric Oncology.

2) Uveal melanoma

Uveal 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 brachytherapy is only available in our institute. Patients with much larger tumors are referred to the National Institute of Radiological Science, Research Center for Charged Particle Therapy, for carbon ion therapy. Uveal 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) 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 treaded with orbital exenteration.

4) 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.

5) 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.

Clinical Trials

One of the unique techniques in our department is

local chemotherapy for retinoblastoma via selective ophthalmic artery infusion using a balloon catheter. Injection of melphalan (7.5 mg/m^2) directly into the affected side of the ophthalmic artery can be performed for two to three patients a week. From 1987 to 2007 1470 injections for 408 retinoblastoma eyes were examined, and the procedure success rate was 98.8%. This technique has been modified and performed until 2009 in more than 20 countries. We are planning the clinical trial on selective ophthalmic artery injection therapy for initial treatment methods.

Direct injection of diluted melphalan (0.016 mg/0.05 ml) 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% eyes were rescued using this strategy.

Neoadjuvant chemotherapy for eye-preservation in retinoblastoma cases is available in selected patients in collaboration with the Department of Pediatrics, the Jikei University School of Medicine. A reduction of systemic chemotherapy using selective ophthalmic artery injection and vitreous injection strategies is now ongoing.

Published Papers

1. Suzuki S, Yamane T, Mohri M, Kaneko A. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. Ophthalmology, 118:2081-2087, 2011

Table 1. Number of patients

Retinoblastoma	48
Choroidal melanoma	14
Other intraocular tumors	22
Eyelid tumor	15
Conjunctival tumor	16
Orbital tumor	22
Others	5

Table 2. Operative procedure

Retinoblastoma	
Selective ophthalmic arterial injection	106
Laser and/or vitreous injection	118
Ruthenium brachytherapy	43
Enucleation	16
Choroidal melanoma	
Ruthenium brachytherapy	8
Enucleation	2
Resection of eyelid tumor	6
Resection of conjunctival tumor	6
Resection of orbital tumor	13
Orbital exenteration	1
Others	2

DEPARTMENT OF HEAD AND NECK ONCOLOGY AND PLASTIC AND RECONSTRUCTIVE SURGERY, HEAD AND NECK SURGERY DIVISION

Masao Asai, Sei-ichi Yoshimoto, Hiroki Umezawa, Natsuki Matsunaga

Introduction

The strategy of head and neck cancer treatment is to improve the patient's survival rate while preserving the significant functions including speech, mastication, swallowing, and cosmetic appearance. In order to achieve this strategy, our division has tried to select the best treatment modality and devise new surgical strategies based on the clinico-pathological findings and the large database of our head and neck cancer patients.

Our divisions have developed and performed original surgical procedures of partial laryngectomy for newly-diagnosed and radiation-failed early glottic cancer, partial hypopharyngectomy for early hypopharyngeal cancer and total glossectomy without total laryngectomy for advanced tongue cancer. These surgical approaches can be performed without sacrificing the larynx. Compared with the results of conventional surgery, the wound apparently heals with fewer complications. Patients can resume social activities more easily when they maintain their ability to communicate by speech. We have recently started a new treatment trial of concurrent chemo-radiotherapy for advanced and resectable head and neck cancer at the National Cancer Center Hospital East.

Routine Activities

The Head and Neck Division of the NCCH consists of two head and neck surgeons and two plastic surgeons as regular staff, and two residents. In our outpatient service, an NCCH East a plastic surgeon is also engaged in routine outpatient activities, including regular follow-up care, and a resident of the Head and Neck Division of NCCH East performs general and local anesthetic operations, and supportive care of inpatients. Many operations with or without major microsurgical reconstructive surgery under general and local anesthesia and radiotherapy are performed at NCCH, but only chemo-radiotherapy for the head and neck cancer is mainly performed at NCCHE.

In 2011, 264 patients with head and neck cancer had undergone surgery under general and local anesthesia and 45 patients had undergone major surgery with reconstructive surgery in our division. Seventy five of these patients were over 75 years old, ranging from 75 to 90. The oldest patient who was treated with microsurgical reconstructive surgery was 87 years old. There were one serious postoperative complications in 264 cases. With the increasing numbers of high-risk patients, we need to establish a treatment policy for these patients in due course.

Our divisions performed neck dissection, total pharyngo-laryngo-esophagectomy with or without micro-surgical reconstructive surgery and various other surgical procedures in cooperation with other divisions. Over 10 patients have been operated on for other divisions in this year.

Our outpatient service is available from Monday to Friday, and the total number of newly registered patients has exceed 400 annually. The number of new patients in 2011 was similar to 2010. Endoscopic examinations and pharyngo-radiography are routinely performed once a week, and cervical echography twice a week. A weekly clinical head and neck conference is held every Tuesday attended by the head and neck surgeons, radio-oncologists, plastic surgeons, and a dentist. A clinico-pathological meeting is held every Friday to clarify and comprehend the oncological behavior of head and neck tumors.

Research Activities

Our divisions are taking part in multi-institutional studies related to neck dissection and the standardization of function preservation therapeutic strategy for head and neck carcinoma. Although neck dissection in our field is a very popular surgical procedure, the standard therapy has not been established until recently. Our divisions are currently investigating the neck dissection area and recurrences of oral cavity carcinoma, and taking part in multi-institutional studies of sentinel lymph node examination of tongue cancer from this year. There is currently no established standardized function-preserving treatment for head and neck carcinoma that will have an improvement on survival, loco-regional control, and preservation of various functions necessary for life. We conducted a research on the relationship between treatment procedures and the

pattern of recurrence/metastasis of various primary sites of head and neck carcinoma, and came up with the best treatment method with function preservation for each patient.

Clinical Trials

Our divisions were able to perform partial laryngectomy in 2 cases of supraglottic carcinoma and partial hypo-pharyngectomy with free radial forearm flap or free jejunum in 7 cases of pyriform sinus and posterior wall hypopharyngeal carcinoma. Voice function was able to be preserved in all the cases. We have started endoscopic mucosal resection (EMR) for small and superficial hypopharyngeal carcinomas in corporation with the Endoscopic Division from 2006, and 19 cases were treated in 2011. The rate of voice preservation surgery of hypopharyngeal cancer was very high (74%), probably No. 1 in Japan.

Table 1. Number of patients for each primary site (surgical treatment only)

Tongue	29
Mesopharynx	22
Hypopharynx	35
Larynx	9
Oral cavity (without tongue)	32
Nasal and paranasal cavity	11
Thyroid	16
Major salivary gland	12
Neck metastasis (primary unknown, eyelid, melanoma, etc.)	18
Others	2
Total	186

Table 2. Type of procedures

Glossectomy (partial, hemi, subtotal) (+ reconstruction)	29 (6)
Resection of mesopharyngeal tumor (+ reconstruction)	22 (8)
Total pharyngolaryngectomy (TPLE) (+ reconstruction)	9 (9)
Partial hypopharyngectomy (preserve larynx) (+ reconstruction)	7 (6)
EMR	19
Total laryngectomy	8
Partial laryngectomy	0
Extended resection of larynx (+ reconstruction)	1 (1)
Resection of tumor of oral cavity (+ reconstruction)	32 (5)
Maxillectomy (+ reconstruction)	11 (4)
Thyroidectomy (hemi, total)	16
Parotidectomy, etc.	12
Neck dissection	18
Neck tumor	1
Reconstruction and plastic surgery only	16
Tracheotomy	5
Lymphadenectomy	55
Others	3
Total	264

Table 3. Operative morbidity and mortality

Major complications *(major leakage, bleeding, flap necrosis, etc.)*	1 cases (0.4% in total, 1 [2.2%] in 45 major surgeries)
Minor complications *(high fever, infection, pneumonia, minor leakage, etc.)*	10 cases (3.8%)
Operative death within 30 days	0 cases
Postoperative hospital death	0 cases

DEPARTMENT OF HEAD AND NECK ONCOLOGY AND PLASTIC AND RECONSTRUCTIVE SURGERY, PLASTIC AND RECONSTRUCTIVE SURGERY DIVISION

Shimpei Miyamoto, Shuji Kayano, Minoru Sakuraba, Shogo Nagamatsu, Hiroki Umezawa

Introduction

The Plastic and Reconstructive Surgery Division 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 flap, local flap, skin graft and so on are used for reconstructive surgery. The objectives of reconstructive surgery are not only the morphological reconstruction, but also the restoration of postoperative function after ablative surgery. The quality of life (QOL) of the patient can be improved by the dual reconstructive approach to restore function and morphology.

Routine Activities

Two plastic surgeons cover reconstructive operations. Every week three to five reconstructive operations are performed. These reconstructive surgeries are performed in cooperation with the surgeons of another division of hospital, such as Head and Neck Surgery, Orthopaedic Surgery, Esophageal Surgery, Breast Surgery, Dermatology, and so on. We started immediate breast reconstruction with autologous tissue transfer from April, 2010, and the number of the patients who receive breast reconstruction is increasing. Limb reconstruction after limb preservation surgery has increased in accordance with the establishment of the Sarcoma Treatment Group.

Research Activities

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 quality of life 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 of reconstructive surgery and developing new techniques of reconstructive surgery are the most important aims of our studies.

A multi-institutional analysis of postoperative function after total pharyngolaryngectomy is now going on. This study is supported by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan. The aim of the study is to clarify the relationship between operative procedures and postoperative swallowing functions.

Other developments of reconstructive procedures in cooperation with the other divisions such as orthopedic surgery, breast surgery, et cetera, are ongoing.

Table 1. Cooperative projects with other divisions

Head & Neck surgery	50
Orthopaedic surgery	32
Esophageal surgery	11
Breast surgery	77
Dermatology	8
Urologic surgery	0
HB&P surgery	7
Ophthalmic surgery	0
Colorectal surgery	2
Gastric surgery	0
Thoracic surgery	0
Neurosurgery	1
Gynecology	2
Total	190

Table 2. Operative Procedures

Microvascular free flap	111
DIEP	35
Anterolateral thigh	24
Jejunum	22
Latissimus Dorsi	12
RAMC	8
Scapula bone	6
Fibula bone	3
Other flaps	1
Other Microsurgery	18
Supercharge	5
Nerve Graft	1
Limb Salvage	3
Hepatic Artery	7
Others	2
Subtotal	129
Pedicled flaps	43
Latissimus Dorsi	22
PM or PMMC	7
RAMC	3
Anterolateral thigh	3
Other flaps	8
Other Procedures	62
Total	227

Published Papers

1. Miyamoto S, Sakuraba M, Asano T, Hayashi R, Ebihara M, Miyazaki M, Daiko H, Shinozaki T, Kimata Y. Free jejunal patch graft for reconstruction after partial hypopharyngectomy with laryngeal preservation. Arch Otolaryngol Head Neck Surg, 137:181-186, 2011
2. Miyamoto S, Sakuraba M, Nagamatsu S. Reconstruction after partial hypopharyngectomy with larynx preservation. Plast Reconstr Surg, 128:327-328, 2011
3. Miyamoto S, Sakuraba M, Nagamatsu S. Reliable option for salvage pharyngoesophageal reconstruction. Plast Reconstr Surg, 127:1734-1735, 2011
4. Miyamoto S, Sakuraba M, Nagamatsu S, Hayashi R. Current role of the iliac crest flap in mandibular reconstruction. Microsurgery, 31:616-619, 2011
5. Miyamoto S, Sakuraba M, Nagamatsu S, Hayashi R. Salvage total pharyngolaryngectomy and free jejunum transfer. Laryngoscope, 121:947-951, 2011

DEPARTMENT OF BREAST ONCOLOGY AND MEDICAL ONCOLOGY, BREAST AND MEDICAL ONCOLOGY DIVISION

Yasuhiro Fujiwara, Masashi Ando, Kenji Tamura, Chikako Shimizu, Kan Yonemori, Mayu Yunokawa, Makoto Kodaira

Introduction

The Breast and Medical Oncology Division is engaged in the clinical management and research of adult malignancies including breast cancer, gynecologic cancer, soft-tissue sarcoma, tumors of unknown primary sites and other rare types of solid tumors. Our activities involve patient care, clinical and translational research, and the education of young oncologists and co-medical staff.

Our goal is to provide comprehensive, state-of-the-art medical care to individual patients. An evidence-based, research-oriented and multi-disciplinary approach is the core value of our practice.

Routine Activities

Our Division consists of seven full-time attending physicians, two part-time staff physicians, two chief residents and one - three clinical residents. We also provide educational opportunities for short-term residents. Full-time attending physicians are on duty at the outpatient clinic one to three days a week. Residents, especially chief residents, are encouraged to take leadership in the clinical management of inpatients. They also undertake clinical and translational research projects under the supervision of attending physicians. Three board-certified Breast Cancer Specialist Nurses help provide seamless and comprehensive care to breast cancer patients. A pharmacist and a pharmacy resident routinely support patients receiving chemotherapy.

Most patients are treated in an outpatient setting in cooperation with the Ambulatory Chemotherapy Center and Pharmacy Division. New patients are referred from both inside and outside the NCCH. Terminally-ill patients are transferred to palliative care units outside the NCCH. 19 patients passed away in 16A ward in 2011. Other patients were referred to outside hospices or in-home care clinics. Post-operative patients have been encouraged to be referred to local breast cancer specialists participating in the Tokyo Breast Consortium network (http://breastcons.com/).

We regularly have 30-40 inpatients. The Briefing Conference is held every morning to discuss the up-to-date, evidenced-based care for individual patients. A Breast Cancer Specialist Nurse in the clinic and pharmacists attends those conferences. A Grand Round is scheduled every Monday, Wednesday, and Friday and a Phase I conference is held every Monday.

We are supporting the “Cosmetic Program” which encourages self-support for change of appearance due to cancer treatments since 2005. The program is held every 2nd and 4th Wednesday in the 16A-Ward and at the clinic in addition to occasional consultations from other wards by the Appearance Support Team.

Multidisciplinary Case Conferences with diagnostic radiologists, surgeons, and pathologists are held once a week for breast and gynecologic cancer patients. A Breast Cancer Conference is held once a month with the participation of the multidisciplinary specialists to discuss recent topics and new research results in breast oncology and to develop institutional treatment guidelines. The treatment guidelines for primary breast cancer were updated in 2011 following multidisciplinary discussion and distributed as a pocket booklet. The treatment guidelines for metastatic breast cancer are now under revision.

Research Activities

The goal of our research activities is to develop new therapeutic strategies for adult solid tumors based on the biology of neoplasia. We value cancer survivorship not only in the clinic but also as themes of research to develop comprehensive care program. We have conducted several retrospective chart reviews and qualitative studies focusing on fertility issues, appearance, spiritual needs and end-of-life care.

We continued to put our efforts into phase I studies by enhancing team communication through the Phase I conference. An investigator-initiated registration-directed trial that aims to evaluate the activity of carboplatin in HER-2 negative breast cancer in the preoperative setting has terminated its accrual in Autumn, 2011. We actively participate in

global trials as well as studies of national multi-institute clinical trialists' groups such as the Japan Clinical Oncology Group (JCOG), JGOG (the Japanese Gynecologic Oncology Group), and the Japan Breast Cancer Research Group (JBCRG). With the cooperation of Shien Lab, the Research Institute, or other multi-institutional research groups, we have launched several translational research programs that aim to discover biomarkers for patient enrichment, drug-resistance, and potential drug targets. We initiated a clinical study to explore SNPS related to taxane-induced peripheral neuropathy in cooperation with the Tokyo Metropolitan Institute of Medical Science in 2011. A ^{64}Cu-labeled trastuzumab molecular imaging study in cooperation with the RIKEN Center for Molecular Imaging Science is in steady progress since its kick-off in 2010. Other clinical studies including the above-mentioned trials are listed in Table 2.

Table 1. Demographics of Patients at their 1st Visit to the Clinic of the Breast and Medical Oncology Division (Jan-Dec, 2011)

No of 1st Visits	n	%
Total	700	
Breast	372	53
GYN	141	20
Cancer of primary unknown	96	14
Sarcoma	54	8
Others	37	5
Purpose of consultation		
2nd opinion	37	5
Treatment at NCCH	162	23
Referrals from other hospitals	130	19
Referrals from other divisions in NCCH	371	53
Breast surgery	256	
GYN	73	
Urology	6	
Orthopedics	7	
Others	29	
Others	0	0

Published Papers

1. Hashimoto K, Yonemori K, Shimizu C, Hirakawa A, Yamamoto H, Ono M, Hirata T, Kouno T, Tamura K, Katsumata N, Ando M, Fujiwara Y. A retrospective study of the impact of age on patterns of care for elderly patients with metastatic breast cancer. Med Oncol, 28:434-440, 2011
2. Tamura K, Shimizu C, Hojo T, Akashi-Tanaka S, Kinoshita T, Yonemori K, Kouno T, Katsumata N, Ando M, Aogi K, Koizumi F, Nishio K, Fujiwara Y. FcgammaR2A and 3A polymorphisms predict clinical outcome of trastuzumab in both neoadjuvant and metastatic settings in patients with HER2-positive breast cancer. Ann Oncol, 22:1302-1307, 2011
3. Katsumata N, Hirai Y, Kamiura S, Sugiyama T, Kokawa K, Hatae M, Nishimura R, Ochiai K. Phase II study of S-1, an oral fluoropyrimidine, in patients with advanced or recurrent cervical cancer. Ann Oncol, 22:1353-1357, 2011
4. Hirata T, Yonemori K, Ando M, Hirakawa A, Tsuda H, Hasegawa T, Chuman H, Namikawa K, Yamazaki N, Fujiwara Y. Efficacy of taxane regimens in patients with metastatic angiosarcoma. Eur J Dermatol, 21:539-545, 2011
5. Yonemori K, Hirakawa A, Ando M, Hirata T, Shimizu C, Katsumata N, Tamura K, Fujiwara Y. Compliance with Good Clinical Practice in oncology registration trials in Japan. Ann Oncol, 22:1451-1456, 2011
6. Tanioka M, Katsumata N, Yonemori K, Kouno T, Shimizu C, Tamura K, Ando M, Fujiwara Y. Second platinum therapy in patients with uterine cervical cancer previously treated with platinum chemotherapy. Cancer Chemother Pharmacol, 68:337-342, 2011
7. Yonemori K, Hirakawa A, Ando M, Hirata T, Yunokawa M, Shimizu C, Katsumata N, Tamura K, Fujiwara Y. The notorious "drug lag" for oncology drugs in Japan. Invest New Drugs, 29:706-712, 2011
8. Ono M, Ando M, Yonemori K, Yamamoto H, Hirata T, Shimizu C, Tamura K, Katsumata N, Fujiwara Y. Second-line chemotherapy in patients with primary unknown cancer. J Cancer Res Clin Oncol, 137:1185-1191, 2011
9. Yonemori K, Tsuta K, Ando M, Hirakawa A, Hatanaka Y, Matsuno Y, Chuman H, Yamazaki N, Fujiwara Y, Hasegawa T. Contrasting prognostic implications of platelet-derived growth factor receptor-β and vascular endothelial growth factor receptor-2 in patients with angiosarcoma. Ann Surg Oncol, 18:2841-2850, 2011
10. Aogi K, Masuda N, Ohno S, Oda T, Iwata H, Kashiwaba M, Fujiwara Y, Kamigaki S, Ito Y, Ueno T, Takashima S. First-line bevacizumab in combination with weekly paclitaxel for metastatic breast cancer: efficacy and safety results from a large, open-label, single-arm Japanese study. Breast Cancer Res Treat, 129:829-838, 2011
11. Hirata T, Yonemori K, Hirakawa A, Shimizu C, Tamura K, Ando M, Katsumata N, Tanimoto M, Fujiwara Y. Efficacy of pleurodesis for malignant pleural effusions in breast cancer patients. Eur Respir J, 38:1425-1430, 2011
12. Hashimoto K, Yonemori K, Katsumata N, Hirakawa A, Hirata T, Yamamoto H, Shimizu C, Tamura K, Ando M, Fujiwara Y. Use of squamous cell carcinoma antigen as a biomarker of chemotherapy response in patients with metastatic cervical carcinoma. Eur J Obstet Gynecol Reprod Biol, 159:394-398, 2011
13. Katsumata N. Dose-dense therapy is of benefit in primary treatment of ovarian cancer? In favor. Ann Oncol, 22 Suppl 8:viii29-viii32, 2011
14. Fujiwara Y. Genomics, health care, and society. N Engl J Med, 365:2339, 2011

Table 2. Active Clinical Trials (Jan. 2011-Dec. 2011)

Disease	Clinical setting	Phase	Protocol	Regimen	status
Breast	Adjuvant	III	BEATRICE	CTx vs CTx + bevacizumab	Active, not recruiting
		III	ALTTO	lapatinib vs HCN vs lapa/HCN	Active, not recruiting
		III	CREATE-X	capecitabine vs none post-NAC	Active
		III	D-CARE	Denosumab vs placebo	Active
	NAC	R-II	CBDCA (IND trial)	neo.PTX +/- CBDCAf/b FEC	Active
		III	JCOG1017	Surgery vs no surgery for primary Stage IV BC	Active
		III	denosumab vs zolodronate	denosumab vs zolodronate	Active
		III	MARIANNE	RO5304020+/- RO4368451 vs HCN/PTX	Active
		III	RAD001	exemestane +/- RAD001	Active, not recruiting
	Metastatic	III	HKI272 (Neratinib)	HKI272 vs lapa/capecitabine	Active, not recruiting
		II	Avastin/PTX	bevacizumab/paclitaxel	Active, not recruiting
		II	ABI-007	ABI007 vs DTX	Active
		II	RO5304020	RO5304020	Active
		II	lapaHER	lapatinib/HCN	Active
		I/II	CAPIRI	capecitabine/CPT-11	Active
		I/II	S1/docetaxel	S1/docetaxel	Active
		Ib	RO5304020/RO4368451	RO5304020/RO4368451	Active
Ovary	Advanced	III	JCOG0602	primary surgery vs NAC	Active
		III	JGOG3017	TC vs. CDDP/CPT-11	Active
		III	GOG213	TC +/- bevacizumab	Active
		III	GOG218 (RDT)	TC +/- bevacizumab	Active
		III	AMG386	PTX+/-AMG386	Active
		III	GW786034	pazopanib	Active
		II	AZD2281	TC +/- Olaparib	Active
		II	JCOG0503	CPT-11/oral etoposide	Active
		I	BIBF	BIBF/CBDCA/Doxil	Active
Endometrial cancer	Advanced	III	JGOG2043	AP vs. DP vs. TCP	Active
	Advanced	III	JCOG0505	TC vs. TP (1st line)	Active
Cervical cancer	Advanced	III	S1/CDDP	S1/CDDP vs CDDP (1st line)	Active
		II	BKM120	BKM120	Active
		I	S1/CDDP	S1/CDDP chemoradiation	Active
		Feasibility	S1/CDDP	S1/CDDP	Active
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	MORAb-003	MORAb-003	Active
		I	MK2206	MK2206	Active
		I	MK4827	MK4827	Active
		I	AZD5363	AZD5363	Active
Soft tissue sarcoma		I	ET-743	ET-743	Active
CIPN SNPs		translational	Paclitaxel induced peripheral neuropathy	Paclitaxel	Active
Molecular Imaging		0	Molecular imaging JST/MEXT-	nano-dose, radio-labeled trastuzumab	Active

DEPARTMENT OF BREAST ONCOLOGY AND MEDICAL ONCOLOGY, BREAST SURGERY DIVISION

Takayuki Kinoshita, Sadako Akashi, Takashi Hojo, Sota Asaga, Junko Suzuki, Eriko Iwamoto, Nobuko Tamura, Kenjiro Jimbo

Introduction

The Breast Surgery Division deals with treatment of breast cancer, as well as diagnosis of breast diseases and lymph nodes in the axillary and clavicular region which are suspected of being metastatic foci. There was a remarkable change in surgical methods this year. In cooperation with plastic surgeons, immediate breast reconstruction became one of the choices for breast cancer patients since April 2010. While the percentage of breast-conserving surgery decreased to 51.0%, a total of 74 immediate breast reconstructions were performed in 2011, which comprised more than 14% of all the cases. Sentinel lymph node (SLN) biopsies were performed in 81.4% of the cases. Among these cases after SLNB, 71.9% of the cases (58.5% of all the cases) could omit axillary lymph node (ALN) surgery with negative SLN findings. In conjunction with the one-step nucleic acid amplification (OSNA) assay, more positive nodes, including micrometastases, have been detected, compared to traditional diagnosis by frozen section alone, and 28.1% of the cases after SLNB needed additional ALN dissection.

Routine Activities

This Division consists of four staff surgeons, two chief residents, and three or four rotating residents. There have been 3 staff surgeons till March, two new staff breast surgeons joined in April, and one surgeon left in September.

All the staff and the residents go the rounds together for all the inpatients from 7:30 every morning. A journal club and research conference are scheduled for every Tuesday morning after rounds. A weekly conference is held on Wednesdays from 17:00 to 19:00 for shared discussions with surgeons, medical oncologists, radiologists, and medical and radiological technologists. The diagnostic images of pre-operative patients are reviewed and compared to pathological reports in every post-operative patient. A breast pathology conference is held on the last Wednesday of each month from 18:00 to 18:30 to discuss a monthly theme (e.g., problems with diagnostic imaging, pathologically interesting cases). A conference about studies, institutional treatment guidelines and recent topics regarding breast cancer is held once a month by a multidisciplinary team. Treatment Guidelines for primary and metastatic breast cancer have been updated regularly through this multidisciplinary discussion since 2003, and they were updated in 2010.

Breast-Conserving Therapy (BCT) usually consists of local excision of the tumor followed by postoperative irradiation of the remaining breast. BCT is indicated for a tumor smaller than 3 cm. Patients with multi-focal lesions or extensive micro-calcifications detected by mammography are not suitable for BCT. Neo-adjuvant chemotherapy (NAC) and neo-adjuvant endocrine therapy (NAET) for operable advanced breast cancer are performed to avoid mastectomy and to test the sensitivity to therapeutic agents. This year, NAC or NAET was performed in about 11% of all patients. Patients receive adjuvant chemo-endocrine therapy depending upon their prognostic and predictive factors, which include the number of lymph nodes involved, histological grade of the tumor and secondary prognostic markers (HER2/neu, ER, PgR, etc.). Widely accepted factors that predict a response to a specific therapy are estrogen and progesterone receptors for hormone therapy and HER2 for trastuzumab.

Research Activities

New protocols for evaluating the survival merit of primary tumor removal in patients with metastatic breast cancer (Dr. Kinoshita) and the efficacy of sentinel lymph node biopsies after neoadjuvant chemotherapy for primary breast cancer patients who are node-positive (Dr. Hojo) are under consideration. With the recent advance in the development of an aromatase inhibitor, neoadjuvant endocrine therapy (NAET) may become the standard-bearer of tailored treatment. We have conducted a prospective neoadjuvant endocrine study since 1998. A new protocol to evaluate the optimal duration of NAET (4 M vs 6 M) has started (PTEX46). As indications for NAC

become more widespread, the question arises if SLNB is appropriate for axillary staging in patients after NAC. The accuracy and feasibility of SLNB after NAC have been evaluated (Kinoshita et al.). A feasibility study to establish the standard surgery for breast tumors using diagnostic images during surgery in an MRX operating room is ongoing (Hojo et al.). A study to evaluate the utility of the impact of supine MRI on surgical decision making was conducted. Supine MRI had more accuracy in the measurement of invasive ductal carcinoma compared to prone MRI, suggesting the usefulness of supine MRI before breast conserving surgery (Kinoshita et al.). A feasibility study using Real-time Virtual Sonography (RVS) is also being planned for breast conserving surgery. RVS can synchronize the US images and the MRI or CT images using a position tracking system with a magnetic sensor. It is thought to be useful for making an accurate excision line when US cannot detect suspicious daughter lesions or intraductal spread as identified on MRI or CT imaging.

Table 1. Number of patients

		n
Primary breast cancer		497
c Stage	0	100
	I	186
	II	180
	III	29
	IV	1
	unknown	1
Other malignant breast disease		1

Clinical Trials

1) Radiofrequency ablation (RFA)
Non-surgical therapy for early breast cancer has recently attracted attention. We started a Phase 3 trial of image-guided radiofrequency ablation which has been ongoing for early-stage breast carcinomas of less than 1 cm in diameter.
2) Denosumab adjuvant treatment (D-CARE)
A phase 3 multi-center, randomized, double blind, placebo controlled study has started. This study is 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.
3) 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 in order to slow or halt hair loss during chemotherapy.
4) Sentinel lymph node (SLN) biopsy
A multi-center feasibility study to test the SLN identification rate using radioisotope (RI) vs indocyanine green (ICG) has started.

Table 2. Type of procedure

	2007		2008		2009		2010		2011	
Total number of operations	546		462		462		482		576	
Mastectomy (%)	249	(46.7)	197	(44.0)	209	(45.6)	213	(44.2)	250	(47.6)
Breast-conserving surgery (%)	284	(53.3)	251	(56.0)	249	(54.4)	269	(55.8)	269	(51.2)
Radiofrequency ablation (%)									6	(1.1)
Axillary lymph node dissection (ALND) (%)	155	(29.1)	100	(22.3)	89	(19.4)	136	(28.2)	205	(41.5)
Sentinel lymph node biopsy (SLNB) (%)	373	(70.0)	342	(76.3)	368	(80.3)	316	(65.6)	402	(81.4)
ALND after SLNB (%)									113	(22.9)
Immediate breast reconstruction (%)	0		0		0		13	(2.7)	74	(14.1)
Neoadjuvant therapy	70	(13.1)	108	(24.1)	105	(22.9)	72	(14.9)	57	(10.9)

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DEPARTMENT OF THORACIC ONCOLOGY, THORACIC SURGERY DIVISION

Hisao Asamura, Shun-ichi Watanabe, Hiroyuki Sakurai, Mitsumasa Kawago

Introduction

The Thoracic Surgery Division 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 division has four attending surgeons. Three subteams with attending surgeons and residents perform all of the inpatient care, operations, examinations, and outpatient care. In 2011, we performed a total of 520 operations; for lung cancer in 378 patients, metastatic tumor in 83, mediastinal tumor in 19, and others in 40.

The first year of our two-year fellowship program is devoted to patient care as a chief resident, and the second year is devoted to clinical/basic research. We have annually adopted one or two residents who want to major in general thoracic surgery.

In addition to weekly division meetings for the preoperative evaluation and postoperative inpatient review on Friday and for the journal club on Wednesday, the chest group has a plenary meeting to share basic information about the current issues for diagnosis and treatment of patients with lung malignancy on Thursday.

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. 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 recently adopted video-assisted resection of the tumor. VATS resection of mediastinal tumor is indicated exclusively for small thymomas.

Research Activities

We started a new modality, radiofrequency ablation (RFA), for malignant tumors of the lung in 2007. This modality should be effective for patients in whom it would be difficult to perform surgical resection, radiotherapy, or chemotherapy because of their poor risk. We are now conducting a clinical trial to evaluate the feasibility of RFA for poor-risk patients with malignant tumors of the lung. More than 100 patients have enrolled so far.

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 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 total, 40 cases and 31 cases have been registered for JCOG 0802 and 0804 from our division, respectively.

As for postoperative adjuvant therapy, a phase III clinical trial to compare the effectiveness of UFT with that of TS-1 for stage IA more than 2 cm and IB NSCLC planned in JCOG (JCOG 0707) has been conducted since 2008. Twenty six cases have been registered for this trial from our division.

Lung cancer consists of non-small (NSCLC) and small cell lung cancer (SCLC). Large cell carcinoma, which is one of the most common histologies of lung cancer, has been classified as NSCLC. Recently, some large cell carcinomas have been reported to have neuroendocrine features, and this lung cancer is called "large cell neuroendocrine carcinoma (LCNEC)". Sometimes it is difficult to discriminate the histology of LCNEC from that of SCLC. Asamura et al. reported the prognosis of resected LCNEC of the lung. The prognosis of this histology is similar to that of SCLC, and this report stated that both SCLC and LCNEC should be classified into the same category: "high-grade neuroendocrine tumor". The appropriate management of LCNEC is going to be investigated, and the role of adjuvant chemotherapy following resection should be discussed in the near future. A phase II clinical trial of adjuvant chemotherapy for LCNEC is on-going.

(by Shun-ichi Watanabe)

Table 1. Number of patients

Primary lung cancer	378
Metastatic lung tumor	83
Mediastinal tumor	19
Pleural disease	8
Chest wall tumor	6
Benign lung nodule	15
Others	11
Total	520

Table 2. Type of procedure

Lung resection	458
Lobectomy	281
Pneumonectomy	7
Segmentectomy	62
Wedge resection	108
Tracheal resection	0
Surgery for mediastinal tumors	21
Surgery for pleural tumors	14
Surgery for chest wall tumors	8
Others	19
Total	520

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

Pathological stage (TNM-7)	No. of pts	5-yr survival (%)
IA	723	92.7
IB	210	83.9
IIA	195	67.7
IIB	118	70.9
IIIA	222	41.1
IIIB	13	34.6
IV	39	22.8
Total	1,520	

Operation period: 2000.1-2004.12

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DEPARTMENT OF THORACIC ONCOLOGY, THORACIC ONCOLOGY DIVISION

Tomohide Tamura, Noboru Yamamoto, Hiroshi Nokihara, Shintaro Kanda, Hidehito Horinouchi, Shinji Nakamichi

Introduction

The incidence of lung cancer in Japan is increasing, especially in the female and elderly populations, and lung cancer has been the most common death from cancer since 1994. The majority of lung cancer patients are diagnosed at the advanced stage, and the prognosis of these patients is still poor. The goals of the Thoracic Oncology Division are to provide the highest quality treatment and to establish new effective treatments against lung cancer and other thoracic malignancies.

The Thoracic Oncology Division includes 6 staff physicians. A total of 3 chief residents, 8 residents, 2 short-term residents and 2 trainees joined the division during 2011. The Phase I Study Group was organized in 1996. Three staff physicians and 1 chief resident of the Thoracic Oncology Division are also core members of the Phase I Study Group.

Routine Activities

The staff physicians attend outpatient services for thoracic diseases, and the division has approximately 80 beds in the hospital. Inpatient care is carried out by five teams. Each team consists of one staff physician and one or two chief resident/resident/trainee.

Protocol and case conferences are scheduled every Monday morning and afternoon, respectively. The journal club is scheduled on Thursday mornings. The chest conference is held on Thursday evenings to discuss cases with thoracic surgeons, pathologists, radiologists and radiation oncologists.

A total of 305 new patients were admitted in 2011. The diagnosis for these patients and initial treatments for 260 lung cancer patients are listed in Tables 1-2. Thirty-six percent of 208 lung cancer patients receiving chemotherapy or chemoradiotherapy as their initial treatments participated in clinical trials. Survival outcomes of lung cancer patients treated in the Division are shown in Table 3. For the Phase I Study Group, 64 patients with miscellaneous solid tumors were admitted and participated in 10 phase I studies.

Research Activities

The Research activities of the Thoracic Oncology Division can be divided into five subjects: (1) multi-institutional phase III studies to establish new standard treatments against thoracic malignancies; (2) phase I/II studies to develop new effective chemotherapy regimens including new drugs against thoracic malignancies; (3) phase I studies to evaluate new drugs against solid tumors; (4) pharmacokinetic and pharmacodynamic (PK/PD) studies to investigate interpatient variability and optimal drug exposure; and (5) translational research for the development of biomarkers and innovative treatment strategies.

Clinical Trials

Clinical trials carried out in 2011 are shown in Table 4. Some studies were based on the JCOG research program, and some were carried out under contract with pharmaceutical companies.

Table 1. Number of New Inpatients in 2011

Non-small cell lung cancer	217
Adenocarcinoma	170
Squamous cell carcinoma	29
Others	18
Small cell lung cancer	43
Mesothelioma	6
Thymic cancer	5
Others	34
Total	305

Table 2. Initial Treatments for New Inpatients with Lung Cancer in 2011

Chemotherapy	174
Chemoradiotherapy	34
Adjuvant chemotherapy following surgery	25
Preoperative chemoradiotherapy	2
Thoracic radiotherapy	5
Supportive care alone (including palliative radiotherapy)	20
Total	260

Table 3. Survival Outcomes

Non-small cell lung cancer			
Unresectable stage III	204 patients treated with concurrent chemoradiotherapy in 1994-2005	Median	24.0 mo
		1-Year	75.5 %
		3-Year	34.7 %
		5-Year	22.8 %
Stage IV	480 patients treated with initial chemotherapy in 2000-2006	Median	13.2 mo
		1-Year	52.7 %
		3-Year	14.8 %
		5-Year	13.1 %
Small cell lung cancer			
limited disease	50 patients treated with concurrent chemoradiotherapy in 2001-2004	Median	28.8 mo
		2-Year	60.0 %
		5-Year	31.7 %
Extensive disease	108 patients treated with initial chemothrapy in 2001-2004	Median	12.1 mo
		2-Year	15.7 %
		3-Year	5.6 %

Table 4. Clinical Trials in 2011

Target disease	Stage	Phase	Treatment
NSCLC	Advanced	III	S-1 vs. DTX
NSCLC	Advanced	III	PF-00299804 vs. Erlotinib
NSCLC-ALK fusion	Advanced	III	PF-02341066 vs. PEM/CDDP
NSCLC-ALK fusion	Advanced	II	PF-02341066
NSCLC-EGFR mutation	Advanced	II	Erlotinib vs. Erlotinib/Bevacizumab
NSCLC-LCNEC	Advanced	II	CDDP/CPT-11
NSCLC	Advanced	II	Erlotinib vs. Erlotinib/ARQ197
NSCLC-ALK fusion	Advanced	I/II	CH5424802
NSCLC	Advanced	I	CBDCA/PTX+Ipilimumab
NSCLC	Locally advanced	II	CDDP/VNR+high-dose TRT
NSCLC	Locally advanced	II	CDDP/PEM+TRT
NSCLC	Locally advanced	I/II	EMD531444
NSCLC	Post operative	III	JCOG0707: S-1 vs. UFT
SCLC	Extensive	III	PCI vs. observation
SCLC	Recurrent	III	JCOG0605: wkly CDDP/ETP/CPT-11 vs. NGT
SCLC	Recurrent	II	AMR
SCLC	Limited	ii	JCOG1101: CRT- CDDP/AMR vs. CODE
Lung cancer	Advanced	II	CDDP short hydration
Lung cancer	Advanced	PK/PD	AMR
Lung cancer	Advanced	Translational	Circulating endothelial cells
Sokid tumor (Phase I study group)	Advanced	III	Antiemetics
Solid tumor	Advanced	I	10 New agents

DTX; docetaxel, CDDP; cisplatin, PEM; pemetrexed, CPT-11; irinotecan, CBDCA; carboplatin, PTX; paclitaxel, TRT; thoracic radiotherapy, VNR; vinorelbine, AMR; amurubicin, PCI; prophylactic cranial irradiation, EPT; etoposide, NGT; nogitecan, CRT; chemoradiotherapy, CODE; CDDP/vincristine/doxorubicin/etoposide

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DEPARTMENT OF THORACIC ONCOLOGY, RESPIRATORY ENDOSCOPY DIVISION

Takaaki Tsuchida, Shinji Sasada

Introduction

In the field of bronchoscopy, bronchoscopic treatments are coupled with computerized tomography (CT) for the treatment of airway stenosis, minute peripheral lung cancer, and so on. 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

A weekly film-reading conference is held. Furthermore, we attend all clinical conferences in the Surgery, Oncology, Radiology and Pathology Divisions to discuss and decide upon treatment strategies. Four hundred and eighteen cases of transbronchial biopsy were performed. Twenty five cases of bronchio-alveolar lavage were performed. Endobronchial ultrasonography (EBUS) is used not only to evaluate mediastinal or hilar malignant lesions but also to evaluate whether the biopsy devices could lead to the occurrence of peripheral lung lesions. Fifty four cases of EBUS-TBNA (EBUS-trans bronchial needle aspiration) were performed as a less invasive procedure to improve diagnosis for patients with mediastinal or hilar lymph node swelling. Ten endobronchial lesions were treated with endobronchial ablation (2 cases), tracheobronchial prosthesis (6 cases), and transbronchial resection (2 cases).

Research Activitiesa

Our efforts have been focused on new diagnostic and therapeutic strategies including bronchoscopy, which involve CT-screening for lung cancer and lead to cure and less-invasive treatments for lung cancer. To achieve a more accurate endoscopic diagnosis for solitary peripheral lung nodules, we are using three-dimensional computed tomography (3D-CT) navigation, an ultrasound-guided approach and onsite cytology. With 3D-CT navigation and/or the ultrasound-guided approach and onsite cytology, the accuracy and sensitivity of transbronchial biopsy could be improved. To evaluate pleural malignancy or metastasis, we started to perform medical thoracoscopy at the operation suite.

Table 1. Number of patients

Adenocarcinoma	148
Squamous cell carcinoma	55
Small cell carcinoma	29
Other malignant tumor	46
Inflammation	64
Others	76
Total	418

Table 2. Type of procedure

Transbronchial biopsy	418
Conventional procedure	(276)
Endobronchial ultrasound	(142)
Observation	173
Bronchoalveolar lavage	25
Medical thoracoscopy	7
Ablation of tumor	2
Stent	6
Other therapies	2
Total	633

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, ESOPHAGEAL SURGERY DIVISION

Yuji Tachimori, Hiroyasu Igaki, Nobukazu Hokamura

Introduction

More than 300 new patients with esophageal tumors are admitted to the National Cancer Center Hospital every year. The multidisciplinary treatment plans are determined by the stage of the tumor in close cooperation with other teams. The Esophageal Surgery Division particularly cooperates with the Gastrointestinal Oncology Division and the Radiation Oncology Division for preoperative chemotherapy and chemoradiotherapy and salvage surgery after definitive chemoradiotherapy. We also maintain close cooperation with the Head and Neck Surgery Division for cervical esophageal carcinomas and with the Gastric Surgery Division for adenocarcinomas in the esophagogastric junction. In Japan, squamous cell carcinomas still constitute the largest proportion of esophageal tumors, and the proportion of adenocarcinomas was 5% in our institution in 2010.

Routine Activities

The Esophageal Surgery Division consists of three staff surgeons, one chief resident and three rotating senior residents. A multidisciplinary conference 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. A bimonthly conference for pretreatment clinical diagnosis and a pathology demonstration of resected esophageal tumors is held to discuss a wide range of topics.

Every week, three patients with esophageal cancer undergo esophageal surgery. One hundred twelve patients underwent esophagectomy including 3 patients with cervical esophageal cancer and 8 with adenocarcinoma in the esophagogastric junction, and also including two with melanoma and one with GIST. Of the 100 patients who underwent surgery as primary therapy, a curative resection was completed for 96%, which reflects strict preoperative staging, with three hospital deaths due to an operative complication. Preoperative chemotherapy was recommended for 45 patients and preoperative chemoradiotherapy was recommended for 25 patients with resectable Stage II-IV esophageal squamous cell cancer. A three-field dissection, including the whole upper mediastinum and supraclavicular in addition to the lower mediastinum and abdomen, is our standard procedure. Video-assisted thoracic surgery was introduced for esophagectomy as minimally invasive surgery in 39 patients. Increase of laryngeal nerve palsy is serious concern. Feasibility will be evaluated upon morbidity and survival results.

The number of patients who receive definitive chemoradiotherapy as their primary treatment for resectable tumor is decreasing after the report of a clinical trial on definitive chemoradiotherapy (JCOG9906). Persistent or recurrent local disease is not infrequent after chemoradiotherapy. Twelve patients underwent salvage esophagectomy after the failure of definitive chemoradiotherapy without surgery-related death in 2011. A three-field dissection is avoided for salvage esophagectomy.

Clinical Trials

The results of a multi-institutional randomized controlled trial (JCOG9907) confirmed preoperative chemotherapy with cisplatin and 5FU before esophagectomy as standard therapy for resectable Stage II-III esophageal cancer. Preoperative chemotherapy with docetaxel, cisplatin and 5FU and preoperative chemoradiotherapy with cisplatin, 5FU and 41.4 Gy irradiation were conducted as feasibility study for the next trial. In addition, a Phase II trial for definitive chemoradiotherapy with or without salvage esophagectomy (JCOG0909) was started. For a Stage I lesion, a multi-institutional randomized controlled comparison between surgery and definitive chemoradiotherapy (JCOG0502) is continuing registration.

Table 1. Type of surgery

Esophagectomy	100
Salvage esophagectomy	12
Gastric conduit cancer surgery	6
Tumor enucleation	1
Salvage lymphadenectomy	2
Bypass surgery	2
Cervical esophagostomy	1
Exploration	3

Table 2. Type of esophagectomy

Rt. thoracotomy with 3-field	53
Rt. thoracotomy with 2-field	12
Video-assisted with 3-field	31
Video-assisted with 2-field	8
Lt. thoracotomy	1
Transhiatal	1
Cervical	3
Abdominal	3

Table 3. Survival rates after esophagectomy

Clinical stages before preoperative chemo and/or radiotherapy	No. of pts	MST (mo)	5-yr survival (%)
cStage I	151	n.v.	76.8
cStage IIA	161	63	51.4
cStage IIB	124	128	67.2
cStage III	406	32	35.7
cStage IVA	35	14	14.3
cStage IVB	98	23	26.5

Operation period: 1997.1-2006.12 n.v.: not verified

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DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, GASTRIC SURGERY DIVISION

Hitoshi Katai, Takeo Fukagawa, Shinji Morita, Masaki Ohashi, Michihiro Ishida, Yukie Yoda

Introduction

This division 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 Division includes four staff surgeons, two chief residents and three or four rotating residents at any given time. Nine to eleven patients are operated upon every week. The Division shares a ward with the Gastrointestinal Medical Oncology Division, so that specialists from both divisions can treat patients with gastric cancer. 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.

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, medical oncologists 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 surgeons, endoscopists and radiologists 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 is to be an important function. In 2011, more than 20 surgeons from various countries visited this division for 2 weeks to 12 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. The Millennium Genomic Project, which entails the analysis of single nucleotide polymorphisms (SNPs) to investigate susceptibility to gastric cancer, is also ongoing. 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 in cooperation with Kyusyu University and Hamburg-Eppendorf University.

Clinical Trials

Our Division 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. Randomized controlled trials are currently underway in a multi-institutional setting. 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 carried out. JCOG0705 is a trial to evaluate the significance of reduction surgery. JCOG 1001 is designed to evaluate the significance of bursectomy for advanced cancer. This trial includes the evaluation of long-term survival, postoperative morbidity, and mortality. The JCOG 0912 phase III trial is a study to prove the non-inferiority of laparoscopic gastrectomy over its open counterpart for patients with clinical stage IA and IB gastric cancer. The JCOG1002, phase II study of systemic chemotherapy with Docetaxel, CDDP, and S-1 followed by surgery in advanced cancer with extensive lymph node metastasis has just started.

Table 1. Number of Patients

Adenocarcinoma	411
GIST	11
Others	29
Total	451

Table 2. Operative morbidity and mortality after gastrectomy

	Number of patients	%
Major complications	43	11.7
Minor complications	72	19.7
Postoperative hospital deaths	0	0
Total	366	100

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, line infection, etc.

Table 3. Operative Procedures

Distal gastrectomy	133
Total gastrectomy	115
Pylorus-preserving gastrectomy	54
Proximal gastrectomy	28
Wedge resection	10
Pancreaticoduodenectomy	1
Laparoscopic distal gastrectomy	16
Laparoscopic pylorus preserving gastrectomy	18
Laparoscopic total gastrectomy	1
Other (bypass, exploration, etc.)	75
Total	451

Table 4. Survival Rates

Stage	No. of patients	5-yr survival
IA	1766	94.2%
IB	545	91.4%
II	468	78.6%
IIIA	345	60.3%
IIIB	191	45.1%
IV	703	14.5%
Total	4018	73.4%

Stage: Japanese classification (13th ed.)
Period: 1995-2004

Published Papers

1. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol, 29:4387-4393, 2011
2. Isobe Y, Nashimoto A, Akazawa K, Oda I, Hayashi K, Miyashiro I, Katai H, Tsujitani S, Kodera Y, Seto Y, Kaminishi M. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. Gastric Cancer, 14:301-316, 2011
3. Yamashita H, Katai H, Morita S, Saka M, Taniguchi H, Fukagawa T. Optimal extent of lymph node dissection for Siewert type II esophagogastric junction carcinoma. Ann Surg, 254:274-280, 2011
4. Saka M, Morita S, Fukagawa T, Katai H. Present and future status of gastric cancer surgery. Jpn J Clin Oncol, 41:307-313, 2011
5. Tanaka N, Katai H, Saka M, Morita S, Fukagawa T. Laparoscopy-assisted pylorus-preserving gastrectomy: a matched case-control study. Surg Endosc, 25:114-118, 2011

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, COLORECTAL SURGERY DIVISION

Yoshihiro Moriya, Takayuki Akasu, Shin Fujita, Seiichiro Yamamoto, Ryo Inada

Introduction

The Colorectal Surgery Division deals with colorectal cancer and allied malignancies in the colon and rectum. Liver metastasis from colorectal cancer is treated in cooperation with the Hepatobiliary and Pancreatic Surgery Division. Although surgery is 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 Gastrointestinal Oncology Division, Endoscopy Division and Radiology Division every week, and discuss treatment plans for preoperative patients.

Routine Activities

There are four staff surgeons, one chief resident, and four or five rotating residents. Every morning (8:20-8:50), we have a morning conference and rounds in wards 8B and 15A, B. Every Tuesday evening (18:30-19:30), a conference is held for the diagnosis of colorectal cancer: colorectal surgeons, endoscopists, and radiologists discuss the diagnosis for preoperative patients. Every Wednesday evening (17:00-18:30), a conference is held for the treatment of colorectal cancer: colorectal surgeons and medical oncologists discuss treatments for preoperative and postoperative patients.

Twelve operations are performed a week in our division. Thus, we operate upon 600 patients with colorectal cancers and allied diseases annually. Patients with clinical stage I colon and rectal cancers mainly undergo laparoscopic surgery. Patients with clinical stage II or III colon cancer are treated with laparoscopic or conventional surgery. Other patients with T3 or T4 colon cancers are treated with conventional techniques or the no-touch isolation technique as part of a clinical traial (JCOG1006 study). Patients with advanced rectal cancers are treated with conventional surgery. Adjuvant chemotherapy is being used in stage III colorectal cancer patients in a clinical trial (JCOG0910 study). Although preoperative radiotherapy is not performed routinely for advanced rectal cancer, patients with T4 rectal cancers or rectal cancers with multiple lymph node metastases are treated with preoperative chemoradiotherapy and surgery. Patients with symptoms caused by nonresectable tumors are treated with palliative surgery including palliative resection, bypass, and stoma before chemotherapy. Patients with resectable liver metastasis are treated in cooperation with the Hepatobiliary and Pancreatic Surgery Division and adjuvant chemotherapy regimens are being evaluated in a clinical trial (JCOG0603 study).

Research Activities

As described in “Routine Activities”, clinical trials are integrated into our routine work. Four clinical trials are underway, and the details are described in “Clinical Trials”. We are evaluating new surgical procedures, including intersphincteric resection (ISR) for very low rectal cancer, laparoscopic surgery, and surgery for pelvic recurrence of rectal cancer. 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. In 2011, we published 5 papers, and the results of our research in 2011 are summarized as follows.

Clinical research

In multi-institutional retrospective and prospective studies, we clarified the indications of diverting stoma for patients with rectal cancer. Diverting stoma is recommended for an anastomosis within 5.0 cm of the anal verge and very strongly for a very low anastomosis within 2.0 cm.

A multi-institutional randomized trial of adjuvant chemotherapy for colorectal cancer (NSAS-CC) demonstrated that adjuvant chemotherapy with UFT improved the survival of patients with rectal cancer but not of those with colon cancer.

We demonstrated that laparoscopic ISR for lower rectal cancer provides benefits in the early postoperative period without increasing morbidity or mortality in a case-control study.

A case of ceacal schwannoma treated with lapalosocopic wedge resection was reported.

Clinical Trials

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

1. JCOG0205: A randomized study that compares adjuvant oral UFT + LV to intravenous 5-FU + lLV for pathological stage III colorectal cancer. One thousand, one hundred and ten eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
2. 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. Seven hundred and one eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
3. JCOG0404: A randomized study that compares laparoscopic to open colectomy for clinical stage II or stage III colon cancer located at the cecum, ascending colon, sigmoid colon or rectosigmoid cancer. One thousand and fifty-seven eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
4. JCOG0603: A randomized study that compares adjuvant modified FOLFOX (5-FU + lLV + Oxaliplatin) to surgery alone after hepatic resection for liver metastasis from colorectal cancer. One hundred and seven patients have been enrolled and recruitment continues.
5. JCOG0910: A randomized study that compares adjuvant Capecitabine to TS-1 for pathological stage III colorectal cancer. Three hundred and nine patients have been enrolled and recruitment continues.
6. JCOG1006: A randomized study that compares conventional techniques to the no-touch isolation technique for clinical T3 or T4 colon cancer. One hundred and fifty two patients have been enrolled and recruitment continues.

Published Papers

1. Hamaguchi T, Shirao K, Moriya Y, Yoshida S, Kodaira S, Ohashi Y. Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC). Cancer Chemother Pharmacol, 67:587-596, 2011
2. Matsumoto T, Yamamoto S, Fujita S, Akasu T, Moriya Y. Cecal schwannoma with laparoscopic wedge resection: report of case. Asian J Endosc Surg, 4:178-180, 2011

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, GASTROINTESTINAL MEDICAL ONCOLOGY DIVISION

Yasuhiro Shimada, Yasuhide Yamada, Tetsuya Hamaguchi, Ken Kato, Satoru Iwasa, Yoshitaka Honma, Natsuko Okita, Hitoshi Nishitani, Kohei Akiyoshi

Introduction

The Gastrointestinal Medical Oncology Division is focused on the development of new drugs and standard chemotherapy regimens combined with or without surgery and radiation for advanced colorectal, gastric and esophageal cancer, gastrointestinal stromal tumor and other gastrointestinal (GI) malignancies. Over recent years, a new generation of therapeutic agents has been developed. The highlights include the development of a molecular-targeted antibody directed against vascular endothelial growth factor (bevacizumab (BV)), and the finding that it causes changes in the microenvironment of the tumor by inhibiting angiogenesis. Another two molecular target-based drugs are the anti-epidermal growth factor receptor antibodies, cetuximab and panitumumab, which were approved in 2008 and 2010 for metastatic colorectal cancer. In the near future we expect to identify other novel agents for the treatment of metastatic GI cancers that inhibit intracellular signal transduction or cellular interactions. However, many unusual adverse effects and a marked increase in medical cost have led to extensive discussion on more accurate targeting of the population using biomarkers. Although the response rates of these molecular-targeted drugs up to now have not been high (about 10 to 20%) when used broadly in a large population of patients, there are a few new candidate biomarkers that may be useful for identifying patients for whom these molecular-targeted drugs will be effective. For example, *K-ras* mutation in tumor tissue is one of negative predictive factors for the response to cetuximab. Accordingly, the identification of molecular markers that can be used to monitor tumor shrinkage or assist prognosis will be critical for the identification of possible new targets and for tailored treatments based on patient genotype or marker expression.

Routine Activities

The staff of the GI Medical Oncology Division consists of 5 medical oncologists, 2 senior residents, and 3 or 4 residents. We hold a daily case conference together at 8 am before the morning rounds. Inter-group meetings with each surgical division (Colorectal, Gastric, and Esophageal Surgery Divisions) and the Radiation Oncology Division are held weekly to decide upon treatment strategies for each individual case or to discuss future treatment strategies for the disease. Palliative care that considers 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 2011, we treated 2,139 hospitalized patients (568 of whom were newly diagnosed). Of these patients, 230 were entered in protocol studies.

Research Activities

An endoscopic biopsy before chemotherapy provides an excellent opportunity for the use of microarray analysis to study biomarkers related to therapy-induced tumor response rates, overall survival, or time to recurrence. Biopsy specimens and blood samples were taken from patients before chemotherapy. Correlations between gene expression profiles and survival time or tumor shrinkage have been evaluated, and follow-up data in survival or recurrence are still being collected. Gene expression profiling of cancer tissues with microarray and real-time RT-PCR techniques would be useful for predicting outcomes in GI cancer. These studies are being performed in collaboration with the Center for Medical Genomics, National Cancer Center Research Institute, Kinki University, and Kyushu University.

We also quantitatively measured the mRNA levels of possible predictive biomarkers in paraffin-embedded GI cancer specimens obtained from surgical resection or endoscopic biopsy, and investigated the correlation between enzymes related to anti-cancer drug metabolism and clinical outcomes with a real-time RT-PCR assay using laser-captured microdissection. Some of these molecules will be validated with cancer tissues of 365 patients in a large randomized clinical trial

(JCOG9912) to establish a chemotherapeutic regimen tailored for patients according to genotype, and a new protocol for metastatic gastric cancer compares docetaxel/S-1/cisplatin versus standard S-1/cisplatin with further examination of molecular profiles from endoscopic biopsy specimens.

Clinical Trials

We carried out several clinical trials in collaboration with the Surgery and Radiation Oncology Divisions in our hospital and other institutes. These clinical trials are summarized in the Table. Major trials are conducted in collaboration with JCOG (Japan Clinical Oncology Group)

1. Colorectal Cancer

A regimen of infusional 5-fluorouracil (5-FU) and levofolinate (l-LV) with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) is the standard care as first- and second-line chemotherapy for patients with metastatic colorectal cancer. However, infusional 5-FU with l-LV has the disadvantages of inconvenience, cost, and morbidity related to the use of a portable infusion pump and a central venous catheter-port system. We investigated establishing combination chemotherapy regimens based on the oral fluoropyrimidine, S-1 (S-1/oxaliplatin/BV, S-1/irinotecan/BV), for metastatic disease. A phase III study of S-1/oxalipaltin/BV (SOXB) is on-going to compare this approach with modified FOLFOX6/BV in first-line chemotherapy. Combination treatment with oral fluoropyrimidines is an important candidate to improve patient QOL, medical cost and medical staff burden.

In the adjuvant setting, JCOG0205 finished and has now been followed for 5 years. The final results of disease-free survival and overall survival determined at the end of December, 2011, were clearly superior to overseas clinical data. The findings suggested that the Japanese strategy of D3 dissection followed by oral fluoropyrimidines might be better than that of strategies from overseas. A new adjuvant trial, JCOG0910, comparing S-1 with one of the standard regimens, capecitabine alone, started in March 2010. At the end of 2011, more than 800 patients had been accrued from JCOG hospitals. JCOG0603, a randomized study of adjuvant chemotherapy with mFOLFOX6 after complete resection of liver metastasis from colorectal cancer, was restarted with minor revisions. The phase I stage of JCOG0903, a phase I/II trial of chemoradiation with S-1/MMC for anal canal squamous carcinoma, was also completed in 2011.

2. Gastric Cancer

A phase III study comparing three regimens (5-FU vs CPT-11/CDDP vs S-1) (JCOG9912) was already published in 2009. This was a pivotal study that established a new standard care protocol for advanced gastric cancer and cited the "New Japanese guidelines for diagnosis and treatment of carcinoma of the stomach", 2010 edition. Another phase III study (JCOG0106) of methotrexate/5-FU or 5-FU monotherapy against peritoneal dissemination of gastric cancer was presented at ASCO 2008. Methotrexate/5-FU did not prove superior to 5-FU alone in survival. A randomized phase II study of best-available 5-FU versus weekly paclitaxel as second-line therapy against peritoneal dissemination of gastric cancer (JCOG0407) was presented at ASCO 2010. A phase I/II study of 5-FU/l-LV/paclitaxel (FLTAX) combination therapy as first-line therapy against this population has finished. A phase III study of FLTAX is under preparation now for advanced gastric cancer with peritoneal metastases. S-1 has become a new standard treatment in the adjuvant setting for stage II/III gastric cancer. A feasibility study of modified S-1/CDDP after gastrectomy was completed, showing improved tolerability and preliminary favorable survival results.

Molecular-targeted drugs for advanced gastric cancer as well as colorectal cancer have been investigated. An international phase III study with CDDP plus capecitabine, which is also an oral fluoropyrimidine, with or without BV (AVAGAST), was reported with negative results. Trials on lapatinib (EGFR/HER2, a dual tyrosine kinase inhibitor) and RAD001 (an mTOR inhibitor) are ongoing. A phase I study of S-1/CDDP/sorafenib was completed, revealing additional toxicities. The activity of trastuzumab for HER2 positive gastric cancer was reported in a first-line ToGA study. We started to evaluate the second-line activity of trastuzumab with weekly paclitaxel.

3. Esophageal Cancer

The results of our phase III study of preoperative versus postoperative 5-FU/CDDP (FP) (JCOG9907) were reported in 2007. Preoperative FP was proven to be significantly superior to postoperative FP with regard to overall survival. Based on the results of this trial, the standard care for stage II/III esophageal cancer has been changed to preoperative FP followed by surgery. A phase II study on the FP/RT (50.4 Gy) regimen in stage II or III esophageal cancer was completed with similar

activity and tolerability. The next JCOG phase III study is being planned in the preoperative adjuvant setting to compare preoperative FP versus preoperative chemoradiation versus preoperative intensive docetaxel with FP in stage II or III esophageal cancer.

4. Other

A phase I study of weekly NK105 (a micellar nanoparticle formulation of taxol) for GI cancer, and a phase II study with NK012 (a micellar nanoparticle formulation of irinotecan) for second-line colorectal cancer have finished. A phase II study of AMN107 against gastrointestinal stromal tumors has also finished.

UGT1A1, a key enzyme in the metabolism of irinotecan, has been validated in a prospective trial. This is an important milestone for genotype-tailored chemotherapy, since homozygotes of UGT1A1*28 or *6 exhibit a higher incidence of severe neutropenia. The dose of irinotecan based on genetic information can be adjusted before the first administration to avoid severe toxicity.

Number of Patients Treated

Disease/stage	Total no. of hospitalized pts.	No. of newly diagnosed pts.	No. of pts. enrolled in the protocol
1) Esophageal cancer	859	195	
Neo CRT			8
Stage I FP+RT vs surgery　JCOG0502 (phase III)			10
Stage II/III S-1/CDDP+RT　JCOG0604 (phase I)			1
Stage I EMR+5FU/CDDP+RTJCOG0508 (phase II)			2
5FU/CDDP+RT for Ce Esophageal Cancer			2
Docetaxel+FP(DCF)-EC　JCOG0807 (phase I/II)			2
Stage II/III EC-CRT+Salvage　JCOG0909 (phase II)			4
T4/M1LYM DCF (phase I/II)			5
S-488410 (phase I/II)			1
DE766 (phase I)			3
2) Gastric cancer	695	149	
S-1/oxaliplatin （SOX） vs S-1/cis p latin （SP）(phase III)			40
Paclitaxel ± lapatinib (phase III)			1
Cetuximab/cis p latin/capecitabine （phase III）			1
NK105 (phase II)			1
Paclitaxel ±IMC-1121B (ramucirumab/placebo) (phase III)			10
Neo S1/CDDP　JCOG0501(phase III)			2
wPTX/Tmab (phase II)			3
3) Colorectal cancer	509	196	
Capecitabine vs S-1　JCOG0910 (phase III)			41
5FU//-LV/oxaliplatin/bevacizumab vs S-1/oxaliplatin/bevacizumab (phase III)			18
NK012 (phase II)			2
Regorafenib vs BSC （phase III）			9
JCOG0603 (phase II/III)			4
Tri-weekly XELIRI+BV (BIX Study)			6
SOX-RT (phase I)			1
Stage II/III S-1/MMC　JCOG0903 (phase I/II)			2
Sunitinib+5FU//-LV/oxaliplatin vs bevacizumab+5FU//-LV/oxaliplatin (phase IIb)			1
mFOLFOX/bevacizumab　TRICC0808 (phase II)			1
Panitumumab/CPT-11 or Panitumumab (phase II)			34
FOLFOX or FOLFIRI/Panitumumab　Paff-J (phase II)			5
4) Others	76	28	
NK105 weekly (phase I)			6
AMN107 vs imatinib (phase III)			2
Regorafenib vs BSC (GIST) (phase III)			2
total	2139	568	230

Published Papers

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2. Iwasa S, Nakajima TE, Nakamura K, Takashima A, Kato K, Hamaguchi T, Yamada Y, Shimada Y. Systemic chemotherapy for peritoneal disseminated gastric cancer with inadequate oral intake: a retrospective study. Int J Clin Oncol, 16:57-62, 2011

3. Iwasa S, Yamada Y, Fukagawa T, Nakajima TE, Kato K, Hamaguchi T, Morita S, Saka M, Katai H, Shimada Y. Management of adjuvant S-1 therapy after curative resection of gastric cancer: dose reduction and treatment schedule modification. Gastric Cancer, 14:28-34, 2011

4. Tanai C, Nakajima TE, Nagashima K, Kato K, Hamaguchi T, Yamada Y, Muro K, Shirao K, Kunitoh H, Matsumura Y, Yamamoto S, Shimada Y. Characteristics and outcomes of patients with advanced gastric cancer who declined to participate in a randomized clinical chemotherapy trial. J Oncol Pract, 7:148-153, 2011

5. Okita NT, Kato K, Takahari D, Hirashima Y, Nakajima TE, Matsubara J, Hamaguchi T, Yamada Y, Shimada Y, Taniguchi H, Shirao K. Neuroendocrine tumors of the stomach: chemotherapy with cisplatin plus irinotecan is effective for gastric poorly-differentiated neuroendocrine carcinoma. Gastric Cancer, 14:161-165, 2011

6. Satoh T, Ura T, Yamada Y, Yamazaki K, Tsujinaka T, Munakata M, Nishina T, Okamura S, Esaki T, Sasaki Y, Koizumi W, Kakeji Y, Ishizuka N, Hyodo I, Sakata Y. Genotype-directed, dose-finding study of irinotecan in cancer patients with UGT1A1*28 and/or UGT1A1*6 polymorphisms. Cancer Sci, 102:1868-1873, 2011

7. Shimada Y. Liver resection for colorectal metastases: Is there an age limit? The Japanese perspective. Curr Colorectal Cancer Rep, 7:187-190, 2011

8. Nakajima TE, Yamada Y. Gastric cancer metastasis. Cancer Metastasis- Biologic Basis and Therapeutics. UK, Cambridge University Press, pp 325-332, 2011

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, GASTROINTESTINAL ENDOSCOPY DIVISION

Yutaka Saito, Takahisa Matsuda, Ichiro Oda, Takeshi Nakajima, Shigetaka Yoshinaga, Haruhisa Suzuki, Satoru Nonaka and Taku Sakamoto (National Cancer Center Hospital)
Yasuo Kakugawa, Yosuke Otake and Minori Matsumoto (Screening Technology and Development Division)

Introduction

The Gastrointestinal Endoscopy Division has eight staff physicians in the National Cancer Center Hospital, three staff physicians in the Screening Technology and Development Division, three chief residents, five residents, four trainees and several rotating residents.

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

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 10,810, 2,924, 372, 59, 41 and 35 screening and/or diagnostic procedures by gastroscopy, colonoscopy, EUS, EUS-fine needle aspiration (EUS-FNA), endoscopic retrograde cholangiopancreatography (ERCP) and capsule endoscopy, respectively, were performed in 2011.

Due to the increasing number of patients with superficial gastrointestinal neoplasms, the number of therapeutic endoscopy procedures is also increasing in this field. In 2011, 1,914 endoscopic resections were carried out (pharynx 20, esophagus 193, stomach 366 and colon 1,335). Among these, ESD, which was developed for large en-bloc resections with a low-risk of local recurrence, was performed for 61 superficial esophageal cancers, 343 early gastric cancers and 125 superficial colorectal neoplasms. For colorectal ESDs and some esophageal ESDs, the newly developed ball-tip bipolar needle knife (B-knife) and insulation-tipped knife (IT-knife; KD-Y0009) were used together with CO_2 insufflation. These procedures and devices were originally developed by our colleagues.

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. As for emergency endoscopic procedures, 446 endoscopies were performed for gastrointestinal bleeding and other emergencies.

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.

Procedure	Number of Procedures Performed in 2011
Upper GI Endoscopy	10,810
Lower GI Endoscopy	2,924
Pharyngeal EMR/ESD	20
Esophageal EMR/ESD	132/61
Gastric EMR/ESD	23/343
Colorectal Polypectomy, EMR	1,210
Colorectal ESD	125
EUS/EUS-FNA/ERCP	372/59/41
Emergency Endoscopy	446
Capsule Endoscopy	35

Research Activities (Figure 1)

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

A multicenter randomized controlled trial (RCT) was conducted to compare the polyp detection rate between AFI and white light endoscopy (WLE). This large RCT in a multicenter referral setting did not show any objective advantage of AFI over WLE in terms of an improved adenoma detection rate. The use of NBI in the proximal colon, however, appeared to improve small adenoma detection and reduce the miss rate in our previous multicenter study so the combined use of NBI and AFI will play an important role in future colorectal cancer screening.

Gastric cancer is the second leading cause of cancer death worldwide. In order to improve the survival rate, early diagnosis is one of the optimal strategies, but it has been difficult to differentiate early gastric cancer from other non-neoplastic lesions using conventional WLE. We have conducted a multicenter prospective RCT and concluded that magnifying-NBI improved the diagnostic accuracy for discriminating gastric neoplasms from benign small depressed lesions. We reported this paper at a Plenary Session of the American Society for Gastrointestinal Endoscopy (ASGE) in 2011.

Endoscopic submucosal dissection (ESD) is accepted as a minimally invasive treatment for early gastric cancer although not widely used in the colorectum because of increased technical difficulty. We have conducted a multicenter prospective study at 10 specialized institutions to examine the current status of colorectal ESDs at specialized endoscopic treatment institutions. Our conclusion was that ESD performed by experienced endoscopists is an effective alternative treatment to surgery providing high en-bloc and curative resection rates for large superficial colorectal tumors based on a prospective series of 1,111 cases.

We have also participated in a further multicenter prospective study on endoscopic treatment of large early colorectal neoplasia conducted by the Colorectal Endoscopic Resection Standardization Implementation Working Group of the Japanese Society for Cancer of the Colon and Rectum. Our group enrolled the largest number of cases so we presented the study results in the Plenary Session of the 19th United European Gastroenterology Week (UEGW 2011) in Stockholm, Sweden where we received the Top Abstract Prize. The en-bloc resection rate for ESD was significantly higher than for EMR although complication rates were not significantly different. Despite longer procedure times, ESD is becoming a standard treatment in Japan for treatment of early colorectal neoplasms especially for larger lesions.

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. Metachronous gastric cancer after EMR/ESD is now an issue of concern so we need to identify an appropriate biomarker. Based on our recent results, we started a multicenter prospective observational study in 2008 to confirm the usefulness of the methylation level as a risk marker for metachronous gastric cancer after EMR/ESD. The recommended sample size is 1,000 and over 600 patients have already been enrolled in this particular study.

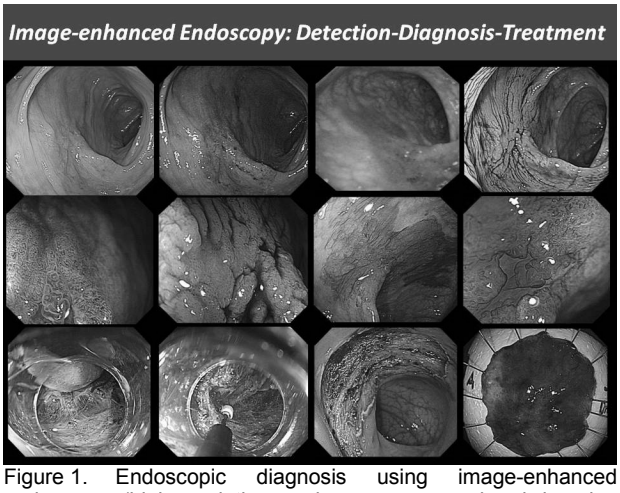

Figure 1. Endoscopic diagnosis using image-enhanced endoscopy (high-resolution endoscopy, narrow-band imaging and autofluorescence imaging) and endoscopic submucosal dissection (ESD) procedure for treating early colon cancer

Clinical Trials

A multicenter clinical trial has been underway 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 chemoradiotherapy for clinical stage I esophageal carcinoma (JCOG 0508).

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. Our division has also cooperated as a participating institution in a Phase II trial of endoscopic submucosal dissection to expand the indications for early gastric cancer (JCOG 0607).

RCTs concerning colorectal neoplasms are ongoing as well. 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. At present, 3,926 patients have been enrolled in this study. This multicenter RCT is scheduled to continue until 2012 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. The final step in the randomization process and complete histopathological assessments are ongoing at the present time.

In late 2009, we initiated an RCT comparing our proposed bowel preparation method for colon capsule endoscopy with the traditional approach. The aim of this trial is to clarify overall cleanliness and determine the anal excretion rate prior to the end of the capsule's battery life using our bowel preparation proposal and a previously reported method.

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DEPARTMENT OF HEPATOBILIARY AND PANCREATIC ONCOLOGY, HEPATOBILIARY AND PANCREATIC SURGERY DIVISION

Tomoo Kosuge, Kazuaki Shimada, Minoru Esaki, Satoshi Nara, Youji Kishi, Seiji Oguro

Introduction

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

Routine Activities

The HBP Surgery Division consists of five staff surgeons along with one chief resident and three or four residents, and we perform around 300 surgeries each year. 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 selected patients. 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 "Journal Club", the latest articles on pancreatic disease are reviewed by surgeons, medical oncologists, radiologists and pathologists.

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. 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 adjuvant chemotherapy in the form of clinical trials have been used for this potentially noncurative disease. Resection of borderline malignancies, such as pancreatic cystic neoplasms and neuroendocrine tumors (NETS) is performed aggressively, since a favorable prognosis can be expected with surgical resection.

Biliary cancer – cholangiocarcinoma & 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 hilar cholangiocarcinoma.

Research Activities and Clinical Trials

Dr. Kosuge et al. reported the results of a multicenter controlled trial to evaluate the effect of adjuvant gemcitabine administration after curative resection in cases of pancreatic cancer (JSAP-02, Ueno, Kosuge et al. Br J Cancer 2009). They are now conducting a randomized phase III study of adjuvant chemotherapy with combination therapy of gemcitabine and S-1 vs. gemcitabine alone in patients with resected pancreatic cancer (JSAP-04).

Dr. Shimada et al. are conducting 3 prospective randomized trials to evaluate the efficacy of surgical devices in HBP surgery: 1) Safety of stapler vs. non-stapler closure of the pancreatic remnant after distal pancreatectomy: a multicenter randomized controlled trial (SNS-RCT); 2) The impact of the use of an energy device during parenchyma transection of the liver: a multicenter randomized controlled trial (EPL-RCT); and 3) The

Table 1. Number of patients

	n
Invasive pancreatic cancer	71
Other pancreatic neoplasms	27
Hepatocellular carcinoma	35
Hepatic metastases	54
Intrahepatic cholangiocarcinoma	19
Bile duct cancer	29
Gallbladder cancer	12
Duodenal cancer	6
Others	46
Total	299

Table 2. Operative procedures

	n
Hepatectomy without biliary resection	105
Hepatectomy with biliary resection	25
Right hemihepatectomy and pancreaticoduodenectomy (HPD)	2
Classical Whipple (CW)	10
Pylorus-preserving pancreaticoduodenectomy (PPPD)	59
Distal pancreatectomy	34
Appleby operation	2
Medial pancreatectomy	6
Total pancreatectomy	3
Extended cholecystectomy	8
Other resections	20
No resection	25
Total	299

Table 3. Long-term survivals

Invasive ductal carcinoma (2000-2008)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	9	62	62
II	8	71	71
III	109	51	40
IVa	172	33	17
IVb	73	25	18
Total	371	38	26

Hepatocellular carcinoma (2000-2008)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	33	87	75
II	144	89	81
III	195	67	54
IV	72	61	44
Total	444	73	59

effect of stapled vs. hand-sewn duodenal reconstruction on delayed gastric emptying during pancreaticoduodenectomy: a dual-center randomized controlled trial (SH-RCT). Dr. Nara et al. are now carrying out a study to evaluate the feasibility of laparoscopic hepatectomy in our environment. These studies are supported by Grants-in-Aid for scientific research from the Ministry of Health, Labour and Welfare of Japan and the National Cancer Center Research and Development Fund.

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DEPARTMENT OF HEPATOBILIARY AND PANCREATIC ONCOLOGY, HEPATOBILIARY AND PANCREATIC ONCOLOGY DIVISION

Takuji Okusaka, Hideki Ueno, Chigusa Morizane, Shunsuke Kondo

Introduction

The Hepatobiliary and Pancreatic Oncology Division 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, we work closely with surgeons and radiologists who have special 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 division consists of four 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 3 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. 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.

Most patients with hepatobiliary and pancreatic tumors, whether they undergo surgical or nonsurgical treatment, are hospitalized in the Hepatobiliary and Pancreatic Ward. 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 multicenter phase II trial in patients with HCC to evaluate the efficacy and safety of SM-11355, using a Zinostatin stimalamer suspension in iodized oil as a reference (Okusaka et al.). Patients with unresectable HCC were randomized 2:1 to receive administration of the SM-11355 or Zinostatin stimalamer suspension into the hepatic artery. Efficacy was evaluated with CT and the therapeutic effect (TE) was categorized as grades V to I, where TE V was defined as disappearance or 100% necrosis of all treated tumors. The TE V rates were 26.5% (22/83) and 17.9% (7/39) in the SM-11355 and Zinostatin stimalamer groups, respectively. The adverse effects with the largest difference between the two groups were hepatic vascular injury (0 vs. 48.4%) and eosinophilia (84.3 vs. 41.0%). The 2-year and 3-year survival rates were 75.9% vs. 70.3% and 58.4% vs. 48.7%, respectively. The results suggest that SM-11355 in iodized oil has similar efficacy to Zinostatin stimalamer and that repeated dosing of SM-11355 is possible without hepatic vascular injury in cases of relapse.

We conducted a phase I/II trial of fixed dose rate infusion of gemcitabine (FDR-Gem) and S-1 (FGS) in patients with Gem-refractory pancreatic cancer (Morizane et al.). The patients received FDR-Gem on day 1 and S-1 orally twice daily on days 1-7. Cycles were repeated every 14 days. Patients were scheduled to receive Gem (mg/m^2/week) and S-1 (mg/m^2/day) at four dose levels in the phase I: 800/80 (level 1), 1,000/80 (level 2), 1,200/80 (level 3) and 1,200/100 (level 4). Forty patients were enrolled in the phase II study at the recommended dose, which was level 3. In the phase II trial, a partial response was confirmed in seven patients (18%). The median overall survival time and median progression-free survival time were 7.0 and 2.8 months, respectively. The common adverse effects were anorexia, leukocytopenia and neutropenia. This combination regimen of FGS is active and well tolerated in patients with Gem-refractory pancreatic cancer.

A multicenter phase II study was conducted to assess the efficacy and toxicity of Gem and S-1 combination therapy for metastatic pancreatic cancer (Ueno et al.). Chemotherapy-naïve patients

with histologically or cytologically proven metastatic pancreatic adenocarcinoma were eligible for this study. A total of 55 patients were included and the efficacy and toxicity were analyzed in 54 patients who received at least one dose of gemcitabine and S-1 combination therapy. Although no complete response was seen, a partial response was achieved in 24 patients, resulting in an overall response rate of 44.4%. The median progression-free survival was 5.9 months and the median overall survival was 10.1 months with a 1-year survival rate of 33.0%. The major Grade 3-4 toxicities were neutropenia (80%), leukopenia (59%), thrombocytopenia (22%), anorexia (17%) and rash (7%). Hematological toxicity was mostly transient and there was only one episode of febrile neutropenia ≥Grade 3. Gem and S-1 combination therapy produced a high response rate with good survival in patients with metastatic pancreatic cancer.

Clinical Trials

Twenty-six clinical trials are ongoing, including eight phase III trials, such as adjuvant chemotherapy versus placebo in HCC patients who had undergone hepatic resection or local ablation therapy, chemotherapy with new agents versus standard chemotherapy in unresectable HCC patients, and chemotherapy with new agents versus standard chemotherapy in advanced pancreatic cancer patients. Two studies are collaboration trials with the Department of Diagnostic Radiology, and one with the Department of Radiation Oncology. Two trials are being conducted to evaluate cancer immunotherapy.

Our studies are supported by Gan-kenkyu-kaihatsuhi (Grant No. 23-A-22, No. 23-A-2 Toku 2, No. 23-A-14, No. 23-A-22, No. 23-A-30, No. 23-A-37, No. 23-A-38), Health and Labour Sciences Research Grants, Clinical Cancer Research (Grant No. H22-ganrinsho-ippan-013,
No. H22-ganrinsho-ippan-015,
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Table 1. Number of patients according to primary tumor site

	No. of pts
Pancreatic cancer	
Invasive ductal	147
Neuroendocrine	16
Others	6
Biliary tract cancer	
Extrahepatic bile duct	7
Gallbladder	29
Papilla of Vater	10
Liver cancer	
Hepatocellular	242
Intrahepatic cholangio	40

Table 2. Number of patients according to type of procedure

	No. of pts
Pancreatic cancer	
Systemic chemotherapy	103
Chemoradiotherapy	5
Biliary tract cancer and Intrahepatic cholangio carcinoma	
Systemic chemotherapy	45
Hepatocellular carcinoma	
Ethanol injection	13
Radiofrequency ablation	41
Transcatheter arterial (chemo)embolization	139
Intra-arterial chemotherapy	43
Systemic chemotherapy	42
Radiotherapy	9

Table 3. Survival

	MST (month)	Survival rate (%)
Pancreatic cancer		
Advanced	10.2	1-yr: 42.4
Biliary tract cancer and Intrahepatic cholangiocarcinoma		
Advanced	11.6	1-yr: 47.7
Hepatocellular carcinoma		
Radiofrequency ablation	NA	5-yr: 63.9
Transcatheter arterial (chemo)embolization	42.2	3-yr: 56.6
Systemic chemotherapy	8.5	1-yr: 40.9

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3. Okusaka T, Ueno H, Ikeda M, Morizane C. Phase I and pharmacokinetic clinical trial of oral administration of the acyclic retinoid NIK-333. Hepatol Res, 41:542-552, 2011

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10. Furuse J, Okusaka T, Bridgewater J, Taketsuna M, Wasan H, Koshiji M, Valle J. Lessons from the comparison of two randomized clinical trials using gemcitabine and cisplatin for advanced biliary tract cancer. Crit Rev Oncol Hematol, 80:31-39, 2011

DEPARTMENT OF UROLOGY

Hiroyuki Fujimoto, Tohru Nakagawa, Motokiyo Komiyama, Hiroyuki Nakanishi

Introduction

In the Urology Division, all urogenital malignant diseases, including kidney cancer, urothelial cancer, prostate cancer, and 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 four 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 tumor 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. A clinicopathological conference is scheduled on alternating Wednesdays.

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 or without neoadjuvant chemotherapy with a M-VAC 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, 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 was indicated.

(4) Testicular germ cell tumor (GCT). Stage I: careful observation regardless of any pathological element. Stage II or higher: EP (etoposide + CDDP) or BEP (BLM + etoposide + CDDP) chemotherapy as the 1st line. In nonseminomatous cases, salvage operation 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 urological malignant tumors.

1. Renal cell carcinoma: Improvement of the treatment outcome in metastatic renal cell carcinoma remains a major problem. Phase II and III studies using a VEGFR inhibitor (AG-013766) are also in progress.
2. Urothelial cancer: The effectiveness of a phase III study to confirm the efficacy of neoadjuvant M-VAC therapy for T2-3N0M0 bladder cancer (JCOG0209) is under review. For metastatic disease, a phase II study using a peptide vaccine (S288310) is in progress and a weekly CBDCA + PTX regimen has been indicated.
3. Prostate cancer: To identify the most effective treatment for the recurrence of PSA failure after radical prostatectomy, a phase III study to evaluate the efficacy of salvage irradiation vs hormone ablation for postoperative PSA failure in T1c-T2 prostate cancer (JCOG0401) is under review. 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. To provide a more precise preoperative diagnosis, a new imaging strategy using 3.0 Tesla MRI has been developed. In local advanced disease, a phase III study to evaluate the survival benefit of continuous endocrine therapy after 3D conformal radiotherapy is still underway. For hormone-refractory prostate cancer, a study on a new hormonal regime with MDV3100 has completed enrollment.

4. Testicular germ cell tumor: 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 tumor, a second line TIP regimen has completed enrollment.

Clinical Trials

We are actively involved in the following ongoing protocol studies;

1. Phase II & III studies: AG-013766 for metastatic renal cell carcinoma
2. A phase II study: S288310 peptide vaccine and weekly CBDCA+PTX for M-VAC-refractory metastatic urothelial cancer
3. A phase III study: Salvage radiation vs hormone ablation for postoperative PSA failure in T1c-T2 prostate cancer (JCOG0401)
4. A phase II study:MDV3100 for hormone-refractory prostate cancer
5. A phase II study: TIP for CDDP-refractory metastatic germ cell tumor.

Published Papers

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Table1. Patients statistics: Major treatment

	2008	2009	2010	2011
Radical/partial nephrectomy	28	43	35	30
Nephroureterectomy	11	16	15	12
Total cystectomy	22	26	31	24
TURBT	161	163	130	140
M-VAC	31	42	62	50
GC		50	71	84
Radical prostatectomy	105	111	98	111
Prostatic biopsy	186	247	168	175
High orchiectomy	7	6	12	8
Retroperitoneal lymphadenectomy	10	7	8	13
Chemotherapy for testicular cancer	10	9	14	30
Retroperitoneal tumor resection	9	9	15	10

DEPARTMENT OF GYNECOLOGY

Takahiro Kasamatsu, Tomoyasu Kato, Takashi Onda, Shun-ichi Ikeda, Mitsuya Ishikawa, Shinich Togami

Introduction

The Gynecologic Oncology Division 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, *i.e.*, cervical, endometrial and ovarian cancer, are now on the rise in Japan. In our institution, the numbers of patients with endometrial and ovarian cancer have increased about 4-fold over the past 30 years. The number of patients with invasive carcinoma of the cervix had decreased by half during the same period, but this trend has reversed since the late 1990s. Consequently, invasive cervical cancer is still the most common gynecologic cancer in Japan.

Routine Activities

The staff members of the Department of Gynecology comprise five gynecologic oncologists. In addition, our division includes two 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 presentation and discussion at the weekly joint conference on Wednesdays. A joint clinicopathological conference is held on the first Tuesday of each month.

1) Treatment strategy for uterine cervical cancer. Either conization or simple total hysterectomy is the treatment of choice for persistent high-grade dysplasia, Stage 0 or Ia1 cervical cancer. Patients with stages Ia2 to IIIa usually undergo radical hysterectomy and pelvic lymphadenectomy. Postoperative total pelvic irradiation following radical hysterectomy is only considered for patients with metastasis to the pelvic nodes or parametrial tissue as confirmed by pathological examination. Radiotherapy alone or concurrent chemo-radiotherapy is given to patients at any stage. Chemotherapy is occasionally used for the treatment of distant metastasis.
2) 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. In our practice, positive peritoneal cytology is not a poor prognostic factor for patients with a well-differentiated tumor confined to the uterus, whereas postoperative chemotherapy is performed for patients with extra-uterine disease.
3) 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. Patients with more advanced stage III and IV disease, who are unlikely to be optimally debulked, are treated with primary chemotherapy. After several courses of chemotherapy, an interval debulking surgery is usually performed for these patients. Surgery alone can offer the chance of cure for patients with recurrence, but only when the disease is completely resectable. The type of surgical procedure, operative morbidity, and survival rates are shown in Tables 1, 2, and 3.

Research Activities

To assess the safety and efficacy of a splenectomy and to analyze the prognostic factors of Müllerian carcinoma with spleen metastasis, Uehara and Onda et al (1). reviewed the medical records of patients with Müllerian carcinoma who underwent a splenectomy between 1997 and 2007 at NCCH. It was concluded that a splenectomy can be performed safely and effectively during debulking surgery for appropriately selected patients with

Table 1. Type of procedure

Procedure	No. of Patients
Radical hysterectomy	28
Simple hysterectomy	164
± Salpingo-oophorectomy	
± Lymphadenectomy	
± Omentectomy	
± Lymphadenectomy	
Radical vulvectomy	3
Conization	11
Others	18
Total	224

Table 2. Operative morbidity and mortality

Item	Value (as % of total patients)
Major complications[a]	2.2%
Minor complications[b]	5.8%
Operative death within 30 days	0
Postoperative hospital death	0

[a] Lymph cystitis requiring drainage, ureterovaginal fistula.
[b] Infection, hemorrhage, bladder atony requiring medication.

Table 3. Survival

FIGO	Cervical cancer[a]		Endometrial cancer[a]		Ovarian cancer[b]	
Stage	No. of patients	5-yr survival	No. of patients	5-yr survival	No. of patients	5-yr survival
I	425	87%	372	91%	80	86%
II	139	74%	62	86%	20	81%
III	120	58%	143	69%	131	32%
IV	46	36%	28	26%	73	16%
Totals	730		605		304	

[a]1993-2002
[b]1990-1999

primary or recurrent Müllerian carcinoma. Onda et al (2). reviewed the outcomes of neoadjuvant chemotherapy (NAC) for advanced ovarian cancer, and demonstrated that NAC followed by surgical cytoreduction is an acceptable management strategy for patients with advanced ovarian cancer.

Clinical Trials

A phase III study to compare treatment starting with neoadjuvant chemotherapy and primary cytoreductive surgery followed by postsurgical chemotherapy (JCOG 0602) for advanced ovarian cancer was completed. A phase II study on irinotecan and etoposide for patients with platinum-resistant taxan-pretreated ovarian cancer (JCOG 0503) is now ongoing. A phase I/II study on Heavy Ion Radiotherapy with concurrent chemotherapy for locally advanced cervical adenocarcinoma using the Heavy Ion Medical Accelerator is ongoing in Chiba (HIMAC, National Institute of Radiological Sciences).

Published Papers

1. Uehara T, Onda T, Togami S, Amano T, Tanikawa M, Sawada M, Ikeda S, Kato T, Kasamatsu T. Safety and efficacy of a splenectomy during debulking surgery for Mullerian carcinoma. Eur J Gynaecol Oncol, 32:269-273, 2011
2. Onda T, Yoshikawa H. Neoadjuvant chemotherapy for advanced ovarian cancer: overview of outcomes and unanswered questions. Expert Rev Anticancer Ther, 11:1053-1067, 2011
3. Onda T, Konishi I, Yoshikawa H, Kamura T. The history of the Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG). Jpn J Clin Oncol, 41:1156-1161, 2011
4. Sawada M, Tochigi N, Sasajima Y, Hasegawa T, Kasamatsu T, Kitawaki J. Primary extraskeletal myxoid chondrosarcoma of the vulva. J Obstet Gynaecol Res, 37:1706-1710, 2011
5. Togami S, Kato T, Oi T, Ishikawa M, Onda T, Ikeda S, Kasamatsu T. A rare case of recurrent ovarian cancer presenting as a round ligament metastasis. World J Surg Oncol, 9:144, 2011
6. Toita T, Ohno T, Kaneyasu Y, Kato T, Uno T, Hatano K, Norihisa Y, Kasamatsu T, Kodaira T, Yoshimura R, Ishikura S, Hiraoka M. A consensus-based guideline defining clinical target volume for primary disease in external beam radiotherapy for intact uterine cervical cancer. Jpn J Clin Oncol, 41:1119-1126, 2011

DEPARTMENT OF ORTHOPEDIC SURGERY

Hirokazu Chuman, Yasuo Beppu, Akira Kawai, Fumihiko Nakatani, Tomoya Matsunobu, Naofumi Asano, Kunihiko Numoto, Shusa Oshika, Shoji Nagano

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 orthopedic surgery 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.

Clinical Practices

The orthopedic surgery division of the NCCH consists of four staff doctors (Drs. Hirokazu Chuman, Yasuo Beppu, Akira Kawai, Fumihiko Nakatani, and Umio Yamaguchi) and five residents. Occasionally, several fellows from Japan and overseas join our group. Outpatient consults are held every weekday. About 30 patients are constantly hospitalized to undergo operation, chemotherapy or radiation therapy. Five or six major operations are routinely performed every week. In 2011, 304 operations were performed under general anesthesia, including palliative operations for pathological fractures or spinal cord compression from metastatic bone and soft tissue tumors. Sarcomas in the trunk, including the thoracic wall, retroperitoneal space and head and neck lesions were excised in cooperation with thoracic, general or head-neck surgeons, respectively. A total of 28 reconstructive operations was 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 neoadjuvant and adjuvant chemotherapy for high-grade bone and soft tissue tumors, palliative chemotherapy for metastatic bone and soft tissue sarcomas, occasionally in collaboration with a medical oncologist. Chemotherapy of children and adolescents with sarcomas is conducted by a pediatric oncologist.

Conferences

Every morning at 8:00 A.M., all staff doctors and residents meet for the morning conference and make rounds of hospitalized patients in the 13B and 12A ward. A weekly clinical conference is held every Monday morning and Tuesdays from 8:00 to 9:00 to discuss the diagnosis, operative procedure, pre-postoperative rehabilitation program, and chemotherapy regimen of each patient.

Research Activities

Since 2004, we have been collaborating with the Research Institute of the National Cancer Center 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 (2D-DIGE) 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 sarcomas of soft tissues. Combined with each patient's clinical information, we have been establishing novel biomarkers for prediction of

Table 1. Numbers treated in our division from 2009 -2011

Year	Benign STT	Malignant STT	Benign BT	Malignant BT	Total
2009	48	142	28	65	283
2010	86	146	44	44	320
2011	57	156	41	69	323

STT, soft tissue tumor; BT, bone tumor

[Statistics]

	Soft tissue sarcoma	Bone Sarcoma	Benign Bone Tumor	Spine or Bone metastasis	biopsy or others	Total
Surgeries performed	95	39	41	21	106	302

	Soft tissue sarcoma	Bone sarcoma	Benign Bone Tumor	Bone metastasis	Total
New patients	116	32	39	24	211

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.

Clinical Trials

We have been conducting clinical trials of image-guided surgery to improve the accuracy of operation procedures using multi-modality imaging systems including open MRI, self-mobile CT and angio-system C-arm in the surgical room (MR/CT operation suite). Using this system, we are trying to establish the optimum minimally invasive surgery but with adequate safe surgical margins to eliminate local recurrences.

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

1. A multi-institutional phase clinical trial of multidrugs adjuvant chemotherapy for osteosarcomas (JCOG 0905) since 2010.
2. A multi-institutional phase study of ridaforlims (an mTOR inhibitor) for controlled sarcomas since 2009.
3. A multi-institutional phase study of Eribulin for uncontrolled sarcoma since 2010.

Published Papers

1. Yanagisawa M, Okada K, Tajino T, Torigoe T, Kawai A, Nishida J. A clinicopathological study of giant cell tumor of small bones. Ups J Med Sci, 116:265-268, 2011
2. Okada K, Hasegawa T, Kawai A, Ogose A, Nishida J, Yanagisawa M, Morita T, Tajino T, Tsuchiya T. Primary (de novo) dedifferentiated liposarcoma in the extremities: a multi-institution Tohoku Musculoskeletal Tumor Society study of 18 cases in northern Japan. Jpn J Clin Oncol, 41:1094-1100, 2011
3. Matsumine A, Ueda T, Sugita T, Yazawa Y, Isu K, Kawai A, Abe S, Yakushiji T, Hiraga H, Sudo A, Uchida A. Clinical outcomes of the KYOCERA Physio Hinge Total Knee System Type III after the resection of a bone and soft tissue tumor of the distal part of the femur. J Surg Oncol, 103:257-263, 2011
4. Ogura K, Hosono A, Yoshida A, Beppu Y, Kawai A. A retroperitoneal mass, systemic lymphadenopathy, and pulmonary nodules in a pregnant woman. Diagnosis: Lymphangioleiomyomatosis (LAM). Skeletal Radiol, 40:631-632, 657-638, 2011
5. Ban J, Jug G, Mestdagh P, Schwentner R, Kauer M, Aryee DNT, Schaefer KL, Nakatani F, Scotlandi K, Reiter M, Strunk D, Speleman F, Vandesompele J, Kovar H. Hsa-mir-145 is the top EWS-FLI1-repressed microRNA involved in a positive feedback loop in Ewing's sarcoma. Oncogene, 30:2173-2180, 2011

DEPARTMENT OF DERMATOLOGIC ONCOLOGY

Naoya Yamazaki, Arata Tsutsumida, Ken-jiro Namikawa, Ryota Tanaka, Junji Kato, Wataru Omata

Introduction

The Department of Dermatologic Oncology has consistently served as the core hospital for the establishment of treatment strategies for malignant skin tumors since the National Cancer Center opened in 1962, and over 1500 cases of malignant melanoma have been accumulated thus far; an impressive number for a hospital or research institution in Japan. Today, patients are referred from throughout Japan. Most of the patients are examined and treated for skin cancer including malignant melanoma. Surgery is the main treatment modality for skin cancer, and multi-disciplinary treatments, consisting of chemotherapy, immunotherapy, and radiotherapy, are also routinely carried out. In addition, this department plays an active role in multicenter trials for skin cancer all over Japan.

Routine Activities

The department has three staff dermatologic oncologists and three residents. We are also engaged in routine outpatient activities on Wednesdays and Thursdays in the National Cancer Center East.

In 2011, a total of 290 patients were examined for the first time in the dermatology department for a malignant skin tumor. The numbers of patients with malignant melanoma (132) and extramammary Paget's disease (22) were particularly large, and were approximately 5 times and 2 times, respectively, the numbers of 15 years ago. There were also 9 cases of the rare cancer, angiosarcoma.

Rounds are made and case presentations are held every morning. A division conference is held every Monday to discuss the therapeutic principles for outpatients and inpatients. A clinicopathological conference that focuses on surgically removed skin specimens is held with pathologists once a month.

Research Activities

Malignant melanoma

The Department of Dermatologic Oncology is part of the melanoma research group in Japan and its work is partly supported by Management Expenses Grants from the Government to the National Cancer Center.

It is extremely important to detect early malignant melanoma lesions accurately and the Department of Dermatologic Oncology adopts dermoscopy for a differential diagnosis. Dermoscopy is very useful for examination of the sole, which is the most frequent site of malignant melanoma in Japanese subjects, since early melanoma frequently shows a parallel ridge pattern, while a parallel furrow, a lattice-like or a fibrillar/filamentous pattern is typical of a pigmented nevus. Based on these findings, our study group proposed a algorithm for the management of acquired acral melanocytic lesions.

We have taken part in a Japanese multicenter joint study on sentinel lymph node (SLN) biopsy. At the Department of Dermatologic Oncology, SLN biopsies for malignant melanoma were performed with the injection of technetium tin colloid, blue dye plus fluorescence method (combination of indocyanine green and the Photodynamic Eye System) in 95 cases. The addition of a real-time fluorescence navigation system with indocyanine green as a new technique achieved a detection rate of 100%. Of all the patients in whom SLN was identified and biopsied, about 35% had metastasis.

We have conducted the DERMA study, the first global study for melanoma patients in Japan. The study investigational product is an Antigen-Specific Cancer Immunotherapeutic agent comprising the recombinant protein MAGE (Melanoma Antigen)-A3. We had a great difficulty in finding candidate patients as the subjects had to be stage IIIb and IIIc cutanous melanoma patients with macroscopic lymph node involvement. Moreover we took part in the study only after a 2-year delay. However, the number of recruited patients is 7 in Japan, a number which is highly regarded in the world. We will continue to follow-up 4 patients recruited in our department for regulatory approval.

Extramammary Paget's disease

When extramammary Paget's disease infiltrates the dermis, it becomes apocrine adenocarcinoma and gives rise to regional lymph node metastasis in

a high proportion of cases. Despite the poor prognosis for patients with lymph node metastasis, management of this disease without clinical evidence of involved nodes is controversial, and yet there is still not a TNM stage classification. We have reported that a favorable outcome is achieved by radical lymph node dissection only when there is a solitary regional lymph node metastasis. The 5-year extramammary Paget's disease-specific survival rate for patients with a solitary regional lymph node metastasis was 100%, although the survival rate for patients with more than three lymph nodes metastases was 0%. Therefore, SLN biopsies for extramammary Paget's disease are important in the initial surgical treatment.

Clinical Trials

This fiscal year we were supported in part by Management Expenses Grants from the Government to the National Cancer Center, and Health and Labour Science Research Grants from the Ministry of Health, Labour and Welfare.

(1) Sentinel lymph node detection in malignant melanoma patients using real-time fluorescence navigation with indocyanine green.
(2) Development and translational research of a peptide vaccine for advanced malignant melanoma.
(3) Serum 5-S-cysteinyldopa and melanoma inhibitory activity levels are periodically measured as tumor markers of malignant melanoma. We are studying their correlation with patient pathophysiological conditions.

The clinical trials (industry-sponsored registration trials) are summarized in Table 3.

(1) We have conducted two kinds of industry-sponsored registration trials for malignant melanoma.
(2) We are carrying out some clinical trials in collaboration with the Investigational Drug Development and Hematology Divisions in our hospital.

Published Papers

1. Iizuka A, Komiyama M, Tai S, Oshita C, Kurusu A, Kume A, Ozawa K, Nakamura Y, Ashizawa T, Yamamoto A, Yamazaki N, Yoshikawa S, Kiyohara Y, Yamaguchi K, Akiyama Y. Identification of cytomegalovirus (CMV)pp65 antigen-specific human monoclonal antibodies using single B cell-based antibody gene cloning from melanoma patients. Immunol Lett, 135:64-73, 2011
2. Noro S, Yamazaki N, Nakanishi Y, Yamamoto A, Sasajima Y, Kawana S. Clinicopathological significance of sentinel node biopsy in Japanese patients with cutaneous malignant melanoma. J Dermatol, 38:76-83, 2011
3. Namikawa K, Yamazaki N. Sentinel lymph node biopsy guided by indocyanine green fluorescence for cutaneous melanoma. Eur J Dermatol, 21:184-190, 2011

Table 1. Number of New Patients

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Malignant melanoma	67	68	74	97	94	79	92	75	94	88	132
Squamous cell carcinoma	27	19	24	31	36	25	25	28	36	52	27
Basal cell carcinoma	40	29	31	47	33	23	25	33	31	28	28
Sweat gland carcinoma	3	10	7	8	10	17	6	10	10	9	9
Trichilemmal carcinoma	0	1	2	0	0	1	7	0	1	0	0
Paget's disease	10	16	13	12	18	16	19	20	21	19	22
Bowen's disease	16	8	7	12	9	8	4	2	10	3	9
Dermatofibrosarcoma protuberans	2	2	3	5	3	7	3	5	10	10	10
Angiosarcoma	7	5	3	3	5	9	6	12	9	9	9
Malignant fibrous histiocytoma	0	0	1	1	1	0	1	1	3	3	1
Epithelioid sarcoma	1	1	0	0	2	1	0	1	0	0	0
Malignant lymphoma	3	10	12	12	15	7	6	15	13	16	16
Merkel cell carcinoma	-	-	-	-	2	3	2	4	3	3	8
others	2	5	5	4	5	12	11	8	7	17	19
Total	178	175	182	232	233	208	207	214	248	257	290

Table 2. Operative Procedures (total number)

Wide local excision	125
Local excision	75
Sentinel node biopsy	36
Lymph node biopsy	12
Lymph node dissection	35
(neck)	5
(axilla)	10
(inguinal)	11
(groin)	8
(popliteal)	0
(epitrochlear)	1
Skin graft	29
Local flap	9
Free flap	5
Amputation	9
others (biopsy/debridement)	3

Table 3. New Agent Studies in 2010

Agent	Eligible Cancer Type	Trial Phase
ONO-4538	Melanoma	II
MAGE-A3	Melanoma	III
BCX1777	T/NK-Cell Lymphoma	I
E7777	Peripheral/Cutaneous T Cell Lymphoma	I
Lenalidomide	ATL, Peripheral T Cell Lymphoma	I
KW0761	T/NK-Cell Lymphoma	II
RO5126766	Solid Tumors	I
RO4987655	Solid Tumors	I
WT4869	Solid Tumors	I
IMC-11F8	Solid Tumors	I
Romidepsin	Peripheral/Cutaneous T Cell Lymphoma	I/II
PF-00299804	Lung Cancer	III

Table 4. Survival rates

	Stage	2002-2007 Number of Patients	5-year Overall Survival Rates
Malignant Melanoma	Stage IA	25	100
	Stage IB	41	100
	Stage IIA	21	85
	Stage IIB	11	65
	Stage IIC	11	76
	Stage IIIA	26	61
	Stage IIIB	29	49
	Stage IIIC	25	60
Squamous Cell Carcinoma	Stage I	39	100
	Stage II	30	96
	Stage III	21	53

DEPARTMENT OF HEMATOLOGY, AND HEMATOPOIETIC STEM CELL TRANSPLANTATION, HEMATOLOGY DIVISION

Kensei Tobinai, Yukio Kobayashi, Takashi Watanabe, Sung-Won Kim, Dai Maruyama, Noriyuki Morikawa, Suguru Fukuhara

Introduction

The Hematology Division is united with the Hematopoietic Stem Cell Transplantation (HSCT) Division, and the research and clinical activity in the Hematology Divisions are devoted to the diagnosis and treatment of hematological malignancies. In the past, our Division introduced new 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). This Division is one of the leading hematology-oncology centers in the world, especially on lymphoid malignancies.

Routine Activities

The number of patients with newly diagnosed hematologic malignancies in the Division increased annually from 1997 to 2004, and then reached a plateau (Table 1). We hold a weekly case conference, where a summary of each hospitalized patient or outpatient 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 microscopic examination, and flowcytometric and molecular-genetic analyses. Five staff physicians, two chief residents, and one to three rotating residents are involved in these activities.

Research Activities

In addition to immunophenotypic analyses, molecular diagnosis is routinely performed, using polymerase chain reaction and fluorescence in-situ hybridization for the detection of t(8;14), t(14;18), t(11;18), t(9;22), t(8;21), t(15;17), and so on. Our recent research has focused on indolent B-cell non-Hodgkin lymphoma (B-NHL). Clinical as well as molecular and cytogenetic analysis of ocular adnexal mucosa-associated lymphoid tissue 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). We are extending the study to determine the spectrum with the mutated A20 gene. We have studied the mechanism of toxicities of bortezomib (Br J Cancer 2010;103:1580-7).

In 2011, we published 20 original articles, and have contributed to the refinement of some subcategories of peripheral T-cell lymphoma (Blood 2011;117:3402-8 / Blood 2011;118:148-55).

Clinical Trials

In 2011, we participated in 39 new-agent studies including 10 international studies, and 7

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

Disease	Year												
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Acute myelocytic leukemia (AML)	12	18	10	8	8	9	8	9	10	6	10	8	13
Acute lymphocytic leukemia (ALL)	6	3	8	3	2	1	2	4	9	8	2	2	1
Chronic myelocytic leukemia (CML)	15	9	24	11	7	5	6	10	11	3	3	2	2
Myelodysplastic syndrome (MDS)	9	9	8	5	6	5	3	3	9	8	20	9	3
Hodgkin lymphoma (HL)	10	10	14	15	16	9	13	21	11	12	7	11	16
Non-Hodgkin lymphoma (NHL)	133	204	215	268	291	299	278	265	210	208	151	185	243
Adult T-cell leukemia-lymphoma (ATL)	3	4	5	4	5	4	6	6	4	5	5	3	6
Chronic lymphocytic leukemia (CLL)	1	2	3	3	2	4	5	4	5	6	4	2	1
Multiple myeloma (MM)	7	7	8	6	9	19	14	9	8	10	12	9	10
Waldenström macroglobulinemia (WM)	3	1	1	1	1	1	0	0	2	3	1	2	2
Total	199	267	295	324	347	356	335	331	279	269	215	233	297

cooperative group studies (Tables 2 and 3). Almost all the new agents that are developed against hematological malignancies in Japan have been evaluated in our Division, and many of them have been approved by the Japanese Ministry of Health, Labour and Welfare (MHLW).

Bendamustine was recently approved by the MHLW, based on its high efficacy for relapsed indolent B-NHL and mantle cell lymphoma in our phase I and II trials (Cancer Sci 2010;101:2054-8 / Cancer Sci 2010;101:2059-64). The agent is now being applied to treat diffuse large B-cell lymphoma and multiple myeloma.

For myelodysplastic syndrome, a phase II study of a hypomethylating agent, azacitidine, was completed, leading to its approval by the MHLW (Cancer Sci 2011;102:1680-6). This year, a phase I study of oligopeptide vaccine against WT1 protein was initiated against acute myelocytic leukemia in complete remission. This is the first vaccine study against hematological malignancies aimed at approval in Japan.

For ATL, based on our published results of a phase III study, JCOG9801 (J Clin Oncol 2007;25:5458-64) and phase I and II studies of KW-0761, a humanized anti-CCR4 (CC chemokine receptor 4) antibody (J Clin Oncol 2010;28:1591-8), we completed patient enrolment to a randomized phase II study comparing an intensified regimen (mLSG15) with or without KW-0761. Based on the encouraging results of a pivotal phase II study against relapsed ATL (J Clin Oncol, in press), KW-0761 will soon be approved by the MHLW.

We have published the results of a phase II/III study to evaluate the dose-dense schedule of rituximab plus CHOP (R-CHOP) chemotherapy for untreated indolent B-NHL (JCOG 0203) (J Clin Oncol 2011;29:3990-8). Although the dose-dense R-CHOP-14 arm did not show superior progression-free survival to the standard R-CHOP-21 arm, the survival data are outstanding. JCOG 0203 has provided important evidence in the treatment of indolent B-NHL for the oncology society (J Clin Oncol 2011;29:3954-6).

Currently, a phase III trial for newly diagnosed diffuse large B-cell lymphoma (JCOG 0601) is

Table 2. Clinical trials for new agent development

Disease	Agents	Phase	Enrolled Patients in 2011	Enrolled Patients in Total
CML	Nilotinib	III	0	1
	Bostinib	I/II	0	2
MDS	Azacitidine	I/II	0	8
	Decitabine	I/II	0	7
AML	WT1 vaccine	I	1	1
MM	MP + Bortezomib	I/II	0	7
	Vorinostat + Bortezomib	I	0	2
	Bendamustine + PSL	II	0	1
	Carfilzomib	I	1	1
	Siltuximab	I	1	1
PTCL	Forodesine	I	0	2
	KW-0761 (ATL)	II	1	2
	KW-0761 (T/NK)	II	1	2
	Lenalidomide	I	1	2
	Romidepsin	I/II	0	0
	E7777	I	0	0
	Darinaparsin	I	0	0
CLL	Alemtuzumab	I	0	1
	Ofatumumab	I/II	0	1
FL	GA101	III	0	0
	CMC-544	III	3	3
	CMC-544 + R-CVP	I	3	8
	Rituximab	II	0	10
	Everolimus	I	0	4
	BM-ca	I	4	4
	Ofatumumab vs. Rituximab	III	10	10
Indolent B-NHL	Vorinostat	II	0	3
MCL	R + Bendamustine	II	0	0
	VcR-CAP	III	0	2
DLBCL	Enzastaurin	III	0	7
	Bendamustine + R	II	1	3
	Ofatumumab	III	0	0
	Everolimus	III	0	1
	CMC-544	III	3	3
CD30+ lymphoma	SGN-35	I	1	1
ML	Vorinostat	I	0	10
AML, ML, MM	OPB-51602	I	1	1

PTCL, peripheral T-cell lymphoma; FL, follicular lymphoma; B-NHL, B-cell non-Hodgkin's 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

ongoing, in which a dose-intense schedule of rituximab in R-CHOP is being compared with that of a standard 3-week R-CHOP regimen. We are also conducting a phase II study of a rituximab-incorporating dose-intensified chemotherapy for untreated mantle cell lymphoma (JCOG 0406).

To develop new effective treatments for B-cell malignancies, we have investigated an anti-CD22 chemoimmunoconjugate (Cancer Sci 2010;101:1840-5), as well as new generation anti-CD20 antibodies (Cancer Sci 2011;102:432-8). Recently we initiated several new agent studies for T-cell malignancies, including forodesine, lenalidomide, romidepsin, darinaparsin, pralatrexate and denileukin difititox. Our continuous efforts will contribute to the further improvement of therapeutic outcomes of patients with hematologic malignancies, world-wide.

Table 3. Cooperative group studies

Disease / Protocol	Phase	Year	No. of pts (a)	%CR (b)	OS (b)
AML					
JALSG-AML 95	III	(96-97)	6	81%	40% (4-yr)
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	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
CML					
JALSG-CML 207	III	(08-10)	1	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					
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-)	23	NA	NA
JCOG 0406	III	(08-)	4	NA	NA
JCOG 0908	III	(08-)	6	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)
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	Iic	(09-)	4	NA	NA

(a) the number of patients enrolled from our Division; (b) As the number of enrolled patients in our Division is relatively small, the %CR or OS for the entire group of patients enrolled 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

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DEPARTMENT OF HEMATOLOGY, AND HEMATOPOIETIC STEM CELL TRANSPLANTATION, HEMATOPOIETIC STEM CELL TRANSPLANTATION DIVISION

Takahiro Fukuda, Yuji Heike, Takuya Yamashita, Sung-Won Kim, Saiko Kurosawa, Nobuhiro Hiramoto

Introduction

At the National Cancer Center Hospital, the Hematopoietic Stem Cell Transplantation (HSCT) Division specializes in patients who undergo allogeneic or autologous HSCT. Twenty-six beds in ward 12B and an additional 3 beds on ward 11A, filtered by a central high-efficiency particulate air filtration system, are solely dedicated to our Transplant Unit.

Routine Activities

Six staff physicians (Drs. Heike, Yamashita, Kim, Kurosawa, Hiramoto, and Fukuda) participate in the transplant program. Children who undergo HSCT are managed in collaboration with the transplant team and Dr. Makimoto, the Chief of Pediatric Oncology Division. In 2011, a total of 101 transplantations were performed. The numbers of each type of HCST and those of HSCT recipients with each disease type in recent years are shown in Tables 1 and 2, respectively. Of note, 54 patients underwent HSCT from unrelated bone marrow donors in 2011, which was the highest level of activity in Japan. At the weekly conference on Monday afternoons, in collaboration with doctors of the Hematology Divisions, about 30 hospitalized HSCT patients and those who were referred for HSCT are reviewed for clinical management and a decision regarding their eligibility for HSCT. The transplant unit is staffed by 26 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. 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 a reduced-intensity stem cell transplant (Mini-transplant) for elderly patients. Three staff physicians (Drs. Heike, Yamashita, and Fukuda) are principal investigators for the Government supported grant projects. Dr. Heike has organized a cell processing facility on the adjoining 12th floor and a facility on the 11th floor specializing in gene therapy in compliance with good manufacturing procedures (GMP). Currently, two clinical trials of gene therapy using the HSV-TK suicide gene are ongoing: one is for donor lymphocyte infusion after related HSCT, and the other is for T-cell add-back following haploidentical HSCT. A clinical trial of post-transplant consolidation with the WT1 vaccine is also ongoing. We have been working on expansion of the indication of drugs used for the treatment of GVHD and infections. In May 2011, foscarnet, an anti-viral agent, was approved for cytomegalovirus infection after HSCT. A prospective feasibility study of the LTFU system after HSCT was approved by the institutional IRB, and will be started in 2012. A nationwide large survey of quality of life (QOL) has been conducted for patients with acute leukemia who received chemotherapy or HSCT. In the Division, about 13 clinical trials are ongoing. In 2011, we have published 7 articles in peer-reviewed international journals and 5 manuscripts have been accepted for E-pub or are in press for publication.

Table 1. Number of each type of HSCT

Year		2008	2009	2010	2011
Allogeneic		77	93	90	76
Unrelated	Bone marrow transplantation	48	59	60	54
	Peripheral blood stem cell transplantation	1	0	0	0
	Cord blood transplantation	1	5	1	4
Related	Bone marrow transplantation	5	2	5	2
	Peripheral blood stem cell transplantation	22	27	24	16
Autologous		8	18	19	25
Total		85	111	109	101

Table 2. Number of patients who underwent HSCT between 2008 and 2011.

Diagnosis	Allogeneic	Autologous
Acute myeloid leukemia	137	1
Myelodysplastic syndrome	29	
Acute lymphocytic leukemia	48	
Malignant Lymphoma (including ATL)	114	39
Multiple Myeloma		16
Solid tumors	2	14
Others	6	
Total	336	70

Published Papers

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DEPARTMENT OF PEDIATRIC ONCOLOGY

Atsushi Makimoto, Ako Hosono, Hiroshi Kawamoto, Yuki Yamamoto, Koji Suzuki, Chika Tanaka

Introduction

Pediatric oncology includes a wide variety of malignancies in children and adolescents such as acute leukemias and malignant lymphomas, as well as solid tumors such as soft tissue sarcomas, neuroblastomas, Wilms tumors and retinoblastomas. All diseases are usually highly chemo-sensitive and curable with appropriate multi-disciplinary treatment. Doctors in the Pediatric Oncology Division manage pediatric cancer patients who are treated with multi-agent chemotherapy, which is usually more toxic than that in adult oncology, as well as with surgery and radiotherapy, which is always radical and sometimes toxic. Hematopoietic stem cell transplantation (SCT) is sometimes indicated in both hematologic malignancies and solid tumors. Regardless of the disease, pediatric oncologists face all of the medical and psychosocial problems in children with cancer with the support of nurses and other medical staff.

The Pediatric Oncology Division includes three staff physicians and two chief residents. The number of doctors does not increase due to the rarity of the diseases. This division handles about 80 patients with pediatric malignancies per year, who are referred from hospitals located throughout Japan and other Asian countries. Due to the need for intensive chemotherapy, most of the patients have to be hospitalized in the pediatric ward (12A). If a patient needs allogeneic SCT, he/she will be transferred to the transplantation ward (12B).

A special nursing care system in the ward helps young patients and their families physically as well as psychologically. Nurses provide appropriate information to help patients and families maintain an ideal relationship. To enhance the quality of hospital life for young patients, educational opportunities ranging from elementary school to high school are available in the pediatric ward, where 8 teachers work daily.

Routine Activities

The pediatric outpatient service is open from Monday through Friday to treat new patients and to provide follow-up treatment to patients who have completed intensive treatment. The pediatric staff and trainees discuss various issues regarding pediatric inpatients on daily rounds. Patients undergo various procedures in a timely manner, sometimes under IV sedation. These procedures include diagnostic bone marrow aspiration/biopsy, central venous catheter placement, and lumbar puncture/intrathecal chemotherapy. A Pediatric Conference is held every morning, mainly to decide upon individual treatment plans. Inter-department conferences between orthopedics, radiation oncology, and palliative care are individually scheduled on a biweekly basis.

The common approach to these diseases is "risk-adapted therapy" regarding long-term life expectancy. Patients receive multidisciplinary therapy, including surgical removal of the tumor, radiation therapy, chemotherapy, and sometimes SCT, as indicated.

The Sarcoma Hot-line, which accepts inquiries and consultations from outside doctors and patients (both children and adults) by phone, is open from Monday to Friday under the management of this division.

Research Activities

I. Designing and planning of clinical trials in a multicenter setting

The Pediatric Data Center (DC) for collaborative pediatric groups, which is independent of the Japan Clinical Oncology Group (JCOG), was established in 2004 with a Grant-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare. Although the DC was transferred to the non-profit organization "Support Unit for Childhood Cancer with Effective Strategy and Solution (SUCCESS)" in 2009, management of the DC is one of the research activities. The DC provides expertise in data management and facilitates administrative matters related to clinical trials. Moreover, the DC studies the methodology of clinical trials. Currently, this DC is managing 2 clinical trials, which are described in the following section.

II. Ancillary studies associated with retrospective case series and clinical trials

(1) Pathology review of case series to identify

correlations between specific molecules and survival.
(2) Determination of the diagnostic value of PET scans for pediatric solid tumors.
(3) Establishment of standard supportive and palliative care for pediatric cancer patients including a special "cosmetic program" for adolescent patients.

Clinical Trials

This department is expanding its focus to include treatment development using relatively new off-label drugs. One of the objectives of the following trials is gathering data on, and assessing the safety and efficacy data of, such off-label drugs.
(1) Phase I-II trial of the combination of topotecan and ifosfamide for recurrent pediatric solid tumors.
(2) Randomized phase II study of two cross-over sequences comprising vinorelbine/cyclophosphamide and temozolomide/etoposide in the outpatient setting for relapsed or refractory solid tumors in children and young adults.
(3) Phase I trial of immunotherapy using HLA-A2- and A24-restricted glypican-3 peptide vaccine for pediatric tumors.

Published Papers

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Table 1. Number of patients

Diagnosis	Newly diagnosed	Pretreated
Rhabdomyosarcoma	7	3
Ewing sarcoma family	6	2
Osteosarcoma	6	2
Neuroblastoma	3	3
Retinoblastoma*	1	1
Germ cell tumor	3	0
Other solid tumors	9	3
Acute lymphoblastic leukemia	0	1
Acute myeloid leukemia	1	1
Non-Hodgkin lymphoma	4	1
Other hematologic diseases	1	0
Total	33	22

*; extended case only

Table 2. Type of procedures

chemotherapy	49
chemotherapy and stem cell transplantation	7
surgery	20
others	3

Table 3. Survival rates (acturarial, 2000-2005)

Diagnosis	Number of pts	5-yr survival (%)
Rhabdomyosarcoma	31	51
Ewing sarcoma family	17	70
Osteosarcoma	8	63
Neuroblastoma	9	44
Non-Hodgkin's Lymphoma	26	85
Acute lymphoblastic leukemia	22	77
Acute myeloid leukemia	8	63

DEPARTMENT OF INTERNAL MEDICINE, GENERAL INTERNAL MEDICINE DIVISION

Masaaki Shoji, Ken Ohashi, Keiichiro Osame, Yukiko Okazaki, Kiyotaka Watanabe, Keiji Okinaka, Tomokazu Matsuura

The Department of Internal Medicine was reorganized in October 2010 to better serve the diverse needs of cancer patients and provide more comprehensive, patient-centered care. The Department consists of the following three divisions.

Indroduction

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. In 2011, four specialists joined the team. Our staffs have experience and expertise in their respective field 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 NCCH.

In 2011, we have expanded diabetes consultation service into NCC Hospital East, improving the quality of diabetes care there.

DEPARTMENT OF INTERNAL MEDICINE, GENETIC COUNSELING DIVISION

Teruhiko Yoshida, Kokichi Sugano

Introduction

Cancer, like many other multi-factorial or common diseases, arises through a complex interplay among life style/environmental factors, genetic predisposition and aging. Cancers are typical polygenic diseases, and an obvious family history (such as 3 or more patients with the same or related cancer types within the 2nd-degree relatives) is not evident in more than 95% of the so-called sporadic cases. However, monogenic Mendelian inheritance patterns have been recognized for certain cancer families. Clinical cancer genetics has been a part of the outpatient service in the National Cancer Center Hospital (Tsukiji) since 1998 as a close collaboration with the Division of Genetics, National Cancer Center Research Institute.

Routine Activities

The major mission of the clinic in a daily practice is to provide cancer genetic counseling in a broad sense, and the clinic accepts any request for information, consultation and other assistance to deal with the clients' concern regarding their own genetic risk or that of their family members. The presence of a nurse with an interest and training in clinical genetics is critical to assist the counseling sessions. Based on a family history, age at diagnosis, type and pattern of cancer development such as multiple primaries, and other accompanying signs and symptoms, genetic risk for the possible hereditary cancer syndromes will be assessed for the clients, followed by explanation of available and appropriate genetic testing, if applicable. Both pre- and post-genetic test counseling is essential to make the genetic testing useful and fruitful to the clients in the long run.

Research Activities

The Division has been participating in several multi-center research activities related to the psychological impact of genetic testing, spectrum of manifestations of hereditary cancer syndromes, and evaluation and development of genetic testing methods. One of the major targets is hereditary retinoblastoma, because about half of the newly diagnosed cases in Japan will visit National Cancer Center Hospital to seek the highly advanced treatment available at the Department of Ophthalmic Oncology. Incidence of retinoblastoma

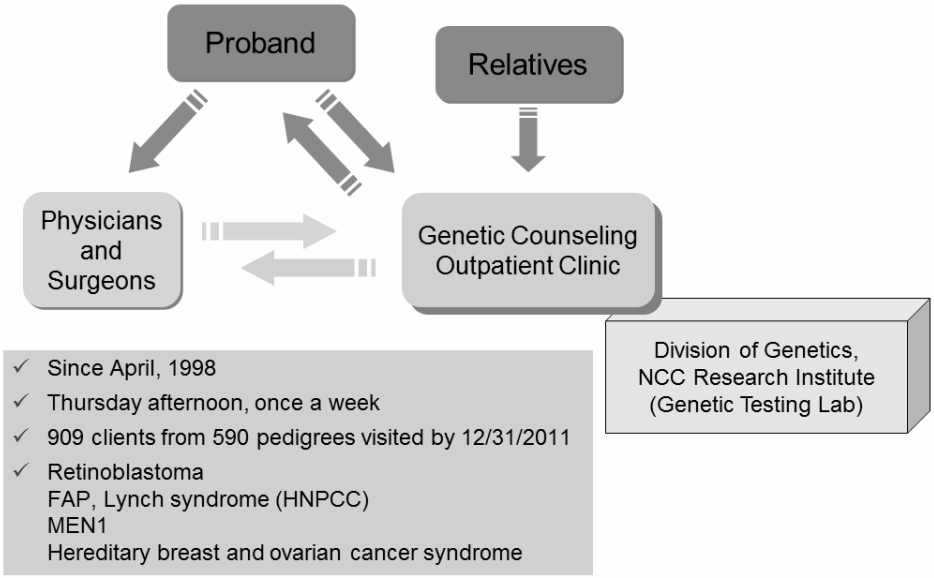

Figure 1. An outline of genetic counseling clinic at NCC hospital

is about 1/16,000-20,000 births, and all bilateral and 10-15% of unilateral retinoblastomas are hereditary with a germline inactivating mutation of the *RB1* gene. Fig. 1 illustrates the current scheme of *RB1* genetic testing. The overall detection rate of the accumulated cases was 64/67 (96%) for bilateral cases and unilateral cases with family history but 3/29 (10%) for unilateral cases without family history. Carrier diagnosis was performed on 93 individuals, including 14 newborns from 11 pedigrees using cord blood samples. Because sensitivity is not sufficient for each single test, and detection of mosaicism and splicing aberration requires FISH and RT-PCR, respectively, the combination of multiple tests is necessary.

Clinical Trials

No clinical trial was performed in 2011.

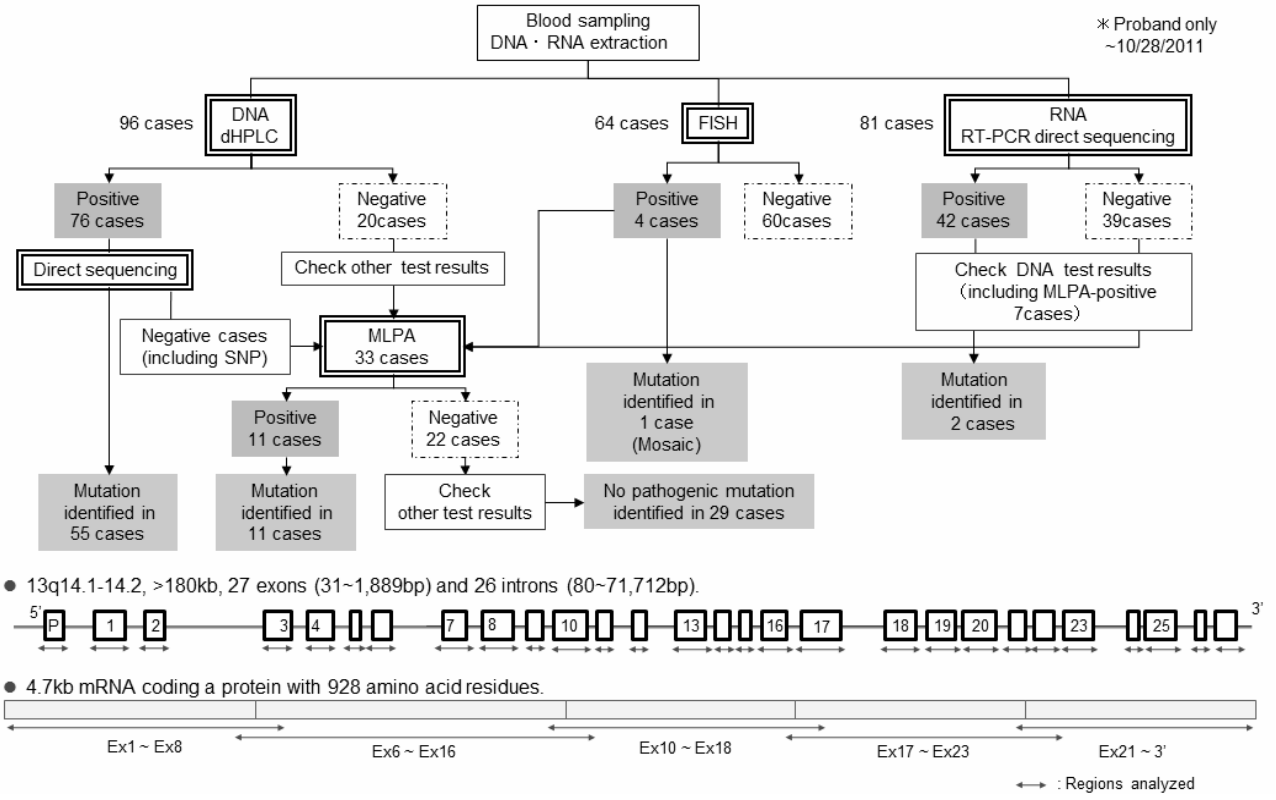

Figure 2. Flowchart of genetic tests for hereditary retinoblastoma.

Table. Number of patients

Type of Disease	Proband	Relative	Total
Lynch syndrome (Hereditary Non-Polyposis Colon Cancer; HNPCC)	11	8	19
Familial Adenomatous Polyposis (FAP)	5	4	9
Retinoblastoma	6	14	20
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	8	3	11
MEN I (Multiple Endocrine Neoplasia Type I)	0	0	0
Other diseases	7	0	7
Counseling only	1	0	1
Total	34	15	49

DEPARTMENT OF INTERNAL MEDICINE, DENTAL DIVISION

Takao Ueno

Introduction

Oral complications are common in patients receiving chemotherapy or undergoing radiation therapy of the head and neck. To prevent and treat oral complications of cancer therapy, we check the oral conditions of the patients, identify the patients at risk, start preventive measures before cancer therapy begins, and treat complications as soon as they appear. Continuing good oral hygiene during cancer treatment can reduce oral complications such as mouth sores, oral mucositis, and infections.

Routine Activities

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 bisphosphonate-associated osteonecrosis
6) Cooperation business of a medical department and dentistry in the Kanto area (for the solution to dental problem of the cancer patient)

Research Activities

Research into the treatment of, and preventive steps against oral complications due to cancer treatment is performed with pan-specialty cooperation.

1) So that all cancer patients may receive dental support during cancer treatment, a coordinated approach has been started with the Japan Dental Association. Problems in the construction of a medical-dental coordinated system are under study.
2) Prospective study about the onset frequency of pneumonia after the operation of esophagus cancer
3) Prospective study of the taste disorder in the stomach cancer adjuvant postoperative treatment

Table. Number of patients

Management of oral complications	622
Introduction to the cooperation dental clinic（oral health care before operation）	306
Total	928

DEPARTMENT OF ANESTHESIOLOGY AND INTENSIVE CARE UNIT, ANESTHESIOLOGY DIVISION

Tetsufumi Sato, Yoko Kinoshita, Tsukasa Satake, Nobuko Yokokawa, Rie Suzuki, Minako Arai, Nohito Tanioka, Yosuke Kawaguchi, Shinji Sugita, Fumie Yamazaki, Keisuke Ishikawa, Kazuhito Mietani, Masashi Yanagi, Megumi Sekikawa

Introduction

The purpose of anesthesiology is to preserve breathing, circulation, and a consistent metabolic state necessary for a person to survive perioperatively. As anesthetists we must prevent any noxious vital reaction due to surgical stress and we must maintain the optimum and safe environment in which the patient is to undergo surgery. The main function of our Division is anesthesia management in the operating room, and we normally perform general anesthesia for 4,000 cases a year or more, and additionally give sedation (approximately 100 a year) during the endoscopic operations performed out of the operating room.

The Division is currently getting ready to introduce improved and state-of-the-art clinical monitoring and information integration systems, namely ORSYS (Philips Japan), designed to automate most intraoperative documentation, and PIMS (Philips Japan) designed to handle the clinical information of patients in the ICU. We will be able to focus even more than before on our patients.

Routine Activity

We hold daily conferences every morning and examine the case of the day, and host a journal club twice a week. An average of 30 daily elective operations are managed, and our Division is ready at any time to support emergency surgery. Preoperative evaluation of the next day's cases and postoperative rounds are performed after surgery.

Research Activity

1) Examination of safe sedative methods for endoscopic operations
2) In cooperation with fundamental university-based studies, we are examining the pituitary function in various kinds of pain

Clinical Trials

1) Examination of the scoring induction for preoperative risk

Table. Number of patients

Surgery in the operation room	4520
General anesthesia	1487
General anesthesia with epidural anesthesia	2450
Epidural anesthesia	6
Epidural anesthesia with spinal anesthesia	5
Spinal anesthesia	144
Others	2

DEPARTMENT OF ANESTHESIOLOGY AND INTENSIVE CARE UNIT, INTENSIVE CARE UNIT

Daisuke Yamaguchi, Yousuke Kawaguchi, Shinji Sugita, Keisuke Ishikawa, Kazuhito Mietani, Tetsufumi Satou

Introduction

The Division of Intensive Care Medicine consists of 6 full time staff members and 5-6 rotating residents who receive critical care medicine training. Since June 2009, we have conducted all patient managements in ward 8A at all hours as a closed management ICU. Compared with other cancer centers in Japan, by providing the largest number of professional staff including intensivists and anesthesiologists, we provide multidisciplinary intensive care. In addition to post surgical patients, without regard to surgical or medical, we treat severe and life-threatening inpatients with acute respiratory failure, septic shock, acute kidney injury, acute hepatic failure, or multiple organ dysfunction which are caused by various types of pathophysiological entities.

Routine Activities

A division conference is held every morning which is attended by intensivists, anesthesiologists, surgeons, physicians, psychiatrists, ICU nurses, staff of the medical engineer division, and other specialists who are involved in the intensive care treatment. We discuss the treatment plans for all ICU patients of the day, with particular attention to critical or life-threatening cases. For these patients, careful management with multidisciplinary cooperation is essential. We are frequently consulted about patients in critical condition who require intensive care, and we discuss these cases at any time. The timing of ICU admission and the treatment plan in our division are also discussed at this conference.

Highly-advanced medical treatments in our ICU include some types of mechanical ventilation especially for acute lung injury patients, renal replacement therapy including continuous hemofiltration and plasma exchange, cardiovascular support for patients with the use of various vasoactive and inotropic agents, temporary pacing devices, and even percutaneous cardiopulmonary bypass (A-V ECMO systems). In performing and delivering these ICU treatments, we observe evidence-based critical care medicine according to the latest guidelines.

From April 2010 to March 2011, 306 new patients were admitted to the ICU, with a total of 1,294 patients treated in our ICU. Of these, although 60% of the admissions were post-surgical status, we treat not only surgical patients but sudden medical change inpatients or outpatients who require chemotherapy, and even oncology emergency patients who have been brought to the ER by ambulance.

With the exception of routine post surgical management, the most frequent cases which require admission to our division are patients with severe respiratory failure as typified by acute lung injury (ALI/ARDS), acute exacerbation of idiopathic pulmonary fibrosis (IPF) and acute interstitial pneumonitis (AIP). As these severe respiratory failure patients often require prolonged mechanical ventilation, we aggressively provide early mobilization of mechanical ventilated patients in cooperation with physiotherapists even if they are intubated and sedated.

Secondly, severe sepsis and septic shock in post surgical patients or neutropenic patients who have hematological disease or who are given chemotherapy have accounted for more than 70 cases per year. We provide sepsis treatments following the Surviving Sepsis Campaign Guidelines (so called “SSCG2008”), and sometimes resuscitate patients with life-threatening sepsis.

Blood purification therapy is one of the important functions in our ICU. In cooperation with the medical engineering division, we provided renal replacement therapy (mainly continuous venovenous hemodiafiltration), plasma exchange, and polymyxin B hemoperfusion for more than 80 cases since June 2009.

If a cardiovascular event occurs, for example acute coronary syndrome or severe congestive heart failure which requires catheter intervention or mechanical cardiac support devices, our intensivists transfer these patients to a cardiac specialized hospital with thorough medical safety management, as if it were a “mobile ICU”.

Critical Care Medical (CCM) training to rotating residents is also important work for us. Both surgical and medical residents must receive CCM training for 2 or 3 months during their first year. Our ICU is a really adequate environment for them to learn oncology emergency and critical care

medicine. We restrict resident duty hours according to the recommendations of The Accreditation Council for Graduate Medical Education (ACGME) in the USA, and provide CCM training program with reference to the educational guidelines of Society of Critical Care Medicine (SCCM) in the USA.

Perspective

In recent years, as the number of operations performed in our hospital has rapidly increased, a concomitant increase has also been seen in the number of patients who require intensive care treatment. Therefore, the significance of the function of our ICU in the hospital has been well-recognized.

Since December 2010, the Rapid Response System (so called "ER call") was established, and at the same time our Medical Emergency Team was organized with a core of intensivists.

The number of ICU beds was expanded from 4 to 8 in November 2011. We are totally prepared to go to greater effort for all cancer patients who require critical care.

Department of Palliative Care and Psycho-Oncology, Palliative Care Division

Motohiro Matoba, Osamu Saito, Satoshi Murakami, Kosuke Miura, Chio Shuto

Introduction

It was in June, 1999, that a palliative care team was established as a multi-disciplinary team, and the Department of Palliative Care and Psycho-Oncology was established in April, 2010, with the reorganization of the National Cancer Center Hospital. The team provides palliative care to attenuate the total pain of cancer patients and their families. About 300 patients yearly are referred to the division mainly for pain management. As a multi-disciplinary team, we provide palliative care for total pain which includes physical, psychological, social, and spiritual pain. Other than physicians, various paramedical professionals such as psychiatrists, pharmacists, acupuncturists, psychologists, cosmetic specialists, and social workers take part in the team. Under the auspices of our team, regular seminars and conferences are held to facilitate the partnership with other hospitals and organizations.

Routine Activities

The main routines of the team are to manage the symptoms of terminal patients and to educate the residents to get them to acquire the knowledge and skills required of a palliative care physician. We are usually in charge of about 30 inpatients, and make a morning round and hold conferences twice-daily. In the outpatient department, we treat approximately 20 patients per week. Besides conventional drug therapy, we perform various neuronal blockades, place emphasis on mental support for the patient and their families and sometimes refer the patients to the Division of Psycho-Oncology, Department of Orthopedic Surgery, Department of Pediatric Oncology and Department of Diagnostic Radiology to attain better symptom management. For the porpose of equilibration of palliative medicine, bimonthly conferences are held, and consequently coordination with the community palliative care in the vicinity is strengthened.

Education for Residents

With regard to their clinical education and training, all the residents of the NCCH are required to train with our team for 1 month, within which a one-week home hospice course is mandatory. In total, 25 residents trained with our team during 2011. The course is whole-person-care oriented. The home hospice course offers an opportunity to understand the role of various occupations other than doctors, such as visiting nurses and care managers. Moreover, a summer training program is carried out for medical students and junior residents. Four medical students and 2 junior residents participated in the program during 2011.

Research Activities

Several translational studies are ongoing in collaboration with the Cancer Pathophysiology Division in the National Cancer Center Research Institute, Hoshi University, Chiba University, and Nihon University.

The effect of lidocaine on the adverse symptoms of cancerous peritonitis, the impact of adjuvant analgesics on sleep disturbance associated with neuropathic pain, the effects of ketamine on pain on movement using the novel spinal bone metastasis model which was developed by us, impact of capsaicin on TRPV-1, and the role of glia cells in cancer pain have been investigated.

Clinical Trials

The main purpose of our clinical trials is to develop a standard therapy to ameliorate terminal symptoms. We have been investigating the usefulness and efficacy of adjuvant analgesics for neuropathic pain, the effect of ketamine on the pain of patients with spinal bone metastasis, the palliation of breathlessness with intravenous trometamol and inhaled furosemide, and the efficacy of oral transmucosal fentanyl citrate (OraVescent fentanyl; OVF). In addition, we have investigated the efficacy and safety of oxicodene injection and presented our findings at the 12th congress of the European Association for Palliative Care.

Table 1. Number of patients.

Lung cancer	43
Sarcoma	38
Rectal cancer	21
Breast cancer	20
Leukemia	16
Uterine cancer	16
Renal cancer	13
Gastric cancer	9
Pancreatic cancer	8
Colon cancer	8
Gallbladder cancer	8
Bladder cancer	8
Esopahageal cancer	8
Malignant lymphoma	6
Primary unknown cancer	6
Prostate cancer	5
Multiple melanoma	4
Ovarian cancer	4
Malignant melanoma	2
Liver cancer	2
CNS cancer	2
Skin cancer	2
Bone cancer	2
Head and neck cancer	2
Others	36
Total	289

Table 2. Type of procedure

Adjustment of non-opioid analgesics	76
Commencement of opioid analgesics	22
Adjustment of opioid analgesics	92
Opioid rotation	38
Adjustment of adjuvant analgesics	61
Nerve block	13
Management of side effect of analgesics	71
Other symptom management	6
Reference to other specialists	8
Others	2

Published Papers

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DEPARTMENT OF PALLIATIVE CARE AND PSYCHO-ONCOLOGY, PSYCHO-ONCOLOGY DIVISION

Ken Shimizu, Yu Yamada, Masashi Kato, Yoshio Oshima

Introduction

The Psycho-Oncology Division was reestablished in September 1995, together with establishment of the Psycho-Oncology Division, National Cancer Center Research Institute East (reorganized to Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East in 2005). One of the most important clinical activities of the Psycho-Oncology Division is the management of cancer patients' behavioral and social problems as well as their psychological distress. Furthermore, this division's aim is to alleviate 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 Psychiatry Division consists of two full time staff psychiatrists, one part time psychiatrist and one clinical resident. Two part-time psychotherapists are available four days a week. The division provides two major services; a clinic for outpatients (four 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 division has played an active role as a member of the palliative care team.

The range of psychiatric diagnoses is based on the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) shown in the Table. In 2011, a total of 641 patients were referred for psychiatric consultation. The mean age was 66 years and 22.8% percent of the referrals were outpatients. Three hundred and thirty-three (52.0%) of the total number of referred patients were males. The most common psychiatric diagnosis was delirium (26.4%), followed by adjustment disorders (25.4%), and major depression (8.3%), while 8.0% of the referrals had no psychiatric diagnosis. The three common mental disorders, adjustment disorder, major depression and delirium, were responsible for half of the psychological problems. The most common cancer referrals were patients with hematological cancer (11.7%), followed by lung cancer (11.2%), breast cancer (8.6%), esophageal cancer (7.6%) and stomach cancer (6.7%).

A clinical and research activities conference is held every Thursday evening with staff members from the Psycho-Oncology Division of the National Cancer Center Hospital East, the psychiatry division of the Chugoku Cancer Center, plus members of the Kyushu Cancer Center, Saitama Cancer Center, Hokkaido Cancer Center, Chiba Cancer Center, Hiroshima University, Chiba cancer center, and Nagoya City University Graduate School of Medical Sciences. Difficult cases are discussed with the attendees. Ongoing and planning protocols are also discussed. Important relevant articles from international medical journals are reviewed together with the members of the Psycho-Oncology Division of the National Cancer Center Hospital East every Tuesday evening. Additionally, the members of the division have played active roles in the palliative care team. There is a joint meeting with other members of the team every Friday evening.

Research Activities

Although implementation of routine screening for cancer patients' distress is desirable, it is hard to perform adequately in a busy clinical oncology practice. We are now developing Distress Screening tools which can be practical in the real world, the purpose of which is to facilitate treatment for patients with major depression and adjustment disorders, and we have proved the feasibility and usefulness of these tools.

Table 1. Patient demographics

Patients	Total number	641	
	Age	66 years	
	Male	333	52.0%
	Inpatients	495	77.2%

Table 2. Number of cancers by site

Cancer site	Hematological	75	11.7%
	Lung	72	11.2%
	Breast	55	8.6%
	Esophageal	49	7.6%
	Stomach	43	6.7%

Table 3. Breakdown of diagnoses

Diagnosis	Delirium	169	26.4%
	Adjustment Disorders	163	25.4%
	Major Depression	53	8.3%
	No Diagnosis.	51	8.0%

Published Papers

1. Ito T, Shimizu K, Ichida Y, Ishibashi Y, Akizuki N, Ogawa A, Fujimori M, Kaneko N, Ueda I, Nakayama K, Uchitomi Y. Usefulness of pharmacist-assisted screening and psychiatric referral program for outpatients with cancer undergoing chemotherapy. Psychooncology, 20:647-654, 2011

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3. Kobayakawa M, Inagaki M, Fujimori M, Hamazaki K, Hamazaki T, Akechi T, Tsugane S, Nishiwaki Y, Goto K, Hashimoto K, Yamawaki S, Uchitomi Y. Serum brain-derived neurotrophic factor and antidepressant-naive major depression after lung cancer diagnosis. Jpn J Clin Oncol, 41:1233-1237, 2011

DEPARTMENT OF DIAGNOSTIC RADIOLOGY

Yasuaki Arai, Masahiko Kusumoto, Yoshito Takeuchi, Yasunori Mizuguchi, Kenichi Takayasu, Gen Iinuma, Hiroaki Kurihara, Hirokazu Watanabe, Tomoko Manabe, Yoko Kawawa, Kentaro Shibamoto, Keitaro Sofue, Mototaka Miyake, Hiroaki Onaya

Introduction

The Department of Diagnostic Radiology offers a wide range of modalities, including interventional radiology (IR), general radiology, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, mammography and nuclear medicine. 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.

Routine Activities

	Modality	Number of examinations
1	CT	38,857
2	MRI	7,731
3	IR	4,025
4	RI	4,294
5	Ultrasound	12,003
6	Radiograph	78,397
7	Gastrointestinal study	2,493

Research Activities

Because of their increased signal to noise ratio, 3.0 T MR machines have improved the ability to detect disease. We have been studying the efficacy of high resolution MR mammography using 3.0 T MRI for the detection and the lesion distribution of invasive ductal cancer or DCIS. Nowadays, we are also investigating the efficacy of the prediction of neo-adjuvant chemotherapy using breast MR spectroscopy.

We have also been performing studies into the efficacy of the detection of liver metastases using Gd-EOB-DTPA-enhanced 3.0 T MR imaging. Prospective studies were performed to compare the images on Gd-EOB-DTPA-enhanced MR imaging for chronic liver disease with 1.5 T and 3.0 T systems.

We have correlated the MR imaging findings with the histopathological findings of ovarian endometrioid tumors, borderline malignancy and ovarian mucinous borderline tumors of the intestinal type to clarify the characteristics of these diseases and to make accurate diagnoses.

CT colonography (CTC) has been developed in the NCC as a new diagnostic technology for the evaluation of colorectal lesions. With the use of 64 multi-slice CT, more than 500 early colorectal cancers have been examined using CTC from 2008 to 2011. We have started a collaboration study with Chicago University to investigate computer-aided detection (CAD) in CTC since last year. Moreover, we have accomplished tagging and electronic cleansing, also CO_2 insufflation systems for standard and efficient CTC preparation. We successfully introduced CTC into colorectal screening in our screening center in 2010, and are now further developing the effective diagnostic methods for the screening process.

Another new CAD systems for lung cancer using MDCT data have been developed in collaboration with Faculty of Engineering in Tokushima University. A newly developed software for lung nodule detection was revised, and a new method of quantitative classification based on CT histogram analysis of lung cancer was proposed.

The Japan RECIST working group improved the tumor response evaluation computer system, which is capable of semiautomatic RECIST evaluation and is compliant with DICOM (Digital Imaging and Communications in Medicine) data.

A multi tracer consisting of F-18 FDG, C-11 choline, C-11methionine and Cu-64 DOTA-antibody PET imaging has been studied for cancer patients to improve the sensitivity and specificity of detecting tumor sites or tumor characteristics. F-18 FDG dynamic PET sampling with Patrak-plot analysis allows us to calculate the glucose metabolic rate of the tumor site. Respiratory-gated PET/CT was evaluated to reduce breathing-induced artifacts using a four-dimensional PET/CT protocol. It provided better localization and quantization of tumors around the lower thorax to the upper abdomen. Another radiopharmaceutical for PET, F-18 FBPA, a derivative of phenylalanine and also an essential evaluator for BNCT, has been synthesized in the hospital, and is waiting for IRB approval for clinical use.

TACE is widely performed for patients with unresectable HCC and has recently been

recommended for those with 2 or 3 tumors >3cm or >=4 tumors in a treatment algorithm proposed by Japanese guidelines. In 4966 HCC patients with no vascular invasion or extrahepatic metastasis who underwent TACE, patients were stratified to two categories of TACE and survival rates were evaluated. The three-year survival for 2 or 3 tumors >3cm or >=4 tumors was 55% and 46% in Child-Pugh A, respectively and 30% and 22% in class B, respectively. These results would help in comparing the outcome of TACE in the East and West, since the treatment algorithm of Japanese guidelines and Barcelona Clinic Liver Cancer (BCLC) staging system might be almost identical.

Clinical Trials

In addition to many company oriented clinical trials, ten clinical trials on interventional radiology are ongoing in the NCC as the flagship hospital of a multi-institutional cooperative study group (JIVROSG: Japan Interventional Radiology in Oncology Study Group): a phase I/II study of RFA for intrapelvic malignant tumors (JIVROSG-0204); a phase I/II study of RFA for malignant bone tumors (JIVROSG-0208); a phase III study evaluating the efficacy of hepatic arterial infusion chemotherapy for metastatic colorectal cancer patients with unresectable liver metastases (JIVROSG-0606); a phase I/II study of RFA for malignant renal tumors (JIVROSG-0701); a phase I/II study of RFA for malignant lung tumors (JIVROSG-0702); 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); a phase III study evaluating the efficacy of stenting for malignant colorectal stricture (JIVROSG-0806); and a phase III study evaluating the efficacy of stenting for SVC/IVC syndrome (JIVROSG-0807).

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DEPARTMENT OF RADIATION ONCOLOGY

Jun Itami, Minako Sumi, Yoshinori Ito, Hiroshi Mayahara, Madoka Morota, Naoya Murakami, Yuki Kuroda

Introduction

The role of the Department is to provide state of art radiation therapy for all relevant patients, to educate and develop the expertise of radiation oncologists, and to lead new developments in radiation oncology both in Japan and worldwide. All Departmental Activities are dedicated to Cancer Patients. In this year, a new building for hospital-based boron neutron capture therapy (BNCT) using an accelerator was begun, and will be finished in 1.5 years. The Department will be fully involved in the development of BNCT.

Routine Activities

The Department of Radiation Oncology of the National Cancer Center Hospital is one of the biggest radiation oncology departments in Japan. Four linear accelerators, one X-ray simulator, one XCT-simulator and 7 treatment planning computers are working together under on-line networks to provide state-of-art precision external beam radiation therapy. In 2010, the X-ray simulator was updated to the newest machine, the Accusim from Varian. In addition to the conventional X-ray and electron therapies, stereotactic irradiations of brain and body tumors and intensity-modulated radiation therapy (IMRT) are employed to improve local control. Stereotactic brain irradiation was originally invented in this Department under the name of stereotactic multiarc radiation therapy (SMART) and has been employed 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. Three of the 4 linear accelerators have on-board kilovoltage CT imagers, which help to align patient and tumor coordinates precisely with the coordinates at the time of simulation. 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. From Dec. 2011, gold markers have been implanted to improve geometric precision of radiation field reproducibility.

Brachytherapy is also performed very frequently to obtain local control. For brachytherapy the following modalities are being employed, an Ir-192 high dose rate (HDR) afterloading system including a dedicated CT simulator and fluoroscopy, an I-125 seed implantation system, and other low dose rate (LDR) brachytherapy systems employing Au grains, Ir-thin wires, and ruthenium eye plaques. The number of patients undergoing HDR brachytherapy continued to rise constantly this year as in the past. This Department is the only one institution in Tokyo, where HDR interstitial as well as intracavitary irradiations can be performed. The HDR interstitial radiation is performed mainly in gynecological, genitourinary, and head and neck tumors. Additionally, there are 2 beds in the shielded ward in Floor 13B. Ruthenium mold therapy is performed by ophthalmologists to treat retinoblastomas. 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 a shortened fractionation regimen for various malignancies, especially for breast cancer and vocal cord cancer; 3) HDR and LDR brachytherapy for genitourinary and gynecologic cancers; 4) hypofractionated stereotactic irradiation of brain and body tumors; and 5) adaptive radiation therapy in accordance with the intratherapeutic tumor and normal tissue change. These studies are financially supported by grants from the Ministry of Health, Labour and Welfare (MHLW), Japan.

The staff in the Division are actively engaged in various prospective trials including JCOG studies.

Clinical Trials

Brain tumors: A multicenter phase II/III trial on

interferon-beta and temozolomide combination therapy for newly diagnosed glioblastomas.

Lung cancer: A 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 nonverified lung tumors.

Pediatrics: A phase II clinical trial on multimodality therapy in localized Ewing sarcomas and related tumors (JESS 04).

Head and Neck cancers: Accelerated fractionation versus conventional fractionation radiation therapy for glottis cancer of T1-2N0M0, a phase III study (JCOG 0701).

Breast cancer: A phase II trial on accelerated partial breast irradiation in T1 breast cancer after partial mastectomy.

Liver cancer: A phase I trial on stereotactic hypofractionated radiation for hepatocellular carcinoma.

Development of an Adaptive Radiation Therapy System

Table 1. Number of Radiation Treatment Plans

Primary Sites	No. of All Treatment Plans					
	2006	2007	2008	2009	2010	**2011**
Head & neck	87	111	115	95	128	**166**
Brain	51	90	117	99	113	**97**
Lung	343	357	397	431	429	**348**
Breast	437	523	549	452	487	**503**
Esophagus	190	276	220	213	265	**237**
Stomach	29	30	34	29	25	**15**
Colorectal	60	101	86	78	66	**119**
Pancreas and hepatobiliary	82	60	38	48	69	**68**
Gynecological	88*	154*	255	331	274	**328**
Genitourinary	137	118	128	159	192	**169**
Bone & soft tissue	55	64	75	69	103	**92**
Skin	12	19	16	26	58	**71**
Pediatric	19	25	22	32	25	**66**
Hematological	141	145	137	220	159	**157**
Other	31	35	47	52	19	**14**
Total	1762	2108	2236	2334	2412	**2450**

*: No. of Cases

Table 2. Purpose of Radiation Therapy

	No. of All Treated Patients					
	2006	2007	2008	2009	2010	**2011**
No. of Treatment Plans	1762	2108	2236	2334	2412	**2450**
Curative Intent	1033	1393	1535	1500	1587	**1662**
Palliative Treatment	729	715	701	834	825	**788**
Curative/Palliative	1.42	1.95	2.19	1.80	1.92	**2.11**
New Patients	1197	1234	1181	1210	1277	**1690**

Table 3. Special Radiation Therapy

	No. of Treated Patients			
	2008	2009	2010	**2011**
IORT	0	0	0	**1**
TBI	23	38	41	**52**
SRT-Brain	4	6	3	**2**
SRT-Body	10	20	33	**45**
Intracavitary RT ^{192}Ir-HDR	32	41	50	**49**
Intracavitary RT ^{192}Ir-LDR	1	0	0	**0**
Interstitial RT ^{192}Ir-HDR	10	22	6	**25**
Interstitial RT ^{192}Ir-LDR	0	0	0	**0**
Interstitial RT ^{198}Au-LDR	6	6	6	**4**
Interstitial RT ^{125}I-LDR	0	16	26	**16**
Interstitial RT ^{106}Ru-LDR	27	7	10	**13**
Non-Sealed Radionuclide Therapy ^{89}Sr	3	3	5	**12**
Non-Sealed Radionuclide Therapy ^{131}I	0	1	14	**21**

IORT ; intraoperative radiotherapy
TBI ; total body irradiation

Published Papers

1. Okamoto H, Kohno T, Kanai T, Kase Y, Matsumoto Y, Furusawa Y, Fujita Y, Saitoh H, Itami J. Microdosimetric study on influence of low energy photons on relative biological effectiveness under therapeutic conditions using 6 MV linac. Med Phys, 38:4714-4722, 2011

2. Okamoto H, Kanai T, Kase Y, Matsumoto Y, Furusawa Y, Fujita Y, Saitoh H, Itami J, Kohno T. Relation between lineal energy distribution and relative biological effectiveness for photon beams according to the microdosimetric kinetic model. J Radiat Res (Tokyo), 52:75-81, 2011

3. Ishikura S, Ito Y, Hiraoka M. JCOG Radiation Therapy Study Group: history and achievements. Jpn J Clin Oncol, 41:1241-1243, 2011

4. Kuroda Y, Hosoya T, Oda A, Ooki N, Toyoguchi Y, Murakami M, Kanoto M, Sugawara C, Honma T, Sugai Y, Nemoto K. Inverse-direction scanning improves the image quality of whole carotid CT angiography with 64-MDCT. Eur J Radiol, 80:749-754, 2011

DEPARTMENT OF PATHOLOGY AND CLINICAL LABORATORIES, PATHOLOGY DIVISION

Hitoshi Tsuda, Ryoji Kushima, Koji Tsuta, Akiko Maeshima, Hirokazu Taniguchi, Masayuki Yoshida, Akihiko Yoshida, Yuko Sasajima

Introduction

In the Pathology Division the practice of, education in and research on 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 work of anatomic pathology consists of managing the autopsy, and post-mortem systemic gross and microscopic examination of patients. Case conferences with each clinical division are held periodically. Residents and trainees are accepted for instruction in diagnostic pathology on a rotating basis. To provide more accurate and informative diagnosis in the future, the staff members are encouraged to conduct research by themselves or in collaboration with other divisions or institutions.

Routine Activities

In 2011, a total of 15 board-certified pathologists, 6 residents and 11 medical technologists, including 10 cytotechnologists, cooperatively performed routine histological and cytopathological diagnosis of specimens obtained at the National Cancer Center Hospital (NCCH) and the Research Center for Cancer Prevention and Screening, and education of the residents. Seven pathologists working exclusively in the NCCH also shared management of the division with regard to infrastructures, risk and human errors, improvement of environment including ventilation of formalin and noxious organic solvents, and so on. Another 7 pathologists were concurrently the staff of the NCC Research Institute (NCCRI) and another one was also the staff of the Center for Cancer Control and Information Services (CCCIS).

1. Surgical pathology

A total of 18,413 histological diagnoses were provided consisting of 15,288 biopsy specimens including 1,858 intraoperative frozen sections and 3,642 surgically resected specimens. The intraoperative frozen sections comprised primary tumors, regional lymph nodes, and surgical margins of specimens. The one-step nucleic acid amplification (OSNA) assay was performed for 374 sentinel lymph nodes to examine metastasis intraoperatively.

2. Cytopathology

Cytopathological diagnoses were provided for a total of 10,232 patients including 402 for intraoperative diagnosis. The specimens comprised smears, sputa, body fluids, urine, and needle aspirates submitted from various departments. Intraoperative cytological examination of body fluids was utilized for disease staging and treatment decisions in the fields of gastric surgery and gynecology.

3. Autopsy

Twenty-eight autopsies were performed to examine the extent of tumor spread, the cause of death, therapeutic and adverse effects, and systemic pathological conditions. Immediately after each autopsy examination, table discussion on gross findings was held among the physicians and the pathologists. These cases were further discussed in the monthly autopsy conference after completion of histological examinations.

4. Conferences

Clinicopathological case conferences were held periodically by diagnostic and treatment groups for cancers of specific organs. The members also participated in the tumor board. We had also monthly joint conferences with the Pathology Division, the NCC East, and trimonthly multi-institutional pathology TV conferences.

Research Activities

In order to improve the quality of pathology practice in future, research projects were conducted in various fields. To establish the basis for the promotion of research activities, we were involved in the construction of the Tsukiji Biobank and reference data base in collaboration with other departments.

1. Gastrointestinal tract

Staff members contributed to multicenter studies on the extramural discontinuous cancer spread in colorectal cancer and on the risk of lymph node metastasis of pedunculated-type early colorectal cancer. The 9th Japan-Korea gastrointestinal-meeting was held, and interobserver variation in the diagnosis of gastric dysplasia and carcinoma was analyzed. The HER2 status and molecular detection of lymph-node metastasis of gastric cancer were studied.

2. Lung and mediastinal tumors

Clinicopathological features of lung carcinomas with *ALK* translocations were studied in the largest case series so far, and diagnostic criteria were proposed for the detection of *ALK* translocation by an *in situ* hybridization test. The utilities of EGFR mutation-specific antibody and of an antibody panel to differentiate squamous cell carcinoma from adenocarcinoma were examined. The diagnostic significances of mitotic counting, phosphohistone H3 immunohistochemistry, and spindle cell and oncocytic features were evaluated in neuroendocrine lung carcinoma. Hormone receptor expression was detected in thymic tumors.

3. Breast and gynecological pathology

MET amplification and PIK3CA mutation were shown to be involved in the genesis and progression of ovarian clear cell carcinoma (OCCC). Histological criteria were proposed for grading OCCC for the purpose of prognosis and for evaluating the therapeutic effect of radiofrequency ablation in early breast cancer. A study to standardize the diagnostic criteria of lobular endocervical glandular hyperplasia of the uterine cervix was conducted in collaboration with gynecologists, diagnostic radiologists, and pathologists.

4. Hematological and soft tissue tumors

Cases of follicular lymphoma with monocytoid/plasmacytoid differentiation and a case of pulmonary epithelioid hemangioendothelioma were reported.

Central pathology review in clinical trials and quality assessment

Central pathology review was performed in clinical trials of breast and gynecological cancers. A study of nationwide quality assurance program for HER2 and hormone receptor tests has been launched.

Table 1. Numbers of Cytopathological Specimens Diagnosed in the Pathology Section in 2011

Field	Number of specimens
	Total
Gynecology	3656
Urology	2872
Respiratory organs	1175
Gastrointestinal tracts	679
Hepatobiliary and Pancreas	380
Head and Neck	175
Breast	130
Hematology	117
Others	159
Research Center for Cancer Prediction and Screening	889
Total	10232

Table 2. Numbers of Autopsies Performed in the Pathology Section in 2011

Department/Division	Number
Hematology and Hematopoietic Stem Cell Transplantation	9
Breast and Medical Oncology	5
Urology	5
Thoracic Oncology	4
Dermatology	3
Neurosurgery	1
Esophageal Surgery	1
Total	28

Table 3. Case Conferences Held Periodically at the Pathology Section

Day	Time	Name of conference	Participants	Frequency
Mon.	16:00-17:00	Monday conference (Jan.-Mar., Sep.-Dec.)	All staff, NCC Hospital East	Monthly
	17:00-18:00	Autopsy conference	All staff, physicians in charge	Monthly
Tue.	17:00-18:00	Gynecological pathology conference	Gynecology Group	Monthly
	1700-19:00	Lymphoma conference	Hematology group	Weekly
	18:00-19:30	Breast cancer pathology workshop	Breast cancer group	Monthly
	12:00-13:00	Pulmonary cytology conference	Pulmonary endoscopy group	Weekly
Wed.	14:00-17:00	GI gross conference	Gastroenterology group	Weekly
	17:30-18:30	GI endoscope conference	Gastroenterology group	Weekly
	18:00-19:00	Gastric histopathology conference	Gastroenterology group	Monthly
	18:30-19:30	Urologic pathology conference	Urology group	Monthly
Thu.	14:00-15:00	Brain tumor pathology conference	Neurosurgery group	Monthly
	18:00-20:00	Hepatobiliary and pancreatic pathology conference	Hepatobiliary and pancreas group	Biweekly
	18:00-19:00	Bone and soft tissue tumor conference	Orthopedics group	Monthly
Fri.	07:15-08:30	Gastric pre-surgery case conference	Gastric surgery group	Weekly
	07:30-08:30	Pulmonary pre-and post-surgery case conference	Pulmonary surgery group	Weekly
	14:30-15:30	Skin tumor pathology conference	Dermatology group	Monthly
	18:00-20:00	Esophageal histopathology conference	Esophageal surgery group	Monthly

Published Papers

1. Ueno H, Mochizuki H, Shirouzu K, Kusumi T, Yamada K, Ikegami M, Kawachi H, Kameoka S, Ohkura Y, Masaki T, Kushima R, Takahashi K, Ajioka Y, Hase K, Ochiai A, Wada R, Iwaya K, Nakamura T, Sugihara K. Actual status of distribution and prognostic impact of extramural discontinuous cancer spread in colorectal cancer. J Clin Oncol, 29:2550-2556, 2011

2. Kushima R, Kim K-M. Interobserver Variation in the Diagnosis of Gastric Epithelial Dysplasia and Carcinoma between Two Pathologists in Japan and Korea. J Gastric Cancer, 11:141-145, 2011

3. Tsuta K, Kalhor N, Raso MG, Wistuba II, Moran CA. Oncocytic neuroendocrine tumors of the lung: histopathologic spectrum and immunohistochemical analysis of 15 cases. Hum Pathol, 42:578-585, 2011

4. Tochigi N, Tsuta K, Maeshima AM, Shibuki Y, Asamura H, Hasegawa T, Tsuda H. Malignant pulmonary epithelioid hemangioendothelioma with hilar lymph node metastasis. Ann Diagn Pathol, 15:207-212, 2011

5. Tsuta K, Raso MG, Kalhor N, Liu DC, Wistuba II, Moran CA. Sox10-positive sustentacular cells in neuroendocrine carcinoma of the lung. Histopathology, 58:276-285, 2011

6. Tsuta K, Raso MG, Kalhor N, Liu DD, Wistuba II, Moran CA. Histologic features of low- and intermediate-grade neuroendocrine carcinoma (typical and atypical carcinoid tumors) of the lung. Lung Cancer, 71:34-41, 2011

7. Hatanaka K, Tsuta K, Watanabe K, Sugino K, Uekusa T. Primary pulmonary adenocarcinoma with enteric differentiation resembling metastatic colorectal carcinoma: a report of the second case negative for cytokeratin 7. Pathol Res Pract, 207:188-191, 2011

8. Tsuta K, Kalhor N, Wistuba II, Moran CA. Clinicopathological and immunohistochemical analysis of spindle-cell carcinoid tumour of the lung. Histopathology, 59:526-536, 2011

9. Kozu Y, Tsuta K, Kohno T, Sekine I, Yoshida A, Watanabe S, Tamura T, Yokota J, Suzuki K, Asamura H, Furuta K, Tsuda H. The usefulness of mutation-specific antibodies in detecting epidermal growth factor receptor mutations and in predicting response to tyrosine kinase inhibitor therapy in lung adenocarcinoma. Lung Cancer, 73:45-50, 2011

10. Mimae T, Tsuta K, Takahashi F, Yoshida A, Kondo T, Murakami Y, Okada M, Takeuchi M, Asamura H, Tsuda H. Steroid receptor expression in thymomas and thymic carcinomas. Cancer, 117:4396-4405, 2011

11. Tsuta K, Liu DC, Kalhor N, Wistuba II, Moran CA. Using the mitosis-specific marker anti-phosphohistone H3 to assess mitosis in pulmonary neuroendocrine carcinomas. Am J Clin Pathol, 136:252-259, 2011

12. Tsuta K, Tanabe Y, Yoshida A, Takahashi F, Maeshima AM, Asamura H, Tsuda H. Utility of 10 immunohistochemical markers including novel markers (desmocollin-3, glypican 3, S100A2, S100A7, and Sox-2) for differential diagnosis of squamous cell carcinoma from adenocarcinoma of the Lung. J Thorac Oncol, 6:1190-1199, 2011

13. Yoshida A, Tsuta K, Nakamura H, Kohno T, Takahashi F, Asamura H, Sekine I, Fukayama M, Shibata T, Furuta K, Tsuda H. Comprehensive histologic analysis of *ALK*-rearranged lung carcinomas. Am J Surg Pathol, 35:1226-1234, 2011

14. Yoshida A, Tsuta K, Nitta H, Hatanaka Y, Asamura H, Sekine I, Grogan TM, Fukayama M, Shibata T, Furuta K, Kohno T, Tsuda H. Bright-field dual-color chromogenic in situ hybridization for diagnosing echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase-positive lung adenocarcinomas. J Thorac Oncol, 6:1677-1686, 2011

15. Yamada K, Maeshima AM, Taniguchi H, Kawabata Y, Nomoto J, Maruyama D, Kim S-W, Watanabe T, Kobayashi Y, Tobinai K, Tsuda H. Follicular lymphoma with marked monocytoid or plasmacytoid differentiation and tiny or indistinct follicles: a case study of four patients. Leuk Lymphoma, 52:804-813, 2011

16. Kawasaki Y, Omori Y, Li Q, Nishikawa Y, Yoshioka T, Yoshida M, Ishikawa K, Enomoto K. Cytoplasmic accumulation of connexin32 expands cancer stem cell population in human HuH7 hepatoma cells by enhancing its self-renewal. Int J Cancer, 128:51-62, 2011

17. Tsuda H. Radiofrequency ablation therapy for primary breast cancer: expectations and problems as a novel breast conservation therapy. Breast Cancer, 18:1-2, 2011

18. Seki K, Tsuda H, Iwamoto E, Kinoshita T. Histopathological effect of radiofrequency ablation therapy for primary breast cancer, with special reference to changes in cancer cells and stromal structure and a comparison with enzyme histochemistry. Breast Cancer, 18:18-23, 2011

19. Tsuda H, Seki K, Hasebe T, Sasajima Y, Shibata T, Iwamoto E, Kinoshita T. A histopathological study for evaluation of therapeutic effects of radiofrequency ablation in patients with breast cancer. Breast Cancer, 18:24-32, 2011

20. Ijichi N, Shigekawa T, Ikeda K, Horie-Inoue K, Fujimura T, Tsuda H, Osaki A, Saeki T, Inoue S. Estrogen-related receptor γ modulates cell proliferation and estrogen signaling in breast cancer. J Steroid Biochem Mol Biol, 123:1-7, 2011

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23. Iwata H, Sato N, Masuda N, Nakamura S, Yamamoto N, Kuroi K, Kurosumi M, Tsuda H, Akiyama F, Ohashi Y, Toi M. Docetaxel followed by fluorouracil/epirubicin/cyclophosphamide as neoadjuvant chemotherapy for patients with primary breast cancer. Jpn J Clin Oncol, 41:867-875, 2011

24. Yamamoto S, Tsuda H, Miyai K, Takano M, Tamai S, Matsubara O. Gene amplification and protein overexpression of *MET* are common events in ovarian clear-cell adenocarcinoma: their roles in tumor progression and prognostication of the patient. Mod Pathol, 24:1146-1155, 2011

25. Yamamoto S, Tsuda H, Shimazaki H, Takano M, Yoshikawa T, Kuzuya K, Tsuda H, Kurachi H, Kigawa J, Kikuchi Y, Sugiyama T, Matsubara O. Clear cell adenocarcinoma with a component of poorly differentiated histology: a poor prognostic subgroup of ovarian clear cell adenocarcinoma. Int J Gynecol Pathol, 30:431-441, 2011

26. Yamamoto S, Tsuda H, Takano M, Iwaya K, Tamai S, Matsubara O. *PIK3CA* mutation is an early event in the development of endometriosis-associated ovarian clear cell adenocarcinoma. J Pathol, 225:189-194, 2011

27. Takatsu A, Shiozawa T, Miyamoto T, Kurosawa K, Kashima H, Yamada T, Kaku T, Mikami Y, Kiyokawa T, Tsuda H, Ishii K, Togashi K, Koyama T, Fujinaga Y, Kadoya M, Hashi A, Susumu N, Konishi I. Preoperative differential diagnosis of minimal deviation adenocarcinoma and lobular endocervical glandular hyperplasia of the uterine cervix: a multicenter study of clinicopathology and magnetic resonance imaging findings. Int J Gynecol Cancer, 21:1287-1296, 2011

28. Shigekawa T, Ijichi N, Ikeda K, Horie-Inoue K, Shimizu C, Saji S, Aogi K, Tsuda H, Osaki A, Saeki T, Inoue S. FOXP1, an estrogen-inducible transcription factor, modulates cell proliferation in breast cancer cells and 5-year recurrence-free survival of patients with tamoxifen-treated breast cancer. Horm Cancer, 2:286-297, 2011

29. Ueda S, Tsuda H, Saeki T, Omata J, Osaki A, Shigekawa T, Ishida J, Tamura K, Abe Y, Moriya T, Yamamoto J. Early metabolic response to neoadjuvant letrozole, measured by FDG PET/CT, is correlated with a decrease in the Ki67 labeling index in patients with hormone receptor-positive primary breast cancer: a pilot study. Breast Cancer, 18:299-308, 2011

30. Tsuda H, Komatsu S. *SMYD2* (SET and MYND domain-containing protein 2). In: Huret JL (ed), Atlas Genet Cytogenet Oncol Haematol. France, INIST, 2011
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DEPARTMENT OF PATHOLOGY AND CLINICAL LABORATORIES, CLINICAL LABORATORIES DIVISION

Ryuji Tanosaki, Koh Furuta

Introduction

The Clinical Laboratories Division, together with the Pathology Division, provides an important service as in-hospital diagnostic unit by examining laboratory specimens and screening for disorders. This division is largely divided into 5 subdivisions. The first subdivision is the clinical laboratory assembly including urinalysis, hematology, biochemistry, endocrinology, immunology, tumor markers and molecular diagnostics. The other subdivisions are the phlebotomy section, the bacteriology laboratory, the blood transfusion service, and physiologic examination facilities consisting of ultrasonography, electrocardiography, electroencephalography, and respiratory function. Along with the transition of our hospital status to an Independent Administrative Institution (IAI), the Clinical Laboratory Division was reorganized and is mainly supervised by 2 medical doctors since June 2010; one medical doctor (K.F.) is responsible for the clinical laboratory assembly, and the other (R.T.) manages the blood transfusion service and supervises the phlebotomy section. The phlebotomy section, which is located adjacent to the outpatient clinics on the 2nd floor, has officially belonged to our division since 2010. The bacteriology laboratory is also supervised by a staff physician of the Infectious Control Team (ICT). The physiologic examination facilities are managed by staff physicians from the corresponding departments.

All the clinical laboratories support clinicians in patient care by providing laboratory data, which are subject to strict quality control, and by accepting consultations from members of the medical staff.

Since last year, we have been preparing to obtain an ISO 15189, which is a medical laboratory-oriented accreditation for quality and competence by the International Organization for Standardisation's Technical Committee 212 (ISO/TC 212). This will be a good opportunity to reorganize and maintain a high-quality management system.

Routine Activities

Two medical doctors, 35 full-time and 8 part-time medical technologists, and 4 assistants provide services. An administrative meeting is held weekly, attending members of which consist of three medical doctors from the Pathology Division and two medical doctors from the Clinical Laboratory Division, and the head and vice-head medical technologists. The laboratory management meetings are regularly held twice a month for quality control of laboratory operations. Our Division also participates in several domestic and international programs for inter-laboratory standardization and quality control including the CAP (College of American Pathologists) Survey.

In the molecular diagnostic laboratory, the examinations for mutations, which might exist in certain genes such as epidermal growth factor receptor (EGFR), are performed using fluorescence in situ hybridization (FISH) and high-resolution melting analysis (HRMA) to determine the eligibility of the targeted therapy. As the number of target diseases increases, the kinds and the number of these molecular tests are also increasing.

The phlebotomy section is equipped with an automated system, BC ROBO™, which enables the automatic labeling and selection of blood collection tubes. It facilitates the blood sampling and also allows us to analyze the number and the waiting time of each patient. The working group meeting, consisting of medical doctors, all chief medical technologists and the chief outpatient nurse, is held once a month in order to provide better services to patients and to secure procedural safety.

The blood transfusion service specifically employs 4 medical technologists, including 1 transfusion-accredited member. An absolute hemo-vigilant system has been established in our institution. Reports regarding any adverse events, which might occur associated with blood transfusion, are automatically sent to the blood transfusion laboratory, and a medical technologist makes a round in the ward to collect precise information. Because about 5% of platelet transfusions are associated with non-hemolytic adverse events probably due to certain substances in the plasma of the blood products, the removal of the supernatant is performed by request of clinical

physicians. Special attention is paid to confirming the ABO types of blood products, as many patients undergo allogeneic hematopoietic stem cell transplantation from an ABO-mismatched donor in our institution, to whom mismatched ABO-blood products are intended to be transfused to prevent adverse immunologic reactions.

Research Activities

An in-hospital bio-bank, which was established in 2002, has been maintained for use by various researchers, and more than 800,000 samples have been cryo-preserved as of the end of 2011.

The project of another larger-scale comprehensive bio-bank is underway in collaboration with the CCCIS, NCCRI, and NCC for the purpose of future progress in cancer research, and our division will contribute to it in phlebotomy and processing of clinical materials (see also the Pathology Division).

Flow cytometers are used for analysis of the surface markers of leukemia and lymphoma cells and for confirmation of blood cell types for routine examinations as well as for research purposes: investigations are performed into the kinetic analysis of infused platelets, enumeration of hematopoietic stem cells and analysis of donor-chimerism after HLA-mismatched hematopoietic stem cell transplantation. The project of development of a new enumeration technique of hematopoietic stem cells, which was started in 2006, is continuing in collaboration with a medical diagnostic company.

The chief doctor (R.T.) participates in the establishment of nationwide guidelines for standard cell-processing procedures as a committee member of the corresponding academic societies. He also contributes to transplantation activities, especially for adult T-cell leukemia-lymphoma, and in cord blood transplantation with the support of a grant for an Anti-Cancer Project from the Ministry of Health, Welfare and Labour of Japan, and as a member of the National Marrow Bank.

Published Papers

1. Furuta K, Yokozawa K, Takada T, Fujiwara Y. De-identification procedure and sample quality of the post-clinical test samples at the bio-repository of the National Cancer Center Hospital (NCCH) in Tokyo. Jpn J Clin Oncol, 41:295-298, 2011
2. Choi I, Tanosaki R, Uike N, Utsunomiya A, Tomonaga M, Harada M, Yamanaka T, Kannagi M, Okamura J. Long-term outcomes after hematopoietic SCT for adult T-cell leukemia/lymphoma: results of prospective trials. Bone Marrow Transplant, 46:116-118, 2011

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 15 surgical oncology groups, nurses, and medical-technical staff with support staff from Radiology and the Laboratory. The Plastic Surgery and Pediatric Surgery Groups have newly joined this year.

Routine Activities

During 2011, the Surgical Center supported more than 4,500 surgical cases and more than 3,900 general anesthesia surgical cases, a slight increase in the number of cases and a 2.4% increase in general anesthesia cases over 2010. 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 (http://www.ncc.go.jp/jp/about/mission.html), and occasionally performed in the Surgical Center. Over the years, minimally invasive procedures have increased remarkably. Endobronchial brachytherapy under general anesthesia in lung cancer and endoscopic resection under general anesthesia in GI cancer are also unique treatments (http://www.ncc.go.jp/jp/about/mission.html), and are carried out in the Surgical Center.

A new operative field monitor and operation room monitor have been introduced to ensure safe operations. Peri-operative information management systems have been introduced into the clinical practice to facilitate the anesthesiologists' and nurses' work.

The Surgical Center staff works as part of a multidisciplinary team active in planning the best utilization of operating rooms. Scheduling, equipment usage, and staffing in the 15 operating suites were evaluated to establish an optimal work flow, streamline room turnover, and improve start times.

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 40 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	113	111	132	116	126	130	127	143	109	119	136	128	1487
General and epidural	201	219	226	203	178	192	180	205	224	209	201	212	2450
Epidural and lumbar	0	0	1	0	0	1	2	0	1	0	0	0	5
Epidural and lumbar	0	0	0	0	0	2	2	1	0	1	0	0	6
Lumbar	12	13	15	10	15	11	13	14	7	8	19	7	144
Local	37	32	31	35	27	39	31	33	27	47	38	49	426
Others	0	2	0	0	0	0	0	0	0	0	0	0	2
Total	363	377	405	364	346	375	352	396	368	384	394	396	4520

Table 2. Number of general anesthesia cases

	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Neurosurgery	8	8	12	11	11	7	8	16	10	9	10	10	120
Opthalmology	21	21	24	27	23	27	23	25	30	25	24	23	293
Head & Neck Surgery	11	12	18	11	9	10	13	16	11	13	12	13	149
Breast Surgery	43	41	47	36	42	44	42	45	29	37	38	35	479
Thoracic Surgery	41	38	32	43	34	41	35	41	42	41	45	58	491
Esophageal Surgery	12	10	13	12	12	8	11	11	17	16	15	11	148
Gastric Surgery	38	38	43	38	31	34	36	37	38	34	42	46	455
Colorectal Surgery	42	54	53	47	37	38	40	44	50	47	40	41	533
Hepatobiliary & Pancreatic Surgery	15	19	23	22	28	21	20	20	22	23	20	26	259
Gynecology	19	19	24	22	16	13	16	18	17	17	18	11	210
Urology	21	19	24	18	19	27	21	18	21	24	21	19	252
Dermatology	7	8	8	8	8	8	6	14	6	8	12	7	100
Orthopedic Surgery	18	17	17	17	20	22	20	30	28	20	27	25	261
Others	18	26	20	7	14	22	16	13	12	14	13	15	190
Total	314	330	358	319	304	322	307	348	333	328	337	340	3937

CLINICAL TRIAL COORDINATION (& SUPPORT) OFFICE

Hiroyuki Terakado

Introduction

the Clinical Trial Coordination (& Support) Office aims to promote clinical trials on unapproved drugs and medical devices, with the goal of allowing patients to receive the benefits arising from life science research as quickly as possible.

The task of the Clinical Trial Coordination (& Support) Office is to facilitate smooth implementation of industry-sponsored registration trials ("*Chiken*"), physician-initiated registration directed clinical trials ("*Ishi-shudou-chiken*") and other clinical research studies (investigator-initiated trials)

This office consists of 3 divisions (the Clinical Trial Coordination Division, the Physician-initiated Registration-directed Clinical Trials Support Division and the Clinical Data Management Division). The staff members, nurses, pharmacists and laboratory technologists, participate in this division independently from outpatient divisions, wards, the nursing division and pharmacy, thus breaking through the conventional framework of profession-based organizations.

Routine Activities

The Clinical Trial Coordination (& Support) Office supports a lot of the industry-sponsored registration trials ("*Chiken*") as well as the physician-initiated registration directed clinical trials ("*Ishi-shudou-chiken*"). A total of 22 CRCs (clinical research coordinators), support these trials. The number of the industry-sponsored registration trials is increasing year by year, and we supported 165 registration-directed clinical trials including 4 physician-initiated registration directed clinical trials in 2011 (Table 1). The Clinical Data Management Division supports 20 clinical trials.

The number of the 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 our hospital, all members of this Office will work together to contribute to reinforcing the clinical research capabilities of our hospital and to making this Office a valuable unit for all members of this hospital.

Table 1. Registration-directed Clinical Trials ("*Chiken*") including Investigator-initiated Registration-directed Clinical Trials

Department	Eligible Cancer Type	Trial Phase	number of trials
Department of Neurosurgery and Neurooncology			4
	Glioma	Phase II	1
		Phase III	1
	Glioblastoma	Phase III	2
Department of Breast Oncology and Medical Oncology			
Breast and Medical Oncology Division			24
	Breast cancer	Phase I	1
		Phase II	3
		Phase III	6
		Post-marketing	2
	Ovarian cancer	Phase II	1
	Ovarian cancer/Fallopian tube cancer/Peritoneal cancer	Phase I	1
		Phase III	2
	Cervical cancer	Phase III	1
	Uterine corpus cancer	Phase II	1
	Soft tissue tumors	Phase I	1
	Solid tumors	Phase I	4
	Neutropenia	Phase III	1
Breast Surgery Group			1
	Breast cancer	Phase III	1

Department of Thoracic Oncology			
Thoracic Oncology Division			30
	Solid tumors	Phase I	12
	Lung cancer	Phase I	4
		Phase I/II	2
		Phase II	3
		Phase III	7
		Post-marketing	2
Thoracic Surgery Division			1
	Lung cancer	Phase III	1
Department of Gastrointestinal Oncology			
Gastrointestinal Medical Oncology Division			17
	Colon cancer	Phase II	2
		Phase III	1
		Post-marketing	1
	Gastric cancer	Phase III	6
	Esophageal cancer	Phase I	1
		Phase I/II	2
		Phase II	1
	GIST	Phase III	2
	Solid tumors	Phase I	1
Department of Hepatobiliary and Pancreatic Oncology			
Hepatobiliary and Pancreatic Oncology Division			27
	Hepatocellular cancer	Phase I	1
		Phase I/II	3
		Phase III	9
	Pancreatic cancer	Phase I/II	1
		Phase II	4
		Phase II/III	1
		Phase III	1
		Post-marketing	1
	Pancreatic endocrine tumors	Phase II	1
		Phase III	1
	Neuroendocrine tumor	Phase I/II	1
	Solid tumors	Phase I	3
Department of Urology			5
	Renal cell cancer	Phase II	2
		Phase III	1
	Bladder cancer	Phase I/II	1
	prostatic cancer	Phase I/II	1
Department of Orthopedic Surgery			3
	Soft tissue sarcoma	Phase II	1
		Phase III	1
	Soft tissue tumors, Bone tumors	Phase II	1
Department of Dermatologic Oncology			2
	Malignant melanoma	Phase II	1
		Phase III	1
Department of Hematology, and Hematopoietic Stem Cell Transplantation			
Hematology Division			38
	Malignant lymphoma	Phase I	9
		Phase I/II	2
		Phase II	6
		Phase III	8
	Leukemia	Phase I	3
		Phase I/II	2
		Phase II	1
		Phase III	1
	Multiple Myeloma	Phase I	2
		Phase I/II	2
	MDS	Phase I/II	1
	Hematopoietic organ tumor	Phase I	1
Hematopoietic Stem Cell Transplantation Division			2
	Allogenic stem cell transplant	Phase I	1
		Phase I/II	1
Department of Pediatric Oncology			3
	Nausea/Vomiting	Phase III	1
	Candidiasis, Aspergillosis	Phase II	1
	malignant tumor	Phase I	1
Department of Palliative Care and Psycho-Oncology			
Palliative Care Division			1
	Cancer pain	Phase III	1
Department of Diagnostic Radiology			4
	Hepatocellular cancer	Phase II	2
	hypervascular cancer	medical device	2
Department of Radiation Oncology			1
	Nausea/Vomiting	Phase II	1
Total			165

As of December 2011

NUTRITION MANAGEMENT OFFICE

Setsuko Kuwahara, Masahiro Sunaga, Hiroki Matsubara, Hiroko Takashima

Introduction

2011 was the year for working on a number of research activities for the Nutrition Management Office.

Improving taste disorders as development of supportive care was initiated as a research project. During cancer treatment, many patients have experienced a decrease in appetite and QOL, and it is believed that improving appetite could improve successful treatment rates.

In addition, dietitians and chefs, in order to enhance the ward activities, began ward catering. This aims to review how to improve our team medical care as well as to deliver nutrition care directly and immediately to patients and families. This initiative will enhance the Nutrition Support Team (NST) activity. Five years ago, our Office began working on the nutritional assessment of cancer patients, including the measurement of resting metabolic changes in patients during treatment, and we have continued to accumulate data on post-surgical status following, for example, esophageal surgery and hepatobiliary-pancreatic surgery. In addition, the Office has placed a strong emphasis on planning meals, menu improvements and personal support, based on the comments received from patients regarding their food on a dedicated Food Comments Form: in fact, this form as of December 2011 was being returned by 54% of patients, so the rich data from these comments has been of great assistance to the office, and we believe that our actions on the feedback help to complement the patients' total treatment.

Routine Activities

Dietary meals totaled 549,511 in 2011, and we gave nutrition-related dietary advice to 2,025 persons. There have been 599 requests for consultation to the NST 50 per month on average, and this aspect of the Office has shown strong growth by 20% annually. Following the establishment of the Departments of Gastroenterology and Stem Cell Transplantation, they became in particularthe most active as far as consultations was concerned, as seen in Table 1. The Office also aims to enhance our nutritional teaching content. Following our experience of publishing two books for 100-day recipes for patients who have undergone ovarian cancer surgery and uterine colorectal surgery, we were involved in the publication of a 100-day recipe book for those who have undergone esophageal surgery, designed as a reference book for the nutritional management of patients after discharge. As for food service, improvements were carried out regarding breakfasts. In the field of human resource development, we have a strong commitment to education and training and we conducted 10 University courses for registered dietitians within the University. By strengthening our cooperation with universities, our aim is to enhance research activities in the future through the development of human resources.

Research Activities and National Workshops

1) The Nutritional Management Workshop for Cancer Patients continues educational activities to underline the importance of nutritional management and giving opportunities to learn practical techniques to maintain such management. In 2011, it celebrated its 30th anniversary, in Okayama, with "Nutrition Past, Present and Future" being the title of the the President's lecture.
2) The Hospital Group for Disease Prevention Study Group of Japan, under the slogan Beneficial and Smooth Formula Diet", investigated the development of the effective use of rice powder in a study of hospital food intake.
3) In cooperation with nutritionists of the Nutritional Management of Cancer Course we held lectures to help target the general public regarding a cancer-preventative diet (Venues: Akita, Tokyo, Toyama, Nagano, Iwate, band Kanagawa)
4) Research project
   ① Survey of dysgeusia
   ② Full medical team. Enhance and expand the role of the dietitian
   ③ Studies on nutrition in the surgical treatment of esophageal cancer
   ④ Perioperative nutritional assessment after pancreaticoduodenectomy

Future Prospects

The central goal of the Nutrition Management Office continues to be promotion of nutritional management for cancer patients to help them, and their families, across the country. Studies continue to lead to a practical research project that will seek to enhance the outcomes for cancer patients and their families.

Table 1. Number of NST consultations in 2011

Clinical Departments	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sept	Oct	Nov	Dec	total
Esophageal Surgery	5	4	4	2	2	1	4	3	5	4	2	2	38
Head and Neck Surgery		2	1	2	3	1	1	2	1	2			15
Gastrointestinal Medical Oncology	18	14	6	11	11	8	11	5	7	8	9	6	114
Hematopoietic Stem Cell Transplantation	12	8	10	11	11	8	9	9	9	10	14	5	116
Thoracic Oncology	5	4	8	2	6	4	5	6	2	1	5	2	50
Thoracic Surgery			1	1			1	1	2	1			7
Hepatobiliary and Pancreatic Oncology	2	2	1	1		4	8	2	3	4	1		28
Hepatobiliary and Pancreatic Surgery	4	1	5	2	3	4	3	4	2	1	1	1	31
Breast Oncology and Mecal Oncology	1	2	1	2	8	10	7	5	5	4	6	7	58
Gynecology			1	2	2	5		1	1	2	1		15
Neurosurgery and Neuro-Oncology	1			1	1		1		2			2	8
Gastric Surgery	2		1		1			1	1	2	2		10
Colorectal Surgery	2	2	1	1	1	1	1		1	1			11
Urology	3	3	3	6	1	3	2	3	2	1	2	4	33
Pediatric Oncology		2		1	1	1						5	10
Orthopedic Surgery	1	1	1	1				2		3	1		10
Dermatologic Oncology			1	1	4	2	2	1	1	1			13
Hematology			1	2	2	1			2	3	2	3	16
Radiation Oncology	1	1	1	1	1	2	1	1	1	4		2	16
Total	57	46	47	50	58	55	56	46	47	52	46	39	599
												mean	50

HEALTH INFORMATION MANAGEMENT OFFICE

Hiroshi Nishimoto, Shinobu Fukuoka, Hisayo Nishizawa

Introduction

The Health Information Management Office is a new division, established in April, 2011. We are taking over several duties from the Cancer Information Services and Surveillance Division. One of them was the **Audit of Discharge Summary**, and another was the **National Cancer Center Hospital Cancer Registry** which is executed as a hospital-based cancer registry. Some statistical duties 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

Auditing Discharge Summary (Quantitative inspection)

Data on discharge summaries should be entered by the attending physician. We inspected and checked about 10,000 summaries and, where required, gave some advice regarding correct input.

National Cancer Center Hospital Cancer Registry (Hospital-based Cancer Registry)

The Office has managed the National Cancer Center Hospital Cancer Registry since 2004, handling more than 6,000 records a year. We have provided our data for the Japanese Institutional Cancer Database that is handled by the Center for Cancer Control and Information Services of the NCC.

Table. National Cancer Center Hospital Cancer Registry

Year of Diagnosis	Number of New Cancer Cases		
	Total	Male	Female
2008	6,684	3,929	2,755
2009	6,721	3,895	2,826
2010	6,636	3,926	2,710

DEPARTMENT OF PHARMACY

Hiroshi Yamamoto

Introduction

The 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 in response to 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 Pharmacy 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 Pharmacy. The importance of providing drug information to 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. The Pharmacy also provides outpatients with guidance in the proper use of opioids and anti-cancer agents.

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 which provides drug information. The medicine-package information and easy-to-understand-by-patients explanations and instructions for the proper use of drugs, such as 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 which makes it possible to check the dose as well as the interval of chemotherapy. In 2011, Pharmacy acquired a robot which prepares injection preparations without human assistance.

Research Activities

Since an important mission of the Pharmacy 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.

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 Pharmacy 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 a three-year postgraduate pharmacist residency in clinical oncology. In the first year, the program is heavily weighted toward technologic 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. Moreover, residents provide pharmaceutical care to ambulatory care patients and participate in an oncology-focused Drug Information Program. This clinical acumen coupled with didactic training in the basic science of oncology will prepare the resident to investigate therapeutic questions related to the care of cancer patients. In the third year, residents participate in specialized pharmaco-clinical practice and research activities, which may be tailored to the resident's goals. There are also 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

	FY 2010	FY 2009
1) Oral and topical preparations		
Prepared in the hospital pharmacy	141,536	134,627
Inpatients	128,566	122,391
Outpatients	12,970	12,236
Taken to outside pharmacies	66,080	63,528
(% of prescription filled outside)	83.6	83.8
2) Injections		
Inpatients	289,568	299,950
Outpatients	34,097	34,936

Table2. Amounts of Drugs Consumed

	FY 2010 (including sales tax)	(%)	FY 2009 (including sales tax)	(%)
Total	4,564,239	100.0	4,901,870	100.0
Internal medicines	407,375	8.9	364,297	7.4
External	33,747	0.7	44,716	0.9
Injection	3,129,818	68.6	3,478,960	71.0
Narcotics	154,469	3.4	153,149	3.1
Blood	430,021	9.4	413,673	8.4
X-ray imaging	249,640	5.5	297,318	6.1
RI	108,945	2.4	91,941	1.9
Others	50,223	1.1	57,816	1.2

Unit:1000 yen

Table 3. Aseptic Preparation of Injectable Drugs

	FY 2010	FY 2009
Anticancer Drugs	59,552	51,071
Others	32,112	34,936

Table 4. House Preparations

	FY 2010	FY 2009
Sterilized	103	93
Nonsterilized	138	131

Table 5. Investigational Drugs

	FY 2010	FY 2009
Newly registered	46	52
Ongoing study	109	106
Total	155	158

NURSING DIVISION

Misae Maruguchi

Activities of the Nursing Division

The Nursing Division bears responsibility for team healthcare at the National Cancer Center Hospital, the core institution for national cancer treatment and control in Japan. The responsibility of the Nursing Division is to develop and improve the quality of cancer nursing as well as to contribute to the appropriate management of the hospital. The Division is also expected to foster nursing staff to achieve the best cancer nursing.

1) Continuous Nursing for Cancer Survivorship

Based on the philosophy of the Nursing Division, which is to create and provide the best cancer nursing geared to the needs of patients, the Nursing Division is working to provide safe and reliable nursing in response to advances in medicine with consciousness and responsibility as a nurse in the cancer center hospital.

We adopted the two-shift nursing system in 10 units, comprising an 8-hour day shift and a 16-hour night shift. Inpatient unit nurses work together more as 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 many patient education programs produced by Certified Nurse Specialists and Certified Nurses. We have 10 patient education programs. Many patients and families have participated in the educational program for their self-care and survivorship in their daily life.

2) Educational Activities

(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 provided training courses on physical assessment and basic nursing skills for new nurses. New nurses learn about clinical nursing practices by shadowing a senior nurse for the first one month. We ensure that new nurses can work in an adverse work-related stress-free environment.

(2) Development knowledge and skills for cancer nursing

To develop the skill of cancer nursing, the Nursing Division 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 9 specialized nurse training courses: Cancer chemotherapy nursing I and II; Clinical trial nursing; Palliative care nursing I and II; Lymphedema care; Wound care nursing; Dysphagia nursing; and Radiotherapy and IVR nursing. A total of 198 nurses have participated, all of whom have over 4 years' nursing experiences. Many nurses want to participate in the courses. Through evaluation of the result 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, 7 certified nurse specialists and 22 certified nurses are working at the National Cancer Center Hospital. They represent the role model for cancer nursing practice in both the 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.

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, 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 the education and coordination for ethical issues in the clinical setting. They support and empower not only patients and families, but also nursing

staffs.

Certified Nurse Specialists and Certified Nurses also engage in educational activities both within and outside the hospital, and contribute to the development of educational program by giving lectures and practice training for the curricula of Certified Nurse Specialists or Certified Nurses.

4) Research Activities and Publications

We presented 10 studies on nursing at some annual conferences in 2011. One of those studies was "Problems and needs related to physical and psychosocial rehabilitation at long-term follow-up nursing consultation for allogeneic hematopoietic stem cell transplantation recipients in Japan", which was presented by our Certified Nurse Specialist in Cancer Nursing at the ASBMT/CIBMTR annual conference in the US.

This year, 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 to challenge nursing research based on their clinical questions. We expect our nurses from the National Cancer Center Hospital to create and develop cancer nursing to even higher levels of proficiency and expertise.

Hospital East

Preface

Nearly ten months have passed from the unforgettable '3-11 disasters' in north-east Japan. I would like once again to deliver my sincere condolences and prayers for the earthquake and tsunami victims and their families.

Fortunately the degree of damage to the hospital buildings due to the earthquake was minimal. No patients and no staff members sustained any serious injury. Considering the days after the disaster, all members of the hospital labored under many difficulties including the planned electric power outages, the so-called rolling power outages, and stringent electricity-saving initiatives during the summertime. The problems associated with the nuclear power plants in Fukushima prefecture still continue to the present day. Kashiwa city is one of the radioactive 'hot spot' areas even though it is around 200 km away from Fukushima and is the home to our NCCHE Kashiwa campus, but I am glad to report that radioactive contamination measured at several spots in the hospital area has recently reached a relatively stable level.

Apart from the natural disasters of 2011, we had some internal ones of our own. In April, 2011 the number of the staff members of in our Anesthesiology Division dropped from 2 to 1 with the loss of the Division chief. We had to limit the number of operations until a new chief came to the division. Now three staff members work hard to bring the number of operations up to where it should be with the help of two part-timers.

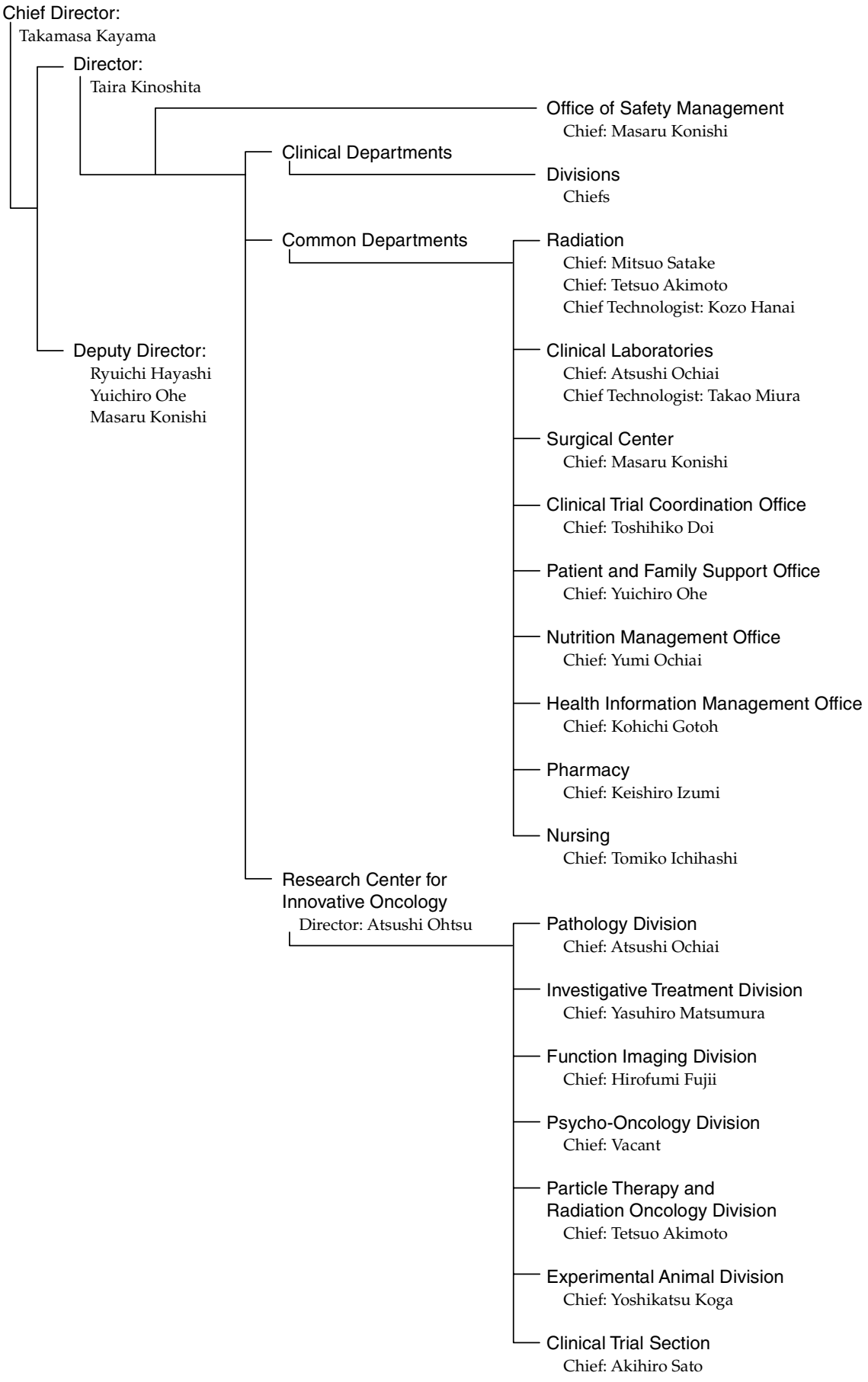
2011 was also a year of expansion and change. In the operating theater, the number of laparoscopic surgeries as a less invasive procedure has been increasing. The Palliative Care Unit changed its remit from terminal care to control of the symptoms before the terminal stage to extend the opportunity to use the limited number of beds for increasing patients. In the Research Center for Innovative Oncology several clinical trials of new anticancer drugs, peptide vaccine and endoscopic instrument are successfully ongoing.

We are in the second year of a new Independent Administrative Institution putting administrative reforms into place under the powerful chief director, Dr. Takamasa Kayama. In this situation, the Hospital East has had to show a different flag from that flown by Central Hospital. Hospital East has been trying to promote innovative works together with the Research Center for Innovative Oncology. I would like to congratulate them on their gaining of a strategic foothold regarding early phase trials from the government to accelerate their innovative activity in the development of new drugs and medical instruments.

2012 is a memorial year, encompassing both the 50th anniversary of the National Cancer Center and the 20th anniversary of the Hospital East. It is my great pleasure and honor to present the summary of the achievements of 2011 in the Hospital East, which were only accomplished through the hard work of the NCCHE staff members. I would like to express my sincere thanks and to send my warmest regards to all the members of the NCCH. At the same time I express my appreciation to all the member of the Tsukiji Campus for their extensive corporation.

Taira Kinoshita M.D., Ph.D.
Director, National Cancer Center Hospital East

Organization



Clinical Departments

Director:

Taira Kinoshita

- **Department of Head and Neck Oncology and Plastic and Reconstructive Surgery**
  - Chief: Ryuichi Hayashi
  - Chief: Shin Tahara
  - Chief: Minoru Sakuraba
  - Head and Neck Surgery Division
  - Head and Neck Oncology Division
  - Plastic and Reconstructive Surgery Division
- **Department of Breast Oncology and Hematology/Medical Oncology**
  - Chief: Kuniaki Ito
  - Chief: Noriaki Wada
  - Breast Surgey Division
  - Hematology/Breast and Medical Oncology Division
- **Department of Thoracic Oncology**
  - Chief: Kanji Nagai
  - Chief: Yuichiro Ohe
  - Chief: Hironobu Ohmatsu
  - Thoracic Surgery Division
  - Thoracic Oncology Division
  - Respiratory Endoscopy Division
- **Department of Gastrointestinal Oncology**
  - Chief: Taira Kinoshita
  - Chief: Norio Saito
  - Chief: Atsushi Ohtsu
  - Chief: Mitsuyo Nishimura
  - Chief: Toshihiko Doi
  - Chief: Kazuhiro Kaneko
  - Esophageal Surgery Division
  - Gastric Surgery Division
  - Colorectal Surgery Division
  - Gastrointestinal Medical Oncology Division
  - Gastrointestinal Endoscopy Division
- **Department of Hepatobiliary and Pancreatic Oncology**
  - Chief: Masaru Konishi
  - Chief: Masafumi Ikeda
  - Hepatobiliary and Pancreatic Surgery Division
  - Hepatobiliary and Pancreatic Medical Oncology Division
- **Department of Urology**
  - Chief: Vacant
- **Department of Anesthesiology and Intensive Care Unit**
  - Chief: Yasuko Miwa
  - Anesthesiology Division
  - Intensive Care Unit
- **Department of Palliative Medicine and Psycho-Oncology**
  - Chief: Hiroya Kinoshita
  - Chief: Asao Ogawa
  - Palliative Medicine Division
  - Psycho-Oncology Division
- **Department of Diagnostic Radiology**
  - Chief: Mitsuo Satake
- **Department of Radiation Oncology**
  - Chief: Tetsuo Akimoto
- **Department of Pathology and Clinical Laboratories**
  - Chief: Atsushi Ochiai
  - Pathology Division

Activities of the Departments

DEPARTMENT OF HEAD AND NECK ONCOLOGY AND PLASTIC AND RECONSTRUCTIVE SURGERY, HEAD AND NECK SURGERY DIVISION

Masakazu Miyazaki, Ryuichi Hayashi, Takeshi Shinozaki, Mitsuru Ebihara, Wataru Okano, Kensuke Suzuki, Shinya Jinnouchi

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 Head and Neck Surgery Division resolves these conflicting requirements mainly by two distinct approaches: (1) conservative surgery and (2) extensive resection with microsurgical reconstruction. The most successful approach for voice preservation has been conservative surgery. This procedure includes a vertical partial laryngectomy which is indicated for T1/T2 glottic carcinoma, recurrent glottis carcinoma after radiotherapy, and early false cord carcinoma. Another example of conservative surgery is partial hypopharyngectomy with preservation of the vocal cords for hypopharyngeal carcinoma with limited extension. On the other hand, extensive resection with microsurgical reconstruction is designed to minimize loss of function following ablative surgery by employing microsurgical transfer of various flaps (further details are available in the annual report of the Plastic and Reconstructive Surgery Division).

Routine Activities

The current treatment policy for head and neck cancer is multimodal therapy. To effectively implement available therapeutic modalities, 4 staff surgeons at the Division 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.

In 2011, 271 new patients were treated: 419 patients underwent surgery under general anesthesia and 32 patients under local anesthesia. Ninety-one patients underwent major surgery with microsurgical reconstruction. The number of surgically treated high-risk patients, including elderly patients aged over 80, is currently increasing owing to the recent advances in surgical techniques and perioperative care. Technically difficult operations, such as surgical resection of advanced oropharyngeal carcinoma with immediate reconstruction, are also being increasingly performed.

The outpatient service of the Division is available from Monday to Friday. Endoscopic, radiographic, and ultrasonic examinations are routinely performed. The dental service is also available to improve the quality of life after ablative surgery using maxillofacial prostheses, to prevent severe odontogenic infection during chemotherapy and / or radiotherapy, and to reduce local infection after major surgery for head and neck cancer.

Research Activities

1. Exploration of factors related to dilation of intraepithelial blood vessels or angiogenesis in the lesions of early-stage esophageal and head and neck cancers

RNA and DNA were extracted from biopsy specimens of cancerous and noncancerous tissues obtained from 13 new subjects using a laser microdissection system. The level of expression of MET, CXCR7, and CD44 was higher in the cancerous tissues than in the noncancerous tissues. In 4 (30.8%) of 13 subjects, p53 mutation was found in the cancerous tissue specimens, and the frequency of mutation was almost the same as that of esophageal squamous intraepithelial neoplasia. It is suggested based on the histopathological findings that the genes identified in this study, which were highly expressed in relation to angiogenesis and induction of inflammation, have an effect leading to carcinogenesis.

2. Study of polyglycolic acid sheet as a wound dressing material

The potential of polyglycolic acid sheet (PGA sheet) as a pharyngeal wound dressing material was studied. The PGA sheet was used in 6 patients with oral and oropharyngeal cancer who underwent peroral resection. Dislocation of the sheet occurred in 2 of 6 patients. In the remaining 4 patients without dislocation, good pain control was obtained. The PGA sheet was usable in 4 patients although touching or scraping frequently occurred in the oral cavity and oropharynx. Thus, the PGA

sheet can be used as a wound dressing material in patients who have undergone endoscopic resection of pharyngeal cancer.

Clinical Trials

1. Multicenter study to establish a suitable approach to resection of advanced tongue cancer

The aim of this study was to establish the pull-through approach as the standard approach for the resection of advanced tongue cancer. 74 patients with T3/4 tongue cancer were enrolled. The pull-through approach was used in 68 patients, whereas the mandibular swing approach was used in only 1 patient. The local control rate did not differ between the partial and total resections performed with the pull-through approach. Thus, the less invasive pull-through approach is considered to be the standard approach for the resection of advanced tongue cancer.

2. Symptom prevalence and functional status among patients with advanced head and neck cancer

A multicenter prospective study is being conducted. The overall QOL of advanced head and neck cancer patients with EORTC-QLQ-C15-PAL, the amount of airway secretions and typical symptoms of head and neck cancer are evaluated. The patient enrollment for this study is ongoing.

Published Papers

1. Ebihara M, Kishimoto S, Hayashi R, Miyazaki M, Shinozaki T, Daiko H, Saikawa M, Sakuraba M, Miyamoto S. Window resection of the trachea and secondary reconstruction for invasion by differentiated thyroid carcinoma. Auris Nasus Larynx, 38:271-275, 2011

2. Shinozaki T, Hayashi R. Nutrition and palliative surgery for head and neck cancer. In: Victor RP (ed), Diet and nutrition in palliative care, USA, CRC Press, pp283-288, 2011

Table 1. Number of new patients

Tongue	58
Oral cavity excluding tongue	48
Oropharynx	35
Hypopharynx	53
Cervical esophagus	15
Larynx	20
Nasal cavity and paranasal sinuses	2
Thyroid gland	33
Major salivary gland	2
unknown	3
Others	2
Total	271

Table 2. Type of procedure

Glossectomy	74
Resection of oral cavity	49
Oropharyngectomy	28
Hypopharyngectomy	27
Cervical esophagectomy	20
Laryngectomy	21
Resection of the nasal and/or paranasal sinuses	8
Thyroidectomy	50
Parotidectomy	17
Submandibulectomy	2
Endoscopic resection	40
Neck dissection	74
Others	41
Total	451

Table 3. Survival rates

Diagnosis	Treatment	No. of Pts.	5-yr survival (%)	
			Crude	Cause-specific
Cancer of the upper gingiva	surgery	41	43.3	n.v.
Cancer of the floor of the mouth	surgery	80	50.3	59.7
Cancer of the oropharynx	surgery	244	58.2	n.v.
Cancer of the hypopharynx	surgery	263	44.3	48.2
Cancer of the thyroid with invasion of the trachea	surgery	41	78.9	n.v.

n.v. : not verified

DEPARTMENT OF HEAD AND NECK ONCOLOGY AND PLASTIC AND RECONSTRUCTIVE SURGERY, PLASTIC AND RECONSTRUCTIVE SURGERY DIVISION

Minoru Sakuraba, Shogo Nagamatsu, Megumi Taji, Nobuko Suesada, Masahide Fujiki

Introduction

The Plastic and Reconstructive Surgery Division 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. In addition, several methods such as tissue transfer with pedicled flaps, local flaps, skin grafts, and so on are used for reconstructive surgery. The objectives of reconstructive surgery are not only the morphological reconstruction, but also the restoration of postoperative function after ablative surgery. The quality of life (QOL) of the patient can be improved with the combination of functional and morphological reconstruction.

Routine Activities

Five plastic surgeons cover reconstructive operations both in the 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 another department of the hospital, such as Head and Neck Surgery, Breast Surgery, Orthopedic Surgery, Esophageal Surgery, Colorectal and Urological Surgery, *et cetera*. In the NCCH East, Head and Neck reconstruction is the most frequently performed operation accounting for 65% of the reconstructive surgery. In the Head and Neck region, a free jejunal graft and a rectus abdominis musculocutaneous flap are the most frequently used procedures. A weekly conference is held with doctors of the Departments of Head and Neck surgery, Radiation Oncology, and Gastro Intestinal Oncology. Breast reconstruction using autologous tissue transfer was employed in 2005, and since then, patients' needs for breast reconstruction have been increasing. Nineteen cases of breast reconstruction were performed in 2011, and a free deep inferior epigastric artery perforator (DIEP) flap transfer is the most frequently used procedure.

Research Activities

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 quality of life 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 of reconstructive surgery and developing new techniques of reconstructive surgery are the most important aims of our studies. Multi-institutional analyses of postoperative complication and swallowing function after total pharyngolaryngo esophagectomy and reconstruction with a free jejunal graft are continuously performed. This study was supported by a Grant in-Aid for Cancer Research. The aim of the study was to clarify the relationship between surgical procedures and postoperative complications and function. We clarified the importance of the tensile strength of the transferred jejunum for better postoperative swallowing functions. Long term results after microsurgical head and neck reconstruction were evaluated to elucidate the risk factors associated with reconstructive failure. We clarified that reconstructive surgery in patients with previous surgical intervention, including reconstructive microsurgery, is at high risk of reconstructive failure. Furthermore, previous radiation therapy was closely related as a risk factor for reconstructive failure.

Table 1. Cooperation with other divisions

NCCH East	No. of patients
Head & Neck surgery	114
Orthopedic surgery	1
Esophageal surgery	2
Breast surgery	42
Dermatology	----
Urologic surgery	1
HB & P surgery	0
Ophthalmic surgery	----
Colorectal surgery	5
Gastric surgery	0
Thoracic surgery	7
Gynecology	----
Plastic & Reconstructive	2
Total	174

Table 2. Operative Procedures

NCCH East	No. of flaps
Microvascular free flap	103
Jejunum	34
RAMC or DIEP	36
Anterolateral thigh	18
Fibula bone	7
Latissimus Dorsi	1
Radial Forearm	0
Other flaps	7
Other Microsurgery	1
Supercharge	0
Nerve Graft	0
Limb Salvage	0
Hepatic Artery	0
Others	1
Subtotal	104
Pedicled flaps	18
PMMC	7
Latissimus Dorsi	3
RAMC	0
Other flaps	7
Other Procedures	52
Total	174

Published Papers

1. Onoda S, Sakuraba M, Asano T, Miyamoto S, Hayashi R, Asai M, Kimata Y. Thoracoacromial vessels as recipients for head and neck reconstruction and cause of vascular complications. Microsurgery, 31:628-631, 2011

2. Tanaka K, Sakuraba M, Miyamoto S, Hayashi R, Ebihara M, Miyazaki M, Shinozaki T, Daiko H, Yano T. Analysis of operative mortality and post-operative lethal complications after head and neck reconstruction with free tissue transfer. Jpn J Clin Oncol, 41:758-763, 2011

3. Onoda S, Kimata Y, Yamada K, Sugiyama N, Sakuraba M, Hayashi R. The best salvage operation method after total necrosis of a free jejunal graft? Transfer of a second free jejunal graft. J Plast Reconstr Aesthet Surg, 64:1030-1034, 2011

4. Tsuchiya S, Sakuraba M, Asano T, Miyamoto S, Kimata Y, Hayashi R, Nakatsuka T. Morphologic study of mandibles in Japanese patients for mandibular reconstruction with fibula free flaps. Head Neck, 33:383-388, 2011

5. Onoda S, Sakuraba M, Asano T, Miyamoto S, Beppu Y, Chuman H, Kawai A, Nakatani F, Kimata Y. Use of vascularized free fibular head grafts for upper limb oncologic reconstruction. Plast Reconstr Surg, 127:1244-1253, 2011

DEPARTMENT OF BREAST ONCOLOGY, HEMATOLOGY, AND MEDICAL ONCOLOGY, HEMATOLOGY AND STEM CELL TRANSPLANTATION DIVISION

Takeshi Yamaguchi, Yoichi Naito, Nobuaki Matsubara, Shunji Nagai, Masahiko Nezu, Hirofumi Mukai, Kuniaki Itoh

Introduction

The Hematology Division is part of the Division of Oncology and Hematology. The staff physicians and residents of this Division carry out clinical and research activities related to chemotherapy of patients with hematological and non-hematological tumors. The overall inpatient care system comprises the management of both oncology and hematology teams, namely, while a monthly rotating attending physician out of three staff physicians is responsible for all inpatient care and education of residents in the oncology team, all physicians including two hematology staff physicians and residents attend to manage all of the inpatient care in the hematology team. In 2011, approximately 180 patients with hematological malignancies, including 23 patients seeking a second opinion, visited the Division for consultation. High-dose chemotherapy with autologous peripheral blood hematopoietic stem cell transplantation is considered the standard treatment for patients with relapsed malignant lymphoma previously responsive to salvage chemotherapy and younger patients with multiple myeloma. Clinical engineers, in collaboration with staff physicians, perform stem cell harvesting by apheresis and cell processing.

Routine Activities

The Division manages patients with various types of hematological malignancies, including non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, macroglobulinemia, acute leukemia, and chronic leukemia. Recently, a tendency has been noted towards an increased number of elderly patients with hematological malignancies. Moreover, the Division is currently providing routine chemotherapy as an outpatient service to an increasing number of patients with both hematological and non-hematological tumors. All patients undergoing aggressive chemotherapy and autologous peripheral blood hematopoietic stem cell transplantation are managed in laminar airflow rooms in the designated ward on the eighth floor. Besides managing patients, the Division also provides consultation on hematological abnormalities. Morning case conferences on inpatient care are held on Mondays and Thursdays, and a weekly case conference on new patients visiting the clinics at the Division is held on Thursday evenings. A weekly conference, including an educational review on hematology, is also conducted on Tuesday evenings. On Wednesday evenings, a weekly joint conference on hematological disorders is held with pathologists. Morning journal clubs also meet on Wednesdays and Fridays at the Division of Oncology and Hematology.

Research Activities and Clinical Trials

Clinical studies on hematological malignancies performed by the Division 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 the local hematology group in Chiba prefecture. The Division also conducts pharmaceutical company-sponsored clinical trials of new anticancer agents 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 (JCOG0601); a randomized phase II trial of biweekly rituximab-CHOP or biweekly rituximab-CHOP/cyclophosphamide, cytarabine, dexamethasone, etoposide and rituximab (CHASER) followed by high dose melpharan, cyclophosphamide, etoposide and dexamethasone (LEED) with autologous peripheral blood hematopoietic stem cell transplantation in patients with newly diagnosed poor risk CD20+ diffuse large B cell lymphoma (JCOG0908); a phase II trial of rituximab-high-CHOP/CHASER followed by high dose LEED with autologous peripheral blood hematopoietic stem cell transplantation in patients with newly diagnosed mantle cell lymphoma (JCOG0406); and a randomized phase II trial of dexamethasone with bortezomib or thalidomide in patients with multiple myeloma in relapse (JCOG0904). An Asian phase II study was

completed on MK-0683 (volinostat), which is a novel inhibitor of histone deacetylase, for patients with low-grade B-cell lymphoma or mantle cell lymphoma in relapse. A randomized double blinded phase III trial of polyethylene glycol (PEG) G-CSF or filograstim for prophylactic use was completed in patients with relapsed malignant lymphoma who were treated with cyclophosphamide, cytarabine, etoposide and dexamethasone (CHASE). A randomized, double-blind study of RAD001 (everolimus), an inhibitor of the mammalian target of rapamycin, is ongoing for poor risk patients with diffuse large B-cell lymphoma in complete remission after first-line treatment with rituximab-CHOP. A global randomized phase III trial of CMC544 (intuzumab ozogamicin) and rituximab or bendamustin and rituximab in patients with relapsed CD22 positive diffuse large B cell lymphoma, who are not eligible for autologous stem cell transplantation, is also ongoing.

Published Papers

1. Tanaka R, Kimura S, Ashihara E, Yoshimura M, Takahashi N, Wakita H, Itoh K, Nishiwaki K, Suzuki K, Nagao R, Yao H, Hayashi Y, Satake S, Hirai H, Sawada K, Ottmann OG, Melo JV, Maekawa T. Rapid automated detection of ABL kinase domain mutations in imatinib-resistant patients. Cancer Lett, 312:228-234, 2011

Table 1. Number of patients

Non-Hodgkin's lymphoma	126
Hodgkin's lymphoma	6
Multiple myeloma	5
Acute leukemia	14
Chronic leukemia	10
Others	21
Total	182

Table 2. Type of procedure

PBSCT non-Hodgkin's lymphoma in relapse	2
Multiple myeloma	2
Total	4

DEPARTMENT OF BREAST ONCOLOGY, HEMATOLOGY, AND MEDICAL ONCOLOGY, INVESTIGATIONAL DRUG DEVELOPMENT FOR SOLID TUMORS DIVISION

Takeshi Yamaguchi, Yoichi Naito, Nobuaki Matsubara, Shunji Nagai, Masahiko Nezu, Hirofumi Mukai, Kuniaki Itoh

Introduction

Patients with different types of cancer, including those with breast and genitourinary tract cancers and malignant lymphomas, are treated with standard chemotherapy and/or managed in clinical trials in daily medical practice at the Division of Oncology and Hematology. Gynecological malignancies and soft tissue sarcomas are also treated with chemotherapy. Another major target of the Division is cancer of unknown primary origin. The clinical and research activities of the Division primarily focus on the following fields: Standard chemotherapeutic treatment in medical practice, disease-oriented clinical trials, particularly for breast cancer and hematological malignancies, developmental therapeutics with 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 diseases of the Division comprised breast cancer and malignant lymphomas. Eligible patients with these cancers were invited to participate in large phase II/III studies. Presently, there is an increasing number of patients with cancers of the genitourinary tract and cancer of unknown primary origin. The Division also treated 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 2011, about 700 patients with different types of cancer, including hematological malignancies, visited the Division for consultation. Approximately 400 patients per month received routine chemotherapy as an outpatient service by the Division. The overall inpatient care system of the Division comprises management of both oncology and hematology teams, namely, a monthly rotating attending physician out of three staff physicians is responsible for all inpatient care and education of residents in oncology team, and all physicians including two hematology staff and residents attend to manage of all the inpatient care in the hematology team. Morning case conferences on inpatient care are held on Mondays and Thursdays, and a weekly case conference on new patients visiting the clinics at the Division is held on Thursday evenings. A weekly educational review on oncology and hematology is also conducted on Tuesday evenings. Moreover, a biweekly joint conference with breast surgeons is held on Wednesday evenings and a monthly urological conference with urologists is held on Monday evenings. Morning journal clubs also meet on Wednesdays and Fridays at the Division of Oncology and Hematology.

Research Activities and Clinical Trials

Phase I/II studies of new anticancer agents for specific disease targets are conducted in collaboration with pharmaceutical companies. Phase I studies of the following anticancer agents were conducted: cabazitaxel (a new taxane derivative) for patients with hormone refractory prostate cancer, abiraterone acetate (a CYP17 inhibitor for androgen antagonist) for patients with castration-resistant prostate cancer who have not received chemotherapeutic agents, eribulin (synthetic halichondrin) for patients with advanced or metastatic breast cancer in whom HER-2 was overexpressed, and NK105 (polymer micelles of paclitaxel) for patients with advanced or metastatic cancer for which standard chemotherapy was unavailable. For patients unresponsive to chemotherapy and those with cancers for which standard chemotherapy was unavailable, a combination phase I study of afatinib with vinorelbine is in progress. Phase II studies of the following anticancer agents were also conducted: AG-013736 (an inhibitor of VEGF receptor tyrosine kinases) as a second-line treatment for patients with metastatic renal cell cancer; and neratinib (erbB1/2/4 inhibitor) as an adjuvant chemotherapy for patients with breast cancer. A phase II study of eribulin for patients with soft tissue sarcomas is

Table 1. Number of patients

Breast cancer	262
Hematological malignancies	182
Genitourinary cancer	171
Gynecological cancer	19
Cancer of unknown primary origin	32
Others	44
Total	710

ongoing.

In addition, a randomized placebo controlled trial of RAD001 (an mTOR inhibitor, everolimus) combined with paclitaxel and trastuzumab is ongoing for patients with HER-2 positive metastatic and/or locally advanced breast cancer in as a primary treatment. BOLERO-3, a randomized placebo controlled trial of RAD001 with vinorelbine and trastuzumab is being conducted for patients with HER-2 positive, trastuzumab-resistant breast cancer in whom taxane therapy has been carried out. A randomized phase III study of neratinib versus a combination with lapatinib and capecitabine for patients with HER-2 positive metastatic and/or locally advanced breast cancer is also being conducted. A randomized phase III study of taxane-based chemotherapy with lapatinib or trastuzumab as a first line therapy for patients with HER-2 positive metastatic breast cancer is also being conducted. In addition, to select an effective chemotherapeutic regimen (SELECT-BC) for patients with metastatic breast cancer in whom hormone therapy has failed and trastuzumab is not indicated, a prospective randomized study of anthracycline versus TS-1 as a front-line chemotherapy is ongoing.

Published Papers

1. Tahara M, Minami H, Kawashima M, Kawada K, Mukai H, Sakuraba M, Matsuura K, Ogino T, Hayashi R, Ohtsu A. Phase I trial of chemoradiotherapy with the combination of S-1 plus cisplatin for patients with unresectable locally advanced squamous cell carcinoma of the head and neck. Cancer Sci, 102:419-424, 2011
2. Ohsumi S, Shimozuma K, Ohashi Y, Shinji M, Hozumi Y, Mukai H, Takatsuka Y, Aihara T. Health-related quality of life and psychological distress of breast cancer patients after surgery during a phase III randomized trial comparing continuation of tamoxifen with switching to anastrozole after adjuvant tamoxifen for 1-4 years: N-SAS BC 03. Breast Cancer Res Treat, 127:143-152, 2011
3. Shigeta K, Miura Y, Naito Y, Takano T. Cabazitaxel for castration-resistant prostate cancer. Lancet, 377:121; author reply 122-123, 2011
4. Shigeta K, Naito Y, Takano T. Early prostate cancer--treat or watch? N Engl J Med, 365:568-569, 2011

DEPARTMENT OF BREAST ONCOLOGY, HEMATOLOGY, AND MEDICAL ONCOLOGY, BREAST SURGERY DIVISION

Noriaki Wada, Kimiyasu Yoneyama, Chisako Yamauchi* (* part-timer)

Introduction

The Breast Surgery Division is responsible for the care of patients with operable breast cancers. The Division is committed to providing the latest, most comprehensive breast treatments for patients in cooperation with other breast care specialists. The multidisciplinary approach to diagnosis and treatment includes working closely with a team of surgeons, radiologists, pathologists, plastic surgeons, medical oncologists, specialized nurses, and technicians.

The division mainly focuses on "minimally invasive surgery" and carries out a thorough investigation for an oncologically safe approach, less morbidity and good cosmesis. In particular, sentinel lymph node (SLN) biopsy has already been established as a standard care for clinical node negative patients. This procedure can be a reasonable alternative to unnecessary axillary lymph node dissection (ALND). On the other hand, preoperative systemic therapy provides the opportunity for 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 of patients with breast cancer.

Routine Activities

For the regular activities of the Division, a daily morning routine round is scheduled for inpatients by all staff and residents. Moreover, Our weekly film conference on breast cancer is conducted every Monday evening to discuss the diagnosis and surgical treatment planning for each patient. Multidisciplinary case conferences with the other breast care team members are held twice a month. A monthly pathological conference on breast cancer is also conducted on the last Friday of each month. At those conferences, the patients' 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 operated patients with breast cancer are shown in Table 1. A total of 285 patients with primary breast cancer and 23 patients with recurrence or other breast disease were operated on. Sixteen immediate breast reconstruction surgeries were included. Of the patients with primary breast cancer, 63 (22%) underwent primary systemic therapy. The types and number of operative procedures performed in 2011 are shown in Table 2. The rate of breast-conserving surgeries (including three radiofrequency ablation alone case) was 72% (204/285). Sentinel node biopsy was performed in 216 patients, and 173 patients were spared from ALND.

Clinical and Research Activities (Trials)

1. Radiofrequency ablation (RFA) using a Cool-tip electrode system.

A feasibility study on RFA followed by partial mastectomy was performed for T1N0 breast cancer patients with no extensive intraductal components using a Cool-tip electrode system. Moreover, a phase II trial of RFA for the nonsurgical treatment of breast cancer is currently about to start.

2. Evaluation for 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.

3. Long term results of SLN negative patients without 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.

4. Effectiveness of primary tumor resection for metastatic breast cancer.

In this multicenter clinical trial (JCOG 1017), the primary tumor resection plus systemic therapy arm is compared to the systemic therapy alone arm in metastatic breast cancer.

Published Papers

1. Ohtani S, Kochi M, Ito M, Higaki K, Takada S, Matsuura H, Kagawa N, Hata S, Wada N, Inai K, Imoto S, Moriya T. Radiofrequency ablation of early breast cancer followed by delayed surgical resection--a promising alternative to breast-conserving surgery. Breast, 20:431-436, 2011

Table 1. Number of primary breast cancer patients operated on during 2002-2011

Clinical stage	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Stage 0	8	18	14	29	34	27	23	38	39	43
Stage I	73	97	100	89	79	94	84	86	80	86
Stage II	110	104	97	94	103	87	87	122	137	112
Stage III	24	33	24	35	34	25	33	42	32	43
Stage IV, unknown	1	1	2	2	1	4	0	3	1	1
Total	216	253	237	249	251	237	227	291	289	285

Table 2. Types of operative procedures performed in 2011 for primary breast cancer

Type of operation	N
BT+SNB	42
BT+SNB→ALND	13
BT+ALND	25
BT alone	1
BP+SNB	128
BP+SNB→ALND	30
BP+ALND	32
BP alone	11
RFA+SNB	3
Total	285

Total mastectomy with immediate breast reconstruction was performed in six-teen patients.
BP, partial mastectomy; BT, total mastectomy; SNB, sentinel node biopsy; ALND, axillary lymph node dissection; RFA, radio frequency ablation

Table 3. Overall survival (OS) rate
OP year: Jan 1993- Dec 2005

Clinical stage	**N**	**5 yr. OS**	**10 yr. OS**
Stage 0	87	99%	93%
Stage I	570	97%	94%
Stage II	1104	90%	80%
Stage III	214	66%	51%
Stage IV, unknown	22	32%	11%
Total	1997		

median follow up period: 104 months [2-218]

DEPARTMENT OF THORACIC ONCOLOGY, THORACIC SURGERY DIVISION

Kanji Nagai, Junji Yoshida, Tomoyuki Hishida, Keiju Aokage, Akikazu Kawase, Masayuki Nakao, Tomohiro Haruki

Introduction

The Thoracic Surgery Division 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 Division 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 bronchoplasty, combined resection with adjacent structures, and perioperative adjuvant treatment.

The Thoracic Surgery Division of the National Cancer Center Hospital East ranks second in Japan following the National Cancer Center Tokyo in providing surgical treatment of primary lung cancer. Since its establishment in 1992, the Division 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 16 scientific papers published in English, and 1 in Japanese, the Division made 59 presentations: 15 international, 37 national, and 7 regional.

Routine Activities

To maintain its leadership position, the Division was seeking more consultant surgeons since Dr. Nagai, chief of the Division, was promoted to hospital management in 2006 and has since then been engaged mostly in administrative duties. After almost 4 years, a new consultant surgeon joined the Division. At the beginning of April, the Division welcomed Dr. Keiju Aokage, one of our former senior residents. The Division is presently composed of 4 consultant surgeons and 5 or 6 residents.

The Division 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, pathologists, 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 Division 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 mediastinal nodes, and small cell primary pulmonary carcinomas in clinical stage I, surgical resection is indicated for 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 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 tumors 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 Division have generally remained similar for the past several years, but we started to employ port-access thoracoscopic surgery more often last year. Approximately 10% of the surgeries are completed via a 3-port access, and 80% of the surgeries are thoracoscopically assisted. To date, the average postoperative hospital stays of patients in the Division have improved and became shorter, 3 days being the shortest with a median of 7 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 1 (0.3%) patient undergoing surgery for primary lung cancer.

Research Activities

In November 2003, the Thoracic Surgery Division initiated a new limited resection trial for small pulmonary ground-glass opacity (GGO) lesions. Patient selection was based solely on high-resolution CT (HRCT) findings: a pure or mixed GGO lesion of 2 cm diameter or smaller in the lung periphery with a tumor disappearance ratio (TDR) of 0.5 or higher on HRCT. TDR is defined as 1−DM/DL, where DM is the maximum tumor diameter on the mediastinal setting and DL on the lung setting. In November 2006, the Department of Thoracic Oncology, Kanagawa Cancer Center Hospital, Yokohama, Kanagawa, Japan, joined the trial, and we achieved our goal of 100 patients in November 2009. We are reviewing the enrolled patients radiologically and pathologically. In view of possible delayed cut-end recurrence cases among patients enrolled in the previous study, diagnosing using the Noguchi classification by intraoperative frozen section, we will have to survey these patients until 10 years after surgery.

The Division is also continuing a negative resection margin technique trial using lavage cytology examination for primary and metastatic lung cancer patients treated with limited resection. This method involves washing the used stapler cartridges followed by intraoperative cytological evaluation of the washed saline sediment.

Clinical Trials

1. Surgical margin lavage cytology examination in limited resection for primary and metastatic lung cancer patients [observational].
2. 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 [phase III].
3. Member of an organized trial of limited resection for small GGO lung tumors [phase II].
4. Member of an organized trial of segmentectomy for peripheral T1aN0M0 non-small cell lung cancers [phase III].
5. Member of an organized trial of CDDP + DOC followed by TS-1 adjuvant chemotherapy for completely resected pathologic stage II/III non-small cell lung cancer [phase II].
6. Member of an organized trial of recMAGE-A3 + AS15 antigen-specific cancer immunotherapeutic as adjuvant therapy in patients with completely resected MAGE-A3 positive stage IB-IIIA non-small cell lung cancer [phase III].
7. Member of an organized trial of WT1 peptide vaccination as adjuvant therapy in patients with completely resected WT1/HLA-A*2402 positive stage IB-II non-small cell lung cancer [randomized phase II].

Table 1. Number of patients

Lung cancer	337
Metastatic lung tumor	55
Mediastinal tumor	17
Others	45
Total	454

Table 2. Type of procedure - Primary lung cancer

Pneumonectomy	26
Lobectomy	256
(Bronchoplasty)	(5)
Limited resection	45
Exploratory thoracotomy	10
Total	337

Table 3. Overall survival rates for resected primary lung cancer (as of 2010)

Pathologic stage#	Number of patients	MST (months)	5-yr survival rate (%)
IA	896	NR	87.9
IB	405	99.9	67.6
IIA	262	65.8	54.1
IIB	120	41.1	43.3
IIIA	306	37.7	37.9
IIIB	32	24.4	35.0

Surgery between 2000 and 2007; #: Stages according to TNM Classification, 6th edition; NR: Not reached.

Published Papers

1. Nakao M, Hishida T, Ishii G, Nagai K. Malignant pleural mesothelioma with osteosarcomatous differentiation: characteristic bone scintigraphy findings associated with enhanced tumorous osteogenesis. Eur J Cardiothorac Surg, 39:421, 2011
2. Ohtaki Y, Yoshida J, Ishii G, Aokage K, Hishida T, Nishimura M, Takeyoshi I, Nagai K. Prognostic significance of a solid component in pulmonary adenocarcinoma. Ann Thorac Surg, 91:1051-1057, 2011
3. Shimada Y, Yoshida J, Aokage K, Hishida T, Nishimura M, Nagai K. Complete left-sided pericardial defect in a lung cancer patient undergoing pneumonectomy without closure of the defect. Ann Thorac Cardiovasc Surg, 17:67-70, 2011
4. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Poor prognostic factors in patients with stage IB non-small cell lung cancer according to the seventh edition TNM classification. Chest, 139:855-861, 2011
5. Ohtaki Y, Ishii G, Hasegawa T, Nagai K. Adult neuroblastoma arising in the superior mediastinum. Interact Cardiovasc Thorac Surg, 13:220-222, 2011
6. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Prognostic impact of histology on early-stage non-small cell lung cancer. Chest, 140:135-145, 2011
7. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. The prognostic impact of cigarette smoking on patients with non-small cell lung cancer. J Thorac Oncol, 6:735-742, 2011
8. Maeda R, Ishii G, Yoshida J, Hishida T, Nishimura M, Nagai K. Influence of cigarette smoking on histological subtypes of stage I lung adenocarcinoma. J Thorac Oncol, 6:743-750, 2011
9. Suzuki K, Koike T, Asakawa T, Kusumoto M, Asamura H, Nagai K, Tada H, Mitsudomi T, Tsuboi M, Shibata T, Fukuda H, Kato H. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). J Thorac Oncol, 6:751-756, 2011
10. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Risk factors for tumor recurrence in patients with early-stage (stage I and II) non-small cell lung cancer: patient selection criteria for adjuvant chemotherapy according to the seventh edition TNM classification. Chest, 140:1494-1502, 2011

DEPARTMENT OF THORACIC ONCOLOGY, THORACIC ONCOLOGY DIVISION

Yuichiro Ohe, Hironobu Ohmatsu, Koichi Goto, Seiji Niho, Kiyotaka Yoh, Shigeki Umemura, Yuki Yamane, Toshihiro Shiozawa, Yoko Yamaguti, Masami Itho

Introduction

The Thoracic Oncology Division provides care for patients with primary lung cancer, mediastinal tumors, and pleural tumors. The Division 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 Division 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 are also receiving oral chemotherapy and/or intravenous chemotherapy in the Ambulatory Care Center. Bronchoscopy for diagnosis is performed on Monday and Thursday afternoon. Fluoroscopic-CT guided needle lung biopsies are carried out on Tuesday afternoon. For patient management, we use approximately 70 beds in wards. 8F, 6A, 6B and 5B.

Case conferences on thoracic surgery and medical oncology are scheduled on Tuesday evenings and Wednesday evenings, respectively. The staff members and residents of the division participate in a journal club on Monday and Wednesday mornings. At monthly meetings with physicians in private practice, the staff members also present case reports and research results for subspecialty education.

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: correlation between gene abnormalities and clinical characteristics; precancerous lesions; and typical adenomatous hyperplasia; and 4) Translational research from bench to bed-side or from bed-side to bench for the development of innovative treatment strategies.

Especially, whole genome analysis of 100 adenocarcinomas of the lung to detect new driver mutations is under investigation in collaboration with the Research Center for Innovative Oncology.

Clinical Trials

The Thoracic Oncology Division 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, some data demonstrated the usefulness of maintenance chemotherapy using pemetrexed orerlotinib for NSCLC but the efficacy has never been definitively established. Thus, an in-house feasibility study of maintenance chemotherapy with TS-1 for stage IV non-small cell lung cancer (NSCLC) is ongoing. Patients received TS-1 as a maintenance chemotherapy after 3 or 4 cycles of platinum-based 1st line chemotherapy and the target number of the patients is 78 in this study.

Crizotinib is a newly developing ALK and MET inhibitor and very effective for EML4-ALK positive NSCLC, although 4-5% of NSCLC are positive for EML4-ALK fusion protein. A global multi-institutional randomized phase 3 study of crizotinib has been started and we are participating in this study. JCOG0509 was a randomized phase 3 study comparing irinotecan with cisplatin vs amrubicin with cisplatin for extensive disease small cell lung cancer (SCLC). The interim analysis of JCOG0509 could not demonstrate non-inferiority of cisplatin and amrubicin compared with cisplatin and irinotecan.

Number of patients in 2011

Lung Cancer		361
	Small cell lung cancer	83
	Adenocarcinoma	174
	Squamous cell carcinoma	53
	Large cell carcinoma	8
	NSCLC NOS	36
	Others	7
Thymic cancer		5
Thymoma		2
Malignant pleural mesothelioma		4

Initial treatment of lung cancer in 2011

Chemotherapy	205
Chemoradiotherapy	54
Surgery followed by chemotherapy	48
Radiotherapy	19
Palliative care	30
Others	5

Survival of lung cancer patients treated in 2004-2008

Disease	Stage	Treatment	N	Survival rate (%)				
				1y	2y	3y	4y	5y
NSCLC	III	Chemoradiotherapy	255	78	49	36	32	26
NSCLC	IIIB-IV	Chemotherapy	830	47	27	15	9	5
SCLC	LD	Chemoradiotherapy	87	80	40	24	17	17
SCLC	ED	Chemotherapy	138	33	2	2	2	0

JCOG0605, a randomized phase 3 study comparing nogitecan vs weekly cisplatin, irinotecan and etoposide for previously treated SCLC and JCOG0901, a phase 2 study of amrubicin for refractory SCLC, have completed patient accrual. JCOG1011 is a newly started randomized phase 2 study for LD-SCLC comparing cisplatin and amrubicin with the CODE regimen (weekly cisplatin, vincristine, Adriamycin, etoposide) after induction chemoradiotherapy with cisplatin and etoposide.

Published Papers

1. Naito Y, Kubota K, Ohmatsu H, Goto K, Niho S, Yoh K, Ohe Y. Phase II study of nedaplatin and docetaxel in patients with advanced squamous cell carcinoma of the lung. Ann Oncol, 22:2471-2475, 2011

2. Nyberg F, Ogiwara A, Harbron CG, Kawakami T, Nagasaka K, Takami S, Wada K, Tu H-K, Otsuji M, Kyono Y, Dobashi T, Komatsu Y, Kihara M, Akimoto S, Peers IS, South MC, Higenbottam T, Fukuoka M, Nakata K, Ohe Y, Kudoh S, Clausen IG, Nishimura T, Marko-Varga G, Kato H. Proteomic biomarkers for acute interstitial lung disease in gefitinib-treated Japanese lung cancer patients. PLoS One, 6:e22062, 2011

3. Nyberg F, Barratt BJ, Mushiroda T, Takahashi A, Jawaid A, Hada S, Umemura T, Fukuoka M, Nakata K, Ohe Y, Kato H, Kudoh S, March R, Nakamura Y, Kamatani N. Interstitial lung disease in gefitinib-treated Japanese patients with non-small-cell lung cancer: genome-wide analysis of genetic data. Pharmacogenomics, 12:965-975, 2011

4. Niho S, Kubota K, Yoh K, Goto K, Ohmatsu H, Nihei K, Ohe Y, Nishiwaki Y. Clinical outcome of small cell lung cancer with pericardial effusion but without distant metastasis. J Thorac Oncol, 6:796-800, 2011

5. Suyama K, Naito Y, Yoh K, Niho S, Goto K, Ohmatsu H, Nishiwaki Y, Ohe Y. Development of Cushing's syndrome during effective chemotherapy for small cell lung cancer. Intern Med, 50:335-338, 2011

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, GASTRIC SURGERY DIVISION

Taira Kinoshita, Masaru Konishi, Shinichiro Takahashi, Takahiro Kinoshita, Naoto Gotohda, Yuichiro Kato, Teruhisa Sakamoto

Introduction

Patients with gastric tumors are treated by the Gastric Surgery Division in the Upper Abdominal Surgical Oncology Group. Our group consists of six staff surgeons, three senior residents and nine resident surgeons. The gastric tumors which we manage include not only common gastric adenocarcinomas but also adenocarcinomas of the esophagogastric junction (AEG), the incidence of which is increasing recently, and gastric submucosal tumors (GISTs), and so on. Annually 260-300 patients are operated on, either with conventional laparotomy or with laparoscopic surgery. The procedure of laparoscopic gastrectomy with nodal dissection was introduced to the division in 2010 to pursue minimal invasiveness and better quality of life (QOL) for the patients. The recent high-definition laparoscopic field of view enables more meticulous and accurate maneuvers. In 2011, about 50% of gastrectomies were performed under laparoscopy, which tendency may continue towards next year. The basis of our surgery is radical extirpation of cancer lesions, but at the same time organ functions and better QOL should be maintained. In addition, we attempt to obtain better clinical outcomes for patients with diseases associated with dismal prognoses (scirrhous gastric cancer or with progressive lymph nodes metastasis) through a surgical approach combined with recent advanced chemotherapy regimen.

Routine Activities

Usually 12-14 patients are hospitalized and 5-7 patients undergo operations per week. A weekly film conference is held every Monday from 17:00 with doctors from the the Department of Diagnostic Radiology and Department of Gastrointestinal Oncology, discussing diagnosis of the patients with gastric tumors from oncological, surgical, endoscopic and radiologic aspects, to determine the optimal treatment strategy for each patient. In principle, patients with superficial gastric cancer lesions (cT1a) of the intestinal histologic type showing a clear margin are treated with endoscopic submucosal dissection (ESD). Some are required to undergo subsequent completion laparoscopic surgery with nodal dissection based on the pathological findings of the specimen obtained with ESD. As the initial interventions, laparoscopic surgery with nodal dissection is indicated for other patients with c-stage I gastric cancer. Not only distal gastrectomy but also total gastrectomy or function preserving procedures (pylorus-preserving gastrectomy or proximal gastrectomy with jejunal interposition/double-tract) can be performed laparoscopically. Basically, all of the procedures, mobilization, lymphadenectomy and reconstruction are carried out under laparoscopy, which we refer to as total laparoscopic procedures. Open gastrectomy with D2 nodal dissection is indicated for patients with c-stage II or III gastric cancer. When the tumor has infiltrated adjacent organs (liver, pancreas, etc.), extended radical operations (pancreaticoduodenectomy, plus hepatectomy) are chosen. For AEGs, when the tumor is over 3 cm long and involves the distal esophagus exceeding, the left thoracoabdominal approach is selected. Otherwise, the abdominal approach with transhiatal dissection is chosen according to the results of JCOG 9502. When the patients are diagnosed as having p-stage II or III in the final postoperative pathological findings, they are subsequently recommended to undergo adjuvant chemotherapy according to the Gastric Cancer Treatment Guidelines (Japanese Gastric Cancer Association).

We place importance on education of gastric surgeons, including those from other institutions, as well as hands-on training for resident surgeons in our hospital. Surgeons from various hospitals regularly visit our division to learn surgical techniques.

Research Activities and Clinical Trials

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. Patients with gastric cancer are, if eligible for a particular study, invited to take part in one of the ongoing clinical trials. Current ongoing multi-institutional clinical

trials, in which we participate, are as follows:

1. JCOG 0501 A phase III randomized study to investigate the effectiveness of neoadjuvant chemotherapy (CDDP+S-1) for resectable gastric cancer with the appearance of large-sized lesions type 3 or type 4. In this trial, the neoadjuvant chemotherapy arm is being compared with the precedent surgery arm, both of which are followed by adjuvant chemotherapy (S-1).
2. JCOG 0705 A phase III randomized study to investigate the efficacy and feasibility of palliative gastrectomy for non-resectable advanced gastric cancer. (REGATTA trial, in collaboration with Korea) In this trial, the palliative gastrectomy arm is compared to the chemotherapy arm.
3. JCOG 0912 A phase III randomized study of laparoscopy assisted versus open distal gastrectomy with nodal dissection for clinical stage IA and IB gastric cancer.
4. JCOG 1001 A phase III randomized study to evaluate the clinical benefits of bursectomy for patients with SS/SE gastric cancer.
5. JCOG 1002 A phase II study of systemic chemotherapy with Docetaxel, CDDP, and S-1 followed by surgery in advanced gastric cancer with extensive lymph node metastasis
6. JCOG 1009/1010 A phase II trial of ESD to expand the indication to early gastric cancer of the undifferentiated type

Published Papers

1. Aizawa M, Gotohda N, Takahashi S, Konishi M, Kinoshita T. Predictive value of baseline neutrophil/lymphocyte ratio for T4 disease in wall-penetrating gastric cancer. World J Surg, 35:2717-2722, 2011
2. Nobuoka D, Gotohda N, Kato Y, Takahashi S, Konishi M, Kinoshita T. Influence of excess body weight on the surgical outcomes of total gastrectomy. Surg Today, 41:928-934, 2011

Table 1. Number of patients

Gastric cancer	268
Others (GIST etc.)	16

Table 2. Type of procedure

Open gastrectomy	129
Distal Gastrectomy	57
Pylorus-preserving Gastrectomy	0
Proximal Gastrectomy	6
Total Gastrectomy	63
Pancreaticoduodenectomy	1
Partial Gastrectomy	1
Others (bypass, exploration, etc.)	17
Laparoscopic Surgery	111
Distal Gastrectomy	82
Pylorus-preserving Gastrectomy	3
Proximal Gastrectomy	16
Total Gastrectomy	5
Partial Gastrectomy	5
Others (exploration, etc.)	7

Table 3. Survival rates of gastric cancer

Stage	No.of pts	5-yr survival(%)
IA	884	99.3
IB	281	91.4
II	242	81.4
IIIA	179	68.2
IIIB	100	37.1
IV	313	18.5

Op.year: 1995.1-2004.12
Stage: Japanese Classification (13th Ed.)

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, COLORECTAL SURGERY DIVISION

Norio Saito, Masanori Sugito, Masaaki Ito, Akihiro Kobayashi, Yusuke Nishizawa

Introduction

The Colorectal and Pelvic Surgery Division was established 13 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 Colorectal and Pelvic Surgery Division comprises 7 consultants (5 colorectal surgeons and 2 urologists) and 10 residents. The outpatient clinic is open 5 days a week. More than 350 new patients with colorectal carcinomas and more than 150 new patients with other pelvic malignancies visited this Division 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) has been performed in about 300 patients with very low rectal tumors and has resulted in cure, preservation of anal function, and better QOL.

Research Activities and Clinical Trials

1) A prospective randomized trial for extending the indications for Lap-Op (JCOG0404 CRC Surg-LAP vs. Open). The criteria for inclusion into this trial include: (1) T3 and T4 tumors located at C, A, and S in the colon and Rs in the rectum; (2) stage N0-2; (3) stage M0; and (4) a maximum tumor size ≤ 8 cm. A total of 77 patients have been registered in this Division. This study is currently in progress.
2) Intersphincteric resection study (ISR Study). APR has been the standard surgery for very low rectal cancer located within 5 cm of the anal verge. However, permanent colostomy causes severe impairment of the 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 by performing ISR in patients with very low rectal cancer. However, patients need to be informed regarding the potential functional adverse effects after ISR preoperatively. This study is in progress, and 43 patients have been registered. The final results will be obtained soon.
3) Bladder-sparing surgery for locally advanced rectal cancer involving the prostate and/or seminal vesicles. Total pelvic exenteration (TPE) is the standard procedure in patients with locally advanced rectal cancer involving the prostate and seminal vesicles. This study aims to evaluate the feasibility of bladder-sparing surgery as an alternative to TPE. This procedure has been performed in 33 patients with primary or recurrent tumors. This technique permits conservative surgery in selected patients with advanced rectal cancer involving the prostate and/or seminal vesicles without compromising local control. The QOL of these patients appears to be better. This 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.]. This study aims to

evaluate the feasibility and effects of lateral node dissection in patients with advanced low rectal cancer (T3, T4) without lateral node metastasis. In this study, 76 patients have been registered intraoperatively. This study is currently in progress.

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 T 1 and a part of T2 rectal cancer without lymph node metastases. In this study, 32 patients have been registered, and itis currently in progress.
6) Other clinical trials are also in progress as follows.
   - The role of diverting stoma in low anterior resection for rectal cancer – A prospective multi-center study under the Japanese Society for Cancer of the Colon and Rectum (JSCCR)
   - Comparing surgical site infection rates in colorectal surgery following closure of abdominal wounds with metallic skin staples or subcuticular absorbing-monofilament suture; A prospective randomized trial
   - A phase I study of preoperative chemoradiotherapy with S-1+L-OHP for locally advanced rectal cancer
   - 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)

Table1. Number of patients (2011.1-2011.12)

Colorectal cases			Other cases		Total
Colon	Rectum	Sub-total	Gastro-intestinal	Others	
140	173	313	7	103	423

Tables 2. Type of procedure
Operative Procedures (2011.1-2011.12)

Colon N=140 Laparoscopic (LAP) : 110, Open : 30		
Sigmoidectomy	44	(LAP:43)
Right (hemi) colectomy	34	(LAP:33)
Ileocecal resection	8	(LAP: 8)
Limited colectomy	26	(LAP:23)
Hartmann procedure	0	
High anterior resection	0	
Low anterior resection	2	
Left (hemi) colectomy	2	(LAP:2)
Stoma	3	
Other	21	

Rectum N=173 Laparoscopic (LAP) : 79, Open : 94		
Low anterior resection	75	(LAP:45)
Abdominoperineal resection(AAR)*	47	(LAP:22)
High anterior resection	11	(LAP:11)
Abdominoperineal resection (APR)	15	
Hartmann procedure	6	
Local excision	5	
Total pelvic exenteration	3	
Stoma	4	
Others	7	

*Conventional coloanal anastomosis : 4
Partial intersphincteric resection (ISR) : 19
Subtotal ISR : 17
Total ISR : 7
Partial external sphincter resection (ESR) : 3

Table 3. Survival rates

Stage	Colon No. of pts	Colon 5-yr survival (%) overall	Colon 5-yr survival (%) cancer specific	Rectum No. of pts	Rectum 5-yr survival (%) Overall	Rectum 5-yr survival (%) cancer specific
Stage0	7	100	100	10	100	100
Stage I	155	96.1	100	119	94.1	99.1
Stage II	239	91.5	95.2	158	83.9	89.9
Stage IIIa	158	82.7	86.3	132	82.2	84.3
Stage IIIb	50	64.9	64.9	89	59.3	62
Stage IV	133	14.3	15.4	77	23.6	23.9

Op:1999.1-2005.12

Published Papers

1. Shiomi A, Ito M, Saito N, Ohue M, Hirai T, Kubo Y, Moriya Y. Diverting stoma in rectal cancer surgery. A retrospective study of 329 patients from Japanese cancer centers. Int J Colorectal Dis, 26:79-87, 2011
2. Yoneyama Y, Ito M, Sugitou M, Kobayashi A, Nishizawa Y, Saito N. Postoperative lymphocyte percentage influences the long-term disease-free survival following a resection for colorectal carcinoma. Jpn J Clin Oncol, 41:343-347, 2011
3. Watanabe K, Saito N, Sugito M, Ito M, Kobayashi A, Nishizawa Y. Predictive factors for pulmonary metastases after curative resection of rectal cancer without preoperative chemoradiotherapy. Dis Colon Rectum, 54:989-998, 2011
4. Kobayashi S, Ito M, Sugito M, Kobayashi A, Nishizawa Y, Saito N. Association between incisional surgical site infection and the type of skin closure after stoma closure. Surg Today, 41:941-945, 2011
5. Nishizawa Y, Fujii S, Saito N, Ito M, Ochiai A, Sugito M, Kobayashi A, Nishizawa Y. The association between anal function and neural degeneration after preoperative chemoradiotherapy followed by intersphincteric resection. Dis Colon Rectum, 54:1423-1429, 2011
6. Shiomi A, Ito M, Saito N, Hirai T, Ohue M, Kubo Y, Takii Y, Sudo T, Kotake M, Moriya Y. The indications for a diverting stoma in low anterior resection for rectal cancer: a prospective multicentre study of 222 patients from Japanese cancer centers. Colorectal Dis, 13:1384-1389, 2011
7. Nishizawa Y, Ito M, Saito N, Suzuki T, Sugito M, Tanaka T. Male sexual dysfunction after rectal cancer surgery. Int J Colorectal Dis, 26:1541-1548, 2011

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, ESOPHAGEAL SURGERY DIVISION

Hiroyuki Daiko, Mitsuyo Nishimura

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, with regard to surgery for esophageal cancer, since transthoracic esophagectomy with 3-field lymphadenectomy has become more safe, reliable, and radical, the Division is striving to improve the surgical procedure further in order to lower the high incidence of postoperative mortality and morbidity that occur following this procedure. The Division is conducting a study to define the role of surgery in the multimodal approach to the treatment of esophageal cancer.

Routine Activities

The Esophageal Surgery Division consists of 2 staff surgeons, 1 chief resident and 2 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 & neck surgeons. Approximately 3 patients are operated upon every week. In 2011, 103 patients underwent esophagectomy. Transthoracic esophagectomy with extended lymph node dissection was performed on 59 nontreated cases or with neoadjuvant chemotherapy before surgery, and modified transthoracic esophagectomy was performed as a salvage procedure in 3 patients in whom other therapeutic modalities had failed. Thoracoscopic esophagectomy in the prone position with radical lymph node dissection was undertaken in 31 cases and transhiatal esophagectomy without thoracotomy was performed in 10 cases. Postoperatively, within 30 days, 1 patient died due to complications after a salvage operation.

Clinical Activities

The prognosis of patients with intramural metastasis or with involvement of more than 4 lymph nodes is very poor compared with patients without these factors. Currently, the Division is examining the role of pre- or postoperative chemotherapy in such patients, in whom two cycles of 5-fluorouracil and cisplatin preoperatively and postoperatively are administered.

For patients without lymph node metastasis in the thoracic inlet, thoracoscopic esophagectomy in the prone position with radical lymph node dissection is being attempted.

Cisplatin and 5-fluorouracil are administered preoperatively to patients with stage II/III esophageal cancer according to the outcome of the JCOG 9907 study. Furthermore, we have developed more effective neoadjuvant therapy for clinical stage II/III; a feasibility trial of neoadjuvant chemotherapy with docetaxel, cisplatin and fluorouracil for clinical stage II/III thoracic esophageal carcinoma has been completed.

For treating patients aged over 80 years who are unable to receive definitive chemoradiotherapy or undergo surgery, transhiatal esophagectomy with upper and middle to lower mediastinal lymph node dissection to as great an extent as possible is being attempted.

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.

JCOG trial 0502: This is a randomized controlled trial of esophagectomy versus chemoradiotherapy in patients with clinical stage I esophageal carcinoma.

Table 1. Type of Operation

Esophagectomy	103
GIST	3
Carcinoma of the reconstructed gastric tube	1
Salvage lymph node dissection	6
Exploratory thoracotomy	3
Emergency operation	4
Others	2
Total	122

Table 2. Type of Approach for Esophageal Cancer

Rt-Transthoracic Esophagectomy	62
Thoracoscopic Esophagectomy	31
Transhiatal Esophagectomy	10
Total	103

Published Papers

1. Daiko H, Hayashi R, Sakuraba M, Ebihara M, Miyazaki M, Shinozaki T, Saikawa M, Zenda S, Kawashima M, Tahara M, Doi T, Ohtsu A. A pilot study of post-operative radiotherapy with concurrent chemotherapy for high-risk squamous cell carcinoma of the cervical esophagus. Jpn J Clin Oncol, 41:508-513, 2011

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, GASTROINTESTINAL ONCOLOGY DIVISION

Atsushi Ohtsu, Toshihiko Doi, Takayuki Yoshino, Nozomu Fuse, Takashi Kojima

Introduction

In 2011, approximately 500 patients were treated by 5 medical oncologists and 7 residents in the Gastrointestinal (GI) Oncology Division, which focuses on the use of chemotherapy with or without radiation for the treatment of GI malignancies.

Routine Activities

Inter-Divisional tumor board conferences with the Surgical/Radiation Oncology Divisions are held regularly to review and direct treatment for each patient or to discuss treatment strategies. Chemotherapy on an outpatient basis for probable candidates was managed passively, and usually approximately 367 patients are hospitalized and the hospital stay with chemotherapy or palliative therapy was short. Our activities for each type of GI cancer in 2011 are shown in Table 1 (Number), Table 2 (Treatment), and Table 3 (efficacy). In clinical trials, both 58 sponsored initiated trials which consisted of 34 phase I trials including first-in-human, first-in-class drugs in a global fashion and 24 phase2/3 global trials to approve investigational new drugs (INDs) were conducted.

Research Activities

Esophageal Cancer (EC)

The result of a multicenter phase II trial of neo-adjuvant combination chemotherapy with docetaxel, cisplatin and 5-FU (DCF) in stage II/III EC was presented at the ASCO (American Society of Clinical Oncology) meeting, 2011. A multicenter phase II trial of neo-adjuvant chemoradiotherapy (CRT) in stage II or III EC, a multicenter phase I/II trial of induction-chemotherapy combination with DCF followed by CRT for advanced EC with T4 or M1, and a multicenter phase I/II trial of chemotherapy combination with DCF in stage IV EC (JCOG0807) have been completed. The enrollment of a multicenter phase I/II trial of CRT concurrent with S-1 and cisplatin in stage II or III EC (JCOG0604) was closed before the registration of the targeted number of patients due to slow accrual.

Gastric Cancer (GC)

The result of the AVAGAST study which evaluated the efficacy of bevacizumab was published in Journal of Clinical Oncology. The results of a global randomized phase II trial comparing irinotecan with nimotuzumab to irinotecan alone was presented at the 9th International Gastric Cancer Congress. The GASTRIC group project which evaluated the surrogacy of progression-free survival for overall survival in gastric cancer patients using individual patient data analysis on 4,102 patients from 20 randomized trials was presented at the 9th annual meeting of Japanese Society of Medical Oncology.

Colorectal Cancer (CRC)

We reported the results of company-sponsored trials, as a randomized phase II trial comparing TAS-102 with BSC (best supportive care), TAS-102 showing overall survival benefit over a placebo. In a global randomized phase III trial comparing regorafenib with a placebo, regorafenib showed survival benefit over the placebo. We also reported the results of investigator-initiated trials, as a cross-sectional study to elucidate *KRAS* mutation in 5,000 CRC, a registration trial to evaluate the Luminex *KRAS* test, an international consortium and a domestic multicenter trial in chemo-refractory KRAS wild-type metastatic CRC patients to evaluate the correlation between the efficacy of cetuximab and FcGR polymorphism and a retrospective trial to evaluate the efficacy of cetuximab to p. G13D *KRAS* mutation.

Others

We also treated GI rare cancers (GIST, NET etc.) as best practice. Recently our division has focused more on early stage clinical development, especially cutting edge phase I trials. Over 100 patients have been registered in phase I or I/II trials as company driven trials. Several results of trials, such as a (PLK1 inhibitor (MK-1496), an IGF-1R inhibitor (AMG 479), a PI3K inhibitor (BKM120), a pan HER inhibitor (TAK285), etc.) were presented at international meetings and published.

Table1. Number of patients

Tumor Type	Number of new patients	Number of hospitalized patients
Esophageal	196	136
Gastric	214	124
Colorectal	313	76
Other type of tumors	58	31
Total	781	367

Table2. Treatment

Tumor Type	Treatment	Number of patients
Esophageal Cancer	Chemotherapy(include CRT*)	118
Gastric Cancer	Chemotherapy	115
	Adjuvant chemotherapy	67
Colorectal Cancer	Chemotherapy	220

*chemoradiation

Table3. Survival of patients who received standard chemotherapy

Tumor Type	Stage	Number of patients	1-year survival	3-year survival
Esophageal Cancer	I	73	94%	86%
	II/III	208	83%	56%
	T4/M1Lym	116	53%	21%
	IV	97	25%	2%
Gastric Cancer	IV	114	50%	9%
Colorectal Cancer	IV	521	82%	34%

Clinical Trials (Describing Only Ongoing Disease-specific Trials)

Esophageal Cancer (EC)

A multicenter phase III trial comparing surgery with CRT concurrent with 5-FU and cisplatin in stage I EC (JCOG0502), and a multicenter phase II trial of combined treatment with endoscopic mucosal resection and chemo radiotherapy for clinical Stage I EC (JCOG0508) are ongoing. A multicenter phase II trial of S-488410 (vaccination with multiple peptides) in stage IV EC is going as a company-led trial.

Gastric Cancer (GC)

The enrollment for a multicenter phase III trial (G-SOX) comparing S-1 plus oxaliplatin with S-1 plus cisplatin (SP) has been completed and the follow-up is ongoing. The follow-up of a multicenter global phase III trial comparing capecitabine plus cisplatin (XP) with cetuximab to XP (EXPAND) and a multicenter global phase III trial comparing everolimus to placebo (GRANITE) are ongoing. The enrollment for a multicenter global phase III trial comparing paclitaxel plus placebo to paclitaxel plus ramucirumab, a multicenter phase II trial of SP plus cetuximab, a multicenter randomized phase II trial of S-1 plus leucovorin (SL), SL plus oxaliplatin and SP, and multicenter phase II trial of neoadjuvant chemotherapy with docetaxel, S-1 plus cisplatin (JCOG 1102) has been opened.

Colorectal Cancer (CRC)

A global randomized phase III trial comparing ramucirumab with placebo in combination with FOLFIRI is ongoing. A phase Ib trial to evaluate FOLFIRI with CS-7017 regimen is ongoing. A phase I/II trial to evaluate capecitabine with perifosine is ongoing. In an adjuvant setting, a multicenter trial to evaluate the FOLFOX regimen is ongoing.

Published Papers

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DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, DIGESTIVE ENDOSCOPY DIVISION

Kazuhiro Kaneko, Tomonori Yano, Yasuhiro Oono, Hiroaki Ikematsu, Takashi Kojima, Yusuke Yoda, Atsushi Yagishita

Introduction

The Digestive Endoscopy Division covers the fields of the gastrointestinal (GI) tract and head and neck regions. In 2011, a total of 10,830 examinations were performed. A narrow band imaging (NBI) system using the LUCERA spectrum (Olympus Optical Co., Ltd.) has been included for routine examination in 5 of 6 endoscopy rooms since September 2009. 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 tissues 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 of the university.

Routine Activities

Routine endoscopic examinations including magnifying NBI and endoscopic ultrasound are presently used for head and neck, esophageal, gastric, and colorectal cancers, and this NBI system has become essential in detecting very early cancer in these areas. With the NBI system, a differential diagnosis between neoplasia and non-neoplasia can be performed without the need for any dye solution. Single-balloon enteroscopy and capsule endoscopy are 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 treatments 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 underway. 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. Furthermore, detection of circulating tumor cells (CTCs) is performed using blood and tissue samples from esophageal, gastric, and colorectal cancer patients.

In contrast, developing research into novel endoscopy systems is being performed. A Micrometer Volumetric Optical Imaging System (μVOIS) is based on Optical Coherence Tomography. In the μVOIS, the three-dimensional microstructure of the intramucosal layer and muscularis mucosa can be visualized in a horizontal direction. Second is hypoxia imaging for neoplastic lesions of the head and neck and alimentary tracts, with blue visualized images. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and nanoparticles of the rare earth, doped

yttrium oxide. This system is capable of penetrating through the intestinal wall and obtaining images. Furthermore, molecular imaging endoscopy for the use of this system with InGaAs CCD has been developed, since nanoparticles of rare earth act as fluorescent agents. With a low-temperature atmospheric pressure plasmas 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, research is ongoing into the development of a new electrosurgical knife as an endoscopic device, which will be used in ESD for esophageal and gastric cancer.

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: 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 phase III randomized trial regarding the efficacy of a proton pump inhibitor followed by EMR for esophageal cancer; a phase II trial of combined treatment of endoscopic mucosal resection and chemoradiotherapy for clinical stage I esophageal carcinoma (JCOG0508); a multicenter clinical study for enrollment of early gastric cancer following endoscopic treatment for enrollment system using the Web; a multicenter clinical trial of ESD for undifferentiated gastric cancer (JCOG1009); 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.

Published Papers

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DEPARTMENT OF HEPATOBILIARY AND PANCREATIC ONCOLOGY, HEPATOBILIARY AND PANCREATIC SURGERY DIVISION

Taira Kinoshita, Masaru Konishi, Shinichiro Takahashi, Takahiro Kinoshita, Naoto Gotohda, Yuichiro Kato, Kazuteru Monden, Motokazu Sugimoto, Teruhisa Sakamoto

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, 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 chemotherapy for malignancies with dismal prognoses have been conducted.

With the refinements in laparoscopic instruments and advances in surgical experience, laparoscopic hepatectomy is a safe alternative for selected patients with hepatic neoplasms, and has fulfilled its indications. In our division, this procedure has been performed since 2002.

Routine Activities

In the National Cancer Center Hospital East, surgeons in the Upper Abdominal Surgical Oncology Group operate on all patients with gastric, hepatobiliary and pancreatic cancer. Our group is composed of 6 attending surgeons, 3 chief residents, and 4–6 residents. The outpatient clinic is open 5 days a week. Staff meetings are held 3 times a week during which treatment strategies from the 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 2011, 228 patients with hepatobiliary and pancreatic diseases underwent surgical treatment at our Division.

Research Activities and Clinical Trials

1) Pancreatic cancer

JASPAC-01 is a randomized phase III trial to compare orally administered S-1 with intravenous gemcitabine as adjuvant chemotherapy for patients with curatively resected pancreatic cancer. Three hundred and fifty-eight patients have been enrolled and recruitment is complete. Follow-up is on-going.

JSAP is a randomized phase III study on adjuvant chemotherapy using combination therapy with gemcitabine and S-1 vs. gemcitabine alone in patients with resected pancreatic cancer. Recruitment is on-going.

JASPAC-05 is a phase II study on neoadjuvant S-1 and concurrent radiotherapy for patients with borderline resectable pancreatic cancer. This study starts in this year.

2) Biliary tract cancer

BCAT is a randomized phase III trial to compare gemcitabine with surgery alone as adjuvant chemotherapy for patients with curatively resected extrahepatic bile duct cancer. Two hundred and twenty-five patients have been enrolled and recruitment is complete. Follow-up is on-going.

BTCS is a phase II feasibility study on adjuvant chemotherapy with S-1 for patients with resected biliary tract cancer. Thirty-three patients have been enrolled and recruitment is complete. The high rate of treatment completion and mild toxicity indicated that S-1 chemotherapy is feasible for patients with resected BTC. A multicenter RCT in to compare S-1 and observation is now under preparation.

3) Hepatocellular carcinoma

STROM is a randomized phase III trial to compare orally administered sorafenib with surgery alone as adjuvant chemotherapy for patients with curatively resected hepatocellular carcinoma. Follow-up is on-going.

Recruitment in a phase II trial on adjuvant immunotherapy with Glypican-3 for patients with hepatocellular carcinoma following curative local treatment is on-going.

4) Liver metastasis from colorectal cancer

JCOG trial 0605 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

Table 1. Number of patients

Invasive pancreatic cancer	30
Other pancreatic neoplasms	13
Hepatocellular carcinoma	41
Hepatic metastases	72
Intrahepatic cholangiocarcinoma	10
Bile duct cancer	20
Gallbladder cancer	5
Total	191

Table 2. Type of procedure

Pancreaticoduodenectomy	36
Distal pancreatectomy	18
Total pancreatectomy	3
Hepatectomy without biliary reconstruction	120
Hepatectomy with biliary reconstruction	8
Laparoscopic hepatectomy	19
Other procedures	24
Total	228

Table 3. Survival rates

Diagnosis	No. of pts	5-yr survival (%)
Invasive pancreatic cancer (2001~2009)	186	22.5
Hepatocellular carcinoma (2001~2005)	350	48.5
Hepatic metastases (2001~2009)	312	56.6
Intrahepatic cholangiocarcinoma (2001~2007)	38	47.2
Extrahepatic bile duct cancer (2001~2007)	83	29.5
Papilla Vater cancer (2001~2007)	45	51.4
Gallbladder cancer (2001~2007)	46	37.7

is on-going.

5) Immune-enhancing enteral diet (IED)

The safety and tolerability of preoperative IED in hepato-biliary surgery is now under investigation in a preliminary study for a future phase II study to evaluate the efficacy of IED in hepato-biliary surgery.

Published Papers

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DEPARTMENT OF HEPATOBILIARY AND PANCREATIC ONCOLOGY, HEPATOBILIARY AND PANCREATIC ONCOLOGY DIVISION

Masafumi Ikeda, Shuichi Mitsunaga, Izumi Ohno, Satoshi Shimizu

Introduction

The Hepatobiliary and Pancreatic Oncology Division is responsible for the treatment and management of patients with hepatic, biliary, and pancreatic cancers. A multidisciplinary treatment strategy is important for the therapy of these cancers, and the treatment plan for each patient is carefully discussed by pharmacologists, surgeons, radiologists, radiation oncologists and medical oncologist. Our goal is to provide high-quality cancer treatment with sufficient palliative care and to develop novel and effective treatments through well-designed clinical trials and research projects.

Routine Activities

Our Division is composed of 4 staff oncologists, and 3 residents, and we have 35-45 beds in the hospital and conduct clinical rounds for admitted patients every morning and evening. Most of the new patients with unresectable hepatobiliary and pancreatic tumors are hospitalized for tumor diagnosis and treatment. Individual patient treatment strategies are discussed in weekly case conferences participated in by medical oncologists, surgeons, radiologists, radiation oncologists, and pharmacologists. For hepatocellular carcinoma (HCC), percutaneous ablation therapy is indicated as a standard treatment in patients with ≤ 3 tumors that are each < 3 cm in diameter. Transcatheter arterial chemoembolization (TACE) is usually used for treating advanced or recurrent HCC when hepatectomy or ablation therapy is not indicated. Sorafenib, an oral multikinase inhibitor, has been used for the treatment of advanced HCCs in patients with portal vein tumor thrombosis and/or distant metastases, or in whom TACE is not indicated. A medical team "Team Nexavar", which is composed of medical oncologists, pharmacologists, and nurses, provides supportive care for the toxicities of sorafenib. Intra-arterial chemotherapy is also available for the treatment of localized advanced HCCs, although it remains unclear whether sorafenib or intra-arterial chemotherapy is better for the treatment of advanced HCCs. For patients with advanced biliary tract cancer, gemcitabine and cisplatin therapy are recognized as the first-line therapies worldwide. S-1 has also been approved for biliary tract cancer, and is administered as the second-line chemotherapy. For patients with advanced pancreatic cancer, gemcitabine plus erlotinib, gemcitabine and S-1 have been approved for the treatment of pancreatic cancer. In our division, gemcitabine plus erlotinib is selected as the first line treatment, if the patient has good general condition. If the general condition is not so good, gemcitabine monotherapy is selected as the first-line chemotherapy. S-1 monotherapy is also considered as the second-line chemotherapy.

Furthermore, we are also responsible for all abdominal ultrasonographic examinations at our hospital, as well as ultrasound-guided biopsies of abdominal masses, particularly those in the liver and pancreas, performed for pathological diagnosis. Percutaneous transhepatic or endoscopic biliary drainage and stenting are performed to relieve jaundice and facilitate the removal of drainage tubes. The endoscopic approach, which is more comfortable than the percutaneous approach, has become the first choice this year, because our endoscopic skill has matured.

Research Activities

Hepatocellular carcinoma

No reliable data from a prospective clinical study for TACE are available in either Korea or Japan. We conducted a single-arm expanded treatment efficacy and safety study of TACE in Japan and Korea, and TACE could be demonstrated to exert a marked favorable efficacy in patients with unresectable HCC who were not suitable for curative treatment.

Sorafenib has been acknowledged as a standard chemotherapy for advanced HCC, but it has some troublesome toxicities including hand-foot syndrome and liver dysfunction. The usefulness of urea-content ointment for prevention of hand-foot syndrome and the efficacy and safety of sorafenib for HCC with Child Pugh B have been clarified.

Intra-arterial chemotherapy has been widely used for advanced HCC in Japan, but no chemotherapeutic agents or regimens have shown any survival benefit. To elucidate the survival benefit of intra-arterial chemotherapy, a

Table 1. Number of patients

Hepatocellular carcinoma	103
Biliary tract cancer	
Intrahepatic cholangiocarcinoma	23
Extrahepatic cholangiocarcinoma	18
Gallbladder cancer	28
Papilla of vater carcinoma	5
Pancreatic cancer	
Locally advanced disease	40
Metastatic disease	114
Other	27
Total	358

Table 2. Type of procedure

Hepatocellular carcinoma	
Radiofrequency ablation	80
Transcatherter arterial chemoembolization	181
Intra-arterial chemotherapy	79
Systemic chemotherapy	84
Proton	10
Biliary tract cancer	
Systemic chemotherapy	68
Radiotherapy	2
Pancreatic cancer	
Systemic chemotherapy	188
Chemoradiotherapy	10
Total	684

Table 3. Survival rates

Diagnosis	No.of pts	MST(mo)	2-yr survival(%)
Hepatocellular carcinoma			
Radiofrequency ablation	191	57.2	83.0
Transcatherter arterial chemoembolization	292	22.7	46.9
Intra-arterial chemotherapy	75	6.5	21.9
Systemic chemotherapy	16	4.7	0
Period:	1992/11-2005/12		
Biliary tract cancer			
Systemic chemotherapy	147	5.4	4.3
Period:	1997/11-2006/2		
Pancreatic cancer			
Locally advanced disease	154	11.2	14.3
Metastatic disease	442	4.8	1.6
Period:	1992/11-2007/3		

randomized trial comparing the combined administration of sorafenib with intra-arterial cisplatin with sorafenib alone is planned and now ongoing for advanced HCC.

Biliary tract cancer

To elucidate the additional efficacy of WT1 vaccine, a randomized trial comparing the combined administration of gemcitabine plus cisplatin with WT1 vaccine with gemcitabine plus cisplatin has been designed for the treatment of advanced biliary tract cancer.

Pancreatic cancer

S-1 with concurrent radiotherapy exerted extremely favorable activity with mild toxicity in patients with locally advanced pancreatic cancer. Based on this result, the two following clinical trials are ongoing: neoadjuvant S-1 and concurrent radiotherapy for borderline resectable pancreatic cancer, and S-1 and concurrent radiotherapy with versus without induction chemotherapy for locally advanced pancreatic cancer. For advanced pancreatic cancer, we have investigated the clinical significance of IL-6, IL-1 and the circulating CRP level, and the symptomatic changes to predict disease control by chemotherapy.

Clinical Trials

Twenty-eight clinical trials (Sponsored, 15 trials; Investigator-initiated, 13 trials) are ongoing, and 8 clinical trials (Sponsored, 3 trials; Investigator-initiated, 5 trials) are planned for the upcoming year. A recent trend in clinical trials has been seen in new molecularly targeted agents for advanced HCC, and new combination chemotherapy for advanced biliary and pancreatic cancer.

Published Papers

1. Kudo M, Imanaka K, Chida N, Nakachi K, Tak W-Y, Takayama T, Yoon J-H, Hori T, Kumada H, Hayashi N, Kaneko S, Tsubouchi H, Suh DJ, Furuse J, Okusaka T, Tanaka K, Matsui O, Wada M, Yamaguchi I, Ohya T, Meinhardt G, Okita K. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer, 47:2117-2127, 2011

2. Iwasa S, Ikeda M, Okusaka T, Ueno H, Morizane C, Nakachi K, Mitsunaga S, Kondo S, Hagihara A, Shimizu S, Satake M, Arai Y. Transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization. Jpn J Clin Oncol, 41:770-775, 2011

3. Suzuki E, Furuse J, Ikeda M, Ishii H, Okusaka T, Nakachi K, Mitsunaga S, Ueno H, Morizane C. A phase I/II study of combined chemotherapy with mitoxantrone and uracil/tegafur for advanced hepatocellular carcinoma. Jpn J Clin Oncol, 41:328-333, 2011

4. Kanai F, Yoshida H, Tateishi R, Sato S, Kawabe T, Obi S, Kondo Y, Taniguchi M, Tagawa K, Ikeda M, Morizane C, Okusaka T, Arioka H, Shiina S, Omata M. A phase I/II trial of the oral antiangiogenic agent TSU-68 in patients with advanced hepatocellular carcinoma. Cancer Chemother Pharmacol, 67:315-324, 2011

5. Inaba Y, Arai Y, Yamaura H, Sato Y, Najima M, Aramaki T, Sone M, Kumada T, Tanigawa N, Anai H, Yoshioka T, Ikeda M. Phase I/II study of hepatic arterial infusion chemotherapy with gemcitabine in patients with unresectable intrahepatic cholangiocarcinoma (JIVROSG-0301). Am J Clin Oncol, 34:58-62, 2011

DEPARTMENT OF UROLOGY

Yasuyuki Sakai, Yoshinobu Komai

Introduction

The Department of Urological Surgery 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: An outpatient clinic is open 2 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 stage D2 prostate cancer are referred to the medical oncology division for chemotherapy or hormone 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. Thirty-four patients newly received ureteral stents and 4 underwent nephrostomy for obstructive uropathy.

Inpatient activities: A daily conference is held with doctors of Department of Pelvic Surgery on diagnosis and treatment of the patients with colorectal and urological cancer. We performed about 50 combination surgeries with colorectal surgeons. In the department of urology, 78 general anaesthesia surgeries, 71 spinal anesthesia surgeries and 54 prostate biopsies were performed.

Other: We have a conference on urogenital cancers every other week among medical oncologists, radiation oncologists and one pathologist. Neoadjuvant chemotherapy for 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 and Clinical Trials

Minimum incision endoscopic surgery was introduced from 2011, the surgery is a gasless, single-port access, cost-effective, and minimally invasive surgery. We intend to make this operation more sophisticated in coordination with the Department of Urology, Tokyo Medical and Dental University.

For those patients (intermediate and high-risk groups) who desired preservation of sexual function, bilateral sural nerve grafting was performed for the recovery of sexual functions. Sural nerve interposition grafting was performed in 46 patients from 2004, and they were followed up for 1 year. Overall, 10 men (22.2%) had return of erectile activity (partial erection).

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 (5 cases in 2011).

Published Papers

1. Komai Y, Fujii Y, Iimura Y, Tatokoro M, Saito K, Otsuka Y, Koga F, Arisawa C, Kawakami S, Okuno T, Tsujii T, Kageyama Y, Morimoto S, Toma T, Higashi Y, Fukui I, Kihara K. Young age as favorable prognostic factor for cancer-specific survival in localized renal cell carcinoma. Urology, 77:842-847, 2011

Table 1. Number of Patients in 2011

Prostate Cancer	35
Bladder Cancer	27
Renal cell carcinoma	19
Upper urothelial carcinoma	10
Testicular cancer	7

Table 2. Number of operative cases in 2006-2011

Section	2007	2008	2009	2010	2011
Radical nephrectomy	27	20	24	24	17
(laparoscopic)	(8)	(6)	(7)	(11)	(2)
(MIES)					(6)
Partial nephrectomy	2	1	4	8	5
(MIES)					(2)
Nephroureterectomy	3	10	5	7	9
(MIES)					(1)
Radical cystectomy	6	9	8	9	11
TUR-Bt	37	32	43	47	59
Radical prostatectomy	32	21	33	33	25

(MIES: Minimum Incision Endoscopic Surgery)

Table 3. Overall Survival Rate after operation (%)

	1 year	3 years	5 years
Prostate cancer	100	97.5	96.3
Renal cell carcinoma	95.8	89.7	76.7
Invasive bladder cancer	87.8	56.0	38.9

DEPARTMENT OF ANESTHESIOLOGY AND INTENSIVE CARE UNIT

Yasuko Miwa, Hiroyuki Yamamoto, Kei Torigoe, Kazuaki Hiraga, Aiko Ooshita

Introduction

Perioperative care for cancer patients with limited vital organ function presents a major challenge for anaesthetists because anaesthesia and surgery itself may cause further deterioration in physical functions. The aim of modern anaesthesia is to protect patients from surgical stress by blocking the noxious stimuli of surgical trauma and enhances their recovery from the operation. The quality of life of the patients and medical ethics must be carefully taken into account.

In 2011, this department faced a crisis followed by the resignation of the senior consultant. However, our remaining young anaesthetist pulled through this difficult situation with the support of the surgeons, nurses, and other staff. Two more anaesthetists took up their posts in the summer. We therefore continue to endeavour to regenerate the department with a broad outlook. We would like to sincerely express our deep appreciation to all who encouraged us during our tough times in 2011.

Routine Activities

Staff members (3 anaesthetists, 2 visiting anaesthetists, 6 part-time anaesthetists and 3 residents serve in various capacities in the department. We performed 2366 cases in 2011 including significant numbers of crucial cases and the cases which had to be treated as difficult airway cases. The annual number of patients admitted to the intensive care unit was 1228.

Daily activity starts with a preanaesthesia case presentation. A journal club is held once a week to sustain up-to-date knowledge of all aspects of anaesthesia.

Research Activities and Clinical Trials

It is extremely important for an academic group to keep up with current research, and although we have been working in somewhat straightened circumstances we still managed to plan some clinical research. Dr Torigoe presented "Unilateral negative pressure pulmonary edema during anaesthesia with a laryngeal mask airway" at the 31st annual meeting of The Japan Society of Anaesthesia in Naha.

Table 1. Number of Patients Managed under General or Spinal/Epidural Anaesthesia

Type of Surgery	2007	2008	2009	2010	2011
Head & Neck	501	458	474	515	424
Thoracic	499	472	503	488	466
Esophageal				137	126
Gastric, Hepatobiliary, Pancreatic	537	508	566	542	556
Colorectal	417	453	418	491	426
Urological	77	59	79	88	78
Breast	247	233	282	297	291
Miscellaneous					2
Total	2278	2183	2322	2558	2366

Table 2. Number of Patients Admitted to the Intensive Care Unit

	2007	2008	2009	2010	2011
Number of the Patients Admitted to ICU	1210	1163	1167	1435	1228

DEPARTMENT OF PALLIATIVE MEDICINE AND PSYCHO-ONCOLOGY, PALLIATIVE CARE SERVICE

Hiroya Kinoshita, Yoshihisa Matsumoto, Mieko Fukui, Keiko Abe, Masao Ogawa, Kazuaki Hiraga

Introduction

The National Cancer Center Hospital East opened the palliative care unit in 1992 for the purpose of providing only palliative care service. The main goal of the unit was to provide end-of-life care to patients with incurable cancer. Approximately 90% of patients cared for in this unit eventually died. Accordingly, outpatient-based chemotherapy was managed passively. The management of devastating symptoms was performed in an outpatient setting, and home care became the preferred option for many cancer patients. Since 2007, many changes to the palliative care service, which provides support to patients and their families, and in which family physicians and visiting nurses provide home care, have been carried out in order to establish a regional palliative care system.

Routine Activities

1. Palliative care unit

This unit is the only designated inpatient setting unit for palliative care in the Toukatu-Hokubu region. Before 2007, the registry system for admittance was adopted wherein patients were admitted in the order of their application. This system was abolished because patients with severe symptoms had to wait for a long time before being admitted. In line with this, criteria for admitting patients were changed to ensure optimal use of limited resources and provide appropriate care to patients with severe physical symptoms and psychological problems. The waiting time for admission was reduced to 5 days.

Since 2008, many conferences on discharge planning have been conducted to facilitate communication concerning end-of life care with family physicians and visiting nurses.

2. Outpatient clinic

From 2007, an outpatient clinic for the assessment and management of patients experiencing devastating symptoms was opened and the clinic provides consultation 5 days a week. Patients undergoing chemotherapy can receive timely palliative care in this clinic. Moreover, the clinic works closely with the Psycho-Oncology Service to provide total care to patients and their family members.

Research Activities

The department participates in the Outreach Palliative care Trial of Integrated regional Model (OPTIM), which is an intervention study for the purpose of dispersing palliative care in four typical regions in Japan.

Clinical Trials

A phase III study on oral buccal fentanyl is ongoing.

Table 1. New referrals to the outpatient clinic (n=395, January - December 2011)

		N (%)
Age	Mean±SD (median, range) (yr)	66.5±11.7 (68, 19-96)
Gender	(male/female)	205/190
Survivors or receiving anticancer therapy		79 (20.0)
Cancer site	Lung	120 (30.4)
	Breast	41 (10.4)
	Colorectal	40 (10.1)
	Head and Neck	35 (8.9)
	Pancreas	21 (5.3)
	Stomach	19 (4.8)
	Esophagus	15 (3.8)
	Liver	15 (3.8)
	Others	89 (22.5)

Table 2. Admission to the palliative care unit (n=378, January - December 2011)

		N (%)
Age	Mean±SD (median, range) (yr)	66.2±11.6 (67, 19-96)
Gender	(male/female)	204/174
Cancer site	Lung	104 (27.5)
	Colorectal	51 (13.5)
	Breast	40 (10.6)
	Head and Neck	26 (6.9)
	Pancreas	26 (6.9)
	Stomach	18 (4.8)
	Prostate	13 (3.4)
	Kidny/Bladder	13 (3.4)
	Others	87 (23.0)
Wating time for admission	Mean±SD (median, range) (days)	5.0±5.3 (3, 0-27)

DEPARTMENT OF PALLIATIVE MEDICINE AND PSYCHO-ONCOLOGY, PSYCHO-ONCOLOGY SERVICE

Asao Ogawa, Daisuke Fujisawa, Hiroyuki Takei, Daisuke Kiuchi, Junko Nouno, Harumi Koga

Introduction

The Psycho-Oncology Division (Psycho-Oncology Service), established in July 1996, aims to manage and alleviate emotional distress of cancer patients, their families and the caring staff. The division, adjunct with the Psycho-oncology Division of Research Center for Innovative Oncology, also aims to study 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 Psycho-Oncology Division is composed of 2 attending psychiatrists, 2 clinical psychologists, and 2 psychiatry residents. The Division's 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-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria. Consultation data included individuals who were family members of cancer patients.

A conference with the Supportive Care Team is held on Wednesdays, and a multicenter joint clinical teleconference involving 6 cancer center hospitals and 2 university hospital is held on Thursdays. In August 2008, the Comprehensive Support Center for Cancer Patients and Families was developed outside the hospital as a part of the regional palliative care project.

Research Activities

Clinical trials

See "Psycho-Oncology Division, Research Center for Innovative Oncology" section.

Table. Psychiatric consultation data (n=1028; January-December, 2011)

Section		N (%)
Age	Mean±SD (median, range) (yr)	64.9±12.6 (67,16～91)
Gender	(male/female)	614 (59.7%) / 414 (40.3%)
Inpatient / Outpatient		666 (64.8%) / 362 (35.2%)
Cancer patient / Family member		987 (96.0%) / 41 (4.0%)
Cancer site	Head and neck	215 (20.9%)
	Lung	208 (20.2%)
	Esophagus	108 (10.5%)
Stage	Recurrent or metastatic	678 (65.9%)
PS	0/1, 2/3, 4	311 (30.2%) / 486 (47.3%) / 231 (22.5%)
Pain	Present	211 (20.5%)
Psychiatric diagnosis	Delirium	309 (30.1%)
	Adjustment disorders	123 (12.0%)
	Major depression	68 (6.6%)
	Dementia	54 (5.3%)
	No diagnosis	176 (17.1%)

DEPARTMENT OF PALLIATIVE MEDICINE AND PSYCHO-ONCOLOGY, SUPPORTIVE CARE TEAM

Hiroya Kinoshita, Asao Ogawa, Daisuke Fujisawa, Yoshihisa Matsumoto, Mieko Fukui, Hiroyuki Takei, Yoichiro Higashi, Tomofumi Miura, Junko Nouno, Harumi Koga, Yuko Tanaka, Chiyuki Terada, Yukie Hosoda, Yasuhiko Ichida, Shinya Motonaga, Kyoko Okada, Aya Matsumaru, 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, psycho-oncologists, a certified nurse specialist, 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.

Research Activities and Clinical Trials

Please refer to the "Psycho-Oncology Division, Research Center for Innovative Oncology" section and "Palliative Care Service" sections.

Table. Supportive Care Team consultation data (n = 839; January-December, 2011)

		N (%)
Age	Mean ± SD (range) (yr)	65.3 ± 12.8 (17-97)
Gender	(male/female)	545 (65%) / 294 (35%)
Service	Palliative care/ Psycho-oncology	173 / 666
Cancer site	Lung	205 (24%)
	Head and Neck	160 (19%)
	Esophagus	90 (11%)
	Colon	73 (9%)
	Stomach	65 (8%)
	Breast (mammary)	35 (4%)
Stage	I / II / III / IV	53 (6%) / 60 (7%) / 82 (10%) / 410 (49%)
	/ recurrence / unknown / others	/ 168 (20%) / 46 (5%) / 17 (2%)
Performance status	0/ 1/ 2/ 3/ 4	129 (15%) / 179 (21%) / 182 (22%) / 206 (25%) / 143 (17%)
Physical symptoms	Pain	343 (41%)
(moderate - severe)	Appetite loss	222 (26%)
	Fatigue	146 (17%)
	Respiratory distress	109 (13%)
Psychiatric diagnosis	Delirium	291 (44%)
(primary diagnosis)	Adjustment disorders	48 (7%)
	Dementia	28 (4%)
	Major Depressive Disorder	17 (3%)
Outcome	Discharge/ Hospital transfer	529 (63%) / 28 (3%)

DEPARTMENT OF DIAGNOSTIC RADIOLOGY

Mitsuo Satake, Ryoko Iwata, Takayuki Hayashi, Yoshihiro Nakagami, Tatsushi Kobayashi, Hirohumi Kuno, Kaoru Shimada

Introduction

The Diagnostic Radiology Division is committed to improving health through excellence in image-oriented patient care and research. Our Division performs more than 73,000 inpatient and outpatient procedures annually. The Division also conducts clinical scientific research as well as basic scientific studies, with the results translated directly into better patient care.

Routine Activities

Our division has four multislice CT scanners, including one area detector CT scanner and one Dual Source CT, two MRI systems (one is 1.5 T, the other is 3 T) one interventional radiology (IVR) CT system, one Multiaxis c-arm CT system, two gamma cameras with the capacity for single photon emission CT (SPECT), two digital radiographic (DR) systems for fluoroscopy, two mammography and four computed radiographic (CR) systems. Our IVR-CT systems use digital subtraction angiography with multidetector computerized tomography (MDCT). One is equipped with a 20 multi-slice CT. A positron emission tomography (PET) scanner and baby cyclotron have been installed, and tumor imaging using ^{18}F-FDG (fluorodeoxyglucose) has been performed. These all-digital image systems enhance the efficacy of routine examination.

This division has 7 consulting radiologists and 32 technologists. As part of our routine activities, every effort is made to produce an integrated report covering almost all examinations, such as MMG, contrast radiologica1 procedures, CT, MRI, RI, PET, angiography and IVR, mainly transarterial chemo-embolization (TACE).

The number of cases examined in 2011 is shown in the Table below.

Several conferences are routinely held at our Division, including teleradiologic, and pre- and postoperative conferences.

Research Activities and Clinical Trials

The Research activities of the Diagnostic Radiology Division focus on Diagnostic imaging, IVR, and teleradiology. These activities consist of: (1) The development of new Nuclear Medicine tracers; (2) the development of new IVR technology; and (3) the construction of a cancer image reference database. The Division also conducts clinical scientific research as well as basic scientific studies, with the results translated directly into better patient care.

(1) Development of new Nuclear Medicine tracers

The small interfering RNA (siRNA) was discovered as a promising gene silencing tool in research and in the clinic, and we succeeded in radiolabeling siRNAs. Briefly, The 3′-end of double strand 21-nucleotide oligoribonucleotides were added to polyadenines using E. coli Poly(A) Polymerase (E-PAP) and ATP conjugated with DTPA and subsequently labeled with Tc-99m or Ga-68 under strict RNase-free conditions. The gene-silencing ability of the siRNA did not change after radiolabeling.

The radiolabeling siRNAs were injected into the tail veins of nude mice and the nude mice were scanned with a micro-SPECT camera (Tc-99m) or a micro-PET camera (Ga-68). Interestingly, the radiolabeling siRNAs accumulated in organs expressing the target genes of the siRNAs. The results of this study could open up a new method of gene imaging *in vivo*.

(2) Development of new CT technology

The accurate evaluation of cartilage invasion is essential for deciding upon appropriate treatment strategies for laryngeal and hypopharyngeal cancer. In dual-energy CT (DECT), two data sets acquired with different tube voltages can be fused to generate weighted-average CT images that have a similar image impression to conventional CT images obtained at 120 kV, in addition to generating images of the distribution of iodinated contrast medium alone. For these applications, the material-specific X-ray energy dependence of the absorption coefficient is used in image postprocessing to mathematically extract iodine and separately calculate color-coded iodine images and virtual non-contrast images.

Dual-energy CT images revealed tumor invasion within the cartilage as red color-coded areas of the

iodine distribution, resulting in contrast enhancement between the tumor and non-calcified cartilage.

Preliminary evidence suggests that dual-energy CT can decrease the overestimation of laryngeal cartilage invasion. This is particularly important for treatment strategy decisions, especially when function-preserving therapy is being considered.

(3) Construction of a cancer image reference database

It is important for multiple hospitals specializing in different fields, designated as collaborative cancer centers, to share the results of cancer imaging and findings on a real-time basis to improve efficiency in performing diagnostic imaging, which contributes to the mutual advancement in diagnostic imaging levels between these facilities. ViewSend Rad-R (VSRR), a web-based device designed to support diagnostic imaging between remote areas, allows us to send original digital imaging and communication in medicine (DICOM) images without any compression to a remote area and hold a real-time consultation without requiring additional servers.

Table 1. Number of Cases Examined

	2007	2008	2009	2010	2011
Plain X-ray examination	35,339	33,913	33,841	34,330	35,032
Mammography (MMG)	2,338	2,272	2,388	2,595	2,434
Fluoroscopic Imaging (GI-series, etc.)	2,531	3,387	3,781	3,478	3,903
CT	18,356	18,014	19,543	21,128	21,967
MRI	4,817	5,053	5,723	5,830	5,708
RI	1,825	1,693	1,718	1,676	1,582
PET	1,541	1,585	1,670	2,048	2,239
Angiography	698	766	711	728	656
Total	67,445	66,683	69,375	71,813	73,521

DEPARTMENT OF RADIATION ONCOLOGY

Tetsuo Akimoto, Mitsuhiko Kawashima, Sadatomo Zenda, Masakatsu Onozawa, Satoko Arahira

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 in 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 dose to the surrounding normal tissues should be kept as low as possible in order to maintain 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) and proton beam therapy (PBT) and expand and establish the important role of RT in cancer treatment. Another important goal is to establish standard treatment and optimal irradiation techniques including PBT.

Routine Activities

At present, the staff of the Department consists of 5 consultant physicians (radiation oncologists), 12 radiation technologists, 4 medical physicists, 1 nurse, and 1 clerk. We have more than 1000 new cases for conventional RT and more than 100 new patients for proton beam therapy every year. Quality assurance for both conventional RT and PBT is performed by medical physicists and radiation technologists, and a 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 the 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. More than 30 clinical trials involving RT as the sole or a combined treatment modalities for various cancers are in progress.

The Department is responsible for conventional (photon-electron) RT, the systems for which comprise 4 linear accelerators, a CT simulator, 4 treatment planning computer workstations, and other important devices. IMRT and IGRT have been routinely applied for head and neck cancer and prostate cancer. The Department is also responsible for PBT, involving 6 operating staff members and 1 technician for fabricating the compensator and aperture; they are sent from the system manufacturers and work in collaboration with the other staff members of the Department. PBT is performed from 2 treatment rooms and both rooms are routinely used for rotational gantry treatment. The Department performs quality assurance and regular maintenance of the PBT machines for precise dose delivery and safe treatment.

Research Activities

In the Department of Radiation Oncology, the following research activities are in progress:

1) Establishment of optimal combined approaches including RT and chemotherapy for locally advanced head and neck cancer.
2) Establishment of the clinical usefulness of IMRT with or without chemotherapy for head and neck cancer.
3) Hypofractionated IMRT for localized prostate cancer.
4) Hypofractionated PBT for localized prostate cancer.
5) Evaluation of the feasibility of PBT combined with chemotherapy for inoperable locally advanced non-small cell lung cancer.
6) PBT for pediatric malignancies.
7) The role of gene polymorphism in the development of acute and late radiation-related complications.

Clinical Trials

The following in-house and multi-institutional clinical trails are in progress.

1) JCOG0701: Accelerated fractionation vs. conventional fractionation radiation therapy for glottic cancer of T1-2N0M0: a phase III study.
2) JCOG0701-A1: Evaluation of single-nucleotide polymorphisms (SNPs) in the development of acute and late complications after accelerated fractionation and/or conventional fractionation radiation therapy for glottic cancer of T1-2N0M0.
3) JCOG0906: A multi-institutional phase II study on post-operative short-term radiation therapy for breast conserving therapy.
4) JCOG1015: A phase II study on intensity modulated radiation therapy (IMRT) with chemotherapy for loco-regionally advanced nasopharyngeal cancer (NPC).
5) A phase II study on PBT for malignant melanoma of nasal cavity.
6) A phase II trial of Concurrent Chemoradiotherapy with 5-FU plus Cisplatin for resectable squamous cellcarcinoma of cervical esophagus.

Published Papers

1. Kawashima M, Kohno R, Nakachi K, Nishio T, Mitsunaga S, Ikeda M, Konishi M, Takahashi S, Gotohda N, Arahira S, Zenda S, Ogino T, Kinoshita T. Dose-volume histogram analysis of the safety of proton beam therapy for unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys, 79:1479-1486, 2011

2. Zenda S, Kawashima M, Nishio T, Kohno R, Nihei K, Onozawa M, Arahira S, Ogino T. Proton beam therapy as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study. Int J Radiat Oncol Biol Phys, 81:135-139, 2011

3. Zenda S, Kohno R, Kawashima M, Arahira S, Nishio T, Tahara M, Hayashi R, Kishimoto S, Ogino T. Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses. Int J Radiat Oncol Biol Phys, 81:1473-1478, 2011

Table 1. Number of patients treated with radiotherapy during 2006-2010

	2006	2007	2008	2009	2010
New patients	1146	1097	1084	1384	1616
New treatments	1418	1363	1388	1363	1388
Head and neck cancers	270	249	289	281	320
Lung and mediastinal cancers	395	391	390	370	411
Breast cancers	300	296	264	297	406
Gastrointestinal cancers	242	202	221	202	228
Hepatobiliary tract cancers	54	63	47	46	54
Urological cancers	94	114	112	120	151
Bone and soft tissue cancers	6	8	8	6	15
Hematological cancers	38	25	33	27	6
Others	19	15	24	35	20
Proton therapy	76	75	81	90	56
IMRT		6	4	31	83

Changes in the number of patients treated with RT

DEPARTMENT OF PATHOLOGY AND CLINICAL LABORATORIES

Atsushi Ochiai, Takeshi Kuwata, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Chisako Yamauchi

Introduction

The Department of Pathology and Clinical Laboratories (DPCL) is composed of two divisions; the Pathology Division (PD) and the Clinical Laboratory Division (CLD). Both divisions play a fundamental role in routine hospital service, and support research activities as well as clinical trial studies at the National Cancer Center Hospital East (NCCHE).

Seven pathologists, including 6 pathologists board-certified by the Japanese Society of Pathology, are assigned to the PD. Two are full-time staff, and another is part-time. The remaining 4 pathologists originally belong to the Pathology Division at the Research Center for Innovative Oncology (RCIO), and are working concurrently at the DPCL. Also working in the division are 6 clinical laboratory technicians and 1 assistant. Two doctors and 3 technicians are cytology experts and cytoscreeners, respectively, board-certified by The Japanese Society of Clinical Cytology.

The CLD consists of 6 subsections for i) general laboratory medicine, ii) hematology, iii) biochemistry/serology, iv) Physiology, v) Bacteriology and vi) blood transfusion. A total of 12 full-time technicians are working at the CLD.

Routine Activities

The primarily routine activities in the PD involve surgical pathology. In 2011, 8,650 biopsy specimens, including 704 frozen sections and 787 review cases, and 2,156 surgically resected specimens were examined and pathologically diagnosed (see Table1 for details). Case conferences are held regularly with almost all of the clinical department/divisions, including 4 weekly case conferences with Head-and-Neck Surgery (Monday), Hematology and Chemotherapy (Wednesday), the Digestive Endoscopy Division (Tuesday) and Thoracic Surgery (Friday). Five thousand hundred and forty five cytology specimens, including 2,320 samples from respiratory organs, were evaluated (Table 2). Ten autopsies were performed, and all cases were presented and discussed in clinic-pathological conferences, which are held monthly. Conference-style training sessions are open every Thursday morning for the residents, where they learn how to present pathological findings through mock case-presentations.

The CLD provides accurate and reliable data to understand the patients' conditions and support prompt decision making for all clinicians working at the NCCHE. Most of the essential laboratory test

Table 1. Number of patholoy samples examined in the Pathology Division in 2011

Origin	Biopsy	Surgical specimen	Autopsy
Hepatobiliary and Pancreatic Oncology	291	1	2
Thoracic Oncology	398		2
Cardiovascular Division			
Thoracic Surgery	502	440	
Esophageal Surgery	86	104	
Breast Surgery	423	296	
Colorectal (Pelvic) Surgery	346	394	
Gastric Surgery	252	509	
Orthopedic Surgery	4		
Dermatology	13		
Urological Surgery	172	7	
Obstetrics and Gynecology	18		
Plastic Surgery	8	3	
Head and Neck Surgery	754	381	
Diagnostic Radiology	0		
Radiation Oncology	137		
Digestive Endoscopy Division	1572		
Gastrointestinal Oncology	3052		3
Hematology and Medical Oncology	403	1	2
Dental Division	2		
Outpatient Unit	177	18	
Palliative Care Unit	1	1	1
Others	39	1	
Total	8650	2156	10

Table 2. Number of cytology samples examined in the Pathology Division in 2011

Sample	
Gynecological	614
Respiratory organs	2320
Gastrointestinal tract	659
Urological	592
Body fluids	341
Hematorogical	95
Head and Neck	227
Breast	182
Skin, CNS, Eye and Soft tissue	35
Others	80
Total	5145

services are available on a-round-the-clock basis. The majority of the general laboratory tests for hematology, biochemistry, serology and urinalysis are performed by an automated analyzer, which enables the division to provide the results within one hour after samples submission. A special computer-based ordering system is equipped to ensure sample-processing and data-transfer to and from outside commercial laboratories. The daily activities of each subsection are as follows (also see Table3 for details):

i) The general laboratory medicine section examines urine (urinalysis) as well as stool, pleural effusion, ascites and spinal fluid samples. Urinalysis includes sugar, protein and blood contamination, 12 of which items are examined by an automated analyzer.
ii) The hematology section performs blood count, blood cell morphology and coagulation tests. Bone marrow samples are also examined morphologically for hematological malignancies.
iii) The biochemistry and serology section examines blood samples and measures protein, sugar, lipid and enzymes/metabolites associated with liver and kidney functions. Most of these tasks are performed by an automated analyzer. The section also performs immunological assays to detect several tumor markers.
iv) The physiology section performs electrocardiography, respiratory function tests, ultrasonography and electroencephalography.
v) The bacteriology section examines various clinical samples to identify the pathogens (bacteria, fungus and virus) which cause infection(s). The section also plays a pivotal role as a part of intramural infection control team at the NCCHE.
vi) The blood transfusion section consolidates any usages of blood preparation/products in the NCCHE. The section is also responsible for collecting and providing up-to-date information related to the safe usage of the blood preparation/products. Daily routine activities for each blood transfusion case include blood typing, irregular antibodies screening and cross-matching.

Research Activities

As a part of the National Cancer Center Biobank project, the DPCL plays a major role in collecting and storing tumor tissue and serum samples in the NCCHE. In 2011, 397 frozen tumor tissue samples from surgery-harvested materials were collected and stored.

All of the pathologists are involved in research activities at the RCIO. The research interests of each pathologist vary, but they all share the same concept; a better understanding of cancer biology to develop new strategies for treating cancer patients. Please refer to the corresponding section in this book for the details.

The laboratory technicians working at the department are also highly motivated to develop advanced diagnostic technology and some results have been presented in several meetings including the one organized by the Japanese Society of Laboratory Medicine.

Clinical Trials

In 2011, as a part of a Phase I Center project, the DPCL played an essential role in 126 clinical trials which were carried out at the NCCHE. The PD in particular participated in a total of 65 trials and supplied paraffin embedded tissue sections for 28 trials in 2011.

Table 3. Number of laboratory tests exmined in the Clinical Laboratory Division in 2006-2011

Section	2006	2007	2008	2009	2010	2011
General laboratory medicine	192,597	176,173	196,233	230,610	265,517	264,452
Hematology	473,416	488,908	527,567	560,110	589,144	622,666
Biochemistry	1,330,853	1,338,116	1,424,263	1,493,858	1,569,963	1,648,755
Serology	121,436	118,468	125,409	136,127	139,759	146,104
Bacteriology	17,834	17,799	21,822	22,466	21,978	21,657
Blood transfusion	20,047	20,240	21,378	24,181	22,441	21,895
Physiology	34,485	34,530	34,258	39,232	43,215	43,275
Total	2,186,307	2,208,652	2,211,641	2,506,584	2,652,017	2,768,804

PHARMACY DIVISION

Keishiro Izumi, Yasuhiko Ichida, Akio Hiroi, Takashi Uemura, Reiko Matsui, Masahito Yonemura, Sonoko Kobayashi, Hideki Funazaki, Ikuyo Ueda, Shinya Motonaga, Tomoka Hagihara, Kenji Kawasumi, Hiroko Ouchi, Mai Itagaki, Tomoko Ogawa, Isami Sakai, Shinya Suzuki, Kazushi Endo

Introduction

The main objectives of our Pharmacy Division are: (1) To promote clinical studies for creating new evidence; (2) To provide chemotherapy based on the most updated evidence; and (3) To pursue patient-centered pharmaceutical care.

Our residents' training program started in 2006. In 2011, six residents joined the Division. Presently, the Division has a total of twenty residents. In addition, the Division has accepted two trainees from other institutions for our oncology-pharmacist training program. In 2010, the two and a half months training course (or an optional advanced training course) has started for the fifth-year pharmacy students on the six-year pharmacy education program in Japan. Our Division has established a special curriculum for them. Through this year, three terms of the training courses, we have educated fifteen pharmacy students and three advanced-training pharmacy students.

The Pharmacy Division 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. The Division reviews the drugs taken by patients before and during their hospitalization. We also check anticoagulants taken by patients undergoing endoscopic mucosal resection. The Division provides a pharmacy outpatient service in which pharmacists check patients' adverse reactions and doses of antineoplastic agents, especially in the case of oral anticancer medications. Then we assess the necessity of the supportive-care medications and suggest them to physicians. Pharmacists are on duty at the Outpatient Chemotherapy Center as dedicated staff members. The pharmacists provide the 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

Over the years, the services of our Division have been under continuous expansion and development. The Division has assigned one pharmacist as a dedicated staff member per ward to provide timely medication counseling and drug information for healthcare providers and patients, to pursue effective pharmaceutical care. The pharmacy outpatient service started reviewing the drugs taken by all patients to evaluate when patients have to stop their anticoagulants before their operation or when they have to stop metformin before examinations with iodinated-contrast material.

	2009	2010	2011
Number of Prescriptions			
Prepared in hospital pharmacy			
Total	82,557	84,492	86,643
Inpatients	77,013	78,327	80,837
Outpatients	5,544	6,165	5,806
Taken to outside pharmacies	49,192	50,731	55,826
(% of prescription filled outside)	(89.9%)	(89.2%)	(90.6%)
Injections			
Total	164,293	157,958	159,730
Inpatients	142,373	132,407	132,969
Outpatients	21,920	25,551	26,761
Number of Prescriptions			
(Investigational new Drugs)	2,997	4,435	4,676
Aseptic Preparation of Injection Mixture			
Anticancer drugs	34,283	32,007	35,082
Others	4,791	4,689	3,320
Number of medication counseling (for inpatients)			
Patients	4,619	5,063	5,067
Counseling sessions which earned a counseling fee	5,746	6,522	6,645
Number of medication counseling sessions (for outpatients)			
in the Outpatient Chemotherapy Center	5,016	5,705	6,364
in the pharmacy outpatient service		479	734
in the 'Sorafenib' outpatient service		416	583
Number of calls on the Chemotherapy Hotline	602	980	1,468
Number of checks on home medications	5,364	5,422	5,364

NURSING DIVISION

Tomiko Ichihashi

Introduction

Recently, In the development of giving better treatment to cancer patients, residential care and treatment has become an integral part of these patients' recovery and their quality of life. The nursing department has dealt with this issue by assigning nurses who exclusively specialized in helping patients go home safely. Our main task is to ensure that patients can be discharged without facing problems medically and physically.

Since 2010, twice a month each ward has organized meetings about residential care which are attended by nurses to support discharge. We have also offered some services to the nurses and care managers who support the patients at home by giving follow-up services on the telephone. Since April 2010 we have encouraged certified nurses to participate in the Nutrition Support Team (NST) to support patient's swallowing and eating processes, and this has made it possible for them to respond smoothly to their patient's nutritional needs. We have also succeeded in intensifying registered nurses' nutritional concerns, which accordingly help them to identify the nutritional problems of each patient. This in turn has led to the patients' awareness of their own dietary-related problems. We have also set up an outpatient section since September, 2010, which offers guidance to the patients on the list of all kinds of surgery for cancers in different sites, such as esophageal, epigastrial, abdominal, respiratory, head and neck and urinary cancer. Participants are given a lecture about prevention of complications after surgery. We work together with other sections to reduce the uneasiness and anxiety which patients experience pre- and postsurgery and to support the each patient's decision about his or her treatment. As for nurses, all wards have introduced a two-working-shift system since September, 2009, and we now have an additional short-time two-working-shift system in order to support nursing care.

Financially, we have contributed to increased profitability by establishing a 7 to 1 system to place nurses. We have a nursery home, which is on the go 24 hours a day. It can take care of a child whose parent has to start working early in the morning.

As part of our own self-help approach, we have established the following goals for the purpose of clarifying our mission and raise the quality of care, under the overall concept: "To shine with learning and act full of life"

1. Respect the patients' will and offer the proper care.
2. Advance medical and nursing skills for the benefit of patients.
3. Try to make our hospital a bright and energetic place to work.
4. Support each other and draw out our ability to achieve the best care for the patients.
5. Take an active part in the hospital's administration.

Routine Activities

In 2011, of the current 311 nurses, 46 were newly employed. The average number of outpatients per day was 769.4, while that of inpatients was 349.9. The average hospitalization term was 14.7 days. The number of chemotherapy treatments in The Medical Treatment Center per day was 66; the number of operations conducted was 2,734 (As of December 2011). We provided educational services to patients undergoing chemotherapy on how to deal with the side effects, and also provided one-on-one telephone-follow-up services and hot-line-telephone services to help solve each patient's problems and allay anxieties in their own home environment.

The Division aims to improve nurse education to provide proper quality nursing services. Four courses have been initiated: (1) an introductory course for new employees; (2) a practical course; (3) a specialized cancer nursing course; and (4) a 'power up' course.

The post of head nurse in charge of nurse's education has been established since April, 2010 to help nurses to study in the optimum way, nurse studying and to support the mental health of our nursing staff.

There are 4 expert nurses, 1 psychiatric mental health nurse and 21 certified expert nurses specializing in wound ostomy care (4), cancer pain (4), cancer chemotherapy (5), palliative care (2), infection control (2), breast care (2), swallowing and eating (1) and radiation (1). They are in charge of

specialized cancer nursing course education programs. We have subsequently accepted trainees for study in the expert nurse course and certified expert nurse course.

Not only expert nurses and certified nurses, but also registered nurses in our hospital have carried out nursing-related research projects and attended external training programs. We gave 20 presentations at academic conference in 2011.

Table 1. The number of trainees (≥1 week)

Category	Year			
	2008	2009	2010	2011
Postgraduate Nurses	8	6	14	6
Certified Expert Nurses	12	13	12	17
Expert Nurses	6	5	4	3
Others	9	1	0	0
Total	35	25	30	26
Nursing Students	208	172	156	141

CLINICAL TRIAL MANAGEMENT OFFICE

Toshihiko Doi

Introduction

The mission of the Clinical Trials Management Office (CTMO) is to facilitate the conduct of quality clinical trials at NCCHE, especially those which are all conducted as a sponsored initiated trial, to achieve registration. The CTMO also will assist investigators with infrastructure support, including Institutional Review Board (IRB) and initial regulatory guidance. A total of 30 staff members support the CTMO: 10 Clinical Research Coordinators (CRCs) (7 Nurses and 3 Pharmacologist), 10 data managers, 4 medical technologists, 1 Free Nurse and 5 secretaries. The CRCs coordinate and conduct patient care visits to ensure that all procedures are conducted with the optimum protocol compliance. The CRC teams interact with the investigators to ensure that patients receive appropriate medical evaluation and care when needed and will alert the investigator of any serious adverse events throughout the course of the protocol study. The clinical data manager teams contribute to the setting up, running and reporting of clinical trials and processes data using a range of computer applications and database systems to support collection, cleaning and management of patient data. They interact with the client as necessary to establish data review guidelines and data flow procedures. The team will also communicate/coordinate with the database manager to ensure accuracy and completeness of the clinical data. Medical technologists conduct and supervise complex medical tests, clinical trials, and control complicated EKG/EUG pharmacokinetic/pharmacodynamic (PK/PD) sampling management. The secretarial team supports the activities of the other teams.

Routine Activities

The CRC function forms the key relationship between the study investigators, sponsor/contract research organization (CRO), subjects and institutional organizations including the IRB, and the clinical trials office. The role of the CRC is critical in helping to ensure that assigned studies are conducted in accordance with human subjects' federal regulations/guidelines regarding human subjects, and meet good clinical practice (GCP) standards as follows:

1) Assist Principal Investigators in the activation and administration of clinical trials.
2) Provide centralized support for operational reviews and ongoing management
3) Provide training and education relevant to all aspects of study management to clinical staff and new investigators.
4) Communicate the availability of clinical trials to physicians, referring physicians and the public
5) Prepare records for internal and external quality and compliance audits, to ensure high-quality standards for data collection and management of clinical trials and to provide a resource for the clinical trial process
6) Assist clinicians in screening and enrolling, managing, and following patients for clinical trials
7) Coordinate and ensure the completion of patient-specific study requirements
8) Provide data management support for clinical trials, including serious adverse events (SAEs)
9) Process, store and ship specimens & support PK/PD sampling
10) Preparing for Audit and Inspection by company and regulatory authorities

A routine staff meeting is held on Fridays to share relevant matters in the management of ongoing clinical trials. An operational committee is also formed and meets with other core members including primary investigations from the clinical laboratory division, pharmacy division and nurse division, and the clinical study support office for the purpose of proper management of trials.

New Achievements and Performance

The number of supported trials and patients under their administration increased in 2011 as in previous years. The CTMO has conducted and supported in excess of 100 registration trials as company sponsored trials. Among them, the numbers of phase 1 clinical trials have increased remarkably over the last few years. We have in particular joined/managed complicated and more early phase clinical trials (1 'first in man' clinical trial and 5 multinational simultaneous phase1 trials, and 1 food effect interaction trial for US-FDA

approval). In 2012, we will be challenged with tougher, more leading edge clinical trials.

In this year, government will provide support to the NCCH & NCCHE with plans to create an infrastructure enabling early-stage and exploratory clinical trials of new drugs and medical devices sponsored by industry and research institutions. We are creating the infrastructure required for exploratory, early-stage clinical trials (for development by specific prospective companies). To realize these trials, Phase 1-specific teams have been started in collaboration with oncology experts to share updated patient and trial information, through regular Phase 1 meetings for patient recruitment, and brief meetings for information sharing.

Drug development is a costly and risky affair and involves lot of money and time. Many compounds that are screened initially fail to make it to the next stage of development. In the past few years, so many phase 3 trials did not meet the endpoint. Many companies re-consider clinical development strategies and have changed their focus (biomarker driven enrichment, IIR for screening etc). The CTMO will meet and overcome the challenge of newer and advanced trials such as combination of unapproved multi-drug trials and new biomarker driven trials. Furthermore, we will contribute to the worldwide network system for phase1 trials to establish the acceleration of the pre-clinical and clinical development of investigational anti-cancer medicines.

PATHOLOGY DIVISION

Atsushi Ochiai, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Takeshi Kuwata, Chisako Yamauchi, Syuichi Mitsunaga

Introduction

The research activities of the Pathology Division of the Research Center for Innovative Oncology currently focus on the application of the morphological study of cancer tissue to the clinical course of the patient. These activities aim to: I) elucidate the new biological roles of cancer epigenetics and cancer-stromal interaction; II) develop a new cancer treatment strategy (Preclinical study); and III) set up and perform experimental and clinicopathological studies on cancer. Prognostic factors and clinicopathological characteristics of various cancers have also been investigated in collaboration with the Department of Pathology and Clinical Laboratories of the National Cancer Center Hospital East (NCCHE) and other institutions.

New Biological Roles of Cancer Epigenetics and Cancer-Stromal Interaction

Overexpression of the polycomb group protein EZH2 (enhancer of zeste homolog 2) occurs in various malignancies and is associated with a poor outcome. EZH2 is an enzyme that controls epigenetical expression of important genes such as E-cadherin and RUNX3 by increasing histone H3K27 tri-methylation. To elucidate the mechanism of EZH2 overexpression in various cancer cells, a promoter analysis of the EZH2 gene was performed and we investigated whether a survival signal that is upregulated in cancer cells could be related to overexpression at the transcription level. The clinical relevance of the signaling pathway that leads to EZH2 overexpression in breast cancer was investigated and the results demonstrated that the MEK-ERK1/2-Elk-1 pathway leads to EZH2 overexpression. The triple-negative and ERBB2-overexpressing subtypes of breast cancer are known to contain more rapidly proliferating breast cancer cells. The signaling pathway connected to EZH2 overexpression was associated with both aggressive subtypes of breast cancer (1). In addition to breast cancer, EZH2 expression and its clinicopathological relationship were investigated in esophageal cancer (2).

Cancer tissue is composed of cancer and stromal cells. The cancer microenvironment generated by the cancer-stromal interaction plays important roles not only in carcinogenesis but also in cancer progression as well as metastasis. Cancer stroma consists of various kinds of cells: fibroblasts, endothelial cells, lymph vessels, macrophages and matrices. The most abundant stromal cells are fibroblasts, however, the origin and biological roles of cancer stromal fibroblasts are still unclear. During the metastatic process, cancer cells interact with vascular adventitial fibroblasts (VAF), which are the main components of the outermost connective tissue layer of blood vessels. The subcutaneous co-injection of human lung adenocarcinoma cell lines (A549, PC-14, and CRL-5807) and human VAF (hVAF) resulted in a high rate of tumor formation. High expression of podoplanin in hVAFs was observed, and sorted podoplanin-positive hVAFs displayed enhanced tumor formation, lymph node metastasis, and lung metastasis of A549 cells. Knockdown and overexpression of podoplanin in hVAFs indicated that podoplanin plays an important role in promoting A549 cancer progression and metastasis. Furthermore, the analysis of small-sized human lung adenocarcinoma (n = 112) revealed that patients with podoplanin-positive cancer-associated fibroblasts had a significantly higher rate of lymph node metastasis and a high risk of recurrence. These results indicate a promotive effect of hVAFs mediated by podoplanin on cancer progression and suggest that the perivascular environment may constitute a specific niche for tumor progression (3). In addition to the importance of fibroblasts on adenocarcinoma progression, squamous cell carcinomas (SqCCs) with a fibrous stroma displayed a higher invasive phenotype and were associated with a significantly poor prognosis. The current results indicate the microenvironment created by both SqCC cells and the peritumoral fibroblasts may facilitate cancer aggressiveness (4).

Development of a New Cancer Treatment Strategy

Trastuzumab is a recombinant antibody drug that is widely used for the treatment of HER2-overexpressing breast and gastric carcinoma. Despite encouraging clinical results, many HER2-overexpressing carcinomas have been primarily resistant to trastuzumab. One of the major roles for trastuzumab in the treatment of

cancer is antibody-dependent cellular cytotoxicity (ADCC) activity with activation of NK cells. To explore trastuzumab resistance, HER2-overexpressing carcinoma cells which were expressing E-cadherin were used to investigate the role of ADCC through the killer cell lectin-like receptor G1 (KLRG1), an inhibitory receptor expressed on subsets of natural killer (NK) cells which recognizes E-cadherin as ligands on NK cells in vitro and in vivo. The results indicated that HER2-overexpressing carcinoma cells were killed by trastuzumab-mediated ADCC and the ADCC activity reflected the degree of E-cadherin expression on carcinoma cells.The results indicated that expression of E-cadherin was shown to be a predictor of the response to trastuzumab-based treatment for HER2-overexpressing carcinomas, furthermore, trastuzumab-mediated ADCC was markedly enhanced by KLRG1-negative peripheral blood mononuclear cells (5).

Experimental and Clinicopathological Studies on Cancer in Collaboration with the Diagnostic Pathology Section

Primary lung adenocarcinomas predominantly composed of goblet cells (APGCs) are relatively rare, and the clinicopathological characteristics have remained unclear. To clarify the clinicopathological characteristics of APGCs, adenocarcinomas with a goblet cell-type component of ≥ 90% from 2228 cases of surgically resected primary lung adenocarcinoma were examined and the clinicopathological characteristics of APGCs (46 cases) were analyzed. APGCs showed a significantly higher rate of tumor location on the left side, in the lower lobe and pathological stage I, when compared with the other types of adenocarcinoma. Furthermore, APGCs displayed a lower frequency of central fibrosis, plural invasion, pulmonary metastasis, lymphatic permeation, and vascular invasion. APGCs demonstrated local recurrence in two of 46 cases (4.3%) and no incidents of distant metastasis. APGCs formed a distinct subset and should be considered separately from lung adenocarcinoma based on frequent involvement of the left and lower lung and lack of central fibrosis (6).

The histological predictive and prognostic factors for gastrointestinal tract cancers such as colon (7, 8), pancreatic tumors (9) and other histologic types of lung cancers (10, 11) were also investigated and reported in collaboration with the clinical divisions of the NCCHE and other institutions.

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INVESTIGATIVE TREATMENT DIVISION

Yasuhiro Matsumura, Masahiro Yasunaga, Yoshikatu Koga, Misato Takigahira, Hikaru Machida, Toshifumi Obonai, Hirobumi Fuchigami, Yoshiyuki Yamamoto, Yohei Hisada, Ryuta Sato, Ryo Tsumura, Yuki Fujiwara, Kengo Oguruma, Kaoru Shiina, Mamiko Shimada, Yukie Katayori

The main goal of the research in this Division is to develop innovative strategies for cancer diagnosis and treatment based on the better understanding of the physiology and biology of cancer tissues and the interaction between cancer and the host. The improvement of preexistent modalities of cancer diagnosis and treatment is also within the scope of our research activity.

Drug Delivery Systems in Cancer Chemotherapy

The main objective of investigating drug delivery systems (DDSs) in cancer chemotherapy is to find methods by which anticancer agents can selectively target solid tumors. The enhanced permeability and retention (EPR) effect in solid tumor tissue was named according to the following pathophysiological characteristics: (a) hypervasculature; (b) incomplete vascular architecture; (c) several vascular permeability factors stimulating extravasation within the cancer; and (d) minimal drainage of macromolecules and particulates (1). Polymeric micelles were expected to increase the accumulation of drugs in tumor tissues utilizing the EPR effect and to incorporate various kinds of drugs into the inner core by chemical conjugation or physical entrapment with relatively high stability. There are several anticancer agent-incorporated micelle carrier systems under clinical evaluation (1, 2).

However, most human solid tumors possess abundant intercellular connective tissue, hindering diffusion of such macromolecules including antibodies. That is why immunoconjugate therapy for stroma rich common solid cancers has not yet proved successful in clinical application. In this context, we have proposed a successful new strategy that overcomes the above contradictory drawbacks by conjugating a small molecular cytotoxic drug with an antibody against particular components of the tumor stroma. In our strategic concept of cancer stroma targeting (CAST) therapy, stromal-targeting immunoconjugates bound to the stroma to create a scaffold, from which sustained release of the cytotoxic agent occurred allowing subsequent diffusion throughout the tumor tissue to damage both tumor cells and tumor vessels (3, 4).

Noninvasive Diagnostic Test for Uterus Cancer

The present medical examination for detecting uterine endometrial cancer has not been proved to be useful. Therefore, we attempted to develop an autoscan-cytology system for detecting endometrial cancer without relying on judgment by the human eye. Our newly developed autoscan-cytology for exfoliated endometrial cells showed overall sensitivity for endometrial cancer patients and overall specificity for healthy volunteers of 53.3% and 94.6%, respectively. This new autoscan-cytology for endometrial cancer deserves further clinical evaluation (5).

Pharmacogenomics Study

Effects of genetic polymorphisms/variations of various genes were analyzed on paclitaxel.

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CANCER PHYSIOLOGY PROJECT

Katsuya Tsuchihara, Chika Miyoshi, Eriko Tomitsuka, Sachiyo Mimaki, Tomomitsu Nasuno, Hiroyasu Esumi

Introduction

Both environmental and genetic factors affect the characteristics of tumor cells. Cancer cells might adapt themselves to the tumor microenvironment by altering their genomes and epigenomes. The Cancer Physiology Project has focused on such adaptations, especially, alterations in the metabolic regulation of cancer cells. Recently developed comprehensive genome and epigenome analyses are powerful tools to reveal the underlying molecular mechanisms for such adaptations as well as exploring novel biomarkers to predict the prognosis of cancers and therapeutic effects of anti-cancer therapies. The final goal of the project is the application of these findings to the development of the rationale of anti-cancer strategies.

Research Activities

Development of Anti-austeric Drugs

Cancer cells in solid tumors frequently encounter a hypoxic and nutrient-deficient microenvironment. The cytotoxicity of conventional anti-cancer drugs was significantly impaired under culture conditions mimicking the tumor microenvironment. Austerity, which is resistance to nutrient starvation, is a characteristic feature of various cancer cells. Since most non-cancerous tissues seldom encounter such nutrient-deficient circumstance, targeting austerity is a promising new strategy for selective cancer treatment. Arctigenin, a major component of *Arctium lappa* (the greater burdock) which is used in traditional herbal medicine, is one of the anti-austerity compounds previously identified in this project. As well as purified arctigenin, a crude extract of *Arctium lappa* possessed equivalent anti-austeric abilities which were exhibited both in culture cell and xenograft models of pancreatic cancer. With the aim of the clinical application of *Arctium lappa*, a phase I/II clinical trial recruiting advanced pancreatic cancer patients has been started, which will examine the efficacy and possible toxicity and determine the appropriate dose for further trials.

Implication of biomarkers for cancer therapy

KRAS mutation testing for metastatic colorectal cancer patients scheduled to receive anti-EGFR antibody treatment has been carried out as a part of the Advanced Medical Technology Programs approved by the Ministry of Health, Labour and Welfare in 2009 and 2010. One-hundred fifty nine tests were performed under the program. Following up the patients who were diagnosed with the KRAS test and received anti-EGFR antibody treatment revealed that sensitive and quality controlled KRAS testing provided improved predictive power to determine the efficacy of the treatment. To further explore more effective genomic biomarkers for anti-EGFR antibody treatment, a multi-centered retrospective study combined with whole exon sequencing and copy number variation analyses has been started.

Molecular epidemiology of lung adenocarcinoma

Whole exon sequencing was adopted to clarify the mutation profiles of Japanese lung adenocarcinoma. Somatic mutations of 97 cases of archived lung adenocarcinoma specimens were identified. An ethnicity-specific mutation profile of known driver mutations was revealed. Furthermore, largely diverse mutation patterns of individual tumors were exhibited.

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CANCER IMMUNOTHERAPY PROJECT

Tetsuya Nakatsura

Introduction

The Cancer Immunotherapy Project aims to investigate evidenced-based cancer immunotherapy, repeating basic research and translational research.

Research Activities

We attempted to compare the induction of the Glypican-3 (GPC3)-specific T-cell-mediated immune response after locoregional therapies in hepatocellular carcinoma (HCC) patients and tumor-bearing mice. Circulating GPC3-specific cytotoxic T lymphocytes (CTLs) were increased in 5 of 9 patients after radiofrequency ablation (RFA) and in 4 of 9 patients after transcatheter arterial chemo-embolization (TACE), but in only 1 of 9 patients after surgical resection. All 7 patients with GPC3-expressing HCCs exhibited an increase in GPC3-specific CTLs after RFA or TACE, whereas none of the 7 patients did after surgical resection. The number of increased GPC3-specific CTLs after RFA was significantly larger than that after surgical resection (P=0.023). Similarly, the frequency of GPC3-specific CTLs after RFA was significantly greater than that after surgical resection in the mouse model (P=0.049). We validated for the first time the stronger effect on the immune system achieved with RFA compared with surgical resection for HCC patients and tumor-bearing mice. Combined treatment with RFA and immunotherapy is a reasonable strategy against HCC. We carried out a phase I clinical trial of HLA-A2-restricted GPC3 (144-152) peptide vaccine in 14 patients with advanced HCC. Immunological responses were analyzed with an *ex vivo* γ-interferon enzyme-linked immunospot assay. The frequency of GPC3 (144-152) peptide-specific CTLs after vaccination (mean, 96; range, 5-441) was significantly larger than that before vaccination (mean, 6.5; range, 0-43) ($P < 0.01$). An increase in the GPC3 (144-152) peptide-specific CTL frequency was observed in 12 (86%) of 14 patients after vaccination. Additionally, there was a significant correlation between the maximum value of GPC3 (144-152) peptide-specific CTLs after vaccination and the dose of the peptide injected ($P = 0.0166$, $r = 0.665$). Moreover, we established several GPC3 (144-152) peptide-specific CTL clones from PBMCs of patients vaccinated with GPC3 (144-152) peptide by single cell sorting using Dextramer and a CD107a antibody. These CTL clones had high avidity (the recognition efficiency showing 50% cytotoxicity was 10(-10) or 10(-11) M) and could recognize HCC cell lines expressing GPC3 in an HLA-class I-restricted manner. These results suggest that GPC3 (144-152) peptide vaccine can induce high avidity CTLs capable of killing HCC cells expressing GPC3 (1). The HLA-A2-restricted GPC3 (144-152) peptide-specific CTL clone recognized naturally processed GPC3-derived peptide on ovarian CCC cells in a HLA class I-restricted manner. Moreover, we confirmed that the level of GPC3 expression was responsible for CTL recognition and that subtoxic-dose chemotherapy made tumor cells more susceptible to the cytotoxic effect of CTL. Thus, it might be possible to treat ovarian CCC patients by combining chemotherapy with immunotherapy. Our data suggest that GPC3 could be an effective target for immunotherapy against ovarian CCC (2). Lengsin is an eye lens protein with a glutamine synthetase domain. Lengsin protein is overexpressed irrespective of the histological type of lung carcinoma, but not in normal tissues other than the lens. Therefore, to significantly extend the use of Lengsin-based T-cell immunotherapy approaches for the treatment of patients with lung carcinoma, we searched for HLA-A*0201-restricted epitopes from this protein by screening predicted Lengsin-derived candidate peptides for the induction of tumor-reactive CTLs. Two of the immunizing peptides, Lengsin (206-215) (FIYDFCIFGV) and Lengsin (270-279) (FLPEFGISSA), induced peptide-specific CTLs in HLA-A*0201 transgenic (HHD) mice, and thus were used to stimulate human peripheral blood lymphocytes *in vitro*. Lengsin (206-215) and Lengsin (270-279) also induced human peptide-specific CTLs, and we were able to generate Lengsin (206-215)- and Lengsin (270-279)-specific CTL clones. The Lengsin (270-279)-specific CTL clone specifically recognized peptide-pulsed T2 cells, COS-7 cells expressing HLA-A*0201 and Lengsin, and HLA-A*0201+/Lengsin+ lung carcinoma cells in an HLA-A*0201-restricted manner. These results suggest that Lengsin (270-279) is naturally processed and presented by HLA-A*0201 molecules

on the surface of lung carcinoma cells and may be a new target for antigen-specific T-cell immunotherapy against lung cancer (3). Dysregulation of the phosphatidylinositol-3-kinase (PI3K)/mammalian target of the rapamycin (mTOR) pathway frequently occurs in human tumors, and is therefore considered to be a good molecular target for treatment. In HCCs, overexpression of p-Akt and decrease of PTEN expression have been reported. NVP-BEZ235 is a novel dual inhibitor of PI3K and mTOR; however, its effect on HCCs has not been documented. Consequently, we investigated the effects of NVP-BEZ235 on the PLC/PRF/5, HLE, JHH7 and HepG2 HCC cell lines *in vitro* and *in vivo*. NVP-BEZ235 decreased the levels of p-Akt and p-p70S6K and inhibited cell proliferation in all HCC cell lines in a dose-dependent manner. Flow cytometric analysis revealed that inhibition of cell proliferation by NVP-BEZ235 was accompanied by G1 arrest in all cell lines, and that NVP-BEZ235 induced apoptosis in PLC/PRF/5 and HLE cells. Tumor growth was suppressed without body weight loss when NVP-BEZ235 was orally administered to JHH-7 tumor-bearing mice for 11 days. These results suggest that NVP-BEZ235 is a potential new candidate for targeted HCC therapy (4).

Clinical Trials

We are performing a Phase II study of GPC3 peptide vaccine as adjuvant treatment for HCC after surgical resection or RFA, and a clinical study to evaluate the immunological efficacy of GPC3 peptide vaccine in patients with advanced HCC.

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FUNCTIONAL IMAGING DIVISION

Hirofumi Fujii, Izumi O. Umeda, Masayuki Yamaguchi, Mistuyoshi Yoshimoto

Introduction

The Functional Imaging Division actively investigated mainly 2 kinds of imaging modalities, namely, radionuclide imaging and magnetic resonance (MR) imaging, to establish strategies for minimally invasive and personalized cancer therapies. For radionuclide imaging, some experimental studies were performed using a small animal single photon emission computed tomography (SPECT) scanner to develop new probes for hypoxia imaging and so on. For MR imaging, some experimental studies were done using both a 9.4T scanner dedicated for small animal imaging and a 3.0T whole-body scanner.

Research Activities

As tumor hypoxia is associated with a poor prognosis and resistance to chemotherapy and radiotherapy, its *in vivo* imaging is quite useful to determine the optimal treatment of cancer. In the experimental radionuclide studies, we developed two different types of hypoxia imaging probes. The first one was a novel ^{99m}Tc-labeled probe containing a 4-nitrobenzyl ester group. It was specifically reduced in hypoxic cells, and the resulting product, carboxylate anions, were successfully trapped in hypoxic cells because of their hydrophilicity and negative charge (1). The other candidate was a ^{125}I-labeled hypoxia-inducible factor 1 (HIF-1) -mimic protein. HIF-1 is a key transcriptional regulator in response to hypoxia. The mimic protein was designed to be stable under hypoxic conditions specifically and degraded in the same manner as HIF-1α under normoxic conditions. *In vivo* SPECT/CT imaging, autoradiography and double-fluorescent immunostaining for HIF-1α and pimonidazole were studied, and it was confirmed that the tumor uptake of this probe corresponded to the HIF-1 expression. Thus, it would be a useful probe for the molecular imaging of HIF-1-activity in tumors (2).

Radiolabeled liposomes are promising radiopharmaceuticals for tumor imaging and radionuclide therapy because of their high affinity to tumors. On the other hand, conventional liposomes also accumulate in the reticuloendothelial systems (RES), such as the liver and spleen. This has hindered their clinical application. In order to solve this problem, we developed a new liposome, the ^{111}In-EC-carrying liposome. It was rapidly washed out and excreted to urine after trapping by the RES, due to the nature of ^{111}In-EC. When ^{111}In was substituted by ^{90}Y, radionuclide therapy could be expected. A patent was applied for ^{111}In-EC-carrying liposomes.

For the early detection of pancreatic cancer, the usefulness of an imaging probe of alpha v beta 3 ($\alpha_v\beta_3$) integrin called ^{111}In-DOTA-c(RGDfK) in SPECT imaging was investigated using a hamster pancreatic carcinogenesis model. ^{111}In-DOTA-c(RGDfK) could clearly visualize pancreatic cancers as small as 3 mm in diameter. ARG analysis and histopathological examination revealed the uptake of ^{111}In-DOTA-c(RGDfK) was strongly correlated with $\alpha_v\beta_3$ integrin expression. On the contrary, no clear uptake of ^{111}In-DOTA-c(RGDfK) was demonstrated in inflammatory lesions. Our findings suggested that SPECT imaging using ^{111}In-DOTA-c(RGDfK) has great potential for early and accurate detection of pancreatic cancer.

Although, MR imaging is originally capable of showing high tissue contrast resolution, administration of contrast agents can further enhance it. We have developed a new contrast agent to visualize mouse tumors in collaboration with The University of Tsukuba (PI: Professor Nagasaki). This contrast agent consisted of iron-oxide nano-particles coated with a plentiful amount of polyethylene glycol (PEG) molecules. These PEG molecules prevent the binding of iron-oxide nano-particles to serum proteins after intravenous administration. As a result, they are not rapidly eliminated from the blood stream by phagocytosis of hepatic and splenic macrophages, and thereby many of them reach the tumor vasculature. We confirmed these iron-oxide nano-particles accumulated very well in subcutaneous mouse tumors on Prussian blue-stained specimens. In addition, we observed the negative enhancement effect of these iron-oxide nano-particles in these tumors on T_2-weighted MR images (3).

Another iron-oxide nano-particle, ferucarbotran, is a clinically approved contrast agent.

Ferucarbotran-enhanced interstitial lymphography has been considered as a useful technique for differentiating metastatic and non-metastatic lesions within sentinel lymph nodes, because it can visualize metastatic and non-metastatic tissues as high and low signal areas, respectively. This technique has, however, a pitfall that radiologists should keep in mind. We investigated inflamed lymph nodes of mice using this technique, and found that non-metastatic tissues like inflammatory tissues can show high signals that are misinterpreted as metastasis. The lack of iron-laden macrophages in inflamed paracortical areas might be the cause of these high signals.

Although MR imaging is a useful tool for preclinical studies, on the negative side, it takes a rather long acquisition time. To improve the though-put of MR imaging, a simultaneous acquisition method with multiple animals is under investigation. We developed a multi-channel coil and simultaneously imaged up to 8 tumor bearing mice using this coil. Our initial study revealed this system could accurately measure the volume of multiple tumors with an acquisition time one third shorter than the conventional method (4).

Clinical Trials

Clinical trials of hypoxia PET tests were ongoing using 2 kinds of radiopharmaceuticals: one was F-18 labeled fluoroarabinofuranosyl nitroimidazole (FAZA) and the other was Cu-62 labeled diacetyl methyl-thiosemicarbazone (ATSM). Patients with lung cancer and those with head and neck cancer were tested to investigate clinical and pathological features of tumors with high avidity to these radiopharmaceuticals.

The effects of systemic chemotherapy on cerebral metabolism and cognitive function in breast cancer patients were evaluated with MR spectroscopy.

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PSYCHO-ONCOLOGY DIVISION

Asao Ogawa, Hiroya Kinoshita, Ken Shimizu, Daisuke Fujisawa

Introduction

The aim of the Psycho-Oncology Division is to develop mind-centered interventions to restore, maintain, and improve the quality of life of patients and their families who face a life-threatening illness, cancer. The Division has focused on developing effective interventions for 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

Research and Development of Interventions for Depression

Major depressive disorders (MDDs) and adjustment disorders (ADs) are common psychiatric disorders in cancer patients but are often overlooked in clinical oncology settings. We developed the 'Distress Screening Program' as a practical means of screening for and facilitating the treatment of major depression and adjustment disorders in cancer patients. We introduced a clinical screening program utilizing the Distress and Impact Thermometer (DIT) to identify MDD and AD in cancer outpatients receiving chemotherapy.

As part of this program, pharmacists administered the DIT to consecutive patients undergoing chemotherapy at an outpatient clinic. Psychiatric treatment was recommended to all the patients with positive screening results. The proportion of patients referred to the Psychiatric Service during the program period was then compared with that during a usual care period.

Of the 520 patients who started chemotherapy during the 6-month program period, 5.0% (26/520) were referred to the Psychiatric Service and 2.7% (15/520) were diagnosed as having an MDD or AD. No statistically significant difference in the referral rates was observed between the two periods (2.7 vs 1.0%, $p = 0.46$). However, the period from the first chemotherapy treatment until the visit to the Psychiatric Service was significantly shorter during the program period than during the period of usual care (12.9±13.2 days vs 55.6±17.6 days, $p<0.001$).

The proportion of patients referred to the Psychiatric Service for the treatment of MDDs or ADs during the program period was not different from that during the usual care period. However, the program was useful for introducing psychiatric treatment at an earlier stage. Further modifications to the program to improve the referral rate are necessary.

Research and Development of the Psychological Support Program for Cancer Patients in Designated Cancer Hospitals

Collaboration between psychiatry and palliative medicine has the potential to enhance the quality of medical practice. The integration between palliative care and psychiatry has been attempted only in discrete medical settings and is not yet firmly established as an institution.

In Japan, the Cancer Control Act was approved in 2006, and prefectural and local cancer hospitals were designated by the government. The designated cancer hospitals were required to provide a hospital-based palliative care team, with a palliative care specialist, a consultation-liaison psychiatrist and a certified advanced nurse practitioner as core members. In addition, national medical insurance covers the services provided by qualified palliative care teams that fulfill the necessary conditions: palliative care teams must be interdisciplinary teams composed of full-time core members with a palliative care specialist, a consultation-liaison psychiatrist, a certified advanced nurse practitioner and hospital pharmacists. The approval of palliative care teams by the insurance plan encourages the dissemination of palliative care service in practice. We investigated the availability and degree of integration between psychiatric consultation-liaison services and palliative care in Japan.

A survey questionnaire was mailed to consultation-liaison psychiatrists at 375 government-designated cancer hospitals regarding their consultation-liaison services. A total of 375 survey questionnaires were sent to consultation-liaison psychiatrists, with a response rate of 64.8%. Designated cancer hospitals with approved palliative care teams were significantly more likely to have a consultation-liaison

psychiatrist in the palliative care team than those in non-approved palliative care teams [80/80 (100%) versus 110/153 (73%); P < 0.008]. Approved palliative care teams had double the number of referrals, conducted rounds more frequently and held conferences more frequently. Psychiatrists of the approved palliative care teams spent more of their time on palliative care consultations, adhered more closely to consultation processes and contributed more actively to the integration of developmental perspectives in treatment plans. In Japan, most designated cancer hospitals with approved palliative care teams were more likely to integrate psychiatric consultation-liaison services into their palliative care programs. Systematic strategies for integration between palliative care and consultation-liaison psychiatry would contribute to the provision of appropriate psychosocial care for cancer patients and families at all stages.

PARTICLE THERAPY AND RADIATION ONCOLOGY DIVISION

Teiji Nishio, Ryosuke Kohno, Satoru Kameoka, Shie Nishioka, Sadamoto Zenda, Mitsuhiko Kawashima, Tetsuo Akimoto

Introduction

The aim of research in the Particle Therapy Division at the National Cancer Hospital East, is to study and develop innovative treatment techniques and pilot clinical trial for radiation therapy (RT). Medical physicists mainly perform development and verification of a beam irradiation system, dose calculation system, dose measurement system, and imaging system. Radiation oncologists mainly perform studies on the clinical benefit, safety and efficacy of RT.

Research Activities

(a): Proton beam therapy as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study

The aim of this pilot study was to assess the clinical benefit of proton beam therapy for mucosal melanoma of the head and neck. Patients with mucosal melanoma of the head and neck with histologically confirmed malignant melanoma and N0 and M0 disease were enrolled. Proton therapy was delivered three times per week with a planned total dose of 60 Gy equivalents (GyE) in 15 fractions. Fourteen consecutive patients were enrolled from January 2004 through February 2008. Patient characteristics were as follows: median age 73 years old (range, 56 to 79 years); male/female ratio, 7/7; and T stage 1/2/3/4, 3/2/0/9. All patients were able to receive the full dose of proton therapy. The most common acute toxicities were mucositis (grade 3, 21%) and mild dermatitis (grade 3, 0%). As for late toxicity, 2 patients had a unilateral decrease in visual acuity, although blindness did not occur. No treatment-related deaths occurred throughout the study. The initial local control rate was 85.7%, and, with a median follow-up period of 36.7 months, median progression-free survival was 25.1 months, and 3-year overall survival rates were 58.0%. The most frequent site of first failure was the cervical lymph nodes (6 patients), followed by local failure in 1 patient and lung metastases in 1 patient. On follow-up, 5 patients died of disease, 4 died due to cachexia caused by distant metastases, and 1 patient by carotid artery perforation caused by lymph nodes metastases. Proton beam radiotherapy showed promising local control benefits and would benefit from ongoing clinical study.

(b): Dose-volume histogram analysis of the safety of proton beam therapy for unresectable hepatocellular carcinoma

To evaluate the safety and efficacy of radiotherapy using PRT for unresectable hepatocellular carcinoma, sixty consecutive patients who underwent PRT between May 1999 and July 2007 were analyzed. There were 42 males and 18 females, with a median age of 70 years (48-92 years). All but 1 patient had a single lesion with a median diameter of 45 mm (20-100 mm). Total PRT dose/fractionation was 76-cobalt Gray equivalent (CGE)/20 fractions in 46 patients, 65 CGE/26 fractions in 11 patients, and 60 CGE/10 fractions in 3 patients. The risk of developing proton-induced hepatic insufficiency (PHI) was estimated using dose-volume histograms and an indocyanine-green retention rate at 15 minutes (ICG R15). None of the 20 patients with ICG R15 of less than 20% developed PHI, whereas 6 of 8 patients with ICG R15 values of 50% or higher developed PHI. Among 32 patients whose ICG R15 ranged from 20% to 49.9%, PHI was observed only in patients who had received 30 CGE (V30) to more than 25% of the noncancerous parts of the liver (n = 5) Local progression-free and overall survival rates at 3 years were 90% (95% confidence interval [CI], 80-99%) and 56% (95% CI, 43-69%), respectively. A gastrointestinal toxicity of Grade $\geq$2 was observed in 3 patients. ICG R15 and V30 are recommended as useful predictors for the risk of developing PHI, which should be incorporated into multidisciplinary treatment plans for patients with this disease.

(c): Development of an activity pencil beam algorithm using measured distribution data of positron emitter nuclei generated by proton irradiation of targets containing ^{12}C, ^{16}O, and ^{40}Ca nuclei in preparation of clinical application

The purpose of this study is to develop a new calculation algorithm that is satisfactory in terms of the requirements for both accuracy and calculation time for a simulation of imaging of the proton-irradiated volume in a patients body in clinical proton therapy. The activity pencil beam

algorithm (APB algorithm), which is a new technique to apply the pencil beam algorithm generally used for proton dose calculations in proton therapy to the calculation of activity distributions, was developed as a calculation algorithm of the activity distributions formed by positron emitter nuclei generated from target nuclear fragment reactions. In the APB algorithm, activity distributions are calculated using an activity pencil beam kernel. In addition, the activity pencil beam kernel is constructed using measured activity distributions in the depth direction and calculations in the lateral direction. ^{12}C, ^{16}O, and ^{40}Ca nuclei were determined as the major target nuclei that constitute a human body that are of relevance for the calculation of activity distributions. In this study, "virtual positron emitter nuclei" was defined as the integral yield of various positron emitter nuclei generated from each target nucleus by target nuclear fragment reactions following irradiation with a proton beam. Compounds, namely, polyethylene, water (including some gelatin) and calcium oxide, which contain plenty of the target nuclei, were irradiated using a proton beam. In addition, depth activity distributions of virtual positron emitter nuclei generated in each compound from target nuclear fragment reactions were measured using a beam ON-LINE PET system mounted on a rotating gantry port (BOLPs-RGp). The measured activity distributions depend on depth or, in other words, energy. The irradiated proton beam energies were 138, 179, and 223 MeV, and measurement time was about 5 h until the measured activity reached the background level. Furthermore, the activity pencil beam data were made using the activity pencil beam kernel, which was composed of the measured depth data and the lateral data including multiple Coulomb scattering approximated by the Gaussian function and were used for calculating activity distributions. The data of measured depth activity distributions for every target nucleus by proton beam energy were obtained using BOLPs-RGp. The form of the depth activity distribution was verified, and the data were constructed in consideration of the time-dependent change of the form. Time dependence of an activity distribution form could be represented by two half-lives. The Gaussian form of the lateral distribution of the activity pencil beam kernel was decided by the effect of multiple Coulomb scattering. Thus, the data of the activity pencil beam involving time dependence could be obtained in this study. The simulation of imaging of the proton-irradiated volume in a patient body using target nuclear fragment reactions was feasible with the developed APB algorithm taking time dependence into account. With the use of the APB algorithm, it was suggested that a system of simulation of activity distributions that has levels of both accuracy and calculation time appropriate for clinical use can be constructed (1).

(d): A feasibility study of a molecular-based patient setup verification method using a parallel-plane PET system

A feasibility study of a novel PET-based molecular image guided radiation therapy (m-IGRT) system was conducted by comparing PET-based digitally reconstructed planar image (PDRI) registration with radiographic registration. We selected a pair of opposing parallel-plane PET systems for the practical implementation of this system. Planar images along the in-plane and cross plane directions were reconstructed from the parallel-plane PET data. The in-plane and cross-plane FWHM of the profile of 2 mm diameter sources was approximately 1.8 and 8.1 mm, respectively. Therefore, only the reconstructed in-plane image from the parallel-plane PET data was used in the PDRI registration. In the image registration, five different sizes of 18F cylindrical sources (diameter: 8, 12, 16, 24, 32 mm) were used to determine setup errors. The data acquisition times were 1, 3 and 5 min. Image registration was performed by five observers to determine the setup errors from PDRI registration and radiographic registration. The majority of the mean registration errors obtained from the PDRI registration were not significantly different from those obtained from the radiographic registration. Acquisition time did not appear to result in significant differences in the mean registration error. The mean registration error for the PDRI registration was found to be 0.93±0.33 mm. This is not statistically different from the radiographic registration which had a mean registration error of 0.92±0.27 mm. Our results suggest that m-IGRT image registration using PET-based reconstructed planar images along the in-plane direction is feasible for clinical use if PDRI registration is performed at two orthogonal gantry angles (2).

(e): Proton dose distribution measurements using a MOSFET detector with a simple dose-weighted correction method for LET effects

We experimentally evaluated the proton beam dose reproducibility, sensitivity, angular dependence and depth-dose relationships for a new Metal Oxide Semiconductor Field Effect Transistor (MOSFET) detector. The detector was fabricated

with a thinner oxide layer and was operated at high-bias voltages. In order to accurately measure dose distributions, we developed a practical method for correcting the MOSFET response to proton beams. The detector was tested by examining lateral dose profiles formed by protons passing through an L-shaped bolus. The dose reproducibility, angular dependence and depth-dose response were evaluated using a 190 MeV proton beam. Depth-output curves produced using the MOSFET detectors were compared with results obtained using an ionization chamber (IC). Since accurate measurements of proton dose distribution require correction for LET effects, we developed a simple dose-weighted correction method. The correction factors were determined as a function of proton penetration depth, or residual range. The residual proton range at each measurement point was calculated using the pencil beam algorithm. Lateral measurements in a phantom were obtained for pristine and SOBP beams. The reproducibility of the MOSFET detector was within 2%, and the angular dependence was less than 9%. The detector exhibited a good response at the Bragg peak (0.74 relative to the IC detector). For dose distributions resulting from protons passing through an L-shaped bolus, the corrected MOSFET dose agreed well with the IC results. Absolute proton dosimetry can be performed using MOSFET detectors to a precision of about 3% (1 sigma). A thinner oxide layer thickness improved the LET in proton dosimetry. By employing correction methods for LET dependence, it is possible to measure absolute proton dose using MOSFET detectors (3).

(f): Multi-institutional Retrospective Analysis of the Inhomogeneity Correction for Radiation Therapy of Lung Cancer

The purpose of this work is to retrospectively analyze the effect of the inhomogeneity correction using a clinically treated plan for stage III non-small-cell lung cancer within multiple institutions in Japan. Twenty-five patients among five radiation therapy facilities were registered for this study. The isocenter dose or D95 of PTV or other important values were compared with and without an inhomogeneity correction using a model-based algorithm. The differences in isocenter dose were 4% average and 10% maximum for the first Anterior-Posterior opposed field plan to 40 Gy and 6% average and 11% maximum for the off-cord boost oblique field plan of 20 Gy. The differences in D95 dose were 1% average and 9% maximum for the first plan and 1% average and 6% maximum for the boost plan. D95 prescription seemed to be a superior method; however, its reliability depends on each clinical case. Additionally, maximum dose, minimum dose and mean dose for both the primary tumor and the metastatic lymph node were analyzed, and the minimum dose had the most impressive results. In some cases, the target volume had an unintended underdose of more than 10%. Finally, an analysis of the organ at risk was added, and this showed no meaningful differences for the V20 of the lung and the maximum dose of the spinal cord. These results provide a standard for the effects of the inhomogeneity correction (4).

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CLINICAL TRIAL SECTION

Akihiro Sato, Yasuhiro Shibasaki, Kayo Onoda, Yuko Kineri, Mie Yamada, Mai Kikuchi, Natsuko Takagi, Yoichi Kisen, Yasuko Nishikubo, Minako Honda, Harumi Nakazima, Hiromi Hasegawa, Yoshihiro Aoyagi, Tomohisa Sudo, Noriko Nabata, Noriko Suzuki, Akiko Nakayama, Izumi Miki, Yukiko Abe, Seiko Kondo, Megumi Nakamura, Kazushi Endo

Introduction

Established in 2008, the Clinical Trial Section supports the Investigator Initiated Clinical Trials (IITs) Program at the National Cancer Center Hospital East (NCCHE) through the Clinical Data Center. Our section consults on development strategy, supports project management and protocol development. The Section consists of the CRC Office for IITs, Clinical Data Center, Protocol Development (Medical Writing) Team, Research Concierge Office, IRB Office and Regulatory Affairs.

Routine Activities

CRC Office for IITs
- Support IITs that are conducted in the NCCHE

Clinical Data Center
- Provides direct oversight of Institutional Investigator Initiated Early-Phase Clinical Trials
- Data Management
- Central Monitoring
- Site Visit Monitoring through direct access to electronic medical records

Protocol Development Team
- Support for protocol writing
- Support for consent form writing
- Consultation on clinical development strategy
- Consultation on trial methodology

Research Concierge Office
- Support for informed consent for genetic research
- Support for trans rational research using genome information.

IRB Office
- Oversees all IRB activities
- Management of Contents of clinical trials on web site
- Call Center for clinical trials
- Intellectual Properties Rights Management commenced in 2010

Regulatory Affairs
- Consultation on regulatory affairs throughout the whole process of drug development by regulatory affairs experts
- All experts have experience either as reviewers in the Minister of Health, Labor and Welfare (MHLW) or in the Pharmaceuticals and Medical Devices Agency (PMDA).

Research Activities and Clinical Trials

CRC Office for IITs
- CRCs, in 2010 supported 34 IITs including a Sponsor Investigator IND trial. A total of 696 patients participated in the IITs.

Clinical Data Center
- Two clinical studies, a medical device and new anticancer drag study, and first-in-man phase 0 study, are active as of 2011.
- Three clinical studies, two medical device studies, and a study on anti-cancer drug are in preparation.

Research Concierge Office
- RCs, in 2011 supported about 3,000 informed consents in 2011.

Protocol Development Team
- Medical writing support and project management were provided for all IITs that were overseen by the Clinical Data Center.

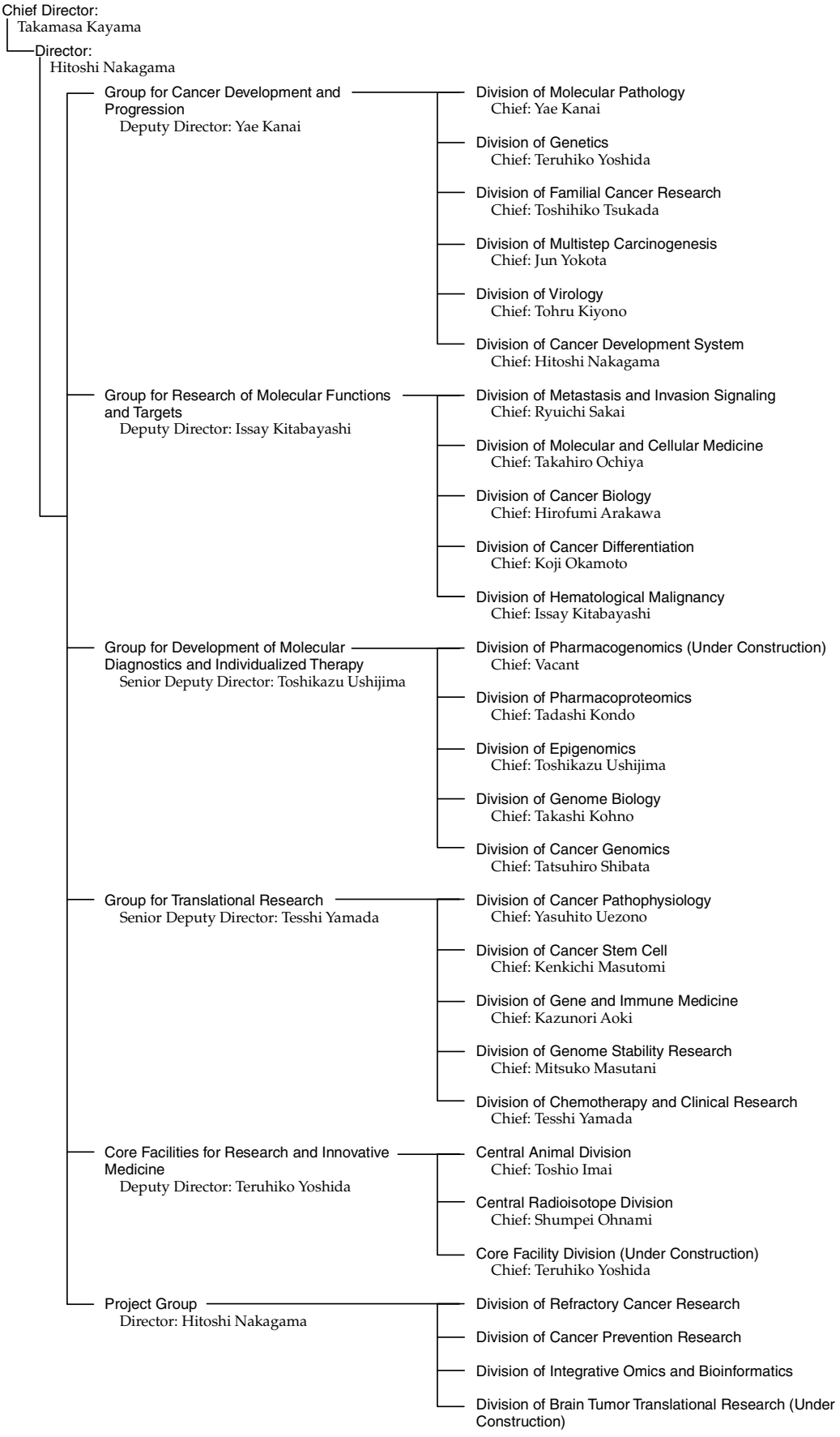
Research Institute

Preface

The National Cancer Center Research Institute (NCCRI) was established in 1962 as a department of the National Cancer Center (NCC), and has been the nation's leading cancer research institute for nearly 50 years. It is now internationally recognized for major contributions to various aspects of cancer research worldwide. The mission of the NCCRI is to advance our knowledge of cancer prevention, diagnosis and therapy, toward the ultimate goal of cancer control. Collaborative research integration between other departments of the NCC, including NCC Hospitals, and the Research Institute is highly encouraged. The NCCRI is now composed of 25 divisions, and they are sub-grouped into four major Research Groups and one Project Group; namely, the Group for Cancer Development and Progression, Group for Research into Molecular Functions and Targets, Group for Development of Molecular Diagnostics and Individualized Therapy and Group for Translational Research and Project Group. Core Facilities for Research and Innovative Medicine, which consist of the Central Animal Division, Central Radioisotope Division and Core Facility Division, provide several kinds of technical support in molecular biology, high-throughput omics-type analyses, biological analysis and animal experiments for researchers in both the Research Institute and Hospital to further encourage and facilitate the development of translational-type studies in our Institute. The NCCRI currently has approximately 90 research staff, around 50 postdoctoral fellows, and more than 100 supporting staff. Foreign scientists and research fellows are also welcomed on a regular basis. The "Annual Report 2011" of the NCCRI summarizes the recent research activities of each division, which cover the following areas: (i) environmental human carcinogens and cancer chemoprevention, including the use of animal models; (ii) clarification of molecular mechanisms underlying cancer development, invasion and metastasis; (iii) investigation of genetic and epigenetic alterations in a variety of cancers; (iv) clarification of the molecular bases underlying the susceptibility to cancer development; (v) exploration of novel biomarkers with diagnostic, therapeutic and prognostic value; and (vi) functional analyses of various cancer-related genes. We have also been participating in worldwide research interactions, such as the International Cancer Genome Consortium (ICGC), International Cancer Biomarker Consortium (ICBC), and International Human Epigenome Consortium (IHEC). We further encourage our members to develop international collaborations in various other areas. The activities of the research institute can also be viewed on the home page: http://www.ncc.go.jp/en/nccri/index.html.

Hitoshi Nakagama, M.D., D.M.Sc.
Director, National Cancer Center Research Institute

Organization



Activities of the Divisions

DIVISION OF MOLECULAR PATHOLOGY

Yae Kanai, Nobuyoshi Hiraoka, Shigeki Sekine, Yoshinori Ishikawa (Ino), Masahiro Gotoh, Hidenori Ojima, Eri Arai, Taisuke Mori

Research in the Division of Molecular Pathology is based on a combination of clinicopathological observations and molecular pathological analyses.

Epigenetic and Genetic Alterations During Multistage Carcinogenesis

To understand the significance of DNA methylation alterations underlying the clinicopathological diversity of human cancers, a genome-wide DNA methylation analysis has been performed. Since renal carcinogenesis is associated with neither chronic inflammation nor persistent viral infection, and hardly any histological change is evident in corresponding non-tumorous renal tissue from patients with renal tumors, precancerous conditions in the kidney have been rarely described. However, the bacterial artificial chromosome (BAC) array-based methylated CpG island amplification method, which may be suitable for overviewing the DNA methylation tendency of individual large regions among all chromosomes, has revealed that non-tumorous renal tissue from patients with renal tumors are already at the precancerous stage. DNA methylation profiles determining the histological subtypes of renal tumors developing in individual patients may be already established in non-tumorous renal tissue at the precancerous stage (1). DNA methylation profiles at the precancerous stage may be basically inherited by the cancers developing in individual patients (2). DNA methylation alterations at the precancerous stage may confer vulnerability to further epigenetic and genetic alterations and determine both the malignant potential of the corresponding cancer and the outcome of patients (2).

Even non-cancerous urothelia showing no remarkable histological features obtained from patients with urothelial carcinomas can be considered to be at the precancerous stage, because they may be exposed to carcinogens in the urine. Actually, genome-wide DNA methylation alterations accumulated in both non-cancerous urothelia obtained from patients with urothelial carcinomas and urothelial carcinomas themselves. An array comparative genomic hybridization analysis revealed that losses of 5q14.1-q23.1, 6q14.1-q27, 8p22-p21.3, 11q13.5-q14.1 and 15q11.2-q22.2 and gains of 7p11.2-q11.22 and 19q13.12-q13.2 were correlated with the development of aggressive non-papillary urothelial carcinomas (3). Losses of 1p32.2-p31.3, 10q11.23-q21.1 and 15q21.3 were correlated with tumor recurrence (3). An unsupervised hierarchical clustering analysis based on copy number alterations clustered urothelial carcinomas into three subclasses: copy number alterations associated with genome-wide DNA hypomethylation, regional DNA hypermethylation on C-type CpG islands associated with frequent chromosomal losses, and genome-wide DNA hypo- and hypermethylation, were accumulated in clusters A, B_1 and B_2, respectively (3). Both epigenetic and genetic events appear to accumulate during urothelial carcinogenesis, reflecting the clinicopathological diversity of urothelial carcinomas.

DNA methylation alterations are stably preserved on DNA double strands by covalent bonds, and they can be detected using highly sensitive methodology. Therefore, genome-wide DNA methylation profiling may be advantageous to establish optimal diagnostic indicators for cancer practice. For example, the diagnostic criteria of ductal adenocarcinomas of the pancreas based on DNA methylation profiling may be advantageous for supporting the histological and cytological assessment of pancreatic biopsy and juice specimens, respectively (4). In order to decide the indications of adjuvant chemotherapy for patients with pancreatic cancers, which should be carried out carefully, paying close attention to adverse reactions, the criteria for prognosis using the 11 BAC clones were established. The DNA methylation status on the 11 BAC clones significantly correlated with both cancer-free and overall survival rates of patients with pancreatic cancers. A multivariate analysis revealed that our criteria were an independent predictor of poor outcome (4).

For appropriate surveillance of patients at the precancerous stage for hepatocellular carcinomas (HCCs), the 45 CpG sites, whose DNA methylation levels differed significantly between normal liver

tissues and non-cancerous liver tissues obtained from HCC patients in the learning cohort, were identified using a highly quantitative pyrosequencing method (5). The criteria combining the DNA methylation status for the 45 CpG sites were able to diagnose non-cancerous liver tissues obtained from HCC patients as being at high risk of carcinogenesis with 100% sensitivity and specificity in both the learning and validation cohorts (5). Pyrosequencing can be performed using a very small amount of degraded DNA extracted from formalin-fixed and paraffin-embedded liver biopsy specimens. These criteria may be applicable for liver biopsy specimens obtained prior to interferon therapy from patients who are followed up because of chronic liver diseases.

Recently, a high-throughput platform using the BeadChip microarray, which is able to interrogate the human DNA methylome at single CpG resolution, has been employed. Such ongoing projects may provide more accurate classifications of human cancers. Such subclassification may yield clues for clarification of distinct mechanisms of carcinogenesis in various organs, and identify possible target molecules for therapy in patients belonging to specific clusters.

Antitumor Immune Responses

The anti-tumor immune reaction changed drastically during carcinogenesis (6, 7). Gene expression analyses using microarray and RT-PCR revealed that CXCL17 and ICAM2 were involved in the immune surveillance during the development of pancreatic cancers (8). CXCL17 and ICAM2 induced infiltration and accumulation of immature myeloid dendritic cells in the tumor epithelial layer. This was followed by an active cellular immune reaction. ICAM2 simultaneously promoted the susceptibility of the tumor cells to cytotoxic T cell-mediated cytolysis. Immune surveillance occurs during the early intraepithelial stages of human pancreatic carcinogenesis, which is mediated by the expression of CXCL17 and ICAM2.

Arginine is essential for T cell activity and survival. Arginase II, an arginine-catabolizing enzyme, in pancreatic ductal carcinoma tissue was clinicopathologically studied. Arginase II was characteristically expressed in cancer-associated fibroblasts under hypoxia. The presence of arginase II-expressing cancer-associated fibroblasts is an independent factor for a worse prognosis, and it is a new hypoxic indicator in pancreatic ductal carcinoma tissue.

Role of β-catenin in Hepatocarcinogenesis

CTNNB1, encoding β-catenin, is one of the most frequently mutated oncogenes in HCCs. However, it has been unclear if active β-catenin signaling confers growth advantage to hepatocytes under physiological conditions. Our analysis of hepatocyte-specific β-catenin-deficient mice showed that hepatocytes with wild-type β-catenin exhibited survival advantage over β-catenin-deficient hepatocytes *in vivo* (9). Furthermore, paradoxically, β-catenin-mutated hepatomas were frequently developed in β-catenin-deficient livers. These suggest that a non-cell autonomous mechanism is involved in the hepatocarcinogenesis mediated by active β-catenin signaling. Our analyses also showed overexpression of AMACR and SLCO1B3, both of which are involved in bile acid metabolism, in *CTNNB1*-mutated human HCCs (10, 11).

Clinicopathological Studies

Breast carcinomas sometimes metastasize to the stomach, and the histopathologic distinction of such metastases from primary gastric adenocarcinomas is often difficult: most metastatic breast and primary gastric carcinomas have contained signet ring cell components. Immunohistochemical examination using a panel of antibodies identified hepatocyte nuclear factor 4A as an excellent marker for differentiating between the 2 lesions (12). Other clinicopathological studies were also conducted to further the understanding of the pathogenesis and promote the diagnosis and treatment of various tumors (13-15).

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DIVISION OF GENETICS

Teruhiko Yoshida, Hiromi Sakamoto, Fumiaki Koizumi, Hiroki Sasaki, Hitoshi Ichikawa, Norihisa Saeki, Kazuhiko Aoyagi, Takao Nishimura, Hiroo Takahashi, Aya Kuchiba, Low Siew Kee, Yusuke Nakadate, Akio Ashida, Sumiko Ohnami, Mineko Ushiama, Yoko Odaka, Misuzu Okuyama, Akiko Takahashi, Masumi Shimizu, He Haiping, Mika Shioya, Sayaka Mito, Mayumi Akitaya, Yuka Kitamura, Yuri Uehara, Rumi Koyama, Rie Komatsuzaki, Fumiko Chiwaki, Sachiyo Mitani, Hiroe Ono, Asami Kikawada

Introduction

In 2011, the three major research areas of the Division of Genetics were 1) molecular understanding of cancer susceptibility for the application to cancer diagnosis and prevention, 2) basic research for the development of molecular targeting and personalized cancer chemotherapy, and 3) transcriptome analyses of solid tumors and leukemia. In addition, the Division has also continued its participation in the biobanking project of the Tsukiji campus of the NCC, particularly in the DNA, RNA and plasma banking of the peripheral blood samples. The Division has been also involved in the construction of the biobank network among the 6 National Centers.

Genetic Susceptibility to Cancers

The Division continued an investigation of the genetic susceptibility of diffuse type gastric cancer by focusing on the second candidate locus at 1q22, which was identified by the previous genome-wide association study (GWAS) by the Division. An LD (linkage disequilibrium) block in the region contained the *MUC1* (mucin 1) gene which was identified as the most likely susceptibility factor based on the annotation and the results of previous candidate gene analyses. Functional studies demonstrated that the rs4072037 SNP (P=1.43x10^{-11}; odds ratio=1.66 by meta-analysis) in *MUC1* affects promoter activity and determines the major splicing variants of *MUC1* in the gastric epithelium. The result suggests that the polymorphism modulates the protective function of the protein against a variety of external insults to the gastric mucosa and thus influences the individual susceptibility to gastric carcinogenesis (1). The researchers of the Division also participated in the international collaboration to identify the *LMO1* (LIM domain only 1) gene as a susceptibility gene of neuroblastoma (2, 3).

Clinical genetic testing on hereditary cancer syndromes has been continued as a long-standing collaboration with the outpatient clinic in the National Cancer Center Hospital to support its genetic diagnosis. Collaboration with other institutions evaluated a role of family history and other general cancer risk factors in the PET cancer screening, but there was no significant association between the cancer risks and detection rate (4).

Basic Research for Molecular Targeting and Personalized Cancer Chemotherapy

Lymphangiogenesis has been considered an important element in the development of metastasis. Sunitinib, a multi-kinase inhibitor and clinically available as an angiogenesis inhibitor, is a promising candidate to suppress the lymphangiogenesis. *In vitro*, sunitinib blocked both VEGFR-2 and VEGFR-3 phosphorylation and downstream signaling induced by VEGF-C or VEGF-D in human lymphatic endothelial cells (LECs). Sunitinib also prevented VEGF-C-induced proliferation, migration and tube formation of the LECs. An *In vivo* breast cancer xenograft model showed that sunitinib significantly reduced the number of blood and lymphatic vessels and suppressed axillary lymph node metastasis, suggesting the usefulness of sunitinib in the treatment of breast cancer (5).

The Division has continued multiple collaborations in the field of pharmacogenetic and pharmacodynamics biomarker development research (pharmacogenomics in a broad sense) with the researchers at the National Cancer Center Hospital and other institutions on cytotoxic or molecular target agents. A GWAS was conducted on 105 chemotherapy-naïve stage IIIB or IV non-small cell lung cancer patients treated with carboplatin and paclitaxel, and 3 SNPs were identified as new prognostic biomarker candidates (6).

Collaborative research found a strong correlation between a high-serum heparan sulfate concentration and a poor treatment outcome of

EGFR-tyrosine kinase inhibitors (TKIs) suggesting the possibility to develop a promising noninvasive and repeatable glycobiological biomarker (7). Acquired resistance to an anti-angiogenic VEGFR2-TKI was analyzed on HUVEC clones. Expression analysis including microarray experiments revealed that an escape from VEGFR2 signaling-dependency is one of the cellular mechanisms of resistance to VEGFR2-TKI in vascular endothelial cells (8).

Gene Expression Profiling Analyses

Surgical specimens have long been used as important subjects for cancer research; however, it is still unclear how concordant the expression profiles of the surgical specimens are with those obtained from biopsy samples. Gene expression profiles were compared between 77 biopsy and 89 surgical samples. Artificially induced epithelial-mesenchymal transition (aiEMT) was found in the surgical specimens, possibly leading to various fundamental misinterpretations in previous cancer research, which relied on surgical archives to establish predictive/ prognostic markers based on biopsy samples (9). As a part of a collaboration on gene expression profiling of esophageal cancers, Reg4 (regenerating islet-derived family, member 4) protein expression was found to be highly specific for adenocarcinoma, but not squamous cell carcinoma, of the esophagus. The diagnostic utility of serum Reg4 concentration will be examined (10).

The researchers in the Division have been involved in gene expression profiling analyses of leukemic and normal hematopoietic cells to understand the molecular pathways leading to leukemia and to develop their clinical applications. This year, the roles of Fbxl10 and Bmi1 in hematopoietic stem cell self-renewal and leukemogenesis were investigated as collaborative works with the researchers in Chiba University (11, 12). Another collaboration also addressed identification and characterization of cancer stem cells in the spheres derived from a canine mammary gland adenocarcinoma model (13).

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DIVISION OF FAMILIAL CANCER RESEARCH

Toshihiko Tsukada, Yuko Nagamura, Satoko Shimazu

Introduction

The Division of Familial Cancer Research is focusing research activities on the development of new methods for diagnosis and treatment of familial cancer syndromes. The genotype-phenotype correlation in multiple endocrine neoplasia type 1 (MEN1) has been investigated. Drug resistance of pituitary tumors and pharmacological actions of rikkunshito, a traditional Japanese herbal medicine, are also being currently investigated.

MEN1

MEN1 is a familial cancer syndrome caused by heterozygous germline mutation of the *MEN1* gene, which encodes a tumor suppressor protein named menin, and is characterized by the multiple occurrences of endocrine tumors in the pituitary, parathyroid, pancreas, gastrointestinal tracts, adrenal cortex and thymus. Because the optimal therapies for MEN1-associated tumors, especially for multicentric parathyroid and pancreatic tumors, are different from those for sporadic endocrine tumors, accurate differential diagnoses between these hereditary and non-hereditary diseases is mandatory before planning treatment. A DNA test for *MEN1* germline mutations is a powerful tool for the differential diagnosis of patients with endocrinopathy suggestive of MEN1. However, it is often difficult to distinguish a disease-causing mutation from a rare benign polymorphism especially when a novel missense mutation is identified in a patient with incomplete forms of MEN1. We previously demonstrated that menin missense mutants associated with typical MEN1 are degraded rapidly by the ubiquitin-proteasome pathway when expressed in culture cells. To examine whether the intracellular stability of mutant menin is correlated with clinical phenotypes, we developed a method of evaluating menin stability, and examined missense mutants associated with typical MEN1 and those associated with incomplete phenotypes such as familial isolated hyperparathyroidism (FIHP) and apparently sporadic parathyroid tumors (ASPTs) (1). All tested mutants associated with typical MEN1 showed reduced stability. Some missense and in-frame deletion mutants associated with FIHP or ASPT were almost as stable as, or only slightly less stable than, wild type menin, while others were as unstable as those associated with typical MEN1. Some stable mutants exhibited substantial biological activities when tested with a JunD-dependent transactivation assay. These findings suggest that certain missense and in-frame mutations are fairly stable and retain intrinsic biological activity, and may be specifically associated with incomplete clinical phenotypes. This menin stability test will provide useful information for the management of patients carrying germline *MEN1* mutations especially when they have missense or in-frame variants of ambiguous clinical significance.

Resistance to Dopamine Agonists in Prolactinoma

The first line treatment of prolactinoma is dopamine (DA) agonists, bromocriptine or cabergoline, which normalize prolactin levels and reduce tumor size of DA-sensitive prolactinoma. However, some tumors (10-15% of cases) are resistant to DA agonists from the beginning of the treatment (primary resistance) and are treated surgically. A few prolactinomas initially respond to DA agonists but become resistant after prolonged treatment with DA (secondary resistance). Although the reduction of the dopamine D2 receptor (DRD2) expression in tumor cells may explain the resistance, the exact mechanism is not fully understood. We examined 13 cases of surgically resected prolactinomas, which were divided into three groups according to the responsiveness to DA agonists: the sensitive, the primary resistant and the secondary resistant tumors. DRD2 expression was investigated by measuring mRNAs of the short isoform (D2S) and the long isoform (D2L) of DRD2. DNA methylation patterns in the promoter region of the *DRD2* gene were also analyzed. The D2L expression was much lower in the secondary resistant tumors than in sensitive or primary resistant tumors. Primary resistant tumors showed lower D2L expression than sensitive tumors. The D2S / D2L receptor mRNA ratio was not correlated with tumor response to DA

agonists. The DNA methylation patterns in the *DRD2* gene promoter region were not different between sensitive and resistant tumors. These findings suggest that the silencing of the *DRD2* gene expression, though not related to promoter methylation, is a possible mechanism for DA resistance in prolactinoma.

Effects of Rikkunshito on Adrenal Chromaffin Cells

Rikkunshito is widely used to treat appetite loss associated with various disorders, and may be a useful regimen for cancer cachexia. Because β-adrenergic agonists have been shown to prevent muscle wasting in experimental cancer cachexia, we investigated the effects of rikkunshito on cAMP-dependent gene expression in PC12 cells, a catecholamine-producing adrenal chromaffin cell line. We previously established modified PC12 cells (PCVG cells) by stable transfection of the bacterial *lacZ* gene fused to the cAMP-dependent vasoactive intestinal peptide gene promoter. β-galactosidase activity is increased in PCVG cells in response to stimuli that increase intracellular cAMP. In PCVG cells, rikkunshito alone increased β-galactosidase expression and also enhanced forskolin-induced expression by two-fold at the forskolin concentration of 0.1 μM. A concomitant increase of cAMP was demonstrated in PCVG cells stimulated with rikkunshito. These findings suggest that rikkunshito increases cAMP levels in adrenal chromaffin cells and may enhance the biosynthesis of epinephrine, which is known to be stimulated by cAMP.

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DIVISION OF MULTISTEP CARCINOGENESIS

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Lung cancer is the leading cause of cancer death worldwide. To develop novel ways of lung cancer prevention, diagnosis and treatment, it is important to elucidate the molecular processes of multistep lung carcinogenesis and genetic/environmental factors involved in the development of lung cancer. For this reason, genetic alterations in lung cancer cells and genetic polymorphisms in lung cancer patients have been studied over the long term in the Division of Multistep Carcinogenesis. In 2011, the following results were obtained.

Even in small-sized (≤2 cm in greatest dimension) and/or stage I lung adenocarcinoma (ADC), a considerable proportion of the patients will show a poor prognosis. Therefore, we conducted a study to identify genetic alterations that define the prognosis of patients with early-stage lung ADC (1). Regions of copy number alterations in 65 small-sized lung ADCs and 40 ADC cell lines were determined with GeneChip Human Mapping 10-K and 250-K single-nucleotide polymorphism (SNP) arrays, respectively. Several regions on chromosomes 5p, 7p, 8q, and 14q were frequently (>10%) amplified in both small-sized ADCs and lung ADC cell lines. In particular, the MYC gene was mapped in the minimum common region at chromosome 8q24.21, and therefore was indicated to be a target of gene amplification in lung ADCs. MYC amplification correlated with a poor prognosis (P=0.031) in patients with small-sized ADCs. MYC amplification detected by SNP array analysis was well reproduced by real-time genomic PCR analysis. Therefore, to investigate the utility of MYC amplification as a prognostic marker for early-stage lung ADCs, 162 stage I lung ADCs were subjected to the analysis. MYC amplification was associated with relapse-free survival in these patients (P=0.013). Thus, it was strongly indicated that MYC amplification is a prognostic marker for patients with early-stage lung ADCs.

Lung cancer cells often show invasive phenotypes; however, causative genetic alterations for the acquisition of invasive phenotypes remain unclear. PTEN is inactivated in a subset of lung cancer; therefore, we investigated the possible involvement of PTEN inactivation in the invasiveness of lung cancer cells (2). AKT at Ser473 was phosphorylated in several lung cancer cell lines with loss of PTEN expression. Therefore, we created a tetracycline inducible expression system of wild-type PTEN (PTEN-WT) as well as catalytically (PTEN-G129R) and lipid phosphatase (PTEN-G129E) inactive PTEN mutants using the PC14, PC9 and PC3 lung ADC cell lines, in which endogenous PTEN expression was not detected and AKT at Ser473 was phosphorylated by Western blot analysis. Induction of PTEN-WT reduced phosphorylation of AKT and inhibited the transcriptional activity of NFkB, whereas PTEN mutants did not, suggesting that PTEN inactivation results in the activation of the AKT/NFkB pathway in ADC cells. Furthermore, overexpression of PTEN-WT suppressed anchorage independent growth and reduced invasiveness in PC14 cells. Neither PTEN-G129R nor PTEN-G129E had suppressive effects on anchorage independent growth and invasiveness. Therefore, it was indicated that activation of the PI3K/AKT/NFkB pathway by PTEN inactivation results in augmented invasiveness in lung ADC cells and lipid phosphatase activity of PTEN plays a key role in this process.

There is increasing evidence that altered microRNA expression is associated with tumor progression and survival in cancer patients. We tested if the expression of specific microRNAs was associated with prognosis and disease progression in early-stage lung ADC (3). Expression of miR-21, miR-17, and miR-155 was measured by quantitative RT-PCR in tissues from 317 non-small cell lung cancer (NSCLC) patients that originated from the U.S., Norway, and Japan. Elevated miR-21 (HR=2.06, 95%CI=1.13-3.75), miR-17 (HR=2.00, 95%CI=1.10-3.61), and miR-155 (HR=2.37, 95%CI=1.27-4.42) was associated with worse cancer-specific mortality in the U.S. cohort. Among three microRNAs, only miR-21 was associated with worse cancer-specific mortality in the Norwegian cohort (HR=2.78, 95%CI=1.22-6.31) and worse relapse-free survival in the Japanese cohort (HR=2.82, 95%CI=1.57-5.07). More advanced stage tumors expressed significantly higher levels of miR-21 compared with stage I tumors. In stage I patients, high levels of miR-21 were associated with worse cancer-specific mortality (HR=2.16,

95%CI=1.11-4.21) and relapse-free survival (HR=3.40, 95%CI=1.57-7.36) independent of other clinical factors. This suggests that the expression of miR-21 may contribute to lung carcinogenesis and could serve as a therapeutic target or early-stage prognostic biomarker for lung ADC.

Recent genome-wide association studies (GWASs) have identified polymorphisms in several genes associated with lung cancer risk. Nevertheless, functional polymorphisms in DNA repair and metabolic genes that had been reported as being associated with risk for lung cancer, particularly for lung squamous cell carcinoma (SQC), were not examined in those studies. Therefore, the significance of these functional polymorphisms was evaluated in a population in which polymorphisms in the GWAS genes showed associations with lung SQC risk. Polymorphisms in three DNA repair genes, TP53, MDM2, and OGG1, and two metabolic genes, CYP1A1 and GSTM1, were examined for associations with lung SQC risk in a hospital-based case-control study consisting of 377 cases and 325 controls, which had been previously subjected to association studies on GWAS genes, CHRNA3, TERT, and HLA-DQA1. Genotypes for two DNA repair genes, TP53 and OGG1, showed significant associations with SQC risk ($P<0.05$), and those for two GWAS genes, CHRNA3 and HLA-DQA1, showed significant associations with SQC risk ($P<0.05$) with odds ratios between 1.65 (95%CI=1.06-2.57 for OGG1) and 2.57 (95%CI=1.03-6.87 for CHRNA3). Marginally significant associations were also observed for the MDM2 and CYP1A1 genes. This result indicates the necessity of reevaluation for the significance of functional polymorphisms in DNA repair and metabolic genes for lung cancer risk in other populations subjected to GWASs.

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DIVISION OF VIROLOGY

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Introduction

Approximately 15% of human cancers have a viral etiology, and seven viruses have been elucidated as being associated with human cancers (Table 1). Among these recognized viruses, research in the Division of Virology is mainly focused on the molecular mechanisms of oncogenesis by the human papillomavirus (HPV). 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). E6 and E7 proteins of HR-HPVs are known to inactivate the major tumour suppressors, p53 and retinoblastoma protein (pRB), respectively. We have developed an *in vitro* multistep carcinogenesis model for both HPV-positive and –negative human oral squamous carcinomas (1), which could be a good model for analyzing the multistep carcinogenesis of other cancers (Figure 1).

HPV and Oral Cancer

Oral squamous cell carcinomas (OSCCs) are considered to arise from human oral keratinocytes. DNAs of human papillomaviruses (HPVs), predominantly types 16 and 18, etiological agents of cervical cancer, have been detected in approximately 25% of OSCCs. In addition to inactivation of the p53 and pRB pathways, other alterations such as overexpression of epidermal growth factor receptor (EGFR) are often observed in both HPV-positive and -negative OSCCs. However, causal-relationships between accumulation of these abnormalities and multi-step carcinogenesis are not fully understood. To elucidate underlying processes, we transduced either HPV16 E6/E7 or mutant CDK4 ($CDK4^{R24C}$), cyclin D1 and human telomerase reverse transcriptase (TERT) into primary human tongue keratinocytes (HTK), and obtained immortal cell populations, HTK-16E6E7 and HTK-K4DT. Additional transduction of oncogenic HRAS or EGFR together with MYC into the HTK-16E6E7 and dominant-negative p53 expressing HTK-K4DT resulted in anchorage-independent growth and subcutaneous tumor formation in nude mice. This *in vitro* model system recapitulating the development of OSCCs should facilitate further studies of mechanisms of carcinogenesis in the oral cavity (Figure 1) (1). Since E6 and E7 are ideal molecular targets for HPV-positive cancers, synthetic small interfering RNA(siRNAs) against E6 and E7 are potent drugs for these cancers. To minimize undesirable effects, including silencing of unintended genes (off-target effect) and nonspecific cytotoxicity, we have developed a new double-strand RNA-DNA chimera (dsRDC) targeting human papillomavirus 16 (HPV16) E6 and E7 oncogenes. The dsRDC modification reduced nonspecific cytotoxicity in two of three siRNAs, while their silencing activity was marginally impaired. Finally, one of the dsRDC induced E6E7-specific growth suppression of cervical cancer cells as well as E6E7-immortalized human keratinocytes (2). By using an *in vitro* multistep carcinogenesis model for cervical cancer, we found that the expression of disintegrin-metalloproteases and their endogenous regulators was dysregulated during cervical carcinogenesis. The aberrant expression of A Disintegrin And Metalloproteases (ADAMs) might contribute to the pathogenesis of cervical cancer formation and progression (3). Matrix metalloproteinase (MMP) production from stroma cells could be stimulated by emmprin expressed in adjacent carcinoma cells. Synthetic peptides carrying a part of the extra-cellular domain of emmprin inhibited emmprin-stimulated production of MMP-2 in co-cultures of fibroblasts and several different human tumor cells types (4).

NF-κB Activation and Progestin-induced FOXO1 Expression in Endometrial Cancer

We have successfully transformed primary endometrial epithelial cells by transduction of several oncogenes, and revealed the importance of the RAS-MAPK and the PI3K-AKT pathways in transformation. In this *in vitro* carcinogenesis model for endometrial cancer, we demonstrated that NF-κB activation is a novel target of oncogenic KRAS in endometrial carcinogenesis, implying the potential utility of NF-κB inhibitors for endometrial cancer chemoprevention, especially with KRAS mutation (5). Despite the therapeutic utility of progestin in invasive and preinvasive endometrial

neoplasias, the molecular mechanisms through which it exerts inhibitory effects on endometrial epithelial growth are largely unknown. We demonstrated that progestin markedly induced FOXO1 gene expression to inhibit cell growth, implicating novel molecular mechanisms of progestin to eradicate endometrial neoplasias (6).

Immortalization of Normal Human cells and Its Application for Cancer Therapy

We have immortalized various types of normal human cells (7-9). Among them, immortalized myoblasts showed normal diploid and conserved differentiation potential (7). Similarly immortalized human peritoneal mesothelial cells (MCs) were used as carrier cells of the oncolytic HSV-1 mutant viruses, HF10 and Hh101, for intraperitoneal therapy against ovarian cancer. In a mouse xenograft model of ovarian cancer, the injection of infected carrier cells led to a significant reduction of tumor volume and prolonged survival in comparison with the injection of the virus alone (8). Several immortalized human epithelial cells were also used for analyzing novel functions of trichoplein and Chk1 (10, 11).

Cell Cycle Regulation of DNA Replication in Mammalian Cells and Its Implication in Oncology

Genomic DNA has to be replicated only once during the cell cycle. During late mitosis through the G1 phase, the MCM complex, a central component of replicative helicase, is loaded onto chromatin by the ORC, CDC6 and Cdt1 proteins. SNF2H, a member of the ATP-dependent chromatin-remodeling complex, was recruited onto DNA replication origins in human cells in a Cdt1-dependent manner and positively regulated MCM loading. Thus SNF2H may promote MCM loading at DNA replication origins via interaction with Cdt1 in human cells (12).

Table 1

Tumor Virus	Malignancy
Human Papillomavirus (HPV)	Cervical Cancer, Anal Cancer, Head and Neck Cancer etc.
Epstein-Barr virus (EBV)	Burkitt Lymphoma, Nasopharyngeal Carcinoma, Gastric Cancer etc.
Hepatitis Virus B (HBV)	Hepatocellular Carcinoma
Hepatitis Virus C (HCV)	Hepatocellular Carcinoma
Human Adult T Cell Leukemia Virus-1 (HTLV-1)	Adult T Cell Leukemia (ATL)
Human Herpes Virus 8 (HHV-8)	Kaposi Sarcoma
*Merkel Cell Polyomavirus (MCPyV)	Merkel Cell Carcinoma

*isolated in 2008, and closely associated with Merkel cell carcinoma, though as yet not defined as a group 1 carcinogen by WHO

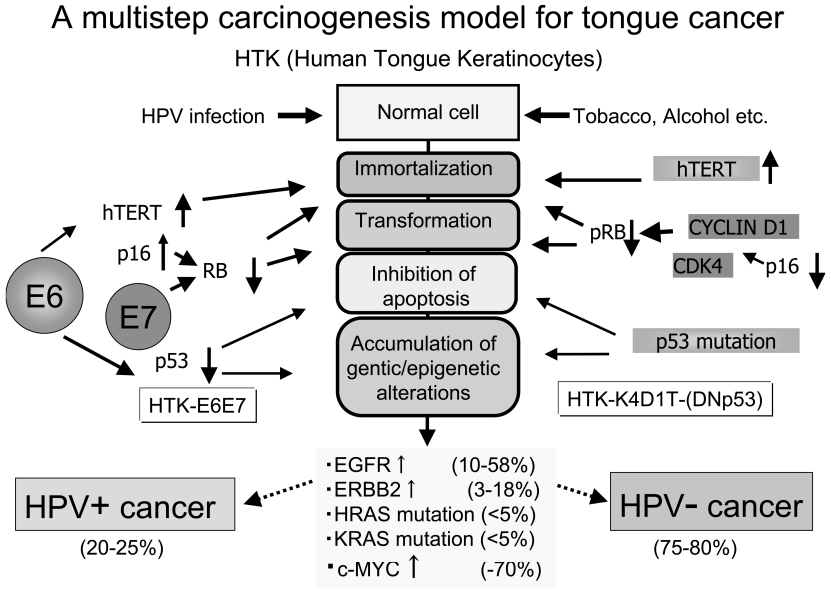

Figure 1

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DIVISION OF CANCER DEVELOPMENT SYSTEM

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Introduction

Research in the Division of Cancer Development System is focused on elucidation of the mechanisms underlying cancer development, which are initiated and promoted by the combination of environmental and genetic factors. Our goal is to dissect the multi-stage carcinogenesis in humans into its component stages, using animal models and *in vitro* systems, for the future development of novel and precise modalities in the field of prevention and early diagnosis of cancer.

In Vitro Reconstitution of Intestinal Tumorigenesis by Genetic and Environmental Factors

We recently developed a cell-based assay that recapitulates intestinal tumorigenesis by genetic reconstitution. Primary murine intestinal cells were transduced with lentivirus vectors for knockdown of tumor suppressor genes, or activation of oncogenes. Tumor formation could be observed within 2 months of the lentiviral infection by the right combinations of genetic alterations, such as inactivation of APC and PTEN. Basically, tumor formation potential observed in this system was concordant with the results from earlier studies using genetically modified mice. Moreover, the generated tumors closely resembled human colorectal adenocarcinoma in their histology. These results suggest that this approach might be indeed mimicking carcinogenesis *in vivo*. Accordingly, this model might allow us to investigate the precise mechanism in the early stage of intestinal carcinogenesis or validate the functional roles of novel cancer-related genes. We further integrated inflammation, as an environmental factor, into this system. Intestinal cells transduced with shAPC were briefly co-cultured with activated inflammatory cells, which resulted in the development of more aggressive tumors, raising the possibility that this model might be useful in dissecting the complex mechanism in inflammation-related carcinogenesis. Reports related to colon carcinogenesis can be found in the attached list of references (1-3).

PhIP-dependent Rat Colon Carcinogenesis

The F344 rat is a sensitive strain for carcinogenesis chemically induced by PhIP, a dietary colon carcinogen. The mechanisms by which PhIP exerts oncogenic effects still remain largely elusive. We previously identified a candidate modifier gene for tumor susceptibility by genetic linkage analysis. Overexpression of the gene in transgenic rats resulted in resistance to PhIP-induced colon carcinogenesis, confirming the tumor suppressive role of the gene. To gain further insight into the mechanism, we asked if miRNA could be involved in mediating the oncogenic properties of PhIP. Six heterocyclic amines (HCAs) with differential carcinogenic potentials have been administered to F344 rats, and the expression profiles of miRNA were obtained. Strikingly, HCAs were separated by hierarchical clustering analysis, and even three miRNAs were sufficient to discriminate carcinogens from non-carcinogens. The *in vitro* responses to PhIP-exposure, including DNA-damage checkpoint, oxidative stress and epigenetic changes, are currently being investigated as well. Reports related to colon carcinogenesis can be found in the attached list of references (4, 5).

Roles of Tumor-suppressor miRNAs in Colon Cancer Development

It has been shown that aberrant expression of miRNA genes, observed in almost all types of human cancers, contributes to cancer development and metastasis. Through functional and comprehensive genomic screens, we recently identified miR-22 as a candidate for a tumor-suppressor gene in human colon cancer (6). The miR-22 gene showed highly frequent hemizygous loss and decreased expression level in human colon cancers. We found that p53 directly regulated the transcription of miR-22, which in turn directly suppressed p21. Indeed, introduction of miR-22 robustly inhibited the accumulation of p21, after activation of p53 by DNA damage, and sensitized cells to p53-dependent apoptosis. The p53-dependent activation of miR-22 was achieved only when the genotoxic stress was so severe that the damaged cells were destined to undergo

apoptosis. These findings indicate that miR-22 is an intrinsic and critical molecular determinant of the p53-dependent response to various oncogenic stresses, partly through p21 repression at a post-transcriptional level (7).

Molecular Targets and Agents for Colon Cancer Prevention

Obesity, consumption of a high-fat diet and hyperlipidemia are epidemiologically associated with the risk of colon cancer. *Apc*-deficient Min mice show age-dependent intestinal polyp development and a hyperlipidemic state, along with suppression of lipoprotein lipase (LPL), which catalyzes the hydrolysis of TG. Statins, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, are clinically used for reducing serum lipid levels. The effects of a novel statin, pitavastatin, on intestinal polyp formation in Min mice were examined. Treatment with pitavastatin decreased the total number of polyps in a dose-dependent manner (8), and reduced serum adipocytokine levels and pro-inflammatory gene levels in the intestinal mucosa. Moreover, lipid oxidation observed in the serum and the small intestinal epithelial cells were reduced (9). These results indicate that statins could thus be a good candidate for colorectal chemopreventive agents.

Identification of Novel Mutagens and Carcinogens

Nanomaterials are commonly used in various fields due to their characteristic properties. Accordingly, risk assessment of their use, especially on genotoxicity, is an issue of serious concern. We examined various nanomaterials, including fullerenes and kaolins, and observed a significant induction of micronuclei, and sister chromatid exchange at a high frequency in cultured cells. Moreover, DNA damage of the lungs, from ICR mice intratracheally instilled with a single dose of these nanomaterials, was about 2-3 fold more intense than vehicle control, as revealed by a comet assay. DNA adducts in the lungs were analyzed in parallel, with stable isotope dilution LC-MS/MS, which identified 2 to 5-fold more 8-oxodeoxyguanosine and other lipid peroxide-related adducts in the nanomaterial-exposed mice. Multiple instillations of C60 or kaolin resulted in higher mutant frequencies in the lungs of gpt delta transgenic mice, involving the increase of G:C to C:G transversions for both C60 and kaolin, and the increase of G:C to A:T specifically for kaolin. Immunohistochemical analysis demonstrated many regions in the lungs that were positively stained for nitrotyrosine. These observations suggest that oxidative stress and inflammatory responses might account for the genotoxicity associated with these nanomaterials (10, 11). We characterized an ADP-ribosyltransferase from *Streptomyces coelicolor* that targets guanine mononucleic acids, including guanosine, deoxyguanosine, cyclic GMP, GTP, and dGTP. ADP-riboyslation of the nucleotide pool was indeed confirmed in HeLa cells constitutively expressing the enzyme.

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DIVISION OF METASTASIS AND INVASION SIGNALING

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Introduction

The malignant characteristics of cancers causing invasion into surrounding tissue and metastasis to distant organs are serious threats to the clinical treatment of cancer. It is suggested that numbers of receptor and non-receptor tyrosine kinases are involved in the multiple steps of cancer progression. 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 tyrosine phosphorylation of signaling molecules during cancer metastasis and invasion. One of the goals of our research is to establish models of the novel therapy for progressed cancer by regulating phosphotyrosine-dependent interactions between signaling molecules.

Molecules Modulating Cancer Invasion and Metastasis

During the analysis of phosphotyrosine-containing proteins in scirrhous gastric carcinoma cell lines, we observed unusual phosphorylation of ARAP3, a multi-modular signaling protein that is a substrate of the Src family kinases. Unlike other phosphotyrosine proteins such as p130Cas, CDCP1 or C9orf10/Ossa that are overexpressed and hyperphosphorylated in scirrhous gastric carcinomas, ARAP3 was underexpressed in cancerous human gastric tissues. Overexpression of ARAP3 in the scirrhous gastric carcinoma cell lines caused marked reduction of peritoneal dissemination without significantly affecting their proliferation. *In vitro* studies also showed that ARAP3 suppressed cell attachment to the extracellular matrix (ECM) as well as invasive activities. These effects were partially lost by mutations in the Rho-GAP domain or in the two tyrosine residues at the C-terminus that are phosphorylated by Src. Our results suggest that ARAP3 is a unique Src substrate that suppresses peritoneal dissemination of scirrhous gastric carcinoma cells (1).

Invadopodia are extracellular matrix-degrading protrusions formed by invasive cancer cells that function in cancer metastasis. We found that PI3-kinase p110α, a frequently mutated gene product in human cancers, and its downstream molecules are essential regulators of invadopodia formation. This study provides evidence that oncogenic activation of p110α promotes invadopodia formation, which contributes to cancer invasion and metastasis (2). We are currently establishing the co-culture system of scirrhous gastric carcinoma cells with fibroblasts for analyzing the cancer-stromal interactions which are characteristic to this type of invasive gastric cancers.

We have reported that CUB-domain-containing protein 1 (CDCP1) regulates anoikis resistance as well as metastatic and invasive properties of cancer cells. It was revealed that CDCP1 phosphorylated at tyrosines by Src family kinases (SFKs) mediates cell migration, invasion and ECM degradation in a tyrosine phosphorylation-dependent manner (3). Cortactin, which was detected as a CDCP1 dependent-binding partner of PKCδ, showed a significant role in migration and invasion but not in the ECM degradation of pancreatic cells. In the invasion model of breast cancer cells, CDCP1 was found to be localized near the invadopodia, which are actin-rich subcellular protrusions with associated proteases used by cancer cells to degrade extracellular matrix cells. On the other hand, human lung cancer tissues or cell lines with Ras mutations show significantly higher expression of CDCP1 than those without Ras mutations. Expression of activated Ras clearly induced CDCP1 expression, while knockdown of CDCP1 abrogated Ras-induced anoikis resistance and enhanced migration/invasion. The cancer progression model of human cervical keratinocytes also validated the involvement of CDCP1 and its phosphorylation by SFKs in the multistep carcinogenesis by Ras and Myc. We demonstrated the CDCP1 protein is required for the functional link between Ras and SFK signaling during the multistage progression of human malignant tumors, highlighting CDCP1 as a potent target for treatment in the broad spectrum of human cancers associated with activating Ras mutations (Figure 1).

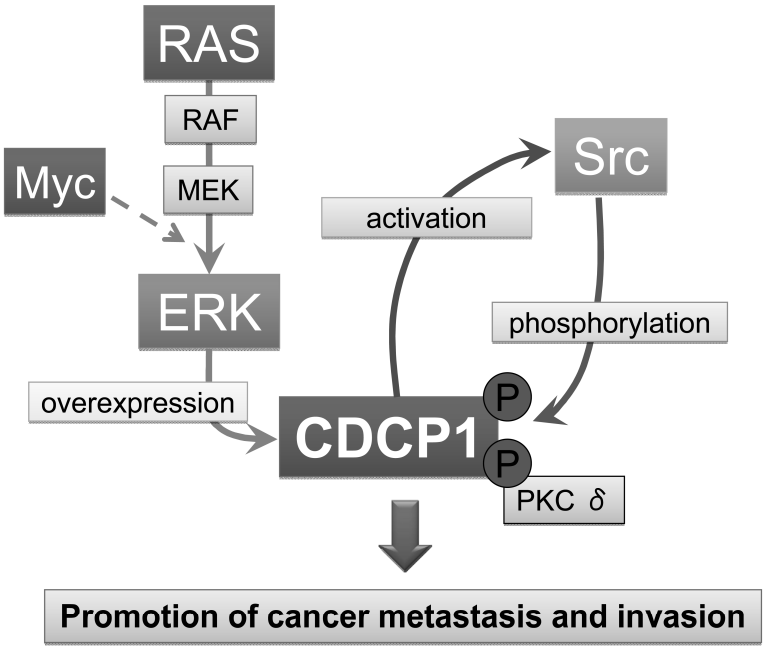

Figure 1

Oncogenic Signals in Neuroblastomas

Neuroblastomas, one of the most common pediatric solid tumors, arise from the immature sympathetic nervous system. Recently, activation of anaplastic lymphoma kinase (ALK) either by mutation or overexpression, has been indicated as a significant oncogenic factor in neuroblastoma formation. During a search of the proteins associating with oncogenic ALK in neuroblastomas, p130Cas (Cas) was detected as forming a complex with activated ALK, and ALK regulates Cas phosphorylation in neuroblastoma cell lines. We previously reported that activated ALK physically binds to the PTB domain of ShcC, while Cas appears to be associated with the SH2 domain of ShcC. Several other phosphortyrosine-containing proteins associated with ALK were identified by mass spectrometry and the oncogenic roles of these molecules in neuroblastoma are being investigated.

On the other hand, it was observed that expression of a receptor tyrosine kinase Ret which is highly expressed in some of the neuroblastoma cell lines was suppressed by knockdown of ALK or by the ALK inhibitor in the neuroblastoma cell lines. Since activation of Ret kinase by its ligands such as GDNF was shown to contribute to the anchorage independent growth of neuroblastoma cells, an indirect effect of ALK activation through Ret kinase might affect the oncogenic aspects of neuroblastomas. The combinatory effect of inhibiting both ALK and Ret kinases are being analyzed for evaluation of its clinical significance.

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DIVISION OF MOLECULAR AND CELLULAR MEDICINE

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Introduction

The main focus of the Division of Molecular and Cellular Medicine is the development of novel strategies to study tumorigenesis, cancer metastasis, and drug resistance. The specific activities in 2011 were as follows: 1) Preclinical studies on RNAi-mediated cancer therapy; 2) An exosome-carrying microRNA as a novel communication tool for cancer development; and 3) The generation of novel animal models for cancer study.

RNAi-mediated Cancer Therapy

Since small interfering RNAs (siRNAs) and microRNAs (miRNAs) are two main types of silencing small RNAs that modulate tumor-related genes and multiple oncogenic pathways, extensive investigation efforts have been directed to siRNAs and miRNAs into clinical therapeutic applications. In our previous study, we identified Ribophorin-2 (RPN2) as a novel regulator of drug resistance in breast cancer and found that RPN2 affects docetaxel resistance through the regulation of *N*-linked glycosylation of P-glycoprotein (1). Further analysis showed that RPN2 is highly expressed in cancer stem cells (CSCs) and regulates tumourigenic and metastatic activities in breast cancer by stabilizing mutant p53. Therefore, RPN2 knockdown profoundly suppressed CSC phenotypes *in vitro* and *in vivo*. Moreover, we demonstrated that therapeutic silencing of RPN2 induced highly significant tumor growth inhibition and regression in a dog with naturally occurring breast cancer. These findings revealed a previously undescribed molecular mechanism for mtp53 stabilization in breast cancer and suggested that the RPN2/mtp53 regulatory network could be a promising target for anti-CSC therapy.

Pulmonary metastases are the main cause of death in patients with osteosarcoma. We identified microRNA-143 (miR-143) as a lung metastasis-related miRNA and found that the treatment with synthetic miR-143 molecules inhibited lung metastasis of mouse model for osteosarcoma (2). Furthermore our data showed that the expression of miR-143 is inversely correlated with its predicted target MMP-13 level in osteosarcoma patients.

Our group also showed that synthetic miR-22 delivery suppresses tumor growth and metastasis by inducing cellular senescence in a mouse model of breast carcinoma (3). Our study suggested that miR-22 restored the cellular senescence program in cancer cells and has a therapeutic potency for cancer treatment. Our *in vivo* studies, tumor growth and metastasis in a mouse model of human cancer have been evaluated *in vivo* by bioluminescence-based imaging analysis (4).

Chronic hepatitis C (CH) can develop into liver cirrhosis (LC) and hepatocellular carcinoma (HCC). We detected several human miRNAs whose expression levels were correlated with the degree of progression of liver fibrosis. In both the mouse and human studies, the expression levels of miR-199 and 200 families were positively correlated to the progression of liver fibrosis (5).

An integrated genomic analysis combined with array-based comparative hybridization, miRNAs, and a gene expression microarray elucidated the mechanism of drug-resistance in a drug-resistant breast cancer cell line (6). One of the down-regulated miRNAs, miR-505, whose genome regions were deleted in a drug-resistant breast cancer cell line, is a novel tumor suppressive miRNA and inhibits cell proliferation by inducing apoptosis. In addition, Akt3, correlated inversely with miR-505, modulated drug sensitivity in a drug-resistant breast cancer cell line. These results showed that various genes and miRNAs can be orchestrated to temper the drug-resistance in cancer cells, and thus acquisition of drug-resistance is intricately controlled by genomic status, gene and miRNA expression changes.

Intercellular Transfer of microRNAs in Living Cells

Evidence is presently increasing to show that miRNAs contained in exosomes are released from mammalian cells and act as a signal transducer. It has already been demonstrated that normal

epithelial cells regulate the secretion of autocrine and paracrine factors that prevent aberrant growth of neighboring cells, leading to healthy development and normal metabolism, indicating that one reason for tumor initiation is considered to be a failure of this homeostatic cell competitive system. Taken together, these findings suggest that secretory miRNAs may have favorable aspects for antiproliferative signals mediating the interaction between cancer cells and non-cancer cells. Through the extension of this concept, it was first found that exosomal tumor-suppressive miRNAs secreted by non-cancerous cells inhibited the proliferation of cancerous cells.

Generation of Genetically Modified Rats from Embryonic Stem Cells

Rats have important advantages as an experimental system for physiological and pharmacological investigations (7). In extensive chemical carcinogenesis studies, rats have been used for a long period. Despite this history, functional genetic studies and generation of human disease models are poor in rats. At present, only a few groups have generated genetically modified rats from embryonic stem (ES) cells because stable ES cells are not available. We have recently established authentic rat ES cells developing a new culture medium composed of 20% fetal bovine serum and cell signaling inhibitors for ROCK, MEK, TGF beta and GSK3 (8). The rat ES cells expressed ES cell markers such as *Oct4*, *Nanog*, *Sox2* and *Rex1* and retained a normal karyotype. Embryoid bodies and teratomas were also produced from the rat ES cells. All six ES cell lines derived from 3 different rat strains successfully achieved germline transmission, which strongly depended on the presence of the inhibitors during the injection process. Most importantly, *Oct4*-Venus transgenic (Tg) rats were successfully generated via the selection of gene-manipulated ES cell clones through germline transmission. In the Tg rats, Venus fluorescence can be detected in cells expressing *Oct4* (9). Since somatic and cancer stem cells expressthe *Oct4* gene, we anticipate that the mechanisms of tumor initiation could be solved using the Tg rats. Our rat ES cell technology has the potential to generate extensive numbers of knockout as well as Tg rats, which will contribute to research for cancer therapy and regenerative medicine for humans (10).

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DIVISION OF CANCER BIOLOGY

Hirofumi Arakawa, Yasuyuki Nakamura, Noriaki Kitamura, Hiroki Kamino, Masaki Yoshida, Ryuya Murai, Izumi Hyo

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 tumor suppressor p53 and the genes that are directly regulated by p53 have been studied to uncover the mechanism of p53-mediated tumor suppression, based on which new cancer therapies could be developed.

Identification and Characterization of p53-target Genes

Using a combination of a microarray analysis and a chromatin immunoprecipitation assay, identification of p53-target genes in the human genome has been conducted at the Division. In 2011, *Mieap* (1) was identified and analyzed as new p53-target genes. The results of these studies enabled us to further understand the physiological functions of p53.

There are a number of p53-target genes, and the function of the p53-target varies from gene to gene. The important question is how p53 regulates a number of target genes and/or functions. Recently, modifications of p53, such as phosphorylation, acetylation and sumoylation have been suggested to play an important role in this process. To clarify the mechanisms, classification of the p53-target genes is being conducted according to their individual functions.

Mieap-induced Accumulation of Lysosome-like Organella within Mitochonria

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 (1). In this mechanism, Mieap induces the accumulation of intramitochondrial lysosome-like organelles 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 ATP synthesis activity, implying MALM plays a role in repairing unhealthy mitochondria.

Mieap-inudced Vacuole

Alternatively, another mechanism has been designated MIV, standing for Mieap-induced vacuole (2). When MALM is inhibited, Mieap induces a vacuole-like structure known as the 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) (1, 2).

Mitochondrial Quality Control and Cancer

Mitochondria play a critical role in a number of cellular functions, being involved in aging, degenerative diseases and cancer. However, the mechanisms involved in maintenance of the quality of healthy mitochondria still remain unclear. A new protein, Mieap, was discovered, which plays a critical role in mitochondrial quality control (1, 2).

Aerobic glycolysis is a common feature of human cancers, which is also known as the Warburg effect. Although the nature of cancer cells has been applied to the development of positron emission tomography (PET) for the whole body screening of human cancers, the mechanism for the phenomenon remains to be elucidated. The p53-Mieap pathway is frequently inactivated in human cancers because of p53 mutations and/or Mieap methylation. This leads to accumulation of unhealthy mitochondria and consequently the Warburg effect (Figure 2). This finding could explain the reason why cancer cells preferentially utilize aerobic glycolysis, as observed by Warburg. Therefore, the mechanisms of maintenance of healthy mitochondria are currently being investigated at this Division.

New Therapeutic Strategies for Cancer Therapy

Several p53-mutants are known to show enhanced apoptosis inducing activity, and are believed to be some kind of activated forms of p53. On the other hand, several p53-target genes have also been reported to induce marked apoptosis in cancer cells. Therefore, to improve p53 gene therapy, adenovirus-mediated gene transfer of the active forms of p53 or apoptotic p53-target genes may well become a new therapeutic strategy for the treatment of p53-resistant cancers. In addition, adenovirus-mediated gene transfer of *Mieap* has been found to strongly suppress the tumor growth, suggesting that normalization of unhealthy mitochondria could be a novel strategy to suppress cancers *in vivo*. Toward the development of new strategies for cancer therapy, the *in vitro* and *in vivo* antitumor effects of these genes are being examined at this Division.

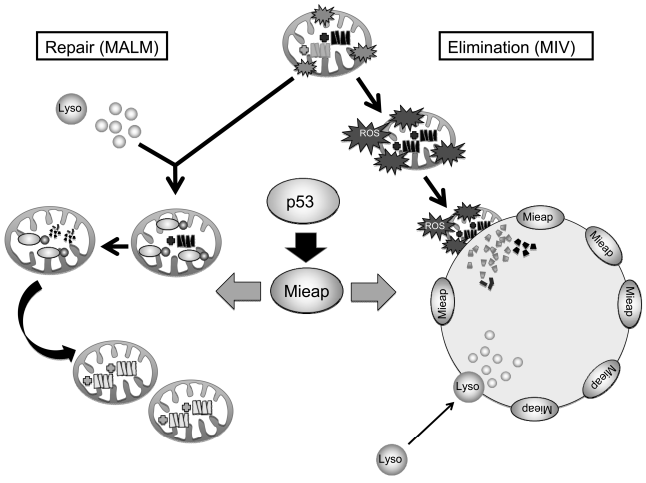

Figure 1

Inactivation of the p53-Mieap pathway in cancer

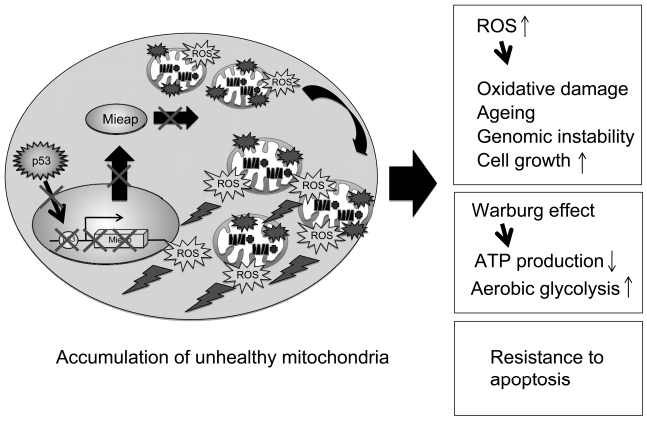

Figure 2

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DIVISION OF CANCER DIFFERENTIATION

Koji Okamoto, Hirokazu Ohata, Tatsuya Ishiguro, Yuki Aihara, Ai Sato, Hiroaki Sakai

Introduction

The main goals of our division center around the elucidation of the biological mechanism behind the metastasis of cancer cells that are refractory to conventional therapy. In general, we took two approaches to understand the mechanism of metastasis. In the first approach, we are attempting to identify crucial regulators of metastasis, especially liver metastasis from colon cancer. In order to identify such regulators, we performed a functional screening in a mouse model of liver metastasis. Once such key regulators are identified we will attempt to understand the mechanism of metastasis via elucidation of their biological roles. In the second approach, we are analyzing human cancer-initiating cells that are derived from refractory cancer of colon or ovary origin. Through analyses of these cancer-initiating cells, we hope to get biological insight into the mechanism of cancer metastasis as it has been reported that metastatic cancer cells share a variety of phenotypic resemblances to cancer stem cells.

Identification of microRNAs (miRNAs) that Inhibit Colon Cancer Metastasis

In order to recapitulate liver metastasis from colon cancer, we developed an experimental model in which cancer metastasis was generated with high efficiency in highly immunocompromised NOG mice. Colon cancer cells were injected into the spleen or tail vein of NOG mice to generate liver or lung metastasis, and generated metastatic foci were visualized with bioimaging or quantified by counting the number of metastatic cells with flow cytometry after dissociation of targeted organs. To determine the role of the regulatory factors of metastasis, lentiviruses that express such factors were introduced in HCT116/GFP, and the effects of the regulatory factors were determined by examining the effects of expression of the factor on generating metastasis.

This metastasis model mentioned above was used to functionally isolate regulatory factors involved in liver metastasis of colon cancer cells. It has been reported that a subset of miRNAs is involved in suppression of metastasis of cancers. Therefore, we looked for miRNAs that can inhibit colon cancer cell metastasis to the liver by applying a systematic screening approach (dropout screening). Through the dropout screening of a miRNA library after the introduction of HCT116 colon cancer cells, one miRNA was isolated that reproducibly inhibited the liver metastasis of colon cancer cells.

The impact of expression of this miRNA on the metastasis and prognosis of colon cancer has been investigated. A functional assay showed that one of the microRNAs identified via the functional screening, miR-493 was capable of inhibiting liver metastasis. miR-493 inhibited retention of metastasized cells in the liver parenchyma and induced cell death. IGF1R was identified as a direct target of miR-493, and its inhibition partially phenocopied the anti-metastatic effects. High levels of miR-493 in primary colon cancer were inversely related to the presence of liver metastasis, and attributed to an increase of miR-493 expression during carcinogenesis. Therefore, in a subset of colon cancer, up-regulation of miR-493 during carcinogenesis may prevent liver metastasis via the induction of cell death in metastasized cells.

Identification of shRNAs that Inhibit Colon Cancer Metastasis

We attempted to isolate genes that regulate liver metastasis of colon cancer by using a functional screening method that is conceptually similar to the dropout screening of miRNA. Screening of the shRNA library for human annotated genes revealed that 8 candidate genes were targeted by two independent shRNAs that inhibit liver metastasis. Individual evaluation of these clones is in progress.

Establishment and Characterization of *in vitro* Culture System of Cancer Stem Cells

Metastatic cells share phenotypic resemblances to cancer stem cells, and acquisition of “stemness” may confer metastatic function to cancer cells. Accumulating reports indicate that “cancer stem cells” exist in various types of cancer, and they are responsible for metastatic processes as well as the tumorigenicity and chemoresistance of cancer. In

order to examine the role of cancer stem cells in metastasis, we isolated cancer stem cells from human colon cancer, and established the condition that allows stable *in vitro* propagation of colon cancer stem cells in a spheroid form (colonosphere).

The difficulty in expanding cancer-initiating cells *in vitro* is one of major obstacles for their biochemical characterization. We found that inhibitors of some kinases greatly facilitated the establishment of spheroids from primary colon cancer. Under such conditions, the spheroid cells expressed cancer stem cell markers, showed the ability to differentiate, and induced tumors in mice. The spheroids were composed of cells that express various levels of CD44, and while $CD44^{high}$ cells exhibited increased sphere-forming ability, $CD44^{-/low}$ cells showed increased levels of differentiation markers and apoptotic cells. As expected from the predicted hierarchy, $CD44^{high}$ cells differentiated into $CD44^{-/low}$ cells. Unexpectedly, a fraction of $CD44^{-/low}$ cells generated $CD44^{high}$ cells, and the kinase inhibitor primed the transition by inducing CD44 expression. In accordance, $CD44^{-/low}$ cells resumed CD44 expression and formed tumors in mice. Therefore, the transition from $CD44^{-/low}$ to $CD44^{high}$ state may enhance tumorigenicity by maintaining a $CD44^{high}$ fraction in colon cancer.

In addition to colon cancer, the attempt to establish similar *in vitro* cultivation system of cancer-initiating cells from ovarian cancer is in progress.

DIVISION OF HEMATOLOGICAL MALIGNANCY

Issay Kitabayashi, Akihiko Yokoyama, Kimiko Shimizu, Kazutsune Yamagata, Takuo Katsumoto, Yutaka Shima

Leukemia is a heterogeneous disease with distinctive biological and clinical properties that are conferred by a variety of acquired genetic mutations. Specific chromosomal translocations and other mutations associated with acute myeloblastic leukemia (AML) often involve transcription factors and transcriptional coactivators. Such target genes include AML1, C/EBPα, RARα, MOZ, p300/CBP, and MLL, all of which are important in the regulation of hematopoiesis. The resultant fusion or mutant proteins deregulate the transcription of the affected genes and disrupt their essential role in hematopoiesis, causing differentiation block and abnormal proliferation and/or survival. Our research focuses on such transcription factors and coactivators, and describes their roles in leukemogenesis and hematopoiesis (1).

Chromosomal translocations of the mixed lineage leukemia (*MLL*) gene account for 5%–10% of acute leukemias and are generally associated with a poor prognosis. The *MLL* gene rearrangements create fusion genes that contain the 5′ portion of *MLL* and the 3′ portion of its fusion partner, whose products cause sustained expression of MLL target genes and consequent enhanced proliferation of hematopoietic progenitors. The MLL proto-oncogenic protein is a histone-lysine N-methyltransferase that is produced by proteolytic cleavage and self-association of the respective functionally distinct subunits (MLL(N) and MLL(C)) to form a holocomplex involved in epigenetic transcriptional regulation. On the basis of studies in Drosophila it has been suggested that the separated subunits might also have distinct functions. In this study, we used a genetically engineered mouse line that lacked MLL(C) to show that the MLL(N)-MLL(C) holocomplex is responsible for MLL functions in various developmental processes. The stability of MLL(N) is dependent on its intramolecular interaction with MLL(C), which is mediated through the first and fourth plant homeodomain (PHD) fingers (PHD1 and PHD4) and the phenylalanine/tyrosine-rich (FYRN) domain of MLL(N). Free MLL(N) is destroyed by a mechanism that targets the FYRN domain, whereas free MLL(C) is exported to the cytoplasm and degraded by the proteasome. PHD1 is encoded by an alternatively spliced exon that is occasionally deleted in T-cell leukemia, and its absence produces an MLL mutant protein that is deficient for holocomplex formation. Therefore, this should be a loss-of-function mutant allele, suggesting that the known tumor suppression role of MLL may also apply to the T-cell lineage. Our data demonstrate that the dissociated MLL subunits are subjected to distinct degradation pathways and thus not likely to have separate functions unless the degradation mechanisms are inhibited (2).

The histone acetyltransferases (HATs) of the MYST family include TIP60, HBO1, MOZ/MORF, and MOF and function in multisubunit protein complexes. Bromodomain-containing protein 1 (BRD1), also known as BRPF2, has been considered as a subunit of the MOZ/MORF H3 HAT complex based on its analogy with BRPF1 and BRPF3. However, its physiologic function remains obscure. Here we show that BRD1 forms a novel HAT complex with HBO1 and regulates erythropoiesis. Brd1-deficient embryos showed severe anemia because of impaired fetal liver erythropoiesis. Biochemical analyses revealed that BRD1 bridges HBO1 and its activator protein, ING4. Genome-wide mapping in erythroblasts demonstrated that BRD1 and HBO1 largely colocalize in the genome and target key developmental regulator genes. Of note, levels of global acetylation of histone H3 at lysine 14 (H3K14) were profoundly decreased in Brd1-deficient erythroblasts and depletion of Hbo1 similarly affected H3K14 acetylation. Impaired erythropoiesis in the absence of Brd1 accompanied reduced expression of key erythroid regulator genes, including Gata1, and was partially restored by forced expression of Gata1. Our findings suggest that the Hbo1-Brd1 complex is the major H3K14 HAT required for transcriptional activation of erythroid developmental regulator genes (3).

In acute promyelocytic leukemia (APL), the promyelocytic leukemia (PML) gene is frequently fused to the retinoic acid receptor α (RARα) gene, generating the PML-RARα fusion gene. While PML normally forms discrete nuclear speckles called nuclear bodies (NBs), PML-RARα disrupts NBs via an unknown mechanism. It is also unclear whether this disruption is related to leukemia pathogenesis. In the present study, PML-RARα was found to mediate NB disruption by inhibiting PML oligomerization while cAMP/PKA-dependent PML-RARα phosphorylation restored NBs and

promoted APL cell differentiation. These results suggest that NB restoration might be an appropriate therapeutic strategy for APL. Recently, cAMP/PKA pathway activators have shown efficacy in t(15;17) APL. The disruption of PML NBs, a defining cellular feature of t(15;17) APL, has been regarded as unimportant in the pathogenesis of the disease because it is not observed in other forms of APL. Therefore, this disruption has also been considered as an inappropriate target for therapy. The present study refutes this view and demonstrates that PML-RARα disrupts NBs by blocking PML oligomerization. Results further show that cAMP/PKA-dependent phosphorylation of PML-RARα restores NBs and that forskolin, a cAMP/PKA pathway activator, restores NBs and promotes ATRA-dependent APL cell differentiation. Thus, the restoration of PML NBs may be a suitable therapeutic approach for t(15;17) APL.

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DIVISION OF PHARMACOPROTEOMICS

Tadashi Kondo, Daisuke Kubota, Hiroshi Ichikawa, Noriyuki Hosoya, Kazutaka Kikuta, Yukiko Nakamura, Youko Takai, Ruriko Sakamoto, Kazuya Arai, Satomi Ikeda, Kano Sakamoto, Fusako Kito, Marimu Sakumoto, Ryousuke Yamaka, Jyunya Otake, Yutaka Sugihara, Hirotaka Yonemori, Ayako Haga, Kazuya Kimura, Chen Chen, Yuka Takaku, Reina Tamura

The Division of Pharmacoproteomics focuses on the identification of novel therapeutic targets, and biomarkers for personalized medicine. The major strategies of the Division are comprehensive protein expression studies using original technologies and clinical samples as well as clinico-pathological information. In collaboration with clinicians, pathologists and researchers inside and outside the Center, and commercial companies, the Division aims to realize the practical use of research outcomes in the clinical field.

Bone and Soft-tissue Sarcoma Study

Response to adjuvant chemotherapy is a major prognostic factor in osteosarcomas. To develop predictive modalities for the response to chemotherapy, the protein and microRNA contents in the incisional biopsy samples before treatments were compared between the responder- and non-responder-groups. A global expression study identified the proteins and microRNA corresponding to the response to the treatments. An *in vitro* function study revealed the molecular backgrounds of these biomarkers.

Prognostic proteins were investigated in synovial sarcomas. The proteomic contents of surgically resected tissues were compared with two-dimensional difference gel electrophoresis (2D-DIGE) and mass spectrometry among patients with different clinical outcomes. Prognostic proteins were identified among more than 3,000 protein species, and the association of sesernin-1 with the prognosis was confirmed in an independent sample set using our original antibody (1). A patent was applied for regarding the utility of the identified protein.

A global expression study on proteins and microRNA for lung-metastasis associated genes in osteosarcomas and a multi-institutional validation study for the prognostic value of nucleophosmin in Ewing sarcoma are on-going with the aims of discovering novel therapeutic targets and biomarkers.

Liver Cancer Study

To develop the prognostic modalities and identify the therapeutic targets in hepatocellular carcinoma (HCC), the expression of 580 unique nuclear factors were examined with an antibody-based proteomics approach. This study included 100 surgical specimens from the patients with HCC in collaboration with Zhongshan Hospital (Shanghai, China). A monoclonal antibody library identified approximately 200 nuclear factors associated with carcinogenesis and early recurrence. A subsequent tissue microarray study revealed the localization of the identified nuclear factors in tumor cells and tumor vascular structures. Among them, function assays identified the nuclear factor with a regulatory function on malignant features of HCC. The proteomic approach using 2D-DIGE also identified the proteins with predictive value for early intrahepatic recurrence in the same sample set. A patent application for the clinical utility of the identified proteins is currently pending.

Colorectal Cancer Study

To develop the biomarkers for the early diagnosis of colorectal cancer, proteomic contents were compared between normal and tumor tissues (2). A 2D-DIGE study of 5000 protein species and an antibody-based proteomics approach for 400 proteins resulted in the identification of the proteins with significant levels of overexpression in the tumor tissues. Further studies revealed that the product of the oncogene was detected in the conditioned medium of colorectal cancer cell lines, and in plasma samples of the patients. A patent application for the clinical utility of the identified proteins is currently pending.

Gastrointestinal Stromal Tumor Study

Our previous proteomic studies using 2D-DIGE identified a novel prognostic biomarker, pfetin, in gastrointestinal stromal tumors. After the prognostic

value of pfetin was validated in 210 cases in the National Cancer Center, a monoclonal antibody was generated for clinical application, and the prognostic value of pfetin was confirmed in 100 cases in Niigata University Hospital. Following this, we further validated the clinical utilities of pfetin in an additional 40 cases in Juntendo University Shizuoka Hospital (3). A multivariate study demonstrated the independent prognostic values of pfetin among the other clinico-pathological parameters in all validation studies. A patent examination for the clinical utility of pfetin is currently pending.

Novel Plasma Proteomics Approach

A novel proteomics protocol for plasma samples was developed using a solid-phase hexapeptide ligand library in combination with a multi-dimensional chromatography system, 2D-DGIE and mass spectrometry. Extensive fractionation resulted in the observation of up-to 8000 intact proteins (4). The application of this protocol to plasma biomarker studies has been undertaken.

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DIVISION OF EPIGENOMICS

Toshikazu Ushijima, Eriko Okochi-Takada, Satoshi Yamashita, Kiyoshi Asada, Tohru Niwa, Hideyuki Takeshima, Naoko Hattori

This Division has been focusing on the epigenetic mechanisms of carcinogenesis, mainly DNA methylation. Using our original genome-wide screening technique for differences in DNA methylation, methylation-sensitive-representational difference analysis, tumor suppressor genes and many aberrantly methylated CpG islands (CGIs) have been identified in various cancers, i.e., gastric cancers, breast cancers, pancreatic cancers, lung cancers, ovarian cancers, neuroblastomas, and melanomas. This led to identification of a novel tumor-suppressor gene in gastric cancers, development of a novel and powerful prognostic marker in neuroblastomas, and revelation of an "epigenetic field for cancerization".

This Division continues its activity in identifying novel epigenetic alterations in various cancers and normal tissues, and is applying its past discoveries to the development of clinically useful biomarkers. It is also interested in the development of epigenetic therapy and clarification of mechanisms of how epigenetic alterations are induced.

Identification of Novel Epigenetic Alterations

Detection of lymph node metastasis is critically important for deciding on the treatment strategy for esophageal squamous cell carcinomas, and this Division identified CGIs whose methylation levels are associated with the presence of lymph node metastasis in human esophageal cancers (1). Aberrant DNA methylation in animal models is useful to analyze modifiers of methylation induction, and such genes were isolated in rat mammary carcinomas (2). The presence of aberrant hypermethylation in predisposed epithelial cells is now known, and hypomethylation of repetitive elements was shown to be present in gastric mucosae with *Helicobacter pylori* (*H. pylori*) infection (3). State-of-the-art technologies are constantly employed for genome-wide methylation analyses, and bead array technology and high-throughput sequencing technologies are now being adopted.

Development of Biomarkers

This Division previously revealed that accumulation of aberrant methylation of multiple genes in normal-appearing gastric mucosae is associated with gastric cancer risk (epigenetic field for cancerization) (4). Levels of such accumulated methylation are expected to be useful as a gastric cancer risk marker, and a prospective study is being conducted to bring this into clinical practice. The presence of an epigenetic field for cancerization is now recognized for various other cancers. In the esophagus, in collaboration with the National Taiwan University Hospital, methylation levels in esophageal mucosae were shown to increase following exposure to carcinogens, such as alcohol, betel quid, and cigarettes, and to be higher in cancer patients ($P<0.05$) (5). The clinical usefulness of prognostic markers in neuroblastomas is being analyzed using materials collected in a prospective manner.

Development of Epigenetic Therapy

Epigenetic therapy is expected as a next-generation strategy in cancer chemotherapy. Since many genes are now known to be silenced in a single cancer, simultaneous reversal of silencing of multiple genes could be an effective treatment. This Division is working on this strategy as a novel therapeutic concept using neuroblastomas as a model. Assay systems for novel epigenetic reagents are also being developed.

Induction Mechanisms of Epigenetic Alterations

Clarification of induction mechanisms of epigenetic alterations is critically important for public health, including cancer prevention. This Division showed that chronic inflammation is critically important for induction of aberrant methylation (Figure 1). The effects of various kinds of inflammation due to different inducers, such as high concentrations of ethanol (EtOH) and saturated sodium chloride (NaCl), were examined. Methylation was induced only in gerbils infected with *H. pylori*. Histologically,

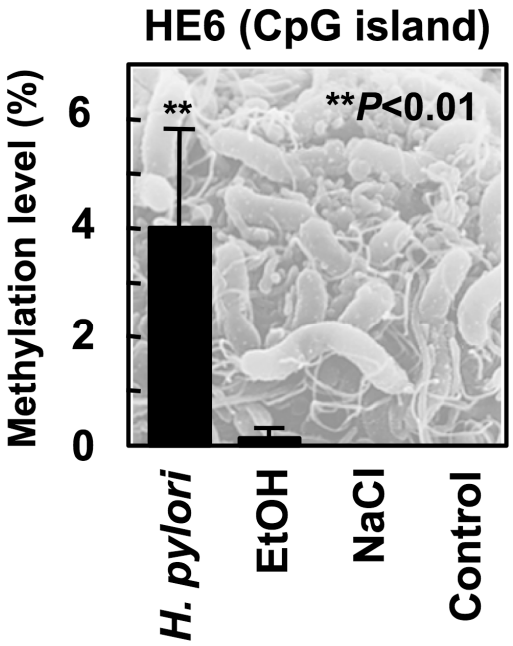

Figure 1. Specific inflammation is critical for aberrant DNA methylation induction

chronic inflammation with lymphocyte and macrophage infiltration was prominent in *H. pylori* infection, whereas neutrophil infiltration was mainly observed in the EtOH and NaCl treatment. Cell proliferation was most strongly induced by the NaCl treatment. Therefore, it was considered that specific types of inflammation are necessary for methylation induction (6).

Aberrant DNA methylation is known to be induced in specific genes, and this Division demonstrated that the absence of RNA polymerase II and the presence of H3K27me3 predispose genes to become methylated. In addition to these epigenetic factors, it was demonstrated that genome architecture, namely a remote location from SINE and from LINE, was associated with increased susceptibility (7).

Other Activities

This Division assisted in a genome-wide screen for aberrant methylation in uterine leiomyoma (8), analysis of histone modifications of the *Bdnf* gene in the brain (9), and analysis of SNPs in the MFSD2A gene in Asian lung cancer patients (10). This Division also contributed to communicating recent technologies in DNA methylation analysis in toxicology (11).

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DIVISION OF GENOME BIOLOGY

Takashi Kohno, Hideaki Ogiwara, Kouya Shiraishi, Yoko Shimada

Introduction

Biological research using genome information is changing medical treatments of cancer. In particular, interindividual variations in the human genome and somatic mutations in the cancer genome have become critical keys to improving the diagnosis and treatment of cancer. The aim of our division is to find "seeds" that improve the prevention, diagnosis and treatment of cancer, by identifying and elucidating the biological significance of somatic mutations in cancer genomes, and genetic polymorphisms of cancer patients. We are working together with NCC staff from hospitals, the Research Center for Cancer Prevention and Screening, and the Center for Cancer Control and Information Service to fight lung cancer, the most common cause of cancer-related deaths in Japan and worldwide.

Research Projects

1. Genes for cancer treatment

Genes involved in DNA repair and/or chromatin remodeling are being analyzed to improve the efficiency of existing therapeutic methods. Non-homologous end joining (NHEJ) is a major repair pathway for DNA double strand breaks (DSBs) generated by ionizing radiation and anti-cancer drugs. Therefore, inhibiting the activity of proteins involved in this pathway is a promising way of sensitizing cancer cells to radio- and chemotherapy. We established an assay for evaluating NHEJ activity against DSBs in chromosomal DNA in human cells. Using this assay, we revealed that CBP and p300, histone acetyltransferases (HATs), promote repair by facilitating accumulation of NHEJ proteins (1). The utility of CBP/p300 as a target for sensitization of tumors to radio- and chemotherapies was indicated. To translate the results into a clinical setting, radiosensitizing effects of natural compounds with an inhibitory activity against HATs involved in NHEJ are being searched for. Up to the present, curcumin (contained in the spice turmeric) and anacardic acid (contained in the shell of the cashew nut), have been identified as promising radiosensitizers (1).

NHEJ is responsible for the repair of DSBs with incompatible DNA ends, which are often generated by ionizing irradiation. Therefore, we defined essential factors involved in incompatible DNA end joining using the *in vivo* assay described above. The results indicate that DNA end resection (Artemis) and ligation (LIG4) factors are critical for the efficient joining of incompatible ends *in vivo*, further emphasizing the importance of synapsis and gap-filling factors (POLλ and POLμ) in preventing illegitimate joining (2). In addition, PALF (Polynucleotide kinase and aprataxin-like forkhead-associated protein) was identified as a novel DNA end resection factor involved in incompatible DNA end joining (3). These essential factors will also be a target for radiosensitization.

Genes that can be used as targets for therapy are also being investigated by analyzing genomic DNA and RNA from lung cancer tissues supplied from the National Cancer Center Biobank. Intragenic mutations in the EGFR gene and rearrangements of the ALK gene are critical information to select patients with lung adenocarcinoma (LADC), which responds to molecular targeting therapy using specific tyrosine kinase inhibitors. In collaboration with the Department of Pathology and Clinical Laboratories, methods to accurately detect EGFR mutations and ALK rearrangements are being investigated. We also demonstrated that N-cadherin signaling contributes to the survival mechanisms of gefitinib-resistant lung cancer cells and N-cadherin is a potential molecular target to cure gefitinib-resistant lung cancer cells (4). Novel genes mutated and/or rearranged in lung cancer are being intensively searched for by conducting whole RNA/exome sequencing using high-speed DNA sequencers.

2. Genes for cancer prevention

By analyzing genetic polymorphisms of cancer patients, we aim to improve cancer prevention through identification of high-risk individuals for cancer development. Recent genome-wide association studies (GWASs) by us and others have identified genes whose polymorphisms are associated with lung cancer risk. However, the significance of functional polymorphisms in DNA repair and metabolic genes that had been reported as being associated with risk for tobacco-related

cancers, particularly for lung squamous cell carcinoma (LSQC), remains unclear, since those polymorphisms were not examined in the GWASs. The significance of such polymorphisms was evaluated here in a cohort of LSQC patients, in which polymorphisms in the GWAS genes showed associations with risk. The association of polymorphisms in TP53 and OGG1 involved in DNA damage response/repair and that in CYP1A1 involved in bio-activation of polycyclic aromatic hydrocarbon, a major tobacco procarcinogen, was validated (5). This result indicates that multiple genes contribute to inter-individual susceptibility to LSQC. GWASs of LADC patients are being conducted to identify genes that enable identification of high risk individuals for targeted screening and/or prevention. LADC, particularly bronchioloalveolar carcinoma, is believed to develop from a benign adenomatous lesion, atypical adenomatous hyperplasia (AAH). AAH is detected as ground-glass opacity (GGO) by computed tomography (CT) examination, therefore, association studies on genetic polymorphisms of CT-based cancer screening examinees with and without GGO are also underway to establish methods to select individuals at high risk for the development of AAH/LADC.

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DIVISION OF CANCER GENOMICS

Tatsuhiro Shibata, Fumie Hosoda, Yasushi Totoki, Yasuhito Arai, Takuya Shirakihara, Hiromi Nakamura, Natsuko Hama, Hiroyuki Takahashi, Wataru Munakata, Naoko Okada, Akiko Kokubu, Tomoko Urushidate, Hiroko Shimizu, Shoko Ohashi

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 global and interconnected "biological systems" that contribute to the pathogenesis of cancer. This Division has also organized the facility and developed new informatics methodologies for the analysis of a next-generation high-performance sequencer.

Whole Genome Sequencing Analysis of Liver Cancer and the International Cancer Genome Project

Thirteen countries including Japan participated in the International Cancer Genome Consortium to generate a comprehensive, high-resolution catalog of genomic changes for major cancer types world-wide. The National Cancer Center has joined this consortium and the Division of Cancer Genomics has taken the initiative in the execution of this international project as a representative research group to analyze virus-associated liver cancer (Figure 1).

Massively parallel sequencing of short-insert genomic libraries of a primary hepatitis C virus-positive hepatocellular carcinoma and matched lymphocytes identified a characteristic mutation signature and potential driver gene candidates (1) (Figure 2). Whole genome sequencing of 10 additional hepatitis B and C virus-associated HCC cases revealed the significant influences of diverse environmental and genetic backgrounds on the somatic mutation patterns and an important role of epigenetic remodeling by genetic alterations in liver carcinogenesis.

Whole Exon Sequencing Analysis of Metastatic Breast Cancer and Other Tumors

Metastasis is the major cause of therapeutic failure and death in cancer patients. The status of metastasis to the axillary lymph nodes is an important prognostic factor in patients with breast cancer. A whole exome sequencing (WES) of three trios of primary breast cancers, their matched noncancerous tissues and lymph node metastatic tumors identified 7 nonsynonymous mutations specific to primary tumors, 4 mutations specific to metastatic tumors and 4 mutations observed in both. This suggests that heterogeneous genetic alterations may occur during the metastatic process in individual breast cancers. WES analysis of hematological cancers and other solid tumors are in progress.

Analysis of Fusion Genes in Lung Cancer

EML4-ALK is a novel transforming fusion product in lung cancer and recent clinical trials for ALK inhibitors reported promising results. The characteristic histopathological features of ALK-positive lung cancer were identified.

To explore molecular genetics and identify new molecular targets in lung cancer, combined sequencing analysis of whole-genome and transcriptome was performed. We identified a novel tyrosine kinase fusion gene which showed oncogenic activity *in vitro* and *in vivo*.

Genome-wide Search for EZH2 Targets in Triple Negative Breast Cancer (TNBC)

Polycomb group proteins, including EZH2, play a master regulatory role in maintaining cancer stem cell population, cell proliferation and metastasis. The primary activity of the EZH2 protein complex is to trimethylate histone H3 lysine 27 at target gene promoters. EZH2 is up-regulated in a broad range of solid human malignancies including TNBC, whose effective therapy remains to be determined. Genome-wide analysis by chromatin immunoprecipitation coupled with sequencing (ChIP-Seq) identified novel EZH2 targets in TNBC cells, which may include potential therapeutic targets.

New Bioinformatics Analysis Pipelines for Cancer Genomics

We developed new algorithms to classify small RNA from RNA sequencing data and applied them to uncover the epigenetic roles of piRNA (2, 3). To support analysis of the huge amount of data generated by a next-generation sequencer, we developed original quality check programs and pipeline programs to efficiently detect somatic mutation, rearrangement, fusion gene, copy number alteration and substitution pattern in cancer genome and transcriptome sequencing. We also estimated the optimum sequence depth for detecting mutations by WES.

Identification of Novel Cancer-related Genes and Their Biology for Translational Research

A resequencing analysis of primary melanoma samples identified somatic *IDH1/2* mutations, which co-exist with *BRAF* and *KIT* mutations (4). Recurrent mutations of *NRF2*, a novel oncogene, in esophageal cancers were associated with therapeutic resistance (5). MET overexpression was a prognostic factor in cholangiocarcinoma (6).

During the EMT process, TGF-beta induced isoform switching of FGF receptors, causing the cells to become sensitive to FGF-2 and combined TGF-beta and FGF-2 stimulation promoted the invasion of cancer cells. TGF-beta and FGF-2 may cooperatively regulate EMT in the cancer microenvironment (7).

Predisposition to cancer is a primary feature of Li-Fraumeni syndrome (LFS). We identified oncogene amplification including BIRC2/3 and TRIB1 along with TP53 missense mutation in LFS-associated tumor (8).

Diagnostic Pathology Research at the Center Hospital

Collaborative clinico-pathological researches have been conducted as a pathologist concurrent in the Division of Clinical Laboratory in the Center Hospital (9).

Figure 1

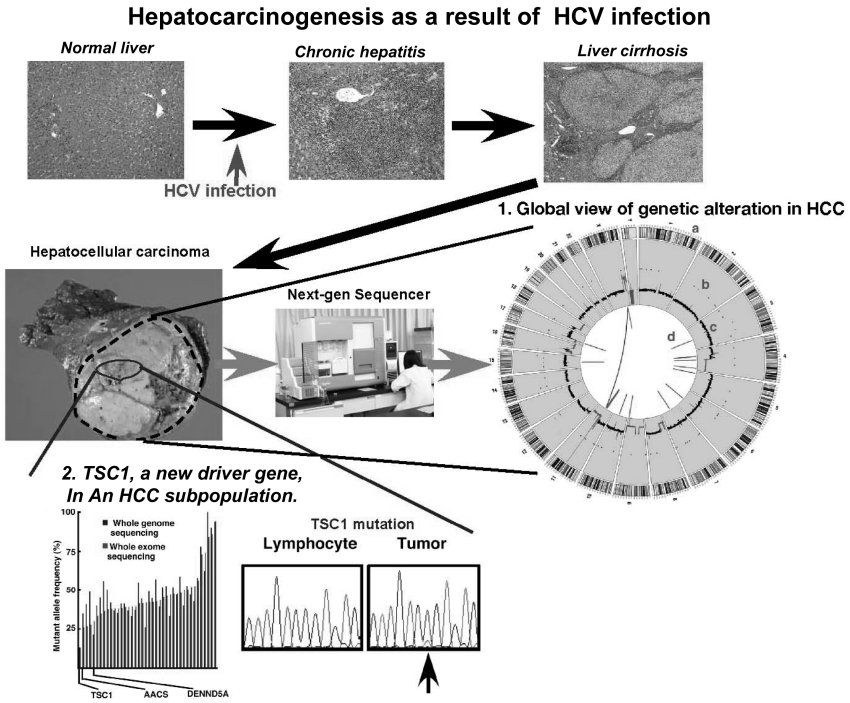

Figure 2

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DIVISION OF CANCER PATHOPHYSIOLOGY

Yasuhito Uezono, Seiji Shiraishi, Kiyoshi Terawaki, Masami Suzuki, Kanako Miyano, Junko Ezuka, Mari Sakamaki, Yuka Sudo, Katsuya Morita, Koichiro Minami, Shun Muramatsu, Tohru Yokoyama, Junichi Ogata, Shiro Tomiyasu, Masato Fukutake, Katsuya Ohbuchi, Naoyo Motoyama, Yohei Kashiwase, Naofumi Oyanagi, Maho Ashikawa, Tempei Miyaji, Miki Inoue, Atsumi Nagasawa

Introduction

Since its establishment in January 2009, the Division of Cancer Pathophysiology has focused on two major research issues regarding 1) improvement of the quality of life of patients with cancer suffering from severe or intolerable pain, and 2) studies on the prevention and development of novel treatment for cancer cachexia. In particular, basic to clinical, and clinical to basic translational interactive collaboration with the Palliative Care and Psychooncology Division in the National Cancer Center Hospital comprises our main research protocols and is now ongoing.

Improvement of Pain Treatment for Patients with Severe and Intolerable Cancer Pain

In the treatment of pain in cancer patients, opioids and related analgesics are mainly and routinely used. However, opioids can prove ineffective in not a few patients. For such patients, several adjuvant analgesics such as anti-convulsants, anti-depressants, anesthetics and anti-arrhythmias are used; they are chosen based mainly on their history of clinical experience. In order to clarify the mechanisms by which adjuvant analgesics have analgesic effects in some particular types of pain, basic research analyses with molecular and cellular biological approaches are conducted in this Division (1, 2, 3, 4).

For instance, voltage-dependent Na^+ channels (Nav) in the peripheral neurons could be involved in certain types of intolerable pain. Accordingly, one of our ongoing studies involves elucidating the mechanisms as to how Nav is modulated by several drugs or endogenous active agents (3, 4). In addition, the transient receptor potential (TRP) channel family, especially the TRP Vanilloid channels 1 (TRPV1) and TRP ankyrin 1 (TRPA1) are reported to transduce a large group of of signal such as pain. We also are trying to investigate the mechanisms of the TRP family functions (2). In addition, analysis of the functions of another analgesic, tramadol, is our current research project (1).

Development of Novel Analgesics with Less Tolerance

Although μ-opioid receptors (μOR) are targets for opioid analgesics, they have been modulated by numerous numbers of drugs and anesthetics. We currently examine whether adjuvant analgesics or anesthetics have a direct or indirect effect on μOR-mediated signaling in cell-based studies and models (5, 6).

γ-Aminobutyric acid receptor type B ($GABA_BR$) is expressed in the central and peripheral neurons, and the $GABA_BR$ agonist baclofen has been used as an anti-spasticity agent. Intrathecal baclofen (ITB) therapy is an established treatment for severe spasticity. Recently, ITB therapy has also been recognized as a powerful antinociceptive tool in patients suffering from chronic pain including cancer pain in whom opioids were ineffective. However, long-term ITB therapy results in the development of tolerance, which makes pain control difficult. Such decreased responsiveness to baclofen is due to $GABA_BR$ desensitization, recognized as occurring due to the formation of complexes of $GABA_BR$ and either G protein-coupled receptor kinase 4 (GRK4) or GRK5.

Some reports have shown that the intrathecal administration of the NMDA receptor antagonist ketamine prevents the development of tolerance against morphine. μ-Opioid receptors are associated with GRK2 or GRK3 and the GRKs are involved in desensitization of μ-opioid receptors. In case of $GABA_BR$, desensitization of $GABA_BR$ would be suppressed by the modification of the properties of GRK4 or GRK5. We showed that ketamine was proved to suppress desensitization of $GABA_BR$ signaling by inhibition of a complex formation between $GABA_BR$ and GRK4 and GRK5 (7). Another project on ketamine concerned its suggested efficacy in the treatment of pain for cancer patients with spinal bone metastasis. We established a mouse spinal bone metastasis model and examined whether ketamine was effective for the pain control in this model. Our data suggested that ketamine was in fact effective for the pain control in the mouse spinal bone metastasis model.

Collectively, ketamine could be a candidate to prevent the development of tolerance against ITB therapy (7) as well as for pain control of bone metastasis from cancers.

Study on the Prevention and Effective Treatment of Cancer Cachexia

Cancer cachexia is often observed in patients with advanced cancer, and is characterized by anorexia and weight loss associated with reduced muscle mass and adipose tissue. The prevention and effective treatment of cachexia are important in the management of patients with cancer because cachexia induces increased morbidity and mortality, and impinges on the patients' quality of life. There is also a trend towards lower response rates with the use of chemotherapy in patients with cancer cachexia. The study of cancer cachexia is indispensable to improve the quality of life in cancer patients and is being conducted in this Division. With support from a Grant-in-Aid for the Third-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare, Japan, we demonstrated that a Japanese *kampo* (traditional Oriental medicine) medication, *rikkunshito*, which is well known to improve gastrointestinal motility, potentiated orexigenic peptide ghrelin signaling attenuated cancer anorexia-cachexia and prolonged survival in an animal model of cancer cachexia (8).

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DIVISION OF CANCER STEM CELL

Kenkichi Masutomi, Seii Ohka, Mami Yasukawa, Keita Kinoshita, Yuko Jincho, Naoko Okamoto

Introduction

Research in the Division of Cancer Stem Cells is focused on deciphering the mechanisms that establish and maintain cancer stem cells and to develop a novel approach targeting cancer stem cells. In particular, the Division studies the molecular links between a) telomerase and RNA dependent RNA polymerase b) telomerase and cancer stem cells and c) telomerase and epigenetics.

Telomerase and RNA Dependent RNA Polymerase

Telomerase is a ribonucleoprotein complex that elongates telomeres. Human telomerase (hTERT) acts as an RNA dependent DNA polymerase (RdDP) and synthesizes telomere DNA from a non-coding RNA (ncRNA) template *human TERC* (*hTERC*). We found that in addition to *hTERC*, hTERT binds a second non-coding RNA, *RMRP*, the RNA component of RNase MRP (1), and TERT and *RMRP* form an RNA dependent RNA polymerase (RdRP) and produce double-stranded *RMRP* that can be processed into an endogenous small interfering RNA (siRNA) to regulate *RMRP* expression levels. To have a deeper understanding of the biological functional role of RdRP (TERT), we generated *RMRP* knockout mice. We have confirmed that the phenotypes of *RMRP* null mice are embryonic lethal (2). These observations indicate the possibilities that the hTERT-*RMRP* complex may essential for ontogeny and biological functions.

Telomerase and Cancer Stem Cells

Accumulating evidence suggests that hTERT has activities beyond telomere maintenance, and it is speculated that the constitutive expression of hTERT not only stabilizes telomere length and facilitates cell immortalization but also increases tumor susceptibility and alters stem cell cycling *in vivo* even when telomere lengths are not limiting. We showed that hTERT forms a protein complex with the SWI/SNF component BRG1 and the nucleolar GTP-binding proteins, nucleostemin (NS) or GNL3L, and the complex composed of hTERT, BRG1 and NS or GNL3L participates in the regulation of tumor initiating cells (TICs) phenotypes (Figure 1) (3). We confirmed that the cells that constitutively express NS/GNL3L exhibited increased beta-catenin signaling and elevated MYC, OCT3/4, KLF4, hTERT and TWIST (master regulator of epithelial mesenchymal transition (EMT)) expression. Moreover, cells that constitutively express elevated levels of hTERT, BRG1 and NS/GNL3L exhibit increased CD133 and CD44 expression and enhanced tumorigenicity at limiting cell numbers. These observations indicate that the TERT–BRG1–NS/GNL3L complex is essential for the maintenance of TICs. Since NS contributes to the maintenance of TICs, we hypothesized that NS may act as a predictive marker for recurrence after neoadjuvant chemotherapy. We examined the expression of CD133, CD44, NS, GNL3L, and TWIST with immunohistochemistry in a series of 54 surgically-resected specimens of esophageal squamous cell carcinomas after neoadjuvant chemotherapy. We identified that that high NS proportion, TWIST intensity, and advanced pathological N (lymph nodes) stage significantly correlated with poor relapse-free survival. Moreover, we confirmed that a high NS proportion, strong TWIST intensity, and advanced pathological N stage were significantly correlated with poor recurrence-free survival in a multivariate analysis adjusted for pathological T (tumor) and N stages. In addition, we examined the correlation between NS and TWIST using several human esophageal cancer cell lines. We confirmed that the ectopic expression of NS induced the upregulation of TWIST expression, and we also found that the endogenous NS expression level correlated with the TWIST expression. These observations implicate NS and TWIST as the predictive markers for postoperative recurrence. Our data suggest that the expression level of NS is correlated with clinical prognosis in esophageal cancer patients. It is noteworthy that this is the first clinical attempt to examine the clinical impact of the cancer stem cell factor(s) of NS in esophageal cancer.

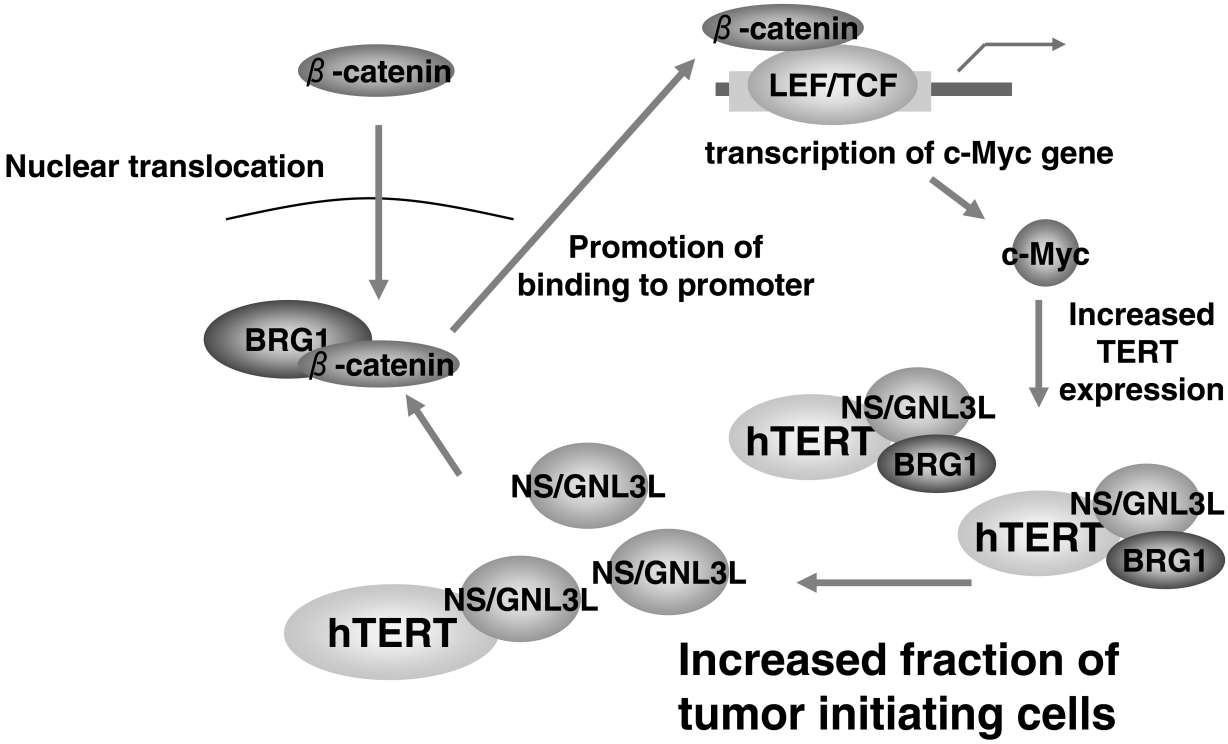

Figure 1

Telomerase and Epigenetics

Functional non-coding RNA is widely involved in the physiology of organisms through its epigenetic regulation. We focus on studying the molecular basis of maintenance of the heterochromatin formation by RNAs, especially by non-coding RNAs such as siRNAs, miRNAs and snoRNAs. It is widely known that epigenetic abnormalities contribute to tumor progression, but the detailed mechanisms are unclear. Since previous studies have shown that hTERT expression reduces the frequency of dicentric chromosomes and suppresses aneuploidy, we speculated that hTERT monitors the genome stability during centromeric heterochromatin maintenance as well as telomere maintenance. Moreover, we have identified that hTERT acts as RdRP, and produces a double-stranded, endogenous siRNA (1). These observations suggest that the mammalian homologue of RdRP (TERT) may regulate heterochromatin formation through its epigenetic regulation, and we are analyzing the link between telomerase and epigenetics.

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DIVISION OF GENE AND IMMUNE MEDICINE

Kazunori Aoki, Naoko Goto, Kouichirou Aida, Koji Suzuki, Kenta Narumi, Takeshi Udagawa, Jun Kimura, Reina Miyakawa, Yuki Yamamoto

Introduction

Research programs in the Division of Gene and Immune Medicine consist of the development of gene and cell therapies for solid cancers based on the analysis of host-immune response against cancer and the development of novel cancer-targeting vectors. In particular, the Division investigates therapeutic methods to inhibit the immune-tolerant environment developed by cancer.

Research Activities

1) Type I IFN Gene Therapy against Solid Cancers

Sarcoma at advanced stages remains a clinically challenging disease. Interferons (IFN) can target cancer cells via multiple antitumor activities including the induction of cancer cell death and enhancement of the immune response. Although the delivery of IFN protein is insufficient and/or results in an unsustainable level in the tumor site in conventional regimens with recombinant IFN proteins, the gene transfer approach allows an increased and sustained local concentration of IFN in the target sites with minimal leakage of the cytokine into the systemic blood circulation. The Division demonstrated that a type I IFN gene transfer significantly suppressed the cell growth of various sarcoma cell lines, and that IFN-β gene transfer was more effective in inducing cell death than was IFN-α in sarcoma cells. Then, to examine the antitumor effect *in vivo*, human sarcoma cells were inoculated in immune-deficient mice, and a lipofection of an IFN-β-expressing plasmid was found to suppress the growth of subcutaneous tumors significantly (Fig. 1). The treated mice showed no significant adverse events. An intratumoral IFN gene transfer could be a promising therapeutic strategy for sarcoma. Based on these basic data, the Division is planning a Phase I clinical trial on intratumoral injection of IFN-β plasmid/liposome complex in patients with sarcoma at advanced stages in collaboration with the Central Hospital.

2) Combination of Hematopoietic Stem Cell Transplantation and Immune Gene Therapy

Allogeneic hematopoietic stem cell transplantation (HSCT) has proved to be an effective therapeutic approach for several types of leukemia and, recently, has also been applied for solid cancers such as renal and breast cancers. The benefit of the graft-versus-tumor (GVT) effect is, however, often offset by the development of graft-versus-host disease (GVHD). Enhancement of the tumor-specific response of allogeneic HSCT against solid cancers is a major issue in clinical oncology. It is commonly believed that the target antigens for a GVT effect include tumor-associated antigens (TAAs) and minor histocompatibility antigens (mHAs), whereas the targets for GVHD are thought to be mHAs. Therefore, efforts to selectively enhance a donor T cell response to TAAs may provide a means to augment antitumor activity without a concomitant increase in toxicity. The Division showed that a combination of immune gene therapy (intratumoral allogeneic major histocompatibility complex gene transfer) can augment the systemic antitumor activity of allogeneic HSCT without exacerbating GVHD (1). The Division also recognizes the utility of autologous HSCT due to the lack of GVHD and independence of donor availability. It is reported that lymphopenia-induced homeostatic proliferation (HP) of T cells after autologous HSCT is driven by the recognition of self antigens, and there is an opportunity to skew the T-cell repertoire during the T-cell recovery by engaging TAAs, leading to an induction of tumor immunity. However, HP-driven antitumor responses gradually decay in association with tumor growth. Type I IFN has important roles in regulating the innate and adaptive immune system. The Division showed that an intratumoral IFN-α gene transfer resulted in marked tumor suppression when administered in the early period of syngeneic HSCT, and was evident even in distant tumors that were not transduced with the IFN-α vector. The intratumoral IFN-α gene transfer creates an environment strongly supporting the enhancement of antitumor immunity in reconstituted lymphopenic recipients.

3) Development of cancer-targeting vectors using the peptide-display adenovirus library

Attempts to redirect adenovirus vectors to alternative receptors by engineering the capsid-coding region have shown limited success because proper targeting ligand-receptor systems on the cells of interest are generally unknown. To overcome the limitation, the Division has developed a direct selection method of the targeted vector from a random peptide library displayed on the adenoviral fiber knob. However the library constructed in the primary method contains residual adenovirus vectors displaying no peptide, which may disturb the extensive exploration of cancer-targeting vectors. To establish more efficient screening methods, the Division is constructing novel adenovirus libraries, which eliminate unnecessary expansion of adenovirus vectors displaying no peptide.

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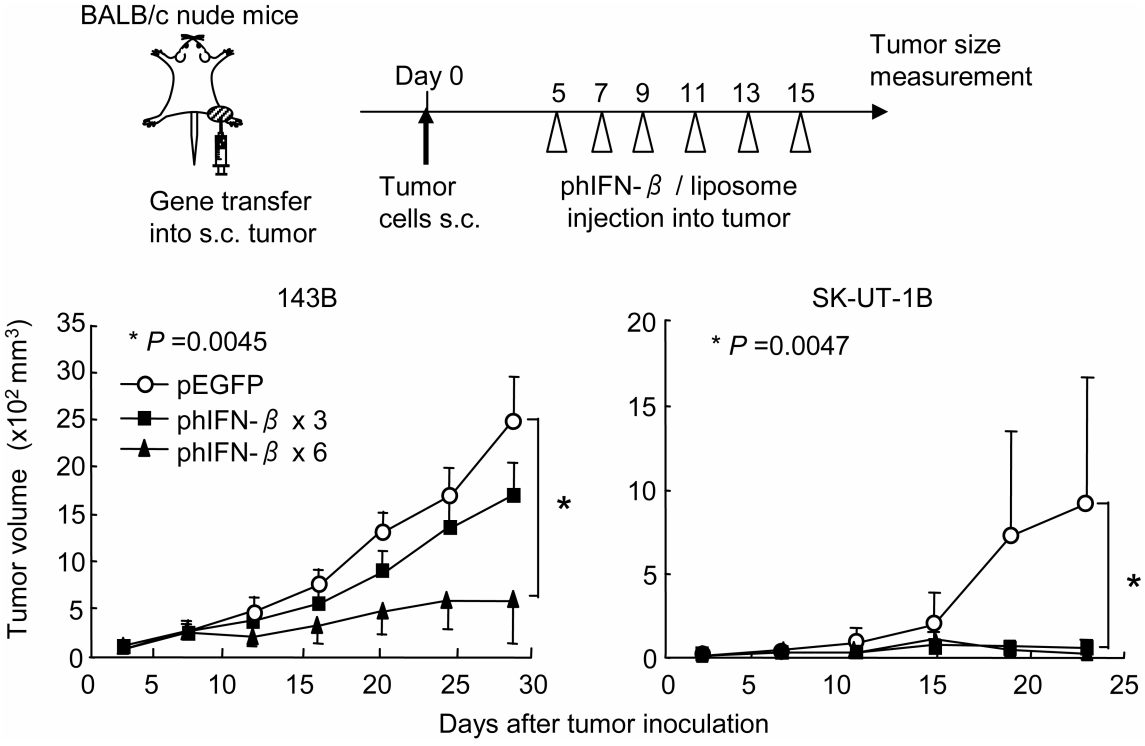

Figure 1

DIVISION OF GENOME STABILITY RESEARCH

Mitsuko Masutani, Ken-ichi Yoshioka, Hiroaki Fujimori-Sakuma, Takahisa Hirai, Anna-Margareta Rydén, Tsubasa Sekiguchi, Hiromi Harada, Kumiko Kinoshita, Junhui Wang, Soichiro Saito, Yuko Atsumi, Yuko Kudo, Tomoyuki Osawa, Hiroaki Mukai

Introduction

The multiple mechanisms for the maintenance of genomic stability contribute to cancer suppression. DNA repair pathways and cell cycle checkpoint systems are the main body of the DNA damage response (DDR) system. Functional studies of the mechanisms for the maintenance of genomic stability are conducted focusing on the poly(ADP-ribosylation) reaction, one of the dynamic post-translational modifications, and key proteins involved in DDRs (1, 2). Elucidation of the DDR is also important in developing novel strategies in chemotherapy and radiation therapy for cancer. The Division started collaborative research with clinical researchers inside and outside of the NCC to develop innovative strategies for chemotherapy and radiation sensitization.

Involvement of PARP-1 in Epigenetic Regulation and Trophoblast Differentiation

Parp-1 deficient embryonic stem cells (ESCs) showed induction and acceleration of trophoblast differentiation of ESCs. *Parp-1* deficient ESCs showed alteration in methylation profiles of the particular CpG islands, including hypomethylation in *H19/Igf2* ICR. Dnmt1 dysregulation and histone H3 acetylation was suggested to be involved in the epigenetic conversion and *H19* transcriptional activation of the ICR in *Parp-1* deficient ESCs. This work, presented by one member of the Division staff (H. F.), was awarded the Koichi Suzuki Memorial Award from the Japanese Biochemical Society.

Cellular DDR Mechanism Suppressing Mutations

Poly(ADP-ribose) polymerase (PARP)-1 is a nuclear enzyme that promotes base excision repair and DNA strand break repair. *Parp-1*$^{-/-}$ mice showed increased frequencies of deletion mutations after treatment with alkylating agents or aging. This could contribute to the augmented susceptibility to carcinogenesis. Using a reconstituted repair assay system, it was shown that processing from 5′-blocked double-strand breaks caused by dephosphorylation was enhanced in the absence of Parp-1, which possibly leads to deletion-type mutations (Fig. 1). Characterization of tumorigenic mutations in a representative tumor suppressor gene, p53 gene, was also analyzed (2).

Radiosensitization by a PARP Inhibitor to Low and High LET Radiation

There are a limited number of factors known to induce sensitization to charged particle radiation. The radiosensitization effect of PARP on low and high linear-energy-transfer (LET) radiation was studied. Treatment of cells with a PARP inhibitor enhanced the effect of γ-, LET 13 and LET 70 carbon-ion irradiation. The mechanism underlying the sensitization effect of PARP inhibitors on γ- and carbon-ion irradiation was a local delay in DNA double-strand break processing. These results suggested that PARP inhibitors might be applicable to a wide therapeutic range of LET radiation through their effects on the DNA damage response. This work, presented by a Division Research Resident (T. H.), was awarded the Radiation and Cancer Biology 1st place Poster Viewing Recognition Award at the American Society for Radiation Oncology in Miami, Florida.

Function of PARG in DNA Damage Response and Cell Death Regulation

Poly(ADP-ribose) glycohydrolase (PARG) is the main enzyme involved in poly(ADP-ribose) degradation. *Parg* and poly(ADP-ribose) polymerase-1 (*Parp-1)* deficiency on ES cell sensitivity to low and high LET radiation was assessed. *Parg*$^{-/-}$ ES cells were more sensitive to γ-irradiation compared to *Parp-1*$^{-/-}$ cells. *Parg*$^{-/-}$ cells also exhibited sensitization to carbon-ion irradiation, whereas *Parp-1*$^{-/-}$ ES cells did not. A further study suggested that *Parg* deficiency sensitizes mouse ES cells to low and high LET radiation through effects on the DNA damage

response and enhanced cell death.

PARG deficiency also causes enhanced cytotoxicity to methylmethanesulfonate (MMS) in mouse ES cells and human cancer cell lines. The mechanism of cell death elevation in these different cell types was characterized. *Parg*$^{-/-}$ ES cells mainly underwent caspase-dependent apoptosis. In *PARG* knocked-down MIAPaCa2, a human pancreatic cancer cell line, enhanced necrotic cell death with augmented HMGB-1 secretion was observed, indicating that different cell death pathways were augmented. This study implies that the functional inhibition of *PARG* may be useful for sensitization of particular cancer cells to alkylating agents.

Arf/p53 Dependent H2AX Diminution and Quiescent Cellular State

Normal cells, both *in vivo* and *in vitro*, attain a growth-arrested state after serial cell proliferation, during which cells are led to a quiescent state but are simultaneously subjected to the risk of developing immortality with genomic instability and mutations, such as in the Arf/p53 module. However, it is still unclear how the cells are regulated for the preservation and the abrogation of cellular homeostasis and how the Arf/p53 module acts in these steps. Addressing these issues, our study showed that a growth-arrested cellular status is produced with histone H2AX diminution in normal cells under the regulation of the Arf/p53 module (Fig. 2) (1). Normal mouse embryonic fibroblast cells undergo growth-arrested status with diminished H2AX only through p53 regulation. Such quiescent status is preserved with genome stability, but is abrogated under continuous growth stimulation because of the induction of DNA replication stress-associated lesions with the resulting genomic destabilization. Although the cells with genomic instability initially remain growth-arrested, immortalized cells eventually appear and become predominant because the Arf/p53 module is mutated with the consequence of genomic instability, resulting in the recovery of H2AX and growth activity. Thus, although cellular homeostasis is preserved under quiescence with genome stability, genomic destabilization induced under growth stimulation disrupts the homeostasis and triggers immortality acquisition.

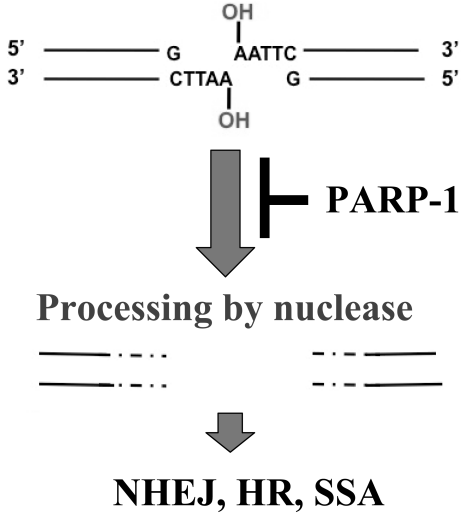

Fig. 1. PARP-1 has been suggested to suppress excessive processing from 5'-blocked termini during double-strand break repair.

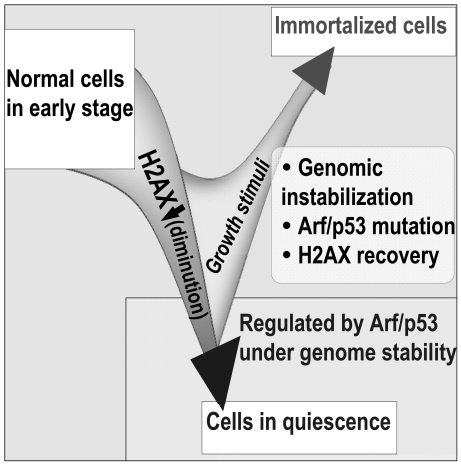

Fig. 2. Life cycle of normal cells, undergoing a growth-arrested phase and developing immortality.

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DIVISION OF CHEMOTHERAPY AND CLINICAL RESEARCH

Tesshi Yamada, Masaya Ono, Kazufumi Honda, Miki Shitashige, Mari Masuda, Nami Miura, Ayako Mimata, Masahiro Kamita, Tomoko Umaki, Ayako Ikarashi, Yuka Nakamura, Miwako Matsuda, Hiroko Ito, Haruyo Tozaki, Akihiko Miyanaga, Takafumi Watanabe

Introduction

Cancer is a genetic disease, but the biological behaviour of cancer is directly regulated by protein quantity, protein post-translational modifications, and protein-protein interactions. These alterations can serve as direct targets for diagnosis and therapy (1, 2). With the aim of discovering molecular biomarkers for early diagnosis and therapy personalization, comprehensive genomic and proteomic analyses of cancer cell lines and clinical samples have been undertaken at the Division of Chemotherapy and Clinical Research.

Combined Functional Genome Survey of Therapeutic Targets for Clear Cell Carcinoma of the Kidney

We adopted a combined functional genomic approach to catalogue potential therapeutic target molecules for clear cell (CC) renal cell carcinoma (RCC). We first selected genes up-regulated in CCRCC relative to surrounding normal kidney tissues in 10 patients using Exon Arrays that detect all potential transcripts predicted in the human genome. The selected genes were subjected to functional screening using small interfering RNA (siRNA) in six CCRCC cell lines. We finally extracted 33 genes over-expressed in CCRCC and required for maintaining cell proliferation in RCC cell lines (3).

Revision of 2-dimensional Image Converted Analysis of Liquid Chromatography and Mass Spectrometry (2DICAL)

Shotgun proteomics has recently attracted considerable attention because of its comprehensive protein identification capacity: protein samples are enzymatically digested into a large array of peptides with uniform physical characteristics, and every peptide is analyzed with low-speed liquid-chromatography (LC) and high-speed scan mass spectrometry (MS). However, LC/MS have been considered unsuitable for quantitative proteomics because of their relatively poor reproducibility. We reviewed various aspects of LC/MS and established a new quantitative proteome platform, namely 2DICAL (Ono et al., Mol Cell Proteomics, 2006). We further refined the algorithm for peak picking and alignment and made 2DICAL ready for large-scale comparative plasma proteomics studies.

We compared the relative quantity of a total of 94,803 peptide peaks between 31 colorectal cancer patients and 59 age/sex-matched healthy controls using the new version of 2DICAL and identified the ninth component of complement (C9) as a novel diagnostic biomarker for colorectal cancer (4).

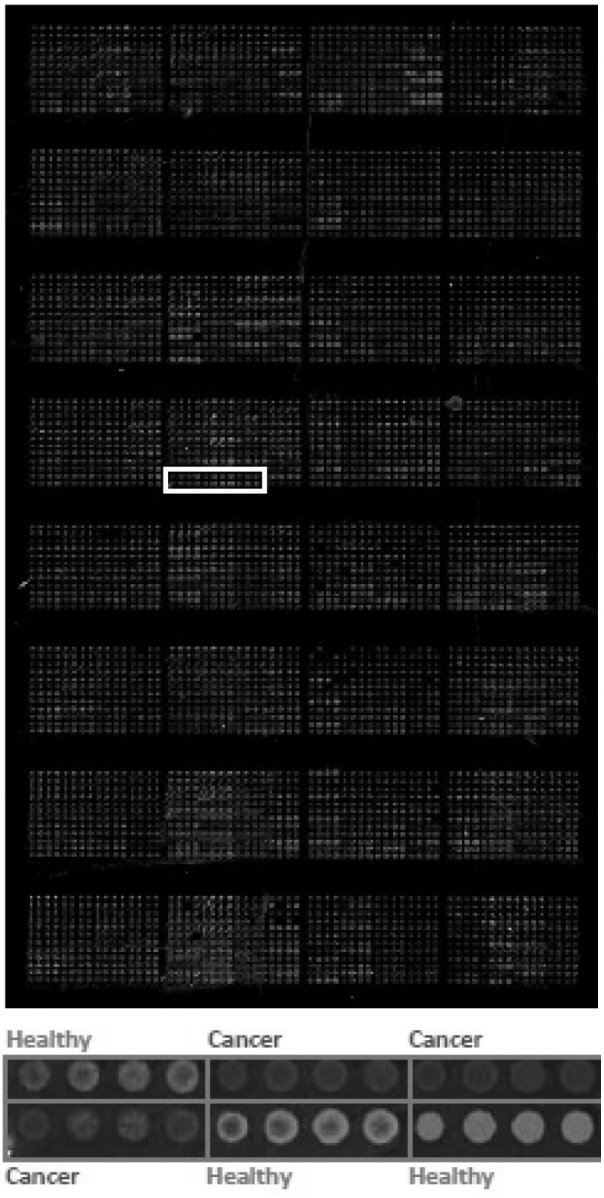
Hollow-fiber-membrane (HFM)-based Low-molecular-weight Protein Enrichment

The proteomics analysis of plasma/serum samples has been hampered by the prominence of a handful of particularly abundant proteins such as albumin and immunoglobulin. The efficient depletion of these proteins is essential for the detection of low-abundant biomarker proteins. We combined a method for the pretreatment of serum/plasma using the HFM filtration technique with 2DICAL. HFM filtration employs multistage filtration and cascaded cross-flow processes, enabling fully automated separation of proteins below a predetermined molecular weight. As the more abundant plasma proteins generally have relatively large molecular weights, they can be efficiently eliminated. Using the combination, we identified a significant decrease in the plasma level of CXC chemokine ligand 7 (CXCL7) in patients with pancreatic cancer. (5).

Biomarker Validation by Protein Microarray

Any biomarker candidates identified using proteomic approaches must be validated in a statistically sufficient number of cases and controls using a different quantitative method before they can be considered for clinical application. We developed a new method of large-scale validation

of proteomics data called high-density reverse-phase protein microarrays (RPPM) and validated the selected biomarker candidates in hundreds of subjects (6).



Dual-color scanning image of a reverse-phase protein microarray (RPPM) on which serially diluted plasma samples of cancer patients and healthy controls were randomly spotted in quadruplicate.

The standard sandwich enzyme-linked immunosorbent assay requires two antibodies, which do not interfere with each other, and more importantly requires a relative large volume of samples. Because the supply of clinical materials is often limited, it may not be possible to use hundreds of microliters of precise samples for preliminary experiments. Our high-density RPPM require a minimal sample volume in the order of the nanoliters and only one antibody. RPPM is considered to be an alternative validation method that can determine rapidly the clinical utility of candidate biomarker protein.

Participation in the International Cancer Biomarker Consortium (ICBC)

Plasma and serum samples were collected prospectively from 7 medical institutions in Japan for biomarker discovery and validation. The multi-institutional collaborative study group was organized by the Third-Term Comprehensive Control Research for Cancer and affiliated to the ICBC (http://www.fhcrc.org/science/international_biomarker/).

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CENTRAL ANIMAL / RADIOISOTOPE DIVISIONS

Toshio Imai, Mami Takahashi, Tetsuya Ishikawa, Yoshinori Ikarashi, Masafumi Yamamoto, Kotomi Otsubo, Naoaki Uchiya, Teruo Komatsu, Masashi Yasuda, Manabu Tsuchida, Masahiro Nakashima, Ayami Kawashima, Daiju Mutoh, Susumu Tezuka, Ikuo Onodera, Daisuke Akagi, Shumpei Ohnami

Introduction

The important role of the Central Animal Division is health management of the experimental animals and maintenance of the animal experimentation facility in the National Cancer Center Research Institute. Some researchers and technical staff act also in the Core Facilities for Research and Innovative Medicine, and several support services are provided based on their biological skills, such as reproductive technologies for animal cleaning/embryo-sperm preservation and histopathological techniques for animal tissues. Research activities have focused on studies of chemical carcinogenesis using laboratory animals, the process of graft-versus-host disease using *in vivo* imaging technologies and human induced hepatic stem cells for anti-cancer drug screening.

The Central Radioisotope 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. Research activities have been performed in collaboration with the Division of Genetics and the Division of Gene and Immune Medicine.

Fatty Infiltration in the Pancreas in Association with Invasive Ductal Carcinogenesis in Hamsters and Man

Obesity is associated with pancreatic cancer risk, but the mechanisms of obesity-associated carcinogenesis have not yet been clearly understood. Syrian golden hamsters, which are susceptible to chemical carcinogenesis in the pancreatic ducts, are in a hyperlipidemic state even under normal diet condition. In the BOP-treated hamster model, a high fat diet increased the levels of serum lipids and leptin, and induced severe fatty infiltration in the pancreas with abnormal adipokine production, which may enhance cell proliferation, and promoted pancreatic cancer development (1). The role of fatty infiltration in pancreatic carcinogenesis is being further investigated in human and animal models.

Pancreatic Ductal Carcinogenesis and Epithelial Mesenchymal Transision in Hamsters

The poor prognosis of pancreatic cancer has been attributed to the difficulty in detection of this cancer in its early operable stages, resulting from its aggressive invasive and distant metastatic activities. To clarify the mechanisms of increased motility and invasiveness of pancreatic carcinoma cells, in the context of epithelial to mesenchymal transition (EMT), the expression of Slug was evaluated in early and advanced stage lesions in a BOP-treated hamster model. Immunohistochemical analysis revealed increased Slug expression not only in invasive carcinomas but also in the early stages of carcinogenesis, suggesting an important role of EMT in the aggressiveness of pancreatic carcinomas. In addition, several invasion-associated proteins, such as kallikrein 7, were found to be over-expressed in the early lesions and carcinomas (2). Investigations for therapeutic target molecules relating to EMT are now ongoing.

Mechanisms of Carcinogenesis by Chemicals in Food

Acrylamide (AA) has been reported to be formed via the baking and frying processes and to show genotoxicities and carcinogenicities in rats and mice (3). Some hormone-related organs, such as the thyroid and mammary gland were revealed as the target organs in the rat model. Therefore, carcinogenic mechanisms associated with systemic hormonal dysregulation have been considered. In a recent study, the effects of 78-week AA exposure on carcinogenic target organs were evaluated in hamsters. Benign and malignant tumor incidences were increased in the forestomach but not in hormone-related organs. Further studies are needed to clarify the cause of species difference in the target organs.

In vivo Fluorescence Imaging of Donor Cells after Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Visualizing the *in vivo* dynamics of donor cells after allogeneic HSCT could be useful for an understanding of the process of graft-versus-host disease (GVHD). *In vivo* fluorescence imaging using green fluorescent protein (GFP)-transgenic mice allowed visualization of GFP donor cells at the single cell level in the tissues after transplantation. Furthermore, *in vivo* cellular fluorescence imaging is a very useful tool for monitoring individual donor cells and for exploring immunomodulatory reagents for allogeneic HSCT as well as understanding the mechanism of GVHD.

Human Induced Hepatic Stem Cells for Anti-cancer Drug Screening

Gene transfer of OCT3/4, SOX2, and KLF4 could induce human hepatic stem (iHS) cells from the skin or gastric tissues. Expandable iHS cells would have an advantage in practical use. They are similar to human embryonic stem (ES) cells and induced pluripotent stem (iPS) cells in morphology and cell surface antigens. Human iHS cells markedly expressed many hepatic genes; in addition, these cells expressed ES cell-specific genes at an equivalent level. Both hepatic and stem cell marker expressions have been confirmed by immunocytochemistry. Human hepatocytes derived from such stem cells would be useful for anti-cancer drug screening.

Possible Role of Genes Related to Folate Metabolism and Global DNA Methylation in Pancreatic Carcinogenesis

Global DNA methylation is known to be involved in the process of carcinogenesis. We have previously shown that a common missense SNP of methionine synthasereductase (MTRR) was a novel pancreatic cancer susceptibility factor. MTRR is an enzyme involved in folate metabolism, and serves as a molecular chaperone for MTR. We thereafter identified a thymidilate synthase (TYMS), a folate dependent enzyme, using a gene-gene interactions analysis based on a data mining method (multifactor-dimensionality reduction) for SNPs in the same study population. Knockdown of MTRR or TYMS expression by siRNAs reduced the global DNA methylation level measured by a methyl-CpG content assay in MIAPaCa-2 cells, in which both genes are highly expressed, as compared to the negative control. It is plausible that the polymorphisms and expression of the genes related to the folate metabolism are involved in pancreatic carcinogenesis through modulation of the methylation status.

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DIVISION OF REFRACTORY CANCER RESEARCH

Hitoshi Nakagama, Masato Enari, Rieko Ohki, Yuko Hibiya, Yukie Aita, Yosuke Ohsawa, Chihiro Otsubo, Ryo Otomo, Makoto Miyazaki, Yoshinori Asano, Issei Ezawa, Kozue Saito, Mayuko Matsumoto

Introduction

Our main focus is to clarify the molecular mechanisms of tumor progression in refractory cancers including lung cancers, pancreatic cancers and brain tumors, and to develop various novel therapeutic strategies for cancer prevention. In particular, the Division studies how cancer cells acquire invasiveness, metastatic activity and drug resistance, which are characteristics of refractory cancers. For this purpose, the functional analyses of a tumor suppressor gene p53, which plays a central role in regulating tumor progression, have been studied using cellular and molecular biological techniques. The specific activities in 2011 were as follows: 1) p53 inactivation and cell-surface proteins during tumor progression in lung cancer; 2) The inhibitory mechanism of p53 function by anaplastic lymphoma kinase (ALK); 3) Involvement of cancer susceptibility polymorphism of p53 at codon 72 in phosphorylation and degradation of the p53 protein.

p53 Inactivation and Cell-surface Proteins During Tumor Progression in Lung Cancer

In lung cancer progression, p53 mutations are often observed more in invasive tumors than in non-invasive tumors, suggesting that p53 is involved in tumor invasion and metastasis. For the understanding of the nature of the function of p53 as a tumor suppressor, it is crucial to elucidate the detailed mechanisms of the alteration in epithelial cells, the main origin of solid tumors, following p53 inactivation. Using immortalized small airway epithelial cells (SAEC) from human lung, many genes altered by p53 inactivation were identified. Among them, two up-regulated genes, *epithelial membrane protein 2* (*emp2*) and *tetraspanin 2* (*tspan2*), encoding a cell-surface protein, were selected because such proteins have emerged as key factors in invasion and cell motility, and may be utilized as targets for cancer therapy such as antibody therapeutics and nucleic acid drugs. Various functional analyses reveal that these cell-surface proteins are involved in cell motility and invasion elicited by p53 inactivation and highly expressed in lung cancer cells with the p53 mutation. Down-regulation of these cell-surface proteins by RNAi suppresses metastasis to the lung organs in immuno-deficient mice, causing prolonged survival. Furthermore, these cell-surface proteins bind to CD44, which is known to be a cancer-initiating cell marker, and regulate the production of reactive oxygen species (ROS) through the modulation of CD44 function. These data suggest that cell-surface proteins induced by p53 inactivation enhance cell motility and invasiveness through the sustained anti-oxidant system to scavenge intracellular ROS (Figure 1).

The Inhibitory Mechanism of p53 Function by Anaplastic Lymphoma Kinase (ALK)

In anaplastic large cell lymphoma, p53 mutations are rarely detected, suggesting that the p53 pathway is inactivated by negative regulators. Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase involved in tumorigenesis and the translocations of the ALK gene locus to various gene loci have recently been identified in many cancers including lung and renal carcinomas. Although ALK-fusion proteins are important for oncogenesis, the relationship between ALK and p53 is poorly understood. Here, we found that oncogenic ALK-fusion proteins inhibit p53 transactivation and that the inhibition of the p53 pathway by ALK is required for its kinase activity. Moreover, three tyrosine residues on p53 are phosphorylated by ALK to inactivate p53 function (Figure 2). This is the first finding of tyrosine phosphorylation on p53 in the world.

Involvement of Cancer Susceptibility Polymorphism of p53 at Codon 72 in Phosphorylation and Degradation of p53 Protein

The common polymorphism of p53 at codon 72, either encoding proline or arginine, has drawn attention for the last 2 decades as a genetic factor associated with clinical outcome or cancer risk. We now show that these two polymorphic variants differ in protein structure, especially within the

N-terminal region and, as a consequence, differ in post-translational modification at the N terminus. The arginine form (p53-72R) shows significantly enhanced phosphorylation at Ser-6 and Ser-20 compared with the proline form (p53-72P). We also show diminished Mdm2-mediated degradation of p53-72R compared with p53-72P, which is at least partly brought about by higher levels of phosphorylation at Ser-20 in p53-72R. Furthermore, enhanced p21 expression in p53-72R-expressing cells, which is dependent on phosphorylation at Ser-6, was demonstrated. Differential p21 expression between the variants was also observed upon activation of TGF-β signaling (1). Collectively, we demonstrate a novel molecular difference and simultaneously suggest a difference in the tumor-suppressing function of the variants.

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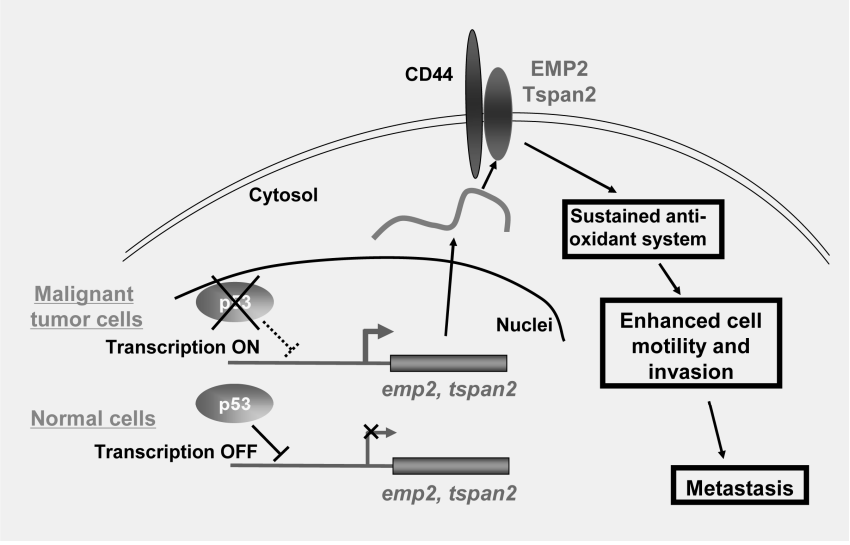

Figure 1. A model of malignant transformation by p53 inactivation

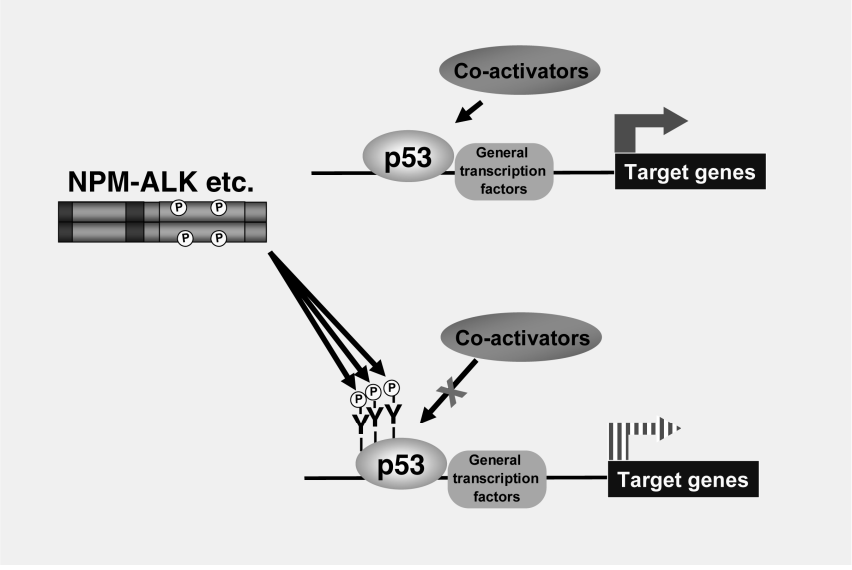

Figure 2. A model of the inhibitory mechanism of p53-mediated transcription by ALK-fusion proteins

DIVISION OF CANCER PREVENTION RESEARCH

Hitoshi Nakagama, Michihiro Mutoh, Gen Fujii, Masafumi Yamamoto

Introduction

Obesity and abnormal lipid metabolism are associated with development of many cancers, including colon and pancreas cancer. Dyslipidemia, alterations of adipocytokine balance and pro-inflammatory status were suggested to be involved in the development of colon and pancreatic cancer. In animal studies, improvement of dyslipidemia and an abnormal adipocytokine balance suppressed both colon and pancreas carcinogenesis. However, underlying suppressive mechanisms are not known in detail, such as lipid metabolism changes in the cancer cells and cross-talk changes between the epithelial cells, adipocytes and macrophages. Thus, we are investigating the mechanisms of obesity- and dyslipidemia-related carcinogenesis in the colon and pancreas to develop effective approaches for human cancer prevention.

Molecular Targets for Cancer Prevention and the Search for a Chemopreventive Agent against Colon Cancer

Obesity is a risk factor for human colorectal cancer development. A colorectal carcinogenesis study using obese KK-A^y mice revealed that the KK-A^y mice are highly susceptible to azoxymethane (AOM)-induced colorectal aberrant crypt foci (ACF) and tumor development. KK-A^y mice showed high serum Pai-1, leptin, IL-6 levels and low adiponectin levels (1). Visceral fat accumulation and low plasma adiponectin levels are reported to be associated with development of human colorectal tumors. Thus, we introduced an adiponectin-knockout mutation into *Min* mice which resulted in an increased total number of intestinal polyps compared with those of adiponectin-wild *Min* mice (2). Moreover, the incidences of AOM-induced tumors in C57BL/6J mice with each genotype, adiponectin (+/-) and (-/-), increased the incidences of colon tumors. Among serum adipocytokines, the levels of serum Pai-1 increased with adiponectin-deficiency. AOM-induced colorectal ACF in adiponectin-deficient mice decreased with administration of a Pai-1 blocker suggesting that adiponectin and its receptors might be good targets for colon cancer chemopreventive agents (3).

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DIVISION OF INTEGRATIVE OMICS AND BIOINFORMATICS

Hitoshi Nakagama, Tsutomu Ohta, Masaru Katoh, Mamiko Miyamoto, Kohtaro Oda, Yuuki Yamamoto, Teruaki Tsuji, Saho Kawamoto

Our Division, consisting of Ohta's and Katoh's Units, contributes to the development of innovative cancer diagnosis and treatment based on an integrative omics approach.

Ohta's Unit

Roles of Nrf2 in Lung Cancer

Oxidative and electrophilic stresses are sensed by Keap1, which activates Nrf2 to achieve cytoprotection by regulating the expression of drug-metabolizing and anti-oxidative stress enzymes/proteins. Since oxidative and electrophilic stresses cause many diseases including cancer, an abnormality in the Nrf2-Keap1 system may provide advantages for the growth of cancer cells. Many synonymous somatic *KEAP1* gene mutations and lower expression of *KEAP1* were identified in lung cancer. In cancer cells, enfeebled Keap1 activity due to the mutations or low-level expression led to nuclear localization and constitutive activation of Nrf2, which resulted in constitutive expression of cytoprotective genes encoding multi-drug resistance pumps, phase II detoxifying enzymes and anti-oxidative stress enzymes/proteins. Up-regulation of these target genes in lung cancer cells led to resistance to anti-cancer drugs. Nrf2 activation also provided growth stimulation in lung cancer-derived *KEAP1*-lower expression and -mutant cell lines and in *Keap1*-null mouse embryonic fibroblasts under homeostatic conditions. These results suggest that inhibition of *NRF2* may provide a new direction for therapeutic approaches in lung cancers with activation of Nrf2. The search system for Nrf2 inhibitors was developed.

Roles of SYT-SSX in Synovial Sarcoma

Chromosomal translocations are frequently associated with soft tissue sarcomas. Fusion proteins generated by such translocations often play critical roles in tumorigenesis. Therefore, it is important to understand the function of the fusion protein to develop therapeutic interventions. The t(X;18)(p11.2;q11.2) translocation found in synovial sarcomas results in a fusion between the SYT gene on chromosome 18 and an SSX gene on the X chromosome. Although SYT-SSX fusion proteins appear to trigger synovial sarcoma development, little is known about the downstream targets of SYT-SSX. The SYT-SSX fusion protein produces a dominant-negative function for the SYT, which is a transcriptional co-activator. To search for the downstream targets of SYT-SSX, the gene expression profiles in SYT-SSX-knockdown SYO-1 cells with a microarray were analyzed. The expression levels of about three hundred genes were increased in the SYT-SSX2-knockdown SYO-1 cells.

Roles of hTERT in Cancer

Telomerase, a ribonucleoprotein enzyme that maintains telomere length, is crucial for cellular immortalization and cancer progression. Telomerase activity is attributed primarily to the expression of telomerase reverse transcriptase (TERT). The gene responsible for the regulation of hTERT transcription was identified with a microarray (1).

Katoh's Unit

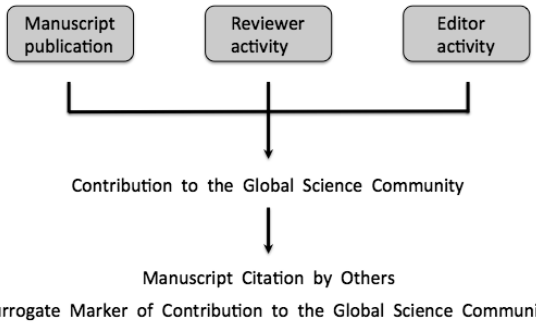
Stem Cell-signaling Network Project

Canonical WNT signaling activation leads to transcriptional up-regulation of the FGF, Notch and non-canonical WNT ligands, the WNT and TGFβ antagonists, and MYC (2). Hedgehog up-regulates the Notch ligand, WNT antagonist, BMP antagonists, and MYCN. TGFβ up-regulates the non-canonical WNT ligand, CDK inhibitors, and NANOG, while BMP up-regulates the Hedgehog ligand. Based on these mutual regulations, WNT, FGF, Notch, Hedgehog, and TGFβ/BMP signaling cascades constitute the stem-cell signaling network, which plays a key role in the maintenance or homeostasis of pluripotent stem cells and cancer stem cells. Human embryonic stem cells (ESCs) are supported by FGF and TGFβ/Nodal/Activin signals, whereas mouse ESCs by LIF and canonical

WNT signals. The combination of a TGFβ inhibitor and a canonical WNT activator alter the character of human induced pluripotent stem cells (iPSCs) from human ESC-like to mouse ESC-like. Because FGF, Hedgehog, TGFβ, and non-canonical WNT signals synergistically induce EMT regulators, such as Snail (SNAI1), Slug (SNAI2), TWIST, and ZEB2 (SIP1), tumor-stromal interaction at the invasion front aids cancer stem cells to acquire a more malignant phenotype (2). Cancer stem cells occur as mimetics of normal tissue stem cells based on germ-line variation, epigenetic change, and somatic mutation of stem-cell signaling components, and then acquire a more malignant phenotype based on accumulation of additional epigenetic and genetic alterations, and tumor-stromal interaction at the invasion front (2).

Contribution to the Global Science Community

Katoh is contributing to the global science community based on manuscript publication, reviewer activity, and editor activity. Katoh carried out peer review of grant proposals or journal manuscripts written in English 73 times/year. Katoh is an editorial board member of several scientific journals, such as PLoS ONE, the Asia-Pacific Journal of Clinical Oncology, and the International Journal of Oncology. PLoS ONE is an open access journal contributing to "Creative Commons." Katoh made an editorial decision on 100 manuscripts submitted to PLoS ONE in 2011.



Manuscript citation count is a surrogate marker of contribution to the global science community. Katoh's citation count by others was 495 in 2011 (Web of Science Database, Thomson Reuters).

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Research Center for Cancer Prevention and Screening

Preface

The Japanese Government initiated the Third-Term Comprehensive 10-Year Strategy for Cancer Control in 2004, aimed at a dramatic decrease in the incidence and mortality rates of cancer in Japan. In order to achieve these aims, development of efficacious methods for cancer screening and cancer prevention and dissemination of information about cancer at the national level are particularly important. Consequently, the Research Center for Cancer Prevention and Screening (RCCPS) was established in the campus of the National Cancer Center, Tokyo, in February 2004. Research on cancer prevention and screening is directly in line with the aim of the Third-Term Comprehensive Cancer Control Project. Initially, this center was composed of four divisions, the cancer screening division, cancer screening technology division, epidemiology and prevention division, and statistics and cancer control division. After the establishment of the Center for Cancer Control and Information Service in October 2006, the last of the above mentioned divisions was transferred from the RCCPS to this new center.

In April 2008, a change in the organization was made to clarify the function of each division in the RCCPS. As a result, in two out of three divisions, names were changed: the cancer screening division became the Screening and Development division, and the cancer screening technology division became the Screening Assessment and Management Division. All clinicians moved to the former division.

The Screening and Development Division is responsible for multiphasic cancer screening using a variety of imaging modalities, such as helical-CT, positron emission tomography (PET) and total colonoscopy, to identify cancer patients among the participants in the study at the RCCPS. The performance characteristics of the screening modalities are measured in collaboration with other Divisions. In addition, clinical evaluation aimed at the application to cancer screening of not only new imaging modalities such as CT-colonography, MRI (3.0 Tesla), and mammography with a tomosynthesis system, but also of PET-pharmaceuticals (except FDG), is under way in collaboration with several divisions of the National Cancer Center Hospital. Among the 9,485 subjects who underwent the general courses for first time, 495 some type of cancers have been detected (5.2%). The Center is planning to provide general screening courses, including vision examinations, fundus examination, tonometry, ECG, and optimal brain checkups in addition to cancer screening.

The Screening Assessment and Management Division is responsible for data collection, integrated management, analysis and dissemination of information on cancer screening at the national level. Studies to evaluate the efficacy of cancer screening programs and development and updating of screening guidelines are undertaken at this division. Guidelines for colorectal, stomach and lung cancer screening have already been published. In addition, construction of a quality assurance system is under way. Studies on developing new technologies for early detection of cancer are performed, as well as measurements of the sensitivities and specificities of such modalities. These studies are intensively promoted to establish screening systems that would allow a reduction in the mortality and incidence rates of cancer in the country.

The Epidemiology and Prevention Division plans and conducts independent and collaborative studies on cancer etiology and prevention, with special focus on dietary factors, gene-environmental interactions and effective measures for cancer prevention. In this respect, several epidemiological projects are currently in progress, including ecological, case-control, cohort and intervention studies, while the methodological backgrounds of dietary assessment (nutritional epidemiology) and molecular biomarkers (molecular epidemiology) are intensively investigated.

I would like to express my sincere appreciation for the support that we have received from the Ministry of Health, Labour and Welfare, other governmental organizations, private organizations, individuals, and also the Foundation for the Promotion of Cancer Research. Moreover, I am grateful for the diligent efforts of my colleagues who have devoted their time and talent to developing the RCCPS.

Noriyuki Moriyama, M.D.
Director, Research Center for Cancer Prevention and Screening

Organization

Chief Director:
Takamasa Kayama

Director:
Noriyuki Moriyama

- Screening Technology and Development Division
  Chief: Yukio Muramatsu
- Screening Assessment and Management Division
  Chief: Hiroshi Saito
- Epidemiology and Prevention Division
  Chief: Shoichiro Tsugane

Activities of the Divisions

SCREENING TECHNOLOGY AND DEVELOPMENT DIVISION

Yukio Muramatsu, Ryutaro Kakinuma, Takashi Terauchi, Nachiko Uchiyama, Yasuo Kakugawa, Minoru Machida, Seiko Kuroki, Minori Matsumoto, Chihiro Tsunoda, Gen Iinuma* Yosuke Otake*, Takahiro Kasamatsu*, Tomoyasu Kato*, Mitsuya Ishikawa*, Syunichi Ikeda*, Takashi Onda*, Shiho Gomi*, Masahiro Suzuki*, Hiromitsu Daisaki*, Takeshi Murano*, Chieko Nagashima*, Naoki Shimada*, Eiko Taguchi*, Hiromi Kimura*, Midori Hashimoto*, Akiko Sakurai*, Emi Masuda*, Daisuke Kano, Yoshie Nagumo*, Yoshi Kosai, Miyuki Mandai, Akiko Kutsuzawa, Michiko Kawakami, Yukiko Okamura, Mari Kanega, Mizuho Nomoto, Miho Ishikawa, Noriko Sasaki, Teiko Oki, Yoshie Iga (*NCCH)

Introduction

In April 2008, a change in the RCCPS organization was made to clarify the function of each of its divisions. As a result, what was originally the Cancer Screening Division became the Screening and Development Division. Cancer screening is performed by medical staff from the new division. There are 7 radiologists, 3 gastroenterologists, 1 pharmacist, 7 radiologic technologists, 2 ultrasonographic technologists, 2 medical laboratory technologists, and 6 nurses. A gynecologist at the NCCH supports gynecological examinations. The division is in charge of multiphasic cancer screening using several imaging modalities to develop new cancer screening systems and to evaluate new screening tests. Our division now has one multi-detector computed tomography (MD-CT) system, two magnetic resonance imaging (MRI) systems (1.5T and 3.0T), two positron emission tomography/computed tomography (PET/CT) systems, one cyclotron system, one digital radiography (DR) system with a newly developed flat panel detector, two mammography (MMG) systems, three ultrasonography (US) systems, and three endoscopy systems. All medical images are digitalized and all imaging diagnosis can be made from CRT monitors.

Routine Activities

1. Course of cancer screening

Basic plan for males consists of screening for cancer of the lung, esophagus, stomach, colon, 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, for both men and women who undergo a complete set of screening, whole body scanning using PET is provided as an option. Other than multi-phasic programs, a screening program is prepared for the lung and female genital cancer, 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 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. Applicants with a cancer diagnosis and/or history of cancer treatment, such as surgery or endoscopic mucosal resection or chemotherapy within the previous one year, are excluded.

3. Cancer screening methods

CT for lung cancer, abdominal US for cancer of the liver, gall bladder, pancreas, and kidney, MRI for cancer of the uterus and ovary, gynecological examinations with Pap-smear, 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.

4. Results of cancer screening

Cancer screening examinations were carried out in 3942 (new, 1575; repeater, 2367) participants from Jan. to Dec. in 2011. Two thousand seven hundred and sixty four participants underwent multi-phasic

programs (new, 1210; repeater, 1554). Cancer screening for the lung, female organs, breast and alimentary tract were independently performed in 565 (new, 15; repeater, 550), 58 (new, 14; repeater, 44), 80 (new, 12; repeater, 68), and 135 (new, 19; repeater, 116) participants, respectively. Moreover, CTC was carried out in 340 (new, 305;repeater,3 5) participants. Recent accurate data on cancers have not been obtained due to lack of adequately long follow-up data from our 2011 patients. We have therefore presented confirmed data from the previous year. Malignant tumors were detected in 76 out of 1260 new participants and in 40 out of 1766 repeaters who underwent multi-phasic clinical programs in 2010.

5. Imaging system

All medical images in our center are digitized. Original or compressed computed radiography (CR), DR, CT, MRI, PET, US, and endoscopy images can be easily and rapidly referenced on the medical information system for research, administration, and clinical expertise (MIRACLE). A reporting system has been established. MIRACLE for cancer screening is used for all routine work.

Research Activity

(1) The first breast tomosynthesis system in Japan was installed at RCCPS in September 2009. Since October 2010, a breast tomosynthesis study has started in cooperation of breast surgeons at the NCC hospital. Regarding the study, NCC IRB approval was granted in December 2008. The sensitivity and specificity of tomosynthesis in comparison with conventional MMG, US, other modalities, and pathological findings have been in the process of evaluation.
(2) CT-colonography with the new method of fecal preparation was provided in November 2011.
(3) In order to establish guidelines for the management of pulmonary nodules detected by 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.
(4) A computer-aided system for detection of pulmonary nodules on low- dose CT images is being developed and a super high-resolution CT scanner is also being developed.
(5) The clinical usefulness of C11-methionine-PET in several kinds of brain tumors detected at the NCCH has been assessed.
(6) The clinical usefulness of MRI (3.0T) in cancer screening has been assessed.

Clinical Trials

Cancer re-screening for those subjects who have finished a follow-up of five years began in February, 2009 in our center. As a result, a new study based on follow-up data has been started.

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SCREENING ASSESSMENT AND MANAGEMENT DIVISION

Hiroshi Saito, Chisato Hamashima, Toshiaki Kobayashi, Kumiko Saika, Yuri Mizota, Ryoko Machii, Ayako Aoki, Yoshiki Ishikawa, Koichi Nagata, Noriaki Takahashi, Sayuri Amanuma, Junko Asai, Kanoko Matsushima, Kazuko Matsuda, Hiromi Sugiyama, Keiko Kawarabata, Akiko Totake, Aoi Sato, Sayaka Kamo

The Screening Assessment and Management 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. Thus, the Screening Assessment and Management Division has developed and updated screening guidelines (Cancer Screening Assessment) and constructed quality assurance systems for the screening programs (Cancer Screening Management).

Studies Evaluating Cancer Screening

A randomized controlled trial evaluating one-time colonoscopic screening (CS) for colorectal cancer was started in 2009. We have been responsible for designing and managing the study as the head office of the study. The study fields were extended to a part of the neighboring Daisen city as of this year. The cumulative number of subjects who were recruited and gave informed consent, and who were thus enrolled in the study, was 3712 during the 29 months after starting recruitment, corresponding to 37% of the planned number. The fields will further be extended to whole areas of Daisen city which has a population 5 times as large as this year's target population, aiming at a marked increase in recruiting study participants.

The results of a case-control study, conducted in four cities in Tottori prefecture, suggested a 33% reduction in the mortality rate of gastric cancer among the population who had undergone endoscopic screening within 12 months. Another case-control study to evaluate gastric cancer screening using endoscopy is ongoing in Niigata city.

Studies on Quality Assurance (QA) in Cancer Screening

Checklists (CLs) as a structure indicator in quality assurance at screening facilities, municipalities, and prefectures have been evaluated regarding their appropriateness by an expert panel. During this year, the appropriateness of cervical and breast cancer screening programs were evaluated. Good consensus on the appropriateness of those CLs was obtained. In addition to the three CLs, which were previously evaluated, panels of the five CLs have been completed this year.

An intervention study to evaluate the efficacy of the feedback on QA results of the data was started in 2009 with the endpoints of improvement of the CL scores and process indicators in subsequent years. The study was conducted by randomly allocating 1270 municipalities, corresponding to 71% of the municipalities in the country, into study and control groups in which data feedback was collected differently. The third feedback was performed this year. The results will be obtained through a planned review in 2014, at the completion of this trial.

Studies on Raising Participation Rates in Screening Programs

We have been conducting several intervention studies to evaluate the call-recall system and various invitation tools for screening participation which were developed by a health-communication technique. We demonstrated that, for breast cancer screening, messages to individual subjects, tailored according to the characteristics of those persons, could raise screening uptake more efficiently than the usual invitation letter.

Assessment and Management of Cancer Screening Programs at the National Level

With regard to assessment of cancer screening, an evidence report on screening for hepatitis-related diseases has been developed. To prepare revision of

the guidelines for breast cancer screening, new evidence has been collected. In addition, we developed the guidelines for the lay population on lung and gastric cancer screening using an original method involving the public, which was developed in 2009.

For Cancer Screening Management, we calculated cancer screening uptake rates in each of the 1800 municipalities in the country in 2009 by the standardized method using the formula which was authorized by the Ministry of Health, Labour and Welfare (MHLW). The data are being published on the website of the Center for Cancer Control and Information Services at the NCC. To disseminate knowledge and skills for quality assurance activity in prefectures to be performed toward municipalities within each prefecture, we are organizing workshops targeting the chief members of the quality assurance committee of each prefecture. The contents of the workshop are also developed using the above mentioned CLs.

The above two activities are performed in part as the project of the Center for Cancer Control and Information Services The former activity will be continued on an annual basis.

EPIDEMIOLOGY AND PREVENTION DIVISION

Shoichiro Tsugane, Manami Inoue, Shizuka Sasazuki, Motoki Iwasaki, Norie Sawada, Taichi Shimazu, Taiki Yamaji, Reiko Suzuki, Azusa Hara, Junko Ishihara, Masayuki Tatemichi, Tsutomu Miura, Yuko Yamano, Sana Yokoi, Minatsu Kobayashi, Ribeka Takachi, Yoshitaka Tsubono, Takehiro Michikawa, Yuri Ishii, Hideyo Ochi, Kayo Ohashi, Michiko Okajima, Yingyan Gong, Yurie Shinozawa, Izumi Suenaga, Ayako Toyama, Tomomi Mukai, Izumi Matsumoto, Ai Noda, Jun Umezawa, Masahiro Matsuyama

The Epidemiology and Prevention Division has planned and conducted independent and collaborative studies on cancer etiology and prevention, with a special focus on dietary, environmental and genetic factors. Several epidemiological projects are currently in progress.

Population-based Prospective Study (the JPHC Study)

Diet has been implicated in the etiology of cancer and in the unique patterns of cancer incidence in Japan. However, the epidemiological evidence for this contention has been limited. The division therefore initiated a cohort study, the Japan Public Health Center-based Prospective Study (JPHC Study), in 1990, in collaboration with 11 public health centers and other institutes, in which approximately 140,000 individuals from 11 areas were scheduled to be followed up for at least 30 years. A total of 21,024 deaths, 16,962 cases of cancers, 5,888 cases of strokes and 1,130 cases of myocardial infarctions, had been documented as of October, 2011.

In the cohort, lifestyle factors that were assessed in the baseline and/or 5 year follow up questionnaire, examination data from health checkups or stored blood samples were examined in relation to the subsequent risk of total death, total or specific cancer and other lifestyle-related diseases.

Total Cancer: In women, past and recent use of vitamin supplements increased the risk of cancer partly explained by preexisting diseases or unhealthy background, while consistent vitamin supplement use might reduce the risk of cardiovascular disease (CVD) (1). **Colorectal Cancer:** Intake of marine n-3 polyunsaturated fatty acids might be inversely related to the risk of cancer in the proximal site of the large bowel (2). Higher consumption of red meat was significantly associated with a higher risk of colon cancer among women as was higher consumption of total meat among men, although the highest quintile of red meat consumption could be considered moderate by Western standards (3). **Liver Cancer:** Compared to the hepatitis virus-negative group, the hazard ratio (HR) of developing hepatocellular carcinoma (HCC) was 35.8-fold higher in HCV monoinfection, but a titer-dependent increase in risk was not identified (4). HBV mono-infected subjects with A1762T/G1764A double mutation could be at high risk of HCC development during the natural course of HBV infection (5). **Lung Cancer:** Plasma genistein concentration was inversely associated with lung cancer risk in Japanese women (6). **Breast Cancer:** Low body mass index (BMI) at age 20 years (y) was substantially associated with an increased risk of breast cancer, while high recent BMI and subsequent BMI gain from age 20 y were associated with increased risk of postmenopausal estrogen receptor (ER)+ progesterone receptor (PR)+ tumors (7). Active participation in leisure-time physical activity may contribute to a decrease in breast cancer risk, particularly for ER+PR+ tumors (8). **Thyroid Cancer:** High green tea consumption was positively associated with thyroid cancer risk in premenopausal women, but inversely in postmenopausal women (9). Coffee consumption and thyroid cancer risk was associated in neither men nor women. **Cardiovascular disease:** Being shorter in height was associated with increased risk of total stroke, either hemorrhagic or ischemic stroke but not with risk of coronary heart disease (CHD) (10). Higher total dietary fiber was associated with reduced risk of CVD only in non-smokers (11). Diabetes mellitus (DM) was a significant risk factor for all types of ischemic stroke, but not for intraparenchymal or subarachnoid hemorrhage (12). Diabetes and elevated glucose levels were also associated with incident CHD (13). Pulse pressure was positively associated with risk of stroke among persons with normal systolic blood pressure levels (14). Higher BMI levels and a weight gain of ≥10% over 5 years were associated with an increased risk of stroke in women, whereas this association was weak in men (15). **Type II Diabetes:** Fish consumption was associated with a lower risk of type 2 DM in men but not in women (16). Weight gain from age 20 y was associated with

an increased risk of type 2 DM, which was further enhanced by weight gain in later life in women (17). Known risk factors for diabetes like age, smoking, family history and so on established in Western populations also increased the risk of diabetes in a Japanese population defined on the basis of HbA1c values (18). **Suicide:** Higher intakes of fish, EPA, or DHA were not associated with a lower risk of suicide (19). Those with the highest level of social support had a significantly decreased risk of suicide, which suggests that avoiding social isolation may decrease the incidence of suicide (20). Men living without a spouse and women living with a parent(s) only were at increased risk of suicide, while women living together with a spouse and child(ren) were at decreased risk of suicide (21). **Metabolic syndrome:** Social support increased the risk of metabolic syndrome among Japanese men, a finding that was opposite to what has previously been reported in Western studies, while there was no such association in women (22). **Validation study:** Validity of the study for the cases of self-reported cancer (23) and self-reported fracture (24) were investigated as well as effect of cooking loss in the assessment of vitamin intake (25).

Epidemiological Study of Japanese Brazilians (São Paulo-Japan Cancer Study)

The ethnic differences in the incidence of cancer suggest an interaction between environmental and genetic factors. Several epidemiologic studies in Brazil, a multi-ethnic nation with 1.2 million people of Japanese ancestry, are in progress. A cross-sectional study was conducted using a control group of case-control studies in Nagano, Japan, and São Paulo, Brazil to clarify the difference in hormone levels (26). In postmenopausal women older than age 55 y, Japanese Brazilians had significantly higher levels of estrogens and androgens than in Japanese and levels similar to or higher than in non-Japanese Brazilians. Hospital-based case-control studies of patients aged 20-74 years with invasive breast cancer and matched controls in Nagano and in São Paulo showed that antibody-dependent cell cytotoxicity (ADCC) might not play a major role in the etiology of breast cancer (27). A colorectal adenoma case-control study in Japanese Brazilians in São Paulo is in progress.

Other Epidemiological Studies

Studies are being conducted to search for the cause of cancer and develop effective cancer prevention methods, using samples from subjects seen at the Research Center for Cancer Prevention and Screening (RCCPS). A self-administered food frequency questionnaire (FFQ) developed for and validated in rural residents was also validated for middle-aged urban cancer screenees (28).

Cancer Prevention Study

To develop an evidence-based cancer prevention strategy in terms of lifestyle intervention suitable for the Japanese population, a systematic literature review project (29-31) and some interventional studies are in progress, as well as some pooled analyses (32). Evidence on smoking, alcohol, anthropometry, fruit and vegetables, other foods and lifestyles and infectious diseases as risk factors of the main cancers in Japan was reviewed to make final or updated judgments, each of which has been made public on the WEB (http://epi.ncc.go.jp/can_prev/). Based on the judgments, current evidence-based cancer prevention recommendations for Japanese provided by the study group were also updated.

International Collaborative Projects

International collaborative projects to contribute on the global scale with a focus on Asian cancer prevention strategies (Japan-China cooperative research work (33, 34), Asia Cohort Consortium (ACC) (35, 36), Asia Breast Cancer Consortium (37, 38), Pooling project of Prospective Studies of Diet and Cancer, WHO Global Burden of Disease Project, etc (39).) are in progress. Most studies that have evaluated the association between BMI and the risks of death from any cause and from specific causes have been conducted in populations of European origin. ACC revealed that being underweight was associated with a substantially increased risk of death in all Asian populations. The excess risk of death associated with a high BMI, however, was seen among East Asians but not among Indians and Bangladeshis.

Other Studies

Analysis of the epidemiological or clinical data was carried out as well as some contribution to The 7th Asia Cancer Forum (40) and The Lancet Special Series on Japan (41), the Hokkaido study (42) and the Nishiaizu Study (43). Risk factors for breast cancer were reviewed with recent evidence in Japan (44).

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Research Conference of the National Cancer Center
Research Center for Cancer Prevention and Screening

JAN 11 Conference 48

Norie Sawada (Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening)

Plasma Testosterone and Sex Hormone-Binding Globulin Concentrations and the Risk of Prostate Cancer among Japanese Men

MAR 01 Conference 49

Chisato Hamashima (Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening)

Summary of the Evidence of Screening for Hepatitis-related Diseases

MAY 10 Conference 50

Ryutaro Kakinuma (Screening Technology and Development Division, Research Center for Cancer Prevention and Screening)

Newly Developed Nodules during Follow-up after Baseline CT Lung Cancer Screening or during Repeat CT Screening

JUL 05 Conference 51

Motoki Iwasaki (Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening)

Colorectal Adenoma Study among Japanese Brazilians in São Paulo

SEP 06 Conference 52

Kumiko Saika (Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening)

Improvement in the Indices of Diagnostic Follow-up Result in Population-based Cancer Screening Programs after Extending the Deadline of Submission

NOV 01 Conference 53

Yasuo Kakugawa (Screening Technology and Development Division, Research Center for Cancer Prevention and Screening)

The Recent Advances and New Insights in Capsule Endoscopy

Center for Cancer Control and Information Services

Preface

The Center for Cancer Control & Information Services (CIS) is a nationally funded program established in 2006, as an essential part of NCC's extramural activities.

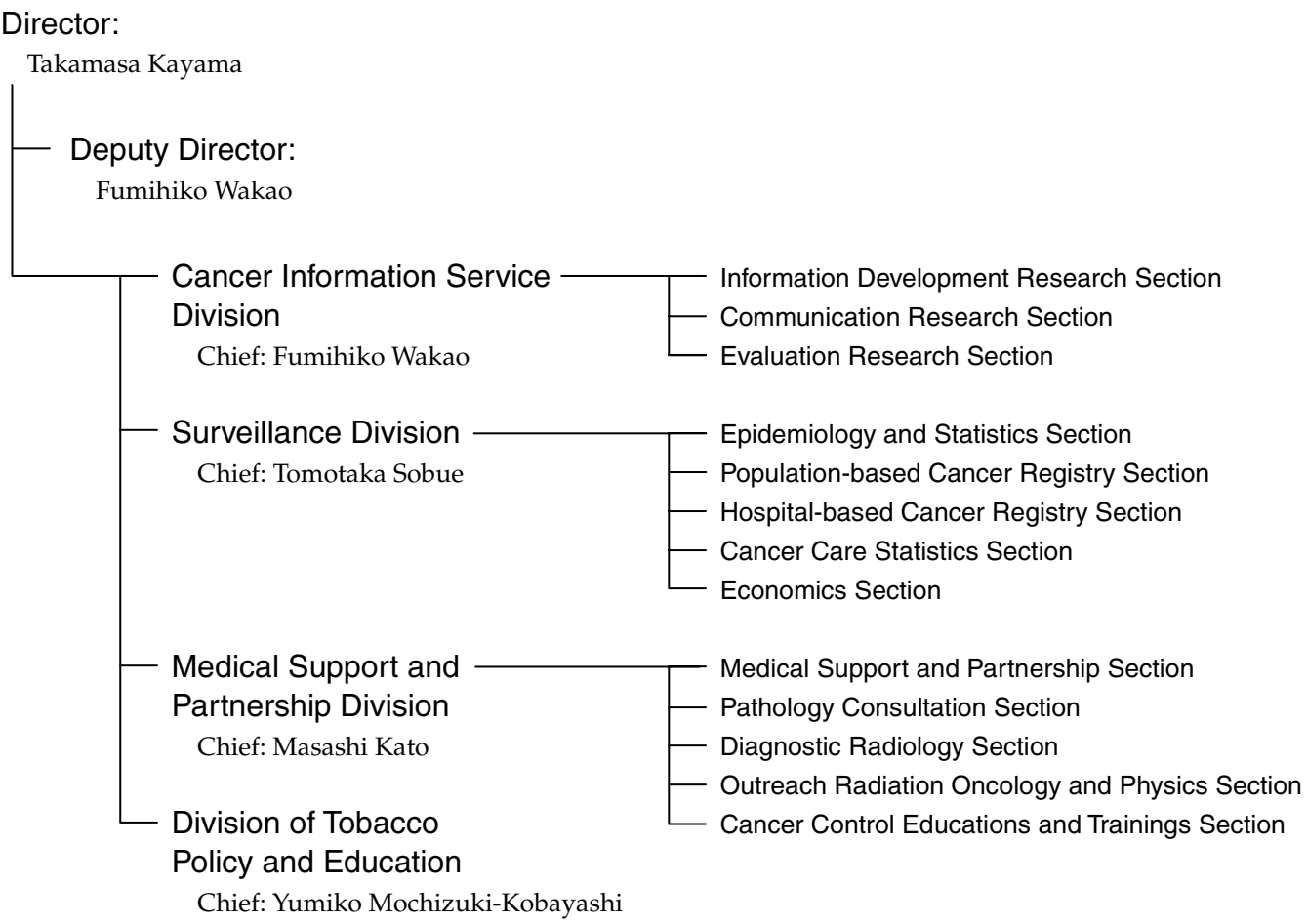
The mission statement of the CIS is as follows: "The Center for cancer control and information services provides information needed to promote comprehensive and systematic cancer control program in Japan. In collaboration with designated cancer care hospitals, Ministry of Health Labour and Welfare and other relevant Ministries, the Center plays a central role to plan, manage and evaluate nation-wide 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."

Since its inception, the CIS has been providing comprehensive, scientifically based, unbiased information to patients, their families, and the general public about all aspects of living with cancer, via its homepage (http://ganjoho.jp) as well as other dissemination channels. The CIS also provides physicians and other health professionals, with up-to-date information on early detection, diagnosis, treatment, care, cancer research, clinical trials and cancer statistics, via our various information channels and professional training programs.

To ensure that we remain relevant to the needs and perspectives of patients, their families, healthcare professionals, and the general public, we are committed to facilitating the participation of all of these stakeholders in shaping both what information we provide, and how this is delivered. In formulating our key publications, we have sought active input from our on-going nationwide panel of cancer patients as well as specialist review boards. The CIS Advisory Board, representing both healthcare professionals and patient advocacy organizations, has also been proactive in helping the CIS prioritize its efforts. We will firmly grasp, every opportunity to improve our services and appreciate your continued support.

Takamasa Kayama, M.D., Ph.D.
Director, Center for Cancer Control and Information Services

Organization



Activities of the Divisions

CANCER INFORMATION SERVICE DIVISION

Fumihiko Wakao, Kiyotaka Watanabe, Tomoko Takayama, Seiichiro Yamamoto, Akiko Urakubo, Maki Hirano, Teruo Ito, Yumiko Yamazaki, Chikako Yamak, Eriko Tao, Nozomu suzuki, Yuri Mizota(joint), Mika Takai, Tamaki Kumagai

Introduction

The mission of the Cancer Information Services is to provide credible information about cancer. In the National Cancer Information Network, the Cancer Information Service Division plays an important role in disseminating cancer-related information directly to our audiences, including patients and their families, the public at large, healthcare professionals, policy makers and researchers. Our dissemination channels also include the 388 designated cancer care hospitals throughout Japan and their respective cancer information & support teams. Currently, multi-channel cancer information services are provided through the internet, brochures, lectures, and public meetings. One of our key mandates is to provide all patients and their dear ones the means to access comprehensive cancer-related information, at the point of need, and with appropriate context. The Spring 2011 launch of a cancer information handbook for patients, the "Kanja Hikkei", represented an important step in this direction. Over 80,000 copies have been disseminated among healthcare professionals, with a view to making this the lingua franca between the cancer patients, their physicians and other healthcare professionals.

Line of Service

Cancer Information Development Research Section

The Cancer Information Development Section has exerted efforts to provide reliable, evidence-based cancer information to patients, their families, citizens, healthcare professionals, researchers, and policy makers. Evidence databases such as clinical practice guidelines and research findings are continuously sourced, assessed, and edited, ensuring that the information is presented in a manner consistent with how the users digest and process the information. Information is disseminated through various media formats, including the website "Cancer Information Service http://ganjoho.jp/", a wide range of patients education brochures and more recently, the handbook ("Kanja-Hikkei") that contains comprehensive cancer information to help empower patients throughout the continuum of cancer survivorship. The Section also helps direct health care providers to access an extensive library of cancer treatment and supportive information that have undergone CIS peer reviews, as well as other cancer information sources that are of interest to health care professionals.

Communication Research Section

In order to disseminate reliable cancer information, the Communication Research Section is in charge of supporting the smooth operation of cancer information services and of encouraging collaboration among relevant stakeholders, such as the cancer information & counseling centers in designated cancer hospitals (388 locations around the nation), support groups, patient advocate groups, prefectural government units responsible for planning and managing their respective regional cancer programs, and other information specialists like public libraries. The Section also handles large volumes of inquiries to cancer information services, prepares and manages collaborative work with a "Patient-civil panel" which consists of 100 supporters of various cancer experience and regional background from throughout Japan, and provides mutual educational forums for media professionals.

Evaluation Research Section

In order to meet our mandate, to continually provide reliable information in an easily understood format, the Section evaluates the credibility of cancer-related information to be disseminated through "ganjoho.jp" (Cancer Information Services). Treatment guidelines are evaluated using the AGREE (Appraisal of Guidelines for Research & Evaluation) instrument and accumulated as evidence repositories. This Section plays a role as the editorial office of cancer information services.

Research Activities

Cancer Information Development Section

To ensure timely dissemination of accurate and pertinent information on cancer, and to more effectively support decision-making by patients, their families and citizens, we conduct extensive surveys to better gauge what type of information is needed, how it needs to be delivered in order to make timely impact, and which stakeholders in the community need to be part of the delivery/dissemination network. Increasingly, we are also involving regional community stakeholders, patients and care providers, in helping to compile more regionally pertinent sets of information, in the effort to improve our community outreach efforts.

Communication Research Section

To overcome the disparities of cancer related information all over Japan and to contribute to building better cancer information and support systems, this Section conducts a portfolio of research in wide ranging areas such as the identification of underserved populations, building a cross-functional network of community care providers, defining the activities of cancer information centers, developing innovative educational programs and training methods that help accelerate best practice adoption among cancer information counselors.

Evaluation Research Section

In collaboration with the Japan Public Health Center-based Prospective Study and other epidemiological and clinical studies, the association of various risk/prognostic factors and cancer have been evaluated. A statistical contribution is being performed for therapeutic development. A new cohort is being established for breast cancer patients, to investigate the effect of lifestyle factors and alternative medicine on their QOL and prognosis. Health communication research using a social marketing method is being conducted in order to fill the gap between practice and evidence of cancer prevention and cancer screening. As for the educational contribution, an e-learning system for clinical research methodology has been established for anyone involved in clinical research.

Published Papers

1. Fujii H, Yamamoto S, Takeda-Imai F, Inoue M, Tsugane T, Kadowaki T, Noda M. Validity and applicability of a simple questionnaire for the estimation of total and domain-specific physical activity. Diabetology International, 2:47-54, 2011
2. Ohuchi N, Ishida T, Kawai M, Narikawa Y, Yamamoto S, Sobue T. Randomized controlled trial on effectiveness of ultrasonography screening for breast cancer in women aged 40-49 (J-START): research design. Jpn J Clin Oncol, 41:275-277, 2011

SURVEILLANCE DIVISION

Tomotaka Sobue, Hiroshi Nishimoto, Kota Katanoda, Tomohiro Matsuda, Akiko Shibata, Koichi B. Ishikawa, Ayako Matsuda, Kumiko Saika (joint), Takahiro Higashi, Yasuko Iba, Yoshiko Emori, Tomomi Kikuchi, Aya Inoue, Kaori Nakano, Mika Mizuochi

Introduction

The Surveillance Division is in charge of providing credible cancer statistics to patients and their families, 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. A newly incorporated economics section will augment epidemiologic data with economic information crucial for formulation of future policy.

Routine Activities

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 the 45 prefectural registries in practical terms and the other 2 prefectures in planning terms, by disseminating up-to-date information through websites and mailing lists; by setting up a Q&A service; by holding a one day seminar in May for administrative officers who were new to their post; and organizing 2-day educational workshops for cancer registrars and administrative officers, a total of 105 participants, in December. The Division also provided site visiting as part of training for the Standard Database System (SDS), for promoting the protection of personal information, and for cancer registry start-up preparation. This activity covered a total of 10 prefectures.

Standardization of the population-based cancer registry has rapidly advanced: 41 registries out of 45 use the standard registry items. Thirty-one registries had introduced the SDS as of December 2011. Introduction is in progress in five registries and 4 are planning to introduce it in 2012. The self-check software on security control in cancer registration, and security educational materials for new workers were developed by the division and are ready for practical use.

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 has been performed at 388 designated cancer care hospitals (DCCHs) and over 100 other hospitals in 2011.

In collaboration with other relevant parties, the division develops data standards for HCR, modifies datasets, and distributes the standardized software "Hos-CanR", which is used in about 250 hospitals. In 2011, individual records for 484,771 cancer cases diagnosed in 2009 were collected from 370 DCCHs. To improve the data quality, the Division devised an education program for cancer registrars through holding three one-week-long workshops for experts in Tokyo per year and 2-day workshops for beginners twice a year at 8 cities in which about 800 registrars participated. Furthermore, the Division performed site visits to 31 DCCHs in 2011.

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 web site and in the book titled "Cancer Statistics in Japan".

Research Activities

Population-based Cancer Registries

The national cancer incidences in 2006 were estimated based on the data from 32 cancer registries. The incidence data were then analyzed in detail by 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. The Division realized a national survey of cancer registries in Japan. The results were effectively utilized to figure out the latest situation in population-based cancer registration in Japan and to promote cancer control.

Quality Indicators

Ensuring quality of cancer care is an important aspect of cancer control. We have developed quality indicators for 5 major cancers in Japan and palliative care. To enable timely feedback, these quality indicators focus on the process of care rather than outcomes. We now are pilot testing the feasibility of these quality indicators in a real practice setting. At the same time, we determined the priority of quality indicators by an expert panel. The high-priority indicators can be incorporated into a future national quality measurement system.

Cancer Statistics

International comparisons of time trends in cancer mortality and screening rate were conducted based on the WHO mortality and OECD database. The population attributable fraction of mortality was estimated for various risk factors among the Japanese population. Cancer mortality was projected according to different scenarios of smoking prevalence among Japanese males. The association between lung cancer mortality and long-term exposure to ambient air pollution was examined by a prospective cohort study.

Economic Studies on Cancer Care

Containing the costs and improving the efficiency of cancer care, while ensuring patient access to required services is an important issue in ageing society. A database on the costs and revenues related to cancer surgery in NCC hospital is developed and analysis on the data for the fiscal year 2010 showed differing levels of performance and profitability among specialties and procedures. For analysis on accessibility to care, DPC survey data are used to capture major cancer treatment facilities and are visualized with GIS to calculate the coverage of the population categorized by driving-time.

Table 1. Cancer Incidence Data from Population-based Cancer Registries

Year of Diagnosis	Prefectures	Number of New Cancer Cases
2006	32 (15 for estimation)	664,398
2007	33 (21 for estimation)	Work in progress

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
2008	357	426,783
2009	370	484,771

Published Papers

1. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T. Cancer incidence and incidence rates in Japan in 2005: based on data from 12 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol, 41:139-147, 2011

2. Katanoda K, Saika K. Comparison of time trends in multiple myeloma mortality (1990-2006) between countries based on the WHO mortality database. Jpn J Clin Oncol, 41:444-445, 2011

3. Katanoda K, Saika K, Yamamoto S, Tanaka S, Oshima A, Nakamura M, Satoh H, Tajima K, Suzuki T, Tamakoshi A, Tsugane S, Sobue T. Projected cancer mortality among Japanese males under different smoking prevalence scenarios: evidence for tobacco control goal setting. Jpn J Clin Oncol, 41:483-489, 2011

4. Katanoda K, Sobue T, Satoh H, Tajima K, Suzuki T, Nakatsuka H, Takezaki T, Nakayama T, Nitta H, Tanabe K, Tominaga S. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. J Epidemiol, 21:132-143, 2011

5. Katanoda K, Yako-Suketomo H. Time trends in lung cancer mortality between 1950 and 2008 in Japan, USA and Europe based on the WHO mortality database. Jpn J Clin Oncol, 41:1046-1047, 2011

6. Machii R, Saika K. Time trends in uterus cancer mortality between 1955 and 2008 in Japan, U.S.A. and Europe based on the WHO Mortality Database. Jpn J Clin Oncol, 41:1313-1314, 2011

7. Matsuda A, Matsuda T. Time trends in stomach cancer mortality (1950-2008) in Japan, the USA and Europe based on the WHO mortality database. Jpn J Clin Oncol, 41:932-933, 2011

8. Matsuda T, Matsuda A. Time trends in prostate cancer mortality between 1950 and 2008 in Japan, the USA and Europe based on the WHO mortality database. Jpn J Clin Oncol, 41:1389, 2011

9. Matsuda T, Matsuda A. Time trends in total cancer mortality (All Sites) between 1950 and 2008 in Japan, USA and Europe based on the WHO mortality database. Jpn J Clin Oncol, 41:833-834, 2011

10. Saika K, Katanoda K. Comparison of time trends in brain and central nervous system cancer mortality (1990-2006) between countries based on the WHO mortality database. Jpn J Clin Oncol, 41:304-305, 2011

11. Saika K, Machii R. Time trends in colon, rectum and anus cancer mortality between 1955 and 2008 in Japan, USA and Europe based on the WHO mortality database. Jpn J Clin Oncol, 41:1153, 2011

12. Saika K, Sobue T. Time trends in breast cancer screening rates in the OECD countries. Jpn J Clin Oncol, 41:591-592, 2011

13. Saika K, Zhang M. Comparison of time trends in non-Hodgkin's lymphoma mortality (1990-2006) between countries based on the WHO mortality database. Jpn J Clin Oncol, 41:154-155, 2011

MEDICAL SUPPORT AND PARTNERSHIP DIVISION

Masashi Kato, Yasunori Arai, Jun Itami, Soichiro Shibui, Hitoshi Tsuda, Fumihiko Wakao, Hiroaki Onaya, Takahiro Hasebe, Hideo Uesugi, Yoshinori Makino, Hiroko Yako-Suketomo, Yoko Nakazawa, Toshiyuki Minemura, Kyouhei Fukata, Chie Kurokawa, Tadakazu Shimoda, Yuko Ogo, Megumi Fukuda, Ritsuko Chinda, Hiroyo Ohchi, Chisako Ito, Yoshiko Suzuki, Hiromi Nakamura, Toshiko Sakaguchi, Shiho Hirai

Introduction

The Division builds partnership with Designated Cancer Care Hospitals to support all health allied professionals concerned with cancer control in Japan. The Medical Support and Partnership Section (MSPS) was established in 2011, and plays a unique role in suggesting the cancer control policy in Japan. The Pathology Consultation Section strives to perform human pathology research based on the histology of tumor cells and tumor-stromal cells to improve diagnostic pathology of the tumors. The Diagnostic Radiology Section (DRS) provides a consultation service and a cancer image reference database (NCC-CIR). A radiology consultation service is aimed 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 the pathology. The Outreach Radiation Oncology and Physics Section (ORPS) provides mailed and on-site dosimetry for monitoring the output for radiotherapy beams and a radiotherapy case review for three-dimensional or more complicated radiotherapy plans. The Cancer Control Educations and Trainings Section (CCET) produces or plans and operates several training programs in the clinical and cancer registry disciplines to provide leadership base for the promotion of a certain level of cancer treatment programs and epidemiological Surveillance. To correct medical inequality in the provision of cancer care throughout Japan, the CCET organizes a number of special training programs for physicians, nurses, pharmacists, cancer information (CI) specialists, other health professionals and cancer registries staff personnel of Designated Cancer Care Hospitals in all parts of the country.

Routine Activities

A. Networking among designated cancer care hospitals

The MSPS formed a network among the designated cancer care hospitals to build partnership for cancer control in Japan. The designated cancer care hospitals are important partners with the NCC to promote comprehensive cancer control; implementing the cancer registry, providing cancer information services, and training oncology professionals, as well as strengthening clinical performance in Japan. Currently, mailing lists have been prepared to allow participants to share their practices or - other information among the participating hospitals.

B. Pathology consultation service

The pathology slides of lesions arising in various sites have been submitted from clients. Eighty-five consultant pathologists who are specialists in various fields are registered, and one pathologist, who was assigned as the consultant, examined the slides and rapidly sent back the report of his or her opinion to each client. Most of the clients expressed satisfaction with the contents of the report and this consultation system. “Pathological diagnosis for soft part pleomorphic sarcoma” has been published as the Geka-byouri-shindan-no-tebiki.

C. Radiology consultation service

Ninety-six consultation reports have been put together for requests mainly from the Kanto and Kyushu region. Hepato-biliary-pancreatic, musculoskeletal, and head-and-neck lesions were the common subjects. Consultation with a specialist was the most frequent reason 46/96 (47.9%) for consultation. The client radiologists have evaluated 194 (85.1%) of the 288 consultation reports as being useful for the presence of clinical impact on the final radiological diagnoses.

D. NCC-CIR

The average number of effective accesses to this site was almost the same as that in 2010, about 100000 per month. Nine cases with adenoma-related lesions of the uterine cervix, pharyngeal cancers, glioblastoma, and neuroendocrine carcinomas with 22 virtual slides have been published, resulting in the total provision of 210 cases.

E. Radiotherapy case reviews

Mailed dosimetry and on-site dosimetry were performed in 23 institutions and 10 institutions, respectively. All data of the institutions were within the permissible limit. In clinical trials, radiotherapy case reviews were performed in 152 institutions.

F. Promotion of medical education programs for cancer control

The CCET organizes medical training programs for allied oncology/hematology professionals to rectify medical inequality in the provision of cancer care throughout Japan as a part of our cancer control projects. The training programs are intended for Health Allied Professionals (physicians, pharmacists, nurses and technologists, CI specialists), for Palliative Care consultation and Chemotherapy teams, for counseling team members, and members of In-hospital cancer registries.

Research Activities

Suggestion for Cancer Control Policy

To suggest a policy for cancer control to the Japanese government, a mailed and web survey was conducted on the next Basic Plan to Promote Cancer Control Programs to the 377 designated cancer care hospitals. The oncology professionals' opinions were analyzed and used for further suggestions to the government.

Trend of Pathology Consultation Services

In 2011, the Pathology Consultation Section received histopathology slides of 364 cases for a specialist's second opinion regarding histopathological diagnosis. The number of consultation cases showed a 20% increase in comparison with the number in 2010.

Develop and Use of a Teleradiology System

The division is investigating methods to improve the way how we can send and receive digital imaging files more easily and more quickly using a teleradiology system. Case presentations with the NCC-CIR English version have almost doubled from 53 to 112.

Develop the RTPS Quality Control Support Program

The division is developing enforcement of "the Radiation Treatment Planning System (RTPS) quality control support program" to confirm the beam modeling data of the RTPS in 45 institutions. In clinical trials, we examine enforcement of the on-site dosimetry regarding the output dose of Intensity Modulated Radiotherapy (IMRT).

Table 1. Training programs conducted during April2010-March 2011

Subjects and programs	Education and Training program title	No. of participants
Oncology nurses education	Continuing education and development of oncology nursing Workshop for trainers	102
	Continuing education and development of oncology nursing Workshop for trainers-Follow up course	48
	Oncology nursing seminar for trainers	218
	Oncology nursing on the job training for trainers	8
CI specialists education	CI Specialist Education Program -Basic course 1	662
	CI Specialist Education Program -Basic course 2	624
	CI Specialist Education Program -Basic course 3	462
	CI Specialist Education Program –"Skill-Up' course	79
Hospital-based cancer registrars training	Training program for instructors of hospital-based cancer registrars	9
	Supplementary training program for instructors of hospital-based cancer registrars	104
	Basic training program for hospital-based cancer registrars	1592
	Supplementary training program for hospital-based cancer registrars of basic course completion	699
	Advanced training program for hospital-based cancer registrars	108
	Site Visiting program on hospital-based cancer registries in national cancer center hospital	72
Cancer registrars and administrative officers training	Basic training programs on a population-based cancer registry for cancer registrars and administrative officers	195
Technologists education	Trainer training for oncologic radiology technologists	16
	Trainer training for oncologic laboratory medical technologists	4
Palliative care physicianseducation	Palliative care education meeting for trainers	64
Psycho-oncologists education	Psycho-oncology education meeting for trainers	63
Palliative care team education	Palliative care team workshops for consultation	120
	Palliative care team workshops for consultation-Basic course	75
Chemotherapy Team education	Chemotherapy Team workshops to introduce safety aspects of new drugs	32

In the hospital-based cancer registrars training section, we have operated a new program four times under the following title :
"Supplementary training program for hospital-based cancer registrars who have completed an advanced course (UICC TNM-7)"

Published Papers

1. Yako-Suketomo H, Inaba Y and Shimanouchi N. Administrators' healthy lifestyle, satisfaction with the process of health policy making and their relationship with municipalities in Japan. Health Promotion Research, 3:26-37, 2011

2. Yako-Suketomo H, Katanoda K. Time trends in breast cancer mortality between 1950 and 2008 in Japan, USA and Europe based on the WHO mortality database. Jpn J Clin Oncol, 41:1240, 2011

3. Hasebe T, Iwasaki M, Akashi-Tanaka S, Hojo T, Shibata T, Sasajima Y, Kinoshita T, Tsuda H. Atypical tumor-stromal fibroblasts in invasive ductal carcinoma of the breast. Am J Surg Pathol, 35:325-336, 2011

4. Hasebe T, Iwasaki M, Akashi-Tanaka S, Hojo T, Shimizu C, Andoh M, Fujiwara Y, Shibata T, Sasajima Y, Kinoshita T, Tsuda H. Atypical tumor-stromal fibroblasts in invasive ductal carcinomas of the breast treated with neoadjuvant therapy. Hum Pathol, 42:998-1006, 2011

5. Hasebe T, Iwasaki M, Akashi-Tanaka S, Hojo T, Shibata T, Sasajima Y, Kinoshita T, Tsuda H. Modified primary tumour/vessel tumour/nodal tumour classification for patients with invasive ductal carcinoma of the breast. Br J Cancer, 105:698-708, 2011

6. Hasebe T, Iwasaki M, Akashi-Tanaka S, Hojo T, Shibata T, Kinoshita T, Tsuda H. Important histologic outcome predictors for patients with invasive ductal carcinoma of the breast. Am J Surg Pathol, 35:1484-1497, 2011

7. Hasebe T, Iwasaki M, Akashi-Tanaka S, Hojo T, Shibata T, Sasajima Y, Kinoshita T, Tsuda H. Prognostic significance of mitotic figures in metastatic mammary ductal carcinoma to the lymph nodes. Hum Pathol, 42:1823-1832, 2011

TOBACCO POLICY AND EDUCATION DIVISION

Yumiko Mochizuki-Kobayashi, Jun'ichi Adachi, Sayuri Takise

Introduction

Every year, tobacco kills more than five million people in the world and 200,000 in Japan. Without immediate action, the number of deaths will reach eight million by 2030. As the tobacco epidemic emerged from human activities and it could be also prevented by human efforts, it is called a "man-made disaster". On the contrary, collective efforts are being made globally to build a tobacco-free society for the next generation, and Japan should not be left behind. Thus, the mission of our Division is to advance tobacco control policy and its implementation with scientific evidence in order to end the tobacco epidemic in our lifetime. The Framework Convention on Tobacco Control (FCTC) entered into force in 2005 and Japan, as a Party to the FCTC, is obliged to implement its provisions and fulfill international responsibilities. The Health Promotion Act and Cancer Control Act as well as the recent political power shift positioned tobacco control as one of the highest priorities among health policies in Japan. Driven by such policy climate changes, our Division serves as a professional think-tank to evaluate tobacco policies and to develop strategies to curb the tobacco epidemic, building concrete partnerships with national and international organizations and institutions.

Knowledge Transfer on Tobacco and Cancer

As a party to the FCTC, Japan is obligated to implement each article. A smoke-free policy (article 8) and a tax policy (article 6) are two prioritized areas to curb the tobacco epidemic, but are the most controversial. The guidelines for article 8, which aims to protect the public from exposure to tobacco smoke, were the first to be implemented rigorously. As the Division is involved in policy development processes at national and local level, accurate and convincing scientific evidence to mobilize political will and obtain public support is essential to dispel emotional and doubtful messages among stakeholders. Regarding the smoke-free policy, we estimated the annual number of deaths from exposure to secondhand smoke in workplaces and homes at 6,800, combining lung cancer and ischemic heart disease. We also conducted a regulatory impact analysis comparing policy options on smoke-free policies. A complete smoke-free policy was found to be a highly cost effective option with the largest number of lives saved but an incomplete ban (with exemptions) was found to generate no significant health benefit, although it was frequently recommended and adopted by government committees in Japan. Regarding a tax policy, we have conducted a rigorous simulation study to support the highest price increase of cigarettes for political debates in the government. Either a gradual increase or a sudden increase in tobacco retail prices was proposed to generate a significant increase in tax revenue, but the sudden increase approach would be more beneficial as far as public health would be concerned, because of its greatest reduction in the smoking population. For the further development of a tobacco control policy, we need a more systematic roadmap as a policy recommendation tool with critical evidence that no policy maker could discard, as well as a precise advocacy plan to mobilize public support.

Stakeholder Analysis and Capacity Building for Programme Implementation

To increase the net resource for tobacco control, the roles of health professionals are essential but still potential. A questionnaire survey to prefectural pharmacist associations was conducted in collaboration with the Japan Pharmacist Association to investigate the current status of their interests in and knowledge on tobacco control and to develop a capacity- building curriculum as well as educational material for cessation services. Most of the pharmacists were involved in some form of tobacco control activities with varied counterparts such as local governments or other health professional organizations, but the quality and the contents of the activities were varied because of lack of standardized materials and access to the appropriate information.

Operational Studies on Tobacco Control

We have conducted workshop-type studies to gather intellectual knowledge and generate political will in order to develop operational work plans on tobacco control, through inviting key academic researchers and advocates as well as politicians. The main purpose of the meetings was to consolidate the best available evidence and to develop a practical roadmap which would lead researchers to the best route for generating the necessary study results for policy development. The next step will be to hold open discussions, inviting other committed stakeholders to operate the given work plans. The outcome of the study is to draft a concrete alternative legislation on tobacco control in Japan.

WHO Collaborating Centre for Reference on Smoking and Health

The National Cancer Center has been designated as a WHO Collaborating Centre (WHO-CC) for Reference on Smoking and Health since 1978 and our Division took over as Head of the WHO-CC since 2009. It has sponsored a series of tobacco control meetings, such as the "World No Tobacco Day (WNTD) Symposium", annually with the Ministry of Health, Labour and Welfare, the "WHO Global Launch on the World No Tobacco Day - Gender and Tobacco" with WHO, and an international seminar entitled "Framework Convention on Tobacco Control" inviting the Head of the Secretariat of the Convention. It also helped the WHO Tobacco Free Initiative to develop WNTD 2011's global campaigns and to launch a monograph on gender, women and tobacco.

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