# Annual Report 2012

## National Cancer Center

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

# CONTENTS

## Hospital East

## Research Institute



## Exploratory Oncology Research & Clinical Trial Center

## Research Center for Cancer Prevention and Screening



## Center for Cancer Control and Information Services

# Greeting from the President

I am pleased to present this report on our activities, which provides an overview of the broad spectrum of accomplishments at the National Cancer Center (NCC), the largest and most comprehensive cancer-oriented facility in Japan.

It has been 50 years since the NCC was founded in 1962 as a leading national cancer care organization where the Naval Hospital used to be. Since then, we have provided the best and latest medical care not only locally but also nationally. In addition, we have been on the cutting-edge of research to unravel the cause of cancer and to develop medical treatment. The NCC has played a key role in training specialists; doctors, nurses, and other health professionals. They practice to become more specialized at the NCC where we perform evidence-based cancer care that is established by properly conducted clinical trials.

From April 2010, the NCC has changed its status to an Independent Administrative Institution (IAI) from being an institution directly controlled by the Ministry of Health, Labour and Welfare of Japan. The NCC is expected to pursue tasks properly and swiftly that are decided by the Government. Those tasks do not necessarily require the Government's direct involvement, but need to be done with absolute certainty because of their public nature. Working together with the Government, we need to have sound financial management including tasks that are not extremely profitable. That is the future image that we believe people expect from us.

Based on the Cancer Control Act enforced in 2007, and the Basic Plan to Promote Cancer Control in Japan, we work on various fields; providing highly advanced medical care, working with designated cancer care hospitals (397, nationwide), promoting a clinical research network, offering palliative care, and constructing a model of support services and information distribution. Through these activities, we pursue the enhancement of our patients' quality of life. To attain the ultimate goal of conquering cancer, we look into effective and new ways of prevention, diagnosis, and development of therapeutic strategies which are led by NCC-promoted basic research and translational research.

We understand our expected leading role in the fields of cancer care, research, screening, prevention, and policy making. "Relieve people in the world from cancer and its pain", "Take the lead to create a society where people live with cancer." With the spirit of our slogan, "All Activities for Cancer Patients", all staff members bring out their maximum specialties and skills, and with enough dialogue and open debate we will share globally what we will have learned from our hard work.

We sincerely appreciate your kind understanding and support.

Tomomitsu Hotta, M.D., Ph.D.
President, National Cancer Center

## Organization of National Cancer Center

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Tomomitsu Hotta

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    - Director: Fumihiko Wakao
  - Administrative Departments
    - Director: Yukio Kosuda
  - Multidisciplinary Research (MDR) Support Office: MDRSO
    - Head: Noriko Yamashita
  - Multi-institutional Clinical Trial Support Center
    - Director: Haruhiko Fukuda

# Sections Directed by President

# Strategic Planning Bureau

**Yasuhiro Fujiwara, Yasuhiro Fujii, Hisao Aasamura, Atsushi Ohtsu, Toshihiko Doi, Teruhiko Yoshida, Fumihiko Wakao, Seiichiro Yamamoto, Ken Ohashi, Ken Shimizu, Minoru Esaki, Akira Kawai, Kenji Tamura, Miyuki Sone, Hidehito Horinouchi, Aayako Mori, Nobuko Ushirozawa, Toshikazu Ushijima, Tatsuhiro Shibata, Takashi Kohno, Kenkichi Masutomi, Taro Shibata, Tetsuo Akimoto, Takayuki Yoshino, Masaaki Ito, Takeharu Yamanaka, Atsushi Ochiai, Kazuya Tsuchihara, Miho Kurihara, Yasuhiro Kuroda, Yasunori Kikuchi, Shoko Koike**

## Introduction

The Strategic Planning Bureau started as a think tank under the supervision of the president of the National Cancer Center in July, 2012. The mission assigned to the Strategic Planning Bureau has been to organize tasks involving not only our center, but also cancer control throughout Japan, and to construct policies for advising industry, government, and academia from the National Cancer Center.

The staff of the Strategic Planning Bureau consists primarily of young members who serve as chief physicians, deputy directors of research groups, or administrators responsible for front-line medical care or research. Therefore we are able to provide system which makes use of the problems which confront staff to make policies.

# Multidisciplinary Research (MDR) Support Office: MDRSO

**Noriko Yamashita, Suga Yamagami, Mari Tomoda, Izumi Kobayashi, Toshinobu Ishibashi**

## 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, develops the infrastructure for research and conducts the audit for clinical studies and investigator initiated trials. 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 the results throughout the NCC in the shift to a new system.

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 new two "Research Concierges" and trained them to be able to handle the explanation to patients. Seven thousand and nine new patients were approached this year, from whom 6,264 agreed to participate, giving a consent rate of 89.4%. Also the Concierges support new patients with processes such as explaining common preliminary diagnosis cards and infection tests. The MDRSO supported 7,841 new patients from January 4 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. The MDRSO held one briefing session for newcomers to the Tsukiji campus on April17, and 154 staff members participated in the session.

Pertinent regulations for the NCC Biobank were updated 3 times for appropriately managing the NCC Biobank and the use of samples by researchers.

The MDRSO has released the Biobank website to the NCC staff on September 13, 2012. This website aims to enhance information about the NCC Biobank allowing sharing among all staff members.

Twenty six visitors from 5 agencies came to see the National Cancer Center Biobank.

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 number of participants was 606 (Table 1).

**Table 1. Research ethics seminars**

| Date | Mar 15, 2012 | Apr 16, 2012 | Oct 10, 2012 |
|---|---|---|---|
| Programs & Speakers | Research Ethics and Human Research Protection<br>by Dr. Akihiro Sato<br>Application procedure for a new protocol<br>by IRB Office | Lecture on the ethical guidelines for clinical Research<br>by Dr. Akihiro Sato<br>Research Ethics and Human Research Protection<br>By Dr. Masashi Ando<br>Application procedure for a new protocol<br>by IRB Office | Research Ethics and Human Research Protection<br>By Dr. Tsutomu Yonemori<br>Application procedure for a new protocol<br>by IRB Office |
| No. of Participants | 104 | 376 | 126 |

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

The MDRSO manages researchers' attendance history at research ethics seminars in a unified manner. The MDRSO also corresponds to helps researchers to give information about attendance history at research ethics seminars for 62 times.

1)-3 Creation of clinical research teaching materials

The MDRSO revised 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 studies and invetigator initiated trials

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

The MDRSO established Standard Operation Procedures (SOPs) on accepting audits and monitoring of clinical studies on March 7.

2)-2 Construction of the audit system for clinical studies and investigator initiated trials

The MDRSO is in charge of auditing investigator initiated trials conducted in accordance with GCP and clinical studies based on the ethical guidelines. SOPs for these audits were established on October 1. Four auditors have been appointed by the Head of NCC as of October 1.

3) Inquiry about clinical research for patients

The MDRSO started a system where receptionists primarily respond to inquiries, complaints and so on from patients regarding 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 studies. Two patients placed quieries by telephone, which were successfully answered by the MDRSO.

4) Planning for and coordinating of research 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 19 researchers made presentations and led discussions. The speakers and the number of participants at each conference were as follows (Table 2).

5) Alliance / partnership activity support

The MDRSO held a meeting to support cooperative activities between the NCC researchers and companies that match alliance contracts, aiming for early development tests. (No. of participants: 35 on Dec 4)

**Table 2. Research conferences**

| Date | Presenter | No. of Participant |
|---|---|---|
| Jan 16, 2012 | Tetsuo Akimoto/Takahiro Ochiya | 253 |
| Feb 15, 2012 | Tomotaka Sobue/Kenji Tamura | 181 |
| Jun 18, 2012 | Yasuhide Yamada/ Toshikazu Ushijima/Toshihiko Doi | 275 |
| Jul 10, 2012 | Takashi Kohno/Koichi Goto | 276 |
| Sep 11, 2012 | Atsushi Ohtsu/Akihiro Sato /Noboru Yamamoto/Teruhiko Yoshida | 247 |
| Oct 9, 2012 | Kazuaki Shimada /Shinichi Yachida/Daisuke Kubotae | 205 |
| Nov 13, 2012 | Ryuzo Ueda / Yuji Heike/Tetsuya Nakatsura | 255 |

# Multi-institutional Clinical Trial Support Center

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

## Introduction

The Multi-institutional Clinical Trial Support Center is a sector reporting directly to the Chief Director of the National Cancer Center. 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 16 disease-oriented or modality-oriented subgroups covering most cancer types except leukemia and pediatric cancer, and approximately 3,000 physicians from 190 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 the JCOG headquarters, the JCOG Data Center and the JCOG Operations Office, in collaboration with a 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 2012, the Center had supported 34 open trials, 22 trials on follow-up, 16 trials in preparation, and the yearly patient accrual was 2,985, which increased by 9% compared to 2011. As for safety management, 54 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 3 interim analysis reports, and 48 protocol amendments/revisions. The Audit Committee made site visits for 34 sites in 10 hospitals, and a total of 106 cases were audited. A central pathology review is on-going in 5 trials (2 on lymphomas, 1 on osteosarcomas, 1 on gastric cancer, and 1 on pancreatic cancer). The quality control program for radiotherapy continued in 13 trials. A web-based 24-hour online patient registration system is available in 25 trials among 34 open trials.

As for activities 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, the 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.

## List of papers published in 2012
## Journal


1. Nakamura K, Shibata T, Takashima A, Yamamoto S, Fukuda H. Evaluation of three definitions of progression-free survival in preoperative cancer therapy (JCOG0801-A). Jpn J Clin Oncol, 42:896-902, 2012

2. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, Nakamura T, Yabusaki H, Aoyama N, Kurita A, Ikeda K, Kanda T, Tsujinaka T, Nakamura K, Fukuda H. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol, 19:68-74, 2012

3. Niho S, Ohe Y, Ishikura S, Atagi S, Yokoyama A, Ichinose Y, Okamoto H, Takeda K, Shibata T, Tamura T, Saijo N, Fukuoka M. Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: a multicenter feasibility study (JCOG 0402). Ann Oncol, 23:2253-2258, 2012

4. Katayama H, Ito S, Sano T, Takahari D, Mizusawa J, Boku N, Tsuburaya A, Terashima M, Sasako M. A Phase II study of systemic chemotherapy with docetaxel, cisplatin, and S-1 (DCS) followed by surgery in gastric cancer patients with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1002. Jpn J Clin Oncol, 42:556-559, 2012

5. Rossi A, Di Maio M, Chiodini P, Rudd RM, Okamoto H, Skarlos DV, Fruh M, Qian W, Tamura T, Samantas E, Shibata T, Perrone F, Gallo C, Gridelli C, Martelli O, Lee S-M. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol, 30:1692-1698, 2012

6. Azuma T, Tobinai K, Takeyama K, Shibata T, Hidaka M, Kurosawa M, Kasai M, Chou T, Fukushima N, Mukai K, Tsukasaki K, Shimoyama M. Phase II study of intensive post-remission chemotherapy and stem cell transplantation for adult acute lymphoblastic leukemia and lymphoblastic lymphoma: Japan Clinical Oncology Group Study, JCOG9402. Jpn J Clin Oncol, 42:394-404, 2012

7. Matsumoto K, Katsumata N, Saito I, Shibata T, Konishi I, Fukuda H, Kamura T. Phase II study of oral etoposide and intravenous irinotecan for patients with platinum-resistant and taxane-pretreated ovarian cancer: Japan Clinical Oncology Group Study 0503. Jpn J Clin Oncol, 42:222-225, 2012

8. Kitagawa Y, Ando N, Nakamura K, Shibata T, Fukuda H. The role of adjuvant chemotherapy for localized squamous cell esophageal cancer: current Japanese standard and the unending role of the drawing board. Ann Surg Oncol, 19:1425-1427, 2012

9. Kagami Y, Itoh K, Tobinai K, Fukuda H, Mukai K, Chou T, Mikuni C, Kinoshita T, Fukushima N, Kiyama Y, Suzuki T, Sasaki T, Watanabe Y, Tsukasaki K, Hotta T, Shimoyama M, Ogura M. Phase II study of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) therapy for newly diagnosed patients with low- and low-intermediate risk, aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG9508. Int J Hematol, 96:74-83, 2012

10. Kunieda F, Kitamura H, Niwakawa M, Kuroiwa K, Shinohara N, Tobisu K, Nakamura K, Shibata T, Tsuzuki T, Tsukamoto T, Kakehi Y. Watchful waiting versus intravesical BCG therapy for high-grade pT1 bladder cancer with pT0 histology after second transurethral resection: Japan Clinical Oncology Group Study JCOG1019. Jpn J Clin Oncol, 42:1094-1098, 2012

11. Shien T, Nakamura K, Shibata T, Kinoshita T, Aogi K, Fujisawa T, Masuda N, Inoue K, Fukuda H, Iwata H. A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017. Jpn J Clin Oncol, 42:970-973, 2012

12. Atagi S, Kawahara M, Yokoyama A, Okamoto H, Yamamoto N, Ohe Y, Sawa T, Ishikura S, Shibata T, Fukuda H, Saijo N, Tamura T. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). Lancet Oncol, 13:671-678, 2012

# International Contribution

Education and international contribution are one of the National Cancer Center's missions. From its very foundation, the NCC has widely accommodated international visiting fellows, mainly as clinical visiting fellows. Although most of them are not allowed to perform clinical work due to the law in Japan, the NCC attracts many visiting fellows.

The NCC has also been a longtime host institution for a group of doctors supported by the Japan International Cooperation Agency (JICA), the biggest Japanese organization supporting developing countries. In the year 2012, too, eight JICA doctors came and underwent training at the six divisions.

About half of the visiting fellows come to the Endoscopy and learn Endoscopic Submucosal Dissection and Chromo-Endoscopic Diagnosis, in which the NCC Endoscopy team takes the lead world-wide, whereas the majority of the rest join surgical departments and learn NCC's unique techniques. Radiation and Pathology are popular, too.

The duration is agreed upon by host divisions and fellows and is from 4 days, the minimal fellowship dates, to up to about one year. The NCC takes many short-term (1- 3 days) visitors, as well.

Most fellows come to the Tsukiji campus but the number of visiting fellows is on the rise at the Kashiwa campus, too.

The fellows are not limited to clinical fields. There are some research fellows, too. They come and join researchers working on studies at our Research Institute departments.

Following their warm welcome from the host divisions and the support they receive from fellowship administrators, overseas fellows complete their fellowship with high satisfaction. Some fellows come back to the NCC for further fellowship. As the NCC staff's international work continues, more and more fellows may continue to visit.

Annual JICA training "Latest Cancer Diagnosis and Treatment" 2012
Dates: October 22 to November 22, 2012
Number of fellows: 8
Countries: Armenia, Costa Rica, Macedonia, Nigeria, Serbia, Sri Lanka and Uruguay
Fellowship divisions:
Gynecology, Colorectal Surgery, Endoscopy, Radiology Oncology, Musculoskeletal Oncology, Thoracic Oncology

**Table 1. Clinical and research visiting fellows by country**

| Citizenship | Number of fellows |
|---|---|
| Armenia | 1 |
| Benin | 3 |
| Bhutan | 1 |
| Brazil | 6 |
| China | 25 |
| Costa Rica | 2 |
| El Salvador | 1 |
| Germany | 1 |
| India | 1 |
| Indonesia | 2 |
| Iran | 1 |
| Iraq | 1 |
| Italy | 2 |
| Korea | 6 |
| Macedonia | 1 |
| Malaysia | 1 |
| Malta | 1 |
| Nigeria | 1 |
| Oman | 1 |
| Peru | 2 |
| Philippines | 1 |
| Russia | 4 |
| Serbia | 1 |
| Singapore | 1 |
| Spain | 2 |
| Sri Lanka | 1 |
| Taiwan | 21 |
| Thailand | 4 |
| Turkey | 1 |
| United Kingdom | 5 |
| United States | 1 |
| Uruguay | 1 |
| Total | 103 |

January - December, 2012
Both campuses of Tsukiji and Kashiwa
short-term visitors are not included.

# Hospital

## Preface

The National Cancer Center Hospital (NCCH) has always set goals in accordance with the principles of striving for the highest level of patient care and clinical research.

The role of the NCCH should cover all facets of medical practice, such as diagnosis and treatment, as well as clinical research to explore better treatment procedures. To provide the most suitable patient care in cancer to all the people in Japan, we must develop new modalities, then evaluate, standardize and share them with domestic and international hospitals. Medical practice should be a constantly advancing field, so our mission includes the development of new agents, devices, techniques and methods for diagnosis and treatment, and also patient support such as palliative symptom control, mental care, family care, appearance care, and so on. We endeavor to be the most active and example of a state-of-the-art cancer hospital in Japan.

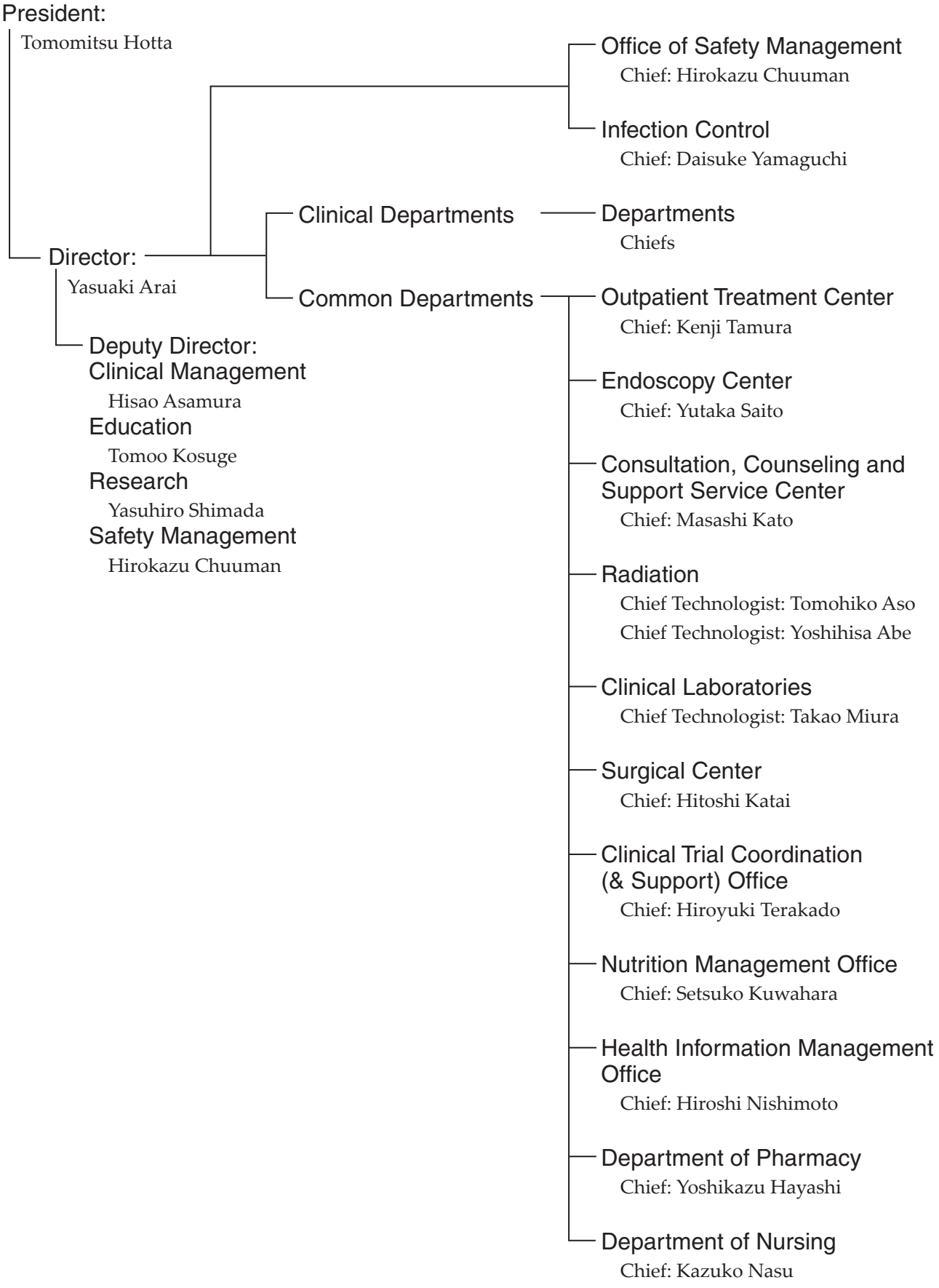
On July 2012, we reorganized the department structures into 30 clinical sections and 11 central clinical facilities to clarify each of their roles and to allow each of them to devote their full attention to their responsibilities.

All members of staff continue to make a full effort to develop better cancer patient care and to be the most reliable medical partner for patients as professionals.

It is my great pleasure and honor to present the summary of our achievements in 2012, and I appreciate your understanding of our recent efforts and results in our ongoing progress towards the continuous advancement of cancer patient care.

Yasuaki Arai, M.D.
Director, National Cancer Center Hospital

## Organization



# Clinical Departments

Director:
Yasuaki Arai

Deputy Director:
Clinical Management
Hisao Asamura
Education
Tomoo Kosuge
Research
Yasuhiro Shimada
Safety Management
Hirokazu Chuuman

- Department of Neurosurgery and Neuro-Oncology
  Chief: Soichiro Shibui
- Department of Ophthalmic Oncology
  Chief: Shigenobu Suzuki
- Department of Head and Neck Surgery
  Chief: Masao Asai
- Department of Plastic and Reconstructive Surgery
  Chief: Shimpei Miyamoto
- Department of Breast Surgery
  Chief: Takayuki Kinoshita
- Department of Breast and Medical Oncology
  Chief: Yasuhiro Fujiwara
- Department of Thoracic Surgery
  Chief: Hisao Asamura
- Department of Thoracic Oncology
  Chief: Tomohide Tamura
- Department of Esophageal Surgery
  Chief: Yuji Tachimori
- Department of Gastric Surgery
  Chief: Hitoshi Katai
- Department of Colorectal Surgery
  Chief: Yukihide Kanemitsu
- Department of Gastrointestinal Medical Oncology
  Chief: Yasuhiro Shimada
- Department of Endoscopy
  Chief: Yutaka Saito
- Department of Hepatobiliary and Pancreatic Surgery
  Chief: Kazuaki Shimada
- Department of Hepatobiliary and Pancreatic Oncology
  Chief: Takuji Okusaka
- Department of Urology
  Chief: Hiroyuki Fujimoto
- Department of Gynecology
  Chief: Takahiro Kasamatsu
- Department of Musculoskeletal Oncology and Rehabilitation
  Chief: Hirokazu Chuman
- Department of Dermatologic Oncology
  Chief: Naoya Yamazaki
- Department of Hematology
  Chief: Kensei Tobinai
- Department of Hematopoietic Stem Cell Transplantation
  Takahiro Fukuda
- Department of Blood Transfusion and Cellular Therapy
  Chief: Ryuji Tanosaki
- Department of Pediatric Oncology
  Chief: Atsushi Makimoto
- Departments of General Internal Medicine, Dentistry, Oncologic Emergency
  Chief: Ken Ohashi
  Chief: Daisuke Yamaguchi
- Department of Genetic Counseling
  Chief: Teruhiko Yoshida
- Department of Anesthesia and Intensive Care
  Chief: Tetsufumi Sato
- Department of Palliative Care
  Chief: Motohiro Matoba
- Department of Psycho-Oncology
  Chief: Ken Shimizu
- Department of Diagnostic Radiology
  Chief: Yasuaki Arai
  Chief: Masahiko Kusumoto
- Department of Radiation Oncology
  Chief: Jun Itami
- Departments of Pathology, Clinical Laboratories
  Chief: Hitoshi Tsuda

# Activities of the Departments

# Department of Neurosurgery and Neuro-Oncology

**Soichiro Shibui, Yoshitaka Narita, Yasuji Miyakita, Makoto Ohno, Yoshiko Okita, Hideyuki Arita**

## Introduction

Patients with primary and metastatic brain tumors are treated by six neurosurgeons in the Neurosurgery Division. Two hundred fifty-seven patients were admitted and 98 craniotomies for tumor removal were carried out in 2012 including 47 gliomas, 33 metastatic brain tumors, 4 primary CNS lymphomas, and 7 meningiomas (Table 1). Nine ventriculo-peritoneal shunts and 4 neuroendoscopic surgeries 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. Five awake surgeries were also performed, particularly for removal of gliomas near the speech center. We started work with our intraoperative MRI system in February 2012 and 80 craniotomies were carried out with use of this system. 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 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 5-year survival rates of the patients with anaplastic astrocytomas and glioblastomas were 66.1% and 10.1%, respectively, which were better than those recorded in the Brain Tumor Registry of Japan. (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. Clinical data during 2001 and 2004 were collected and the report will be published in 2013 as a supplement of the official journal of the Japan Neurosurgical Society.

An analysis of gene expression profiles in malignant gliomas is being carried out in order to determine specific genes that have an influence on the effects of chemotherapy and radiation therapy in cooperation with the Division of Cancer Genomics, 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, the determination of the methylation status of $O^6$-methylguanine-DNA methyltransferase (MGMT) and the mutation of IDH1/2 are also carried out to predict the prognosis of the patients with malignant gliomas.

## Clinical trial

The Japan Clinical Oncology Group (JCOG)-Brain 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: "A Randomized phase III trial of postoperative whole brain radiation therapy compared with salvage stereotactic radiosurgery in patients with one to four brain metastasis (JCOG 0504)". 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 2013. 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.

**Table 1. Number of surgeries by year, 2010-2012**

| | 2012 | 2011 | 2010 |
|---|---|---|---|
| Glioma | 47 | 35 | 51 |
| Metastatic brain tumor | 33 | 39 | 42 |
| Meningioma | 7 | 5 | 9 |
| Primary CNS lymphoma | 4 | 6 | 4 |
| Other brain tumor | 5 | 7 | 6 |
| Others | 36 | 31 | 33 |
| Total | 132 | 123 | 145 |

**Table 2. Survival rates**

| Diagnosis | MST (mo) | 5-yr (%) |
|---|---|---|
| Diffuse astrocytoma | 76.0 | 55.6 |
| Oligoastrocytoma | n.v. | 94.1 |
| Anaplastic oligoastrocytoma | 82.4 | 66.1 |
| Anaplastic astrocytoma | 30.6 | 35.6 |
| Glioblastoma | 13.6 | 10.0 |

MST, median survival time; n.v., not verified

## List of papers published in 2012
### Journal


1. Momota H, Narita Y, Miyakita Y, Shibui S. Intravascular lymphoma of the central nervous system presenting as multiple cerebral infarctions. Nagoya J Med Sci, 74:353-358, 2012
2. Okita Y, Narita Y, Miyakita Y, Ohno M, Nagai S, Shibui S. Management of cytomegalovirus infection in a patient with malignant glioma treated with temozolomide and steroids. Intern Med, 51:2967-2971, 2012
3. Okita Y, Narita Y, Yoshida A, Miyakita Y, Ohno M, Saio M, Yoshimi N, Shibui S. The late recurrence of ganglioneuroma 21 years after initial presentation with neuroblastoma. Pediatr Hematol Oncol, 29:647-651, 2012
4. Ohno M, Narita Y, Miyakita Y, Okita Y, Kayama T, Shibui S. Development of secondary skull sarcoma after treatment for childhood acute myeloid leukemia. Asia Pac J Clin Oncol, 8:e49-52, 2012
5. McCarthy BJ, Shibui S, Kayama T, Miyaoka E, Narita Y, Murakami M, Matsuda A, Matsuda T, Sobue T, Palis BE, Dolecek TA, Kruchko C, Engelhard HH, Villano JL. Primary CNS germ cell tumors in Japan and the United States: an analysis of 4 tumor registries. Neuro Oncol, 14:1194-1200, 2012
6. Matsuda K, Sato A, Okada M, Shibuya K, Seino S, Suzuki K, Watanabe E, Narita Y, Shibui S, Kayama T, Kitanaka C. Targeting JNK for therapeutic depletion of stem-like glioblastoma cells. Sci Rep, 2:516, 2012
7. Ohno M, Narita Y, Miyakita Y, Okita Y, Matsushita Y, Yoshida A, Fukushima S, Ichimura K, Kayama T, Shibui S. Histopathological malignant progression of grade II and III gliomas correlated with IDH1/2 mutation status. Brain Tumor Pathol, 29:183-191, 2012
8. Okita Y, Narita Y, Miyakita Y, Ohno M, Fukushima S, Maeshima A, Kayama T, Shibui S. Long-term follow-up of vanishing tumors in the brain: how should a lesion mimicking primary CNS lymphoma be managed? Clin Neurol Neurosurg, 114:1217-1221, 2012
9. Fukushima S, Narita Y, Shinomiya A, Ohno M, Miyakita Y, Okita Y, Hanakawa K, Ide T, Kayama T, Shibui S, Tsuda H. A case of unclassified high-grade glioma with polar spongioblastoma pattern. Neuropathology, 32:604-610, 2012
10. Okita Y, Narita Y, Miyakita Y, Ohno M, Fukushima S, Kayama T, Shibui S. Pathological findings and prognostic factors in recurrent glioblastomas. Brain Tumor Pathol, 29:192-200, 2012
11. Hashimoto K, Narita Y, Matsushita Y, Miyakita Y, Ono M, Kayama T, Shibui S. Methylation status of O6-methylguanine-DNA-methyl transferase promoter region in non-small-cell lung cancer patients with brain metastasis. Clin Transl Oncol, 14:31-35, 2012
12. Okita Y, Narita Y, Miyakita Y, Ohno M, Aihara K, Mori S, 3Kayama T, Shibui S. Reactivation of cytomegalovirus following treatment of malignant glioma with temozolomide. Int Cancer Conf J, 1:53-57, 2012

# Department of Ophthalmic Oncology

**Shigenobu Suzki, Yukiko Aihara**

## Introduction

Our Department is one of the rare groups specializing in ocular tumors, especially intraocular tumors. Recently, more than 60% of patients nationwide with retinoblastomas, which is the most frequent intraocular malignancy in childhood, and more than 50% of patients with uveal melanomas, 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 complications such as secondary glaucoma or severe hemorrhage, or if extraocular extension of the retinoblastoma is strongly suspected, we can offer the family eye-preserving treatment. Initial systemic chemotherapy and additional local therapies, called "chemoreduction therapy", comprise the main strategy. If the tumor is localized in the peripheral retina, plaque radiotherapy using ruthenium-106 is also available. Transpupillary thermotherapy or cryotherapy is also used in cases with localized small tumors. Patients with extraocular extension, recurrence or metastasis who need 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 radiotherapy 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) Orbital tumors

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

4) Eyelid tumors

The most common malignant eyelid tumors include basal cell carcinoma, sebaceous carcinoma, and squamous cell carcinoma. They are treated with excisional resection and reconstruction. Radiotherapy using electrons is another strategy. Orbital exenteration is selected in cases of orbital invasion.

5) Conjunctival tumors

Conjunctival malignant tumors are treated with 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.

## Research activities

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

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

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

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

Ocular adverse events associated with anti-cancer drugs used for systemic disease have recently been recognized, and ocular examinations are included in clinical trials, especially for molecular targeted drugs. Serous retinal detachment (SRD), retinal vein occlusion (RVO), and ocular surface complications are major adverse events associated with kinase inhibitor drugs, stenosis or occlusion of lacrimal drainage systems are common events following S-1 administration, and some drugs have induced cystoid macular edema (CME). The mechanisms of these events have not been clarified, but most are classified under grade 1-2, and are reversible or self-limited. We examine and follow these adverse events, with or without additional treatment, to support clinical studies, to contribute establishing protocols, and to bring awareness of these events to the general ophthalmologist.



**Table 1. Number of patients**

| | |
|---|---|
| retinoblastoma | 53 |
| Choroidal melanoma | 20 |
| Other intraocular tumors | 23 |
| Eyelid tumor | 9 |
| Conjunctival tumor | 9 |
| Orbital tumor | 13 |
| Ocular adnexal lymphoma | 10 |
| Others | 25 |
| Total | 162 |

**Table 2. Type of procedure**

| | |
|---|---|
| Retinoblastoma | |
| Selective ophthalmic arterial injection | 116 |
| Laser and/or vitreous injection | 143 |
| Ruthenium brachytherapy | 9 |
| Enucleation | 23 |
| Examination under anesthesia (EUA) | 8 |
| Choroidal melanoma | |
| Ruthenium brachytherapy | 7 |
| Enucleation | 3 |
| Resection of ciliary body tumor | 1 |
| Resection of eyelid tumor | 5 |
| Resection of conjunctival tumor | 5 |
| Resection of orbital tumor | 9 |
| Others | 17 |
| Total | 346 |

## List of papers published in 2012

### Journal

1. Suzuki S. A case of recurrent lacrimal gland tumor treated by orbital exenteration. Jpn J Clin Oncol, 42:560, 2012

# Department of Head and Neck Surgery

**Masao Asai, Sei-ichi Yoshimoto, Tsutomu Nomura, Daisuke Maki**

## 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 vocally. We have recently started a new treatment trial of concurrent chemoradiotherapy 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 three head and neck surgeons and a chief resident. Many operations with or without major microsurgical reconstructive surgery under general and local anesthesia are performed. In addition to radiotherapy, chemo-radiotherapy for head and neck cancer have recently been performed at NCCH.

In 2012, 268 patients with head and neck cancer underwent surgery under general and local anesthesia and 52 patients had undergone major surgery with reconstructive surgery in our division. Forty seven of these patients were over 75 years old, ranging from 75 to 85. The oldest patient who was treated with microsurgical reconstructive surgery was 80 years old. There was one serious postoperative complication in 268 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 referred from other divisions have been operated on this year.

Our outpatient service is available from Monday to Friday except Wednesday, and the total annual number of newly registered patients has exceed 400. The number of new patients in 2012 was similar to 2011. 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, no standard therapy was 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 last 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 study 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 6 cases of supraglottic and glottic carcinoma and partial hypo-pharyngectomy with free jejunum in 8 cases of pyriform sinus and posterior wall hypopharyngeal carcinoma. We were able to preserve voice function in all the cases. We have been performing endoscopic mucosal resection (EMR) for small and superficial hypopharyngeal carcinomas in cooperation with the Endoscopic Division from 2006, and 24 cases were treated in 2011. The rate of voice preservation surgery in cases of hypopharyngeal cancer was very high (68%), probably the top in Japan.

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

| | |
|---|---|
| Tongue | 29 |
| Mesopharynx | 18 |
| Hypopharynx | 47 |
| Larynx | 14 |
| Oral cavity (without tongue) | 30 |
| Nasal and paranasal cavity | 10 |
| Thyroid | 16 |
| Major salivary gland | 8 |
| Neck metastasis (primary unknown, eyelid, melanoma, etc.) | 24 |
| Others | 10 |
| Total | 205 |

**Table 2. Type of procedures**

| | | |
|---|---|---|
| Glossectomy (partial, hemi, subtotal) [+ reconstruction] | 29 | [ 9] |
| Resection of mesopharyngeal tumor [+ reconstruction] | 18 | [ 5] |
| Total pharyngolaryngectomy (TPLE) [+ reconstruction] | 15 | [15] |
| Partial hypopharyngectomy (preserve larynx) [+ reconstruction] | 8 | [ 6] |
| EMR | 24 | |
| Total laryngectomy | 7 | |
| Partial laryngectomy | 6 | |
| Extended resection of larynx [+ reconstruction] | 1 | [ 1] |
| Resection of tumor of oral cavity [+ reconstruction] | 30 | [ 5] |
| Maxillectomy [+ reconstruction] | 10 | [ 2] |
| Thyroidectomy (hemi, total) | 16 | |
| Parotidectomy, etc. [+ reconstruction] | 8 | [ 2] |
| Neck dissection [+ reconstruction] | 24 | [ 2] |
| Neck tumor [+ reconstruction] | 6 | [ 1] |
| Reconstruction and plastic surgery only | 3 | |
| Tracheotomy | 5 | |
| Lymphadenectomy | 48 | |
| Others [+ reconstruction] | 10 | [ 2] |
| Total | 268 | [53] |

**Table 3. Operative morbidity and mortality**

| | |
|---|---|
| Major complications | 1 case |
| *(major leakage, bleeding, flap necrosis, etc.)* | (0.4% in total, 1 [1.9%] in 53major surgeries) |
| Minor complications | 12 cases (4.5%) |
| *(high fever, infection, pneumonia, minor leakage, etc.)* | |
| Operative death within 30 days | 0 cases |
| Postoperative hospital death | 0 cases |

## List of papers published in 2012

### Journal

1. Yoshimoto S, Hasegawa Y, Matsuzuka T, Shiotani A, Takahashi K, Kohno N, Yoshida T, Kitano H. Sentinel node biopsy for oral and laryngopharyngeal squamous cell carcinoma: a retrospective study of 177 patients in Japan. Auris Nasus Larynx, 39:65-70, 2012

# Department of Plastic and Reconstructive Surgery

**Shimpei Miyamoto, Shuji Kayano, Minoru Sakuraba, Masanobu Sakisaka**

## Introduction

The Plastic and Reconstructive Surgery Division has mainly focused on surgical reconstruction of defects left after extirpation or excision of cancerous tissue. 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 a pedicled flap, local flap, skin grafting, 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 surgery. The quality of life (QOL) of the patient can be improved by good functional and morphological reconstruction.

## Routine activities

Two plastic surgeons cover reconstructive operations. Every week three to five reconstructive procedures are performed. These reconstructive surgeries are performed in cooperation with the surgeons of another division of the hospital, such as Head and Neck Surgery, Breast Surgery, Orthopedic Surgery, Esophageal Surgery, and Dermatology, *et cetera*. The number of the patients who receive immediate breast reconstruction in our Division is increasing. Limb reconstruction after limb preservation surgery has increased in accordance with 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 surgical removal of cancers.

With the objective of addressing these four aspects, establishing a high standard 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 ongoing: 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.

Further development of reconstructive procedures in cooperation with other Divisions, such as orthopedic surgery, breast surgery and so on, is also ongoing.

**Table 1. Cooperation with other divisions**

| | |
|---|---|
| Breast surgery | 65 |
| Orthopedic surgery | 53 |
| Head & Neck surgery | 51 |
| Esophageal surgery | 14 |
| HB&P surgery | 4 |
| Neurosurgery | 4 |
| Dermatology | 1 |
| Colorectal surgery | 1 |
| Gynecology | 1 |
| Total | 194 |

**Table 2. Operative Procedures**

| | |
|---|---|
| Microvascular free flap | 120 |
| DIEP | 37 |
| Jejunum | 26 |
| Anterolateral thigh | 25 |
| Latissimus Dorsi | 21 |
| Fibula bone | 4 |
| Scapula bone | 2 |
| RAMC | 2 |
| Radial Forearm | 2 |
| Other flaps | 1 |
| Other Microsurgery | 19 |
| Supercharge | 6 |
| Limb Salvage | 7 |
| Hepatic Artery | 4 |
| Others | 2 |
| Subtotal | 139 |
| Pedicled flaps | 46 |
| Latissimus Dorsi | 23 |
| PM or PMMC | 8 |
| DP | 4 |
| Other flaps | 11 |
| Other Procedures | 95 |
| Total | 269 |



## List of papers published in 2012

### Journal


1. Miyamoto S, Sakuraba M, Nagamatsu S, Kayano S, Kamizono K, Hayashi R. Risk factors for gastric-tube dependence following tongue reconstruction. Ann Surg Oncol, 19:2320-2326, 2012
2. Miyamoto S, Sakuraba M, Nagamatsu S, Kamizono K, Hayashi R. Comparison of reconstruction plate and double flap for reconstruction of an extensive mandibular defect. Microsurgery, 32:452-457, 2012
3. Miyamoto S, Sakuraba M, Nagamatsu S. Inadvertent injury of critical perforator vessels during perforator flap surgery. J Reconstr Microsurg, 28:95-98, 2012
4. Kayano S, Sakuraba M, Miyamoto S, Nagamatsu S, Taji M, Umezawa H, Kimata Y. Comparison of pedicled and free anterolateral thigh flaps for reconstruction of complex defects of the abdominal wall: review of 20 consecutive cases. J Plast Reconstr Aesthet Surg, 65:1525-1529, 2012

# Department of Breast Surgery

**Takayuki Kinoshita, Takashi Hojo, Sota Asaga, Junko Suzuki, Eriko Iwamoto, Kenjiro Jimbo**

## Introduction

The Breast Surgery Division deals with treatment of breast cancer, as well as diagnosis of breast diseases and assessment of lymph nodes in the axillary and clavicular regions which are suspected harboring metastases. Although breast-conserving therapy (BCT) has accounted for 53.4% of the cases, BCT was not indicated in more than 40% of the cases even when the cancer was at an early stage. In 2010, immediate breast reconstruction became one of the choices for these patients in whom breast preservation was impossible, and a total of 62 immediate breast reconstructions were performed in 2012, comprising more than 12% of all the cases. Sentinel lymph node (SLN) biopsies (SLNB) were performed in 82.8% of the cases. Following SLNB, the axillary lymph node dissection (ALND) could be avoided when the SLNB was negative. 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 25.2% of the cases after SLNB needed additional ALN dissection.

## Routine activities

The Division is staffed by four staff surgeons, one chief resident, and three or four rotating residents. From 7:30 every morning, all the staff and the residents perform in patient rounds together. A journal club and research conference are scheduled on every Tuesday morning after rounds. A weekly conference is held on Wednesdays from 17:00 to 18:00 for shared discussions with surgeons, medical oncologists, radiologists, and radiology and sonography technicians. The diagnostic images of pre-operative patients are reviewed and compared to pathological reports in every postoperative 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.

BCT usually consists of local excision of the tumor followed by postoperative irradiation of the remaining breast, and is indicated for a tumor smaller than 3 cm. Patients with multi-focal lesions or extensive micro-calcifications detected with mammography are not elegible 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 tumor sensitivity to therapeutic agents. Patients receive adjuvant chemo-endocrine therapy depending upon their prognostic and predictive factors, which include the number of lymph nodes involved, the histological grade of the tumor and secondary prognostic markers (HER2/neu, ER, PgR, and so on). Widely accepted factors that predict a response to a specific therapy are estrogen and progesterone receptors for hormone therapy and HER2 for trastuzumab. Since hormone-receptor positive patients tend to receive less chemotherapy nowadays, NAC has been decreasing and only 7.7% of all patients received neoadjuvant therapy in 2012.

## 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 with node-positive (Dr. Hojo) are under consideration. With the recent advance in development of an aromatase inhibitor, neoadjuvant endocrine therapy (NAET) may become the standard-bearer of tailored treatment. We have been conducting a prospective neoadjuvant endocrine study since 1998. A new protocol to evaluate the optimal duration of NAET (4M vs 6M) 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 revealed with MRI or CT.

## Clinical trials

1) Radiofrequency ablation therapy for early breast cancer as local therapy (RAFAELO study)

   A trial of image-guided radiofrequency ablation (non-surgical therapy) has been ongoing for early-stage breast carcinomas of less than 1 cm in diameter. After these years of trial, indication has just been expanded up to 1.5 cm in diameter and this technique is certified as an advanced medical treatment by Ministry of Health, Labour and Welfare.

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

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

3) Denosumab adjuvant treatment (D-CARE)

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

4) Scalp-cooling device during chemotherapy

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

5) Sentinel lymph node (SLN) biopsy

   A multi-center feasibility study to test the SLN identification rate using a radioisotope (RI) vs indocyanine green (ICG) has been ongoing since 2011.

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

   This multi-center randomized trial started in 2012 and compares disease-free survival in patients with or without TS-1 administration together with adjuvant endocrine therapy.

7) Skin care for patients receiving radiotherapy after breast conserving therapy

   This is a multi-center survey to check the frequency and degree of radiation dermatitis in order to give appropriate skin care and improve cosmetic satisfaction of the patients. Questionnaires were handed out to patients who received radiotherapy.

**Table 1. Type of procedure**

| | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Total number of operations | 462 | | 462 | | 482 | | 576 | | 581 | |
| Mastectomy (%) | 197 | (44.0) | 209 | (45.6) | 213 | (44.2) | 250 | (47.6) | 234 | (45.4) |
| Breast-conserving surgery (%) | 251 | (56.0) | 249 | (54.4) | 269 | (55.8) | 269 | (51.2) | 275 | (53.4) |
| Radiofrequency ablation (%) | | | | | | | 6 | (1.1) | 6 | (1.2) |
| Axillary lymph node dissection (ALND) (%) | 100 | (22.3) | 89 | (19.4) | 136 | (28.2) | 205 | (41.5) | 188 | (38.1) |
| Sentinel lymph node biopsy (SLNB) (%) | 342 | (76.3) | 368 | (80.3) | 316 | (65.6) | 402 | (81.4) | 409 | (82.8) |
| ALND after SLNB (%) | | | | | | | 113 | (22.9) | 103 | (20.9) |
| Immediate breast reconstruction (%) | 0 | | 0 | | 13 | (2.7) | 74 | (14.1) | 62 | (12.5) |
| Neoadjuvant therapy | 108 | (24.1) | 105 | (22.9) | 72 | (14.9) | 57 | (10.9) | 45 | (7.7) |

**Table 2. Number of patients**

| | | 2011 | 2012 |
|---|---|---|---|
| Primary breast cancer | | 496 | 494 |
| | cStage 0 | 100 | 76 |
| | I | 186 | 199 |
| | II | 180 | 194 |
| | III | 29 | 17 |
| | IV | 1 | 8 |
| | unknown | 1 | 2 |
| Other malignant breast disease | | 1 | 3 |
| Total | | 497 | 497 |

**Table 3. Survival (2004-2005)**

| | | No. of patients | 5-yr survival (%) |
|---|---|---|---|
| stage | 0 | 83 | 96.5 |
| | I | 226 | 98.7 |
| | II | 344 | 92.4 |
| | III | 65 | 75.3 |

## List of papers published in 2012
## Journal


1. Asaga S, Kinoshita T. A case of multidisciplinary treatment for a massive locoregional recurrence of breast cancer. Jpn J Clin Oncol, 42:865, 2012
2. Shien T, Nakamura K, Shibata T, Kinoshita T, Aogi K, Fujisawa T, Masuda N, Inoue K, Fukuda H, Iwata H. A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017. Jpn J Clin Oncol, 42:970-973, 2012
3. Kikuyama M, Takeshima H, Kinoshita T, Okochi-Takada E, Wakabayashi M, Akashi-Tanaka S, Ogawa T, Seto Y, Ushijima T. Development of a novel approach, the epigenome-based outlier approach, to identify tumor-suppressor genes silenced by aberrant DNA methylation. Cancer Lett, 322:204-212, 2012
4. Hirokawa T, Kinoshita T, Nagao T, Hojo T. A clinical trial of curative surgery under local anesthesia for early breast cancer. Breast J, 18:195-197, 2012
5. Nagao T, Kinoshita T, Hojo T, Tsuda H, Tamura K, Fujiwara Y. The differences in the histological types of breast cancer and the response to neoadjuvant chemotherapy: the relationship between the outcome and the clinicopathological characteristics. Breast, 21:289-295, 2012
6. Nagao T, Kinoshita T, Hojo T, Kurihara H, Tsuda H. Sentinel lymph node biopsy using indigo carmine blue dye and the validity of '10% rule' and '4 nodes rule'. Breast, 21:455-458, 2012
7. Nagao T, Hojo T, Tanaka-Akashi S, Tsuda H, Kinoshita T. Primary leiomyosarcoma of the breast. Breast J, 18:81-82, 2012
8. Masuda N, Sagara Y, Kinoshita T, Iwata H, Nakamura S, Yanagita Y, Nishimura R, Iwase H, Kamigaki S, Takei H, Noguchi S. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. Lancet Oncol, 13:345-352, 2012
9. Zhang M, Higashi T, Nishimoto H, Kinoshita T, Sobue T. Concordance of hospital-based cancer registry data with a clinicians' database for breast cancer. J Eval Clin Pract, 18:459-464, 2012

# Department of Breast and Medical Oncology

**Yasuhiro Fujiwara, Kenji Tamura, Chikako Shimizu, Kan Yonemori, Harukaze Yamamoto, Mayu Yunokawa, Makoto Kodaira**



## Introduction

The Breast and Medical Oncology Division is engaged in the clinical management of, and research into 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.

We envision becoming a premier oncology department which leads cancer care in Japan and in the World. Our mission is to provide patient-centered, state-of-the-art medical care to individual patients suffering from cancer. 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, four chief residents (fellows) and one - three clinical residents. We also provide educational opportunities to short-term residents. Full-time attending physicians are on duty at the outpatient clinic one to three days a week. Residents, especially the first-year chief residents, are encouraged to take leadership in the clinical management of hospitalized patients. They also undertake clinical and translational research projects under the supervision of attending physicians. Three board-certified Breast Cancer Specialist Nurses help providing seamless and comprehensive care to breast cancer patients. Group-assigned pharmacists support patients receiving chemotherapy both in the ward and in the clinic.

Most of our patients are treated in an outpatient setting in cooperation with the Outpatient Treatment Center and Pharmacy Division. New patients are referred from both inside and outside the National Cancer Center Hospital (NCCH). We regularly have approximately 30 inpatients. Terminally-ill patients are transferred to palliative care units or in-home care clinics outside NCCH, whereas 41 patients of our Division passed away in NCCH in 2012. Post-operative breast cancer patients without disease recurrence have been encouraged to be referred to local breast cancer specialists participating in the Tokyo Breast Consortium network (http://breastcons.com/).

The Briefing Conference is held every morning to discuss the optimal care for individual patients. A Breast Cancer Specialist Nurse in the clinic and group-assigned pharmacists attend those conferences. Grand Rounds are scheduled every Monday, Wednesday, and Friday. A Phase I conference is held every Monday.

We are supporting the "Appearance Care Program" which encourages self-support for change of appearance due to cancer treatments. This 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. The Appearance Support Team consists of a physician, nurses, a clinical psychiatrist sub-specialized in appearance care, and a pharmacist.

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 multidisciplinary specialists to discuss recent topics in breast oncology and to develop institutional treatment guidelines. The treatment guidelines for breast cancer, both primary and metastatic, were updated in 2012.

## Research activities

The goal of our research activities is to develop new therapeutic strategies for adult solid tumors based on the biology of neoplasia. A Research Conference is held every Thursday morning to discuss on-going studies. Three Clinical Research Coordinators are supporting our research activities.

In 2012, we were involved in several international first-in-human studies. We continue to put our efforts into phase I studies by enhancing team communication through in-group and intergroup Phase I conferences. For late-phase studies, 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) and others. A phase II study of CBDCA/S1 triple-negative breast cancer has recently been approved by the Institutional Review Board (IRB) and is waiting for patient accrual.

With the cooperation of Shien Lab, the Research Institute, or outside institutions, we have been conducting several translational studies that aim to discover biomarkers for patient enrichment, drug-resistance, and potential drug targets. Of note, we have published the preliminary results of our $^{64}$Cu-labeled trastuzumab molecular imaging study which is being performed in cooperation with the RIKEN Center for Molecular Imaging Science. We also have recruited more than 130 patients into an observational/translational study to explore SNPS related to taxane-induced peripheral neuropathy in cooperation with the Tokyo Metropolitan Institute of Medical Science and the NCC Research Institute. We are expecting the completion of patient accrual in 2013. Other clinical studies, including the above-mentioned trials, are listed in Table 2.

In addition to clinical trials, we value cancer survivorship as a research theme in order to develop a patient-centered comprehensive care program. We have conducted several qualitative and quantitative studies focusing on patients' and physicians' perception and attitude towards fertility issues, appearance, hereditary breast and ovarian cancer, spiritual needs and end-of-life care.

## List of papers published in 2012
### Journal


1. Yonemori K, Hirakawa A, Ando M, Hirata T, Yunokawa M, Shimizu C, Tamura K, Fujiwara Y. Content analysis of oncology-related pharmaceutical advertising in a peer-reviewed medical journal. PLoS One, 7:e44393, 2012
2. Kojima Y, Hashimoto K, Ando M, Yonemori K, Yamamoto H, Kodaira M, Yunokawa M, Shimizu C, Tamura K, Hosono A, Makimoto A, Fujiwara Y. Comparison of dose intensity of vincristine, d-actinomycin, and cyclophosphamide chemotherapy for child and adult rhabdomyosarcoma: a retrospective analysis. Cancer Chemother Pharmacol, 70:391-397, 2012
3. Yunokawa M, Koizumi F, Kitamura Y, Katanasaka Y, Okamoto N, Kodaira M, Yonemori K, Shimizu C, Ando M, Masutomi K, Yoshida T, Fujiwara Y, Tamura K. Efficacy of everolimus, a novel mTOR inhibitor, against basal-like triple-negative breast cancer cells. Cancer Sci, 103:1665-1671, 2012
4. Shoji H, Hashimoto K, Kodaira M, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Ando M, Fujiwara Y. Hematologic safety of breast cancer chemotherapies in patients with hepatitis B or C virus infection. Oncology, 82:228-233, 2012
5. Ijichi N, Shigekawa T, Ikeda K, Horie-Inoue K, Shimizu C, Saji S, Aogi K, Tsuda H, Osaki A, Saeki T, Inoue S. Association of double-positive FOXA1 and FOXP1 immunoreactivities with favorable prognosis of tamoxifen-treated breast cancer patients. Horm Cancer, 3:147-159, 2012
6. Kojima Y, Hashimoto K, Ando M, Yonemori K, Hirakawa A, Kodaira M, Yunokawa M, Shimizu C, Tamura K, Katsumata N, Hosono A, Makimoto A, Fujiwara Y. Clinical outcomes of adult and childhood rhabdomyosarcoma treated with vincristine, d-actinomycin, and cyclophosphamide chemotherapy. J Cancer Res Clin Oncol, 138:1249-1257, 2012
7. Hashimoto K, Shimizu C, Tsuda H, Saji S, Osaki A, Shigekawa T, Aogi K. Immunohistochemical detection of breast cancer stem cells in hormone receptor-positive breast cancer and their role in response to endocrine therapy and clinical outcome. Oncology, 82:168-174, 2012
8. Bock AJ, Dong HP, Trope CG, Staff AC, Risberg B, Davidson B. Nucleoside transporters are widely expressed in ovarian carcinoma effusions. Cancer Chemother Pharmacol, 69:467-475, 2012
9. Nakamura S, Ando M, Masuda N, Aogi K, Ino H, Iwata H, Tokuda Y, Yamamoto N, Kasai H, Takeuchi M, Tsuda H, Akiyama F, Kurosumi M, Fujiwara Y. Randomized phase II study of primary systemic chemotherapy and trastuzumab for operable HER2 positive breast cancer. Clin Breast Cancer, 12:49-56, 2012
10. Fujiwara Y, Takatsuka Y, Imoto S, Inaji H, Ikeda T, Akiyama F, Tamura M, Miyoshi K, Iwata H, Mitsuyama S, Noguchi S. Outcomes of Japanese breast cancer patients treated with pre-operative and post-operative anastrozole or tamoxifen. Cancer Sci, 103:491-496, 2012
11. Kitagawa R, Katsumata N, Ando M, Shimizu C, Fujiwara Y, Yoshikawa H, Satoh T, Nakanishi T, Ushijima K, Kamura T. A multi-institutional phase II trial of paclitaxel and carboplatin in the treatment of advanced or recurrent cervical cancer. Gynecol Oncol, 125:307-311, 2012
12. Martin M, Bell R, Bourgeois H, Brufsky A, Diel I, Eniu A, Fallowfield L, Fujiwara Y, Jassem J, Paterson AHG, Ritchie D, Steger GG, Stopeck A, Vogel C, Fan M, Jiang Q, Chung K, Dansey R, Braun A. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. Clin Cancer Res, 18:4841-4849, 2012
13. Hashimoto K, Sasajima Y, Ando M, Yonemori K, Hirakawa A, Furuta K, Tsuda H, Fujiwara Y. Immunohistochemical profile for unknown primary adenocarcinoma. PLoS One, 7:e31181, 2012

**Table 1. Demographics of Patients at their 1st Visit to the Clinic of the Breast and Medical Oncology Division (Jan - Dec, 2012)**

| No of 1st Visits | n | % | |
|---|---|---|---|
| Total | 759 | | |
| Breast | 361 | 47.5 | |
| GYN | 136 | 17.9 | |
| Cancer of primary unknown | 106 | 14.0 | |
| Sarcoma | 78 | 10.3 | |
| Others | 78 | 10.3 | |
| Purpose of consultation | | | |
| 2nd opinion | 38 | 5.0 | |
| Treatment at NCCH | 76 | 10.0 | |
| Referrals from other hospitals | 252 | 33.2 | |
| Referrals from other divisions in NCCH | 393 | 51.8 | (100) |
| Breast surgery | 243 | | (61.8) |
| GYN | 68 | | (17.3) |
| Urology | 19 | | (4.8) |
| Orthopedics | 10 | | (2.5) |
| Others | 53 | | (21.8) |
| Others | 0 | | |

**Table 2. Active Clinical Trials (Jan. 2012-Dec. 2012)**

| 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, not recruiting |
| | | III | D-CARE | Denosumab vs placebo | Active, not recruiting |
| | | III | APHINITY | CTx+HCN/placebo vs CTx/HCN/ pertuzumab | Active |
| | | III | POTENT | HTx+S1 vs HTx alone | Active |
| | Metastatic | III | JCOG1017 | Surgery vs no surgery for primary Stage IV BC | Active |
| | | III | MARIANNE | RO5304020+/- RO4368451 vs HCN/ PTX | Active |
| | | III | NK105 | NK105 vs paclitaxel | Active |
| | | III | ELTOP (WJOG) | lapa/capecitabine vs HCN/capecitabine | Active |
| | | II | RO5304020 | RO5304020 | Active |
| | | II | lapaHER | lapatinib/HCN | Active |
| | | II | CBDCA/S1 for TNBC | CBDCA/S1 | 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 |
| | | II | GOG268 | TC+temsirolimus | 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 | RO5304020/RO5368451 | RO5304020/RO5368451 | Active |
| | | I | AZD1208 | AZD1208 | Active |
| | | I | AZD5363 | AZD5363 | Active |
| | | I | PD0332991 | PD0332991 | 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 Thoracic Surgery

**Hisao Asamura, Shun-ichi Watanabe, Hiroyuki Sakurai, Kazuo Nakagawa, Takashi Makino**

## 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 656 operations; for lung cancer in 486 patients, metastatic tumor in 89, mediastinal tumor in 17, and 64 in others.

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

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

For mediastinal tumors, thymic epithelial tumors are most commonly encountered for resection. In the mediastinum, where a variety of tumor histologies can arise, the treatment must be carefully determined by the cytologic/histologic diagnosis before surgery. For this purpose, CT-guided needle biopsy is replacing the formerly common biopsy under X-ray fluoroscopy. For patients with thymoma, we have already adopted video-assisted resection of the tumor. VATS resection of mediastinal tumor is indicated exclusively for small thymomas less than 4 cm in size.

As for meetings, there are two division meetings. One is for the preoperative evaluation and postoperative inpatient review on Fridays and the other is for the journal club on Wednesdays. In addition, 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 Thursdays.

## 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.

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" has been developed 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 as early adenocarcinomas. 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 adenocarcinomas 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. The accrual for JCOG 0804 trial closed last year. Fifty-eight cases have been registered for JCOG 0802 from our division.

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. In total, 34 cases have been registered for this trial from our division.

**Table 1. Number of patients**

| | |
|---|---|
| Primary lung cancer | 486 |
| Metastatic lung tumor | 89 |
| Mediastinal tumor | 17 |
| Pleural disease | 12 |
| Chest wall tumor | 8 |
| Benign lung nodule | 31 |
| Others | 13 |
| Total | 656 |

**Table 2. Type of procedure**

| | |
|---|---|
| Lung resection | 606 |
| Lobectomy | 356 |
| Pneumonectomy | 12 |
| Segmentectomy | 68 |
| Wedge resection | 170 |
| Tracheal resection | 0 |
| Surgery for mediastinal tumors | 15 |
| Surgery for pleural tumors | 9 |
| Surgery for chest wall tumors | 8 |
| Others | 18 |
| Total | 656 |

**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

## List of papers published in 2012
## Journal


1. Rusch VW, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, Pass H, Asamura H, Waller D, Edwards J, Weder W, Hoffmann H, van Meerbeeck JP. Initial analysis of the international association for the study of lung cancer mesothelioma database. J Thorac Oncol, 7:1631-1639, 2012
2. Kawaguchi K, Miyaoka E, Asamura H, Nomori H, Okumura M, Fujii Y, Nakanishi Y, Eguchi K, Mori M, Sawabata N, Yokoi K. Modern surgical results of lung cancer involving neighboring structures: a retrospective analysis of 531 pT3 cases in a Japanese Lung Cancer Registry Study. J Thorac Cardiovasc Surg, 144:431-437, 2012
3. Yoshino I, Yoshida S, Miyaoka E, Asamura H, Nomori H, Fujii Y, Nakanishi Y, Eguchi K, Mori M, Sawabata N, Okumura M, Yokoi K. Surgical outcome of stage IIIA- cN2/pN2 non-small-cell lung cancer patients in Japanese lung cancer registry study in 2004. J Thorac Oncol, 7:850-855, 2012
4. Van Schil PE, Asamura H, Rusch VW, Mitsudomi T, Tsuboi M, Brambilla E, Travis WD. Surgical implications of the new IASLC/ATS/ERS adenocarcinoma classification. Eur Respir J, 39:478-486, 2012
5. Hosako M, Muto T, Nakamura Y, Tsuta K, Tochigi N, Tsuda H, Asamura H, Tomonaga T, Kawai A, Kondo T. Proteomic study of malignant pleural mesothelioma by laser microdissection and two-dimensional difference gel electrophoresis identified cathepsin D as a novel candidate for a differential diagnosis biomarker. J Proteomics, 75:833-844, 2012
6. Shiraishi K, Kunitoh H, Daigo Y, Takahashi A, Goto K, Sakamoto H, Ohnami S, Shimada Y, Ashikawa K, Saito A, Watanabe S, Tsuta K, Kamatani N, Yoshida T, Nakamura Y, Yokota J, Kubo M, Kohno T. A genome-wide association study identifies two new susceptibility loci for lung adenocarcinoma in the Japanese population. Nat Genet, 44:900-903, 2012
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# Department of Thoracic Oncology

**Tomohide Tamura, Noboru Yamamoto, Hiroshi Nokihara, Yutaka Fujiwara, Shintaro Kanda, Hidehito Horinouchi, Shinji Nakamichi, Satoru Kitazono, Hidenori Mizugaki, Shigehiro Yagishita**

## Introduction

Lung cancer has been the most common cause of death from cancer since 1994, and the incidence of lung cancer in Japan is still increasing in females and the elderly. The majority of lung cancer patients are diagnosed at the advanced stage, and the prognosis of these patients is poor. The standard treatments are chemoradiotherapy for locally advanced disease and platinum doublet chemotherapy for metastatic disease. Recently, several driver gene alterations such as EGFR mutation and ALK, Ros 1 or RET fusion gene, have been identified in non-small cell lung cancer. Inhibitors for these molecules show excellent response against tumors with these driver gene alterations. Optimal treatment selection based on tumor molecular analysis and biomarker analysis is a major research issue in this field.

The goals of the Department of Thoracic Oncology are to provide high quality treatment for each patient and to establish new effective treatments against lung cancer and other thoracic malignancies. The Department of Thoracic Oncology includes 6 staff physicians. A total of 3 chief residents, 9 residents, 3 short-term residents and 1 trainee joined the department during 2012.

## Routine activities

The staff physicians attend outpatient services for thoracic diseases, and the division has 55-60 beds in the hospital. Inpatient care is carried out by five teams. Each team consists of one staff physician and one or two chief residents and residents.

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 328 new patients were admitted in 2012 (305 and 276 patients in 2011 and 2010, respectively). The diagnoses for these patients and initial treatments for 288 lung cancer patients are listed in Tables 1 and 2. Thirty-four percent of 182 advanced lung cancer patients receiving chemotherapy as their initial treatments participated in clinical trials. The survival outcomes of lung cancer patients treated in the Department are shown in Table 3. Thirty-four patients with miscellaneous solid tumors were admitted to, and participated in 8 phase I studies of new agents.

## Research activities

The Research activities of the Department can be divided into four subjects: (1) phase I/II studies to develop new effective chemotherapy regimens including new drugs against thoracic malignancies; (2) multi-institutional phase III studies such as Japan Clinical Oncology Group (JCOG) studies to establish new standard treatments against thoracic malignancies; (3) translational research using clinical samples for the development of biomarkers and innovative treatment strategies; and (4) pharmacokinetic and pharmacodynamic (PK/PD) studies to investigate optimal drug exposure and interpatient variability.

## Clinical trials

Clinical trials carried out in 2012 are shown in Table 4. More than 30 clinical trials have been carried out in the Department. Some studies were based on the JCOG Lung Cancer Study Group research program, and some were carried out under contract with pharmaceutical companies.

**Table 1. Number of New Inpatients in 2012**

| | |
|---|---|
| Non-small cell lung cancer | 240 |
| Adenocarcinoma | 187 |
| Squamous cell carcinoma | 36 |
| Others | 17 |
| Small cell lung cancer | 48 |
| Mesothelioma | 2 |
| Thymic cancer | 3 |
| Thymoma | 1 |
| Others | 34 |
| Total | 328 |

**Table 2. Initial Treatments for New Inpatients with Lung Cancer in 2012**

| | |
|---|---|
| Chemotherapy | 182 |
| Chemoradiotherapy | 42 |
| Adjuvant chemotherapy following surgery | 33 |
| Preoperative chemoradiotherapy | 2 |
| Thoracic radiotherapy | 4 |
| Supportive care alone (including palliative radiotherapy) | 25 |
| Total | 288 |

**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 2012**

| Target disease | Stage | Phase | Treatment |
|---|---|---|---|
| NSCLC | Advanced | III | S-1 vs. DTX |
| NSCLC | Advanced | III | PF-00299804 vs. Erlotinib |
| NSCLC | Advanced | III | Erlotinib vs. Erlotinib/ARQ197 |
| NSCLC | Advanced | III | CBDCA/PTX vs. CBDCA/PTX/AMG706 |
| NSCLC MET+ | Advanced | III | Erlotinib vs. Erlotinib/MetMAb |
| NSCLC | Advanced | III | Eribulin vs. Physician's choice |
| NSCLC | Advanced | III | Bevacizumab beyond PD |
| NSCLC-ALK fusion | Advanced | III | PF-02341066 vs. PEM/CDDP |
| NSCLC | Advanced | II | DTX+IMC1121B |
| NSCLC-ALK fusion | Advanced | II | PF-02341066 |
| NSCLC-EGFR mutation | Advanced | II | Erlotinib vs. Erlotinib/Bevacizumab |
| NSCLC-EGFR mutation | Advanced | II | Gefitinib+PEM |
| NSCLC-ALK fusion | Advanced | I/II | CH5424802 |
| NSCLC | Advanced | I | CBDCA/PTX+Ipilimumab |
| NSCLC | Advanced | I | CBDCA+PTX+ABT888 |
| 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 | Limited | II | JCOG1101: CRT- CDDP/AMR vs. CODE |
| SCLC | Extensive | I/II | CPT-11 maintenance |
| Lung cancer | Advanced | II | CDDP short hydration |
| Lung cancer | Advanced | Translational | Circulating endothelial cells |
| Lung cancer | Advanced | PK/PK | Erlotinib |
| Solid tumor | Advenced | PK/PD | TS-1 |
| Solid tumor | Advanced | I | 8 New agents |

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

## List of papers published in 2012
## Journal


1. Makihara RA, Makino Y, Yamamoto N, Yokote N, Nokihara H, Sekine I, Ohe Y, Tamura T, Yamamoto H. Gender difference in hematological toxicity among lung cancer patients receiving amrubicin monotherapy. Jpn J Clin Oncol, 42:1187-1191, 2012

2. Niho S, Ohe Y, Ishikura S, Atagi S, Yokoyama A, Ichinose Y, Okamoto H, Takeda K, Shibata T, Tamura T, Saijo N, Fukuoka M. Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: a multicenter feasibility study (JCOG 0402). Ann Oncol, 23:2253-2258, 2012

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17. Tomioka H, Mukohara T, Kataoka Y, Ekyalongo RC, Funakoshi Y, Imai Y, Kiyota N, Fujiwara Y, Minami H. Inhibition of the mTOR/S6K signal is necessary to enhance fluorouracil-induced apoptosis in gastric cancer cells with HER2 amplification. Int J Oncol, 41:551-558, 2012

# Department of Esophageal Surgery

**Yuji Tachimori, Hiroyasu Igaki, Nobukazu Hokamura, Takayoshi Kishino**

## Introduction

More than 300 new patients with esophageal tumors are admitted to the National Cancer Center Hospital (NCCH) every year. The multidisciplinary treatment plans are determined by the stage of the tumor in close cooperation with other teams. The Esophageal Surgery Division cooperates with the Gastrointestinal Oncology Division and the Radiation Oncology Division particularly 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 6% in our division in 2012.

## Routine activities

The Esophageal Surgery Division consists of three staff surgeons, one chief resident and 2-3 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 conference for pretreatment clinical diagnosis and a pathology demonstration of resected esophageal tumors has been held irregularly this year to discuss a wide range of topics.

Every week, 2-3 patients with esophageal cancer undergo esophageal surgery. One hundred nineteen patients underwent esophagectomy including 2 patients with cervical esophageal cancer and 11 with adenocarcinoma in the esophagogastric junction, and also including two with carcinosarcoma and one with small cell carcinoma. Six of 11 adenocarcinomas arose from Barrett's epithelium. Of the 92 patients who underwent surgery as primary therapy, a curative resection was completed for 88%, significantly decreased from previous year. There was 1 hospital death due to an operative complication (1%). Preoperative chemotherapy was recommended for 52 patients and preoperative chemoradiotherapy was recommended for 2 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 21 patients, which is a decrease from the previous year and reflecting the stricter application of this method. Feasibility will be evaluated upon morbidity and survival results.

The number of patients who receive definitive chemoradiotherapy as their primary treatment for resectable tumors 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 2012. A three-field dissection is avoided for salvage esophagectomy.

## Research activities

Several translational studies are being carried out in cooperation with the National Cancer Center Research Institute. Establishing a cell line of squamous cell carcinoma floating in the thoracic duct is being carried out. A study of DNA methylation in biopsied specimens is also ongoing to estimate the efficacy of preoperative chemotherapy in patients with advanced esophageal cancer.

## Clinical trials

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. A new multi-institutional randomized controlled trial comparing standard preoperative chemotherapy (5FU and cisplatin), an intensive regimen (5FU and cisplatin plus docetaxel), and preoperative chemoradiotherapy (5FU and cisplatin plus 41.4

Gy irradiation) for Stage II-III esophageal cancer (JCOG1109) has launched on December, 2012. A Phase II trial for definitive chemoradiotherapy with or without salvage esophagectomy (JCOG0909) is continuing registration. For a Stage I lesion, a multi-institutional randomized controlled comparison between surgery and definitive chemoradiotherapy for a Stage I lesion (JCOG0502) has almost finished registration.

**Table 1. Type of surgery**

| | |
|---|---|
| Esophagectomy | 90 |
| Salvage esophagectomy | 12 |
| Gastric conduit cancer surgery | 1 |
| Salvage lymphadenectomy | 10 |
| Bypass surgery | 3 |
| Cervical esophagostomy | 2 |
| Exploration | 1 |

**Table 2. Type of esophagectomy**

| | |
|---|---|
| Rt. thoracotomy with 3-field | 46 |
| Rt. thoracotomy with 2-field | 23 |
| Video-assisted with 3-field | 15 |
| Video-assisted with 2-field | 6 |
| Lt. thoracotomy | 1 |
| Lt. thoraco-abodominal | 3 |
| Transhiatal | 2 |
| Cervical | 4 |
| Abdominal | 4 |

**Table 3. Survival rates after esophagectomy**

| Clinical stages before preoperative chemo and/or radiotherapy | No. of pts | MST (mo) | 5-yr survival (%) |
|---|---|---|---|
| cStage I | 171 | n.v. | 80.1 |
| cStage IIA | 195 | 86 | 71.1 |
| cStage IIB | 157 | n.v. | 72.6 |
| cStage III | 494 | 34 | 36.9 |
| cStage IVA | 42 | 17 | 21.4 |
| cStage IVB | 112 | 22 | 28.0 |

Operation period: 1999.1-2008.12 n.v.: not verified

## List of papers published in 2012

### Journal

1. Ozawa S, Tachimori Y, Baba H, Fujishiro M, Matsubara H, Numasaki H, Oyama T, Shinoda M, Takeuchi H, Teshima T, Udagawa H, Uno T, Barron JP. Comprehensive Registry of Esophageal Cancer in Japan, 2004. Esophagus, 9:75-98, 2012

# Department of Gastric Surgery

**Hitoshi Katai, Takeo Fukagawa, Shinji Morita, Masaki Ohashi, Yukie Yoda, Masahiro Maeda**



## Introduction

This Division treats not only gastric adenocarcinomas 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. Neoadjuvant chemotherapy is frequently used for patients with locally advanced tumors.

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

We consider the education of foreign surgeons is to be an important function. In 2012, 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. DNA methylation as a gastric cancer metastasis risk factor has been investigated. A mini-chip assay of peritoneal washing specimens or prediction of gastric cancer recurrence is being developed. Research on the detection of small amounts of cancer cells in the 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 on systemic chemotherapy with Docetaxel, CDDP, and S-1 followed by surgery in advanced cancer with extensive lymph node metastasis has been conducted. A phase II study has just started to check the feasibility of Oxaliplatin, and S-1 neoadjuvant chemotherapy for stage III disease.

**Table 1. Number of Patients**

| | |
|---|---|
| Adenocarcinoma | 413 |
| GIST | 11 |
| Others | 57 |
| Total | 481 |

**Table 2. Operative morbidity and mortality after gastrectomy**

| | Number of patients | % |
|---|---|---|
| Major complications | 55 | 16.1 |
| Minor complications | 77 | 22.5 |
| Postoperative hospital deaths | 0 | 0 |
| Total | 342 | 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 | 146 |
| Total gastrectomy | 90 |
| Pylorus-preserving gastrectomy | 48 |
| Proximal gastrectomy | 19 |
| Wedge resection | 10 |
| Pancreaticoduodenectomy | 1 |
| Laparoscopic distal gastrectomy | 15 |
| Laparoscopic pylorus preserving gastrectomy | 22 |
| Laparoscopic total gastrectomy | 1 |
| Other (bypass, exploration, etc.) | 129 |
| Total | 481 |

**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

## List of papers published in 2012
### Journal


1. Terashima M, Kitada K, Ochiai A, Ichikawa W, Kurahashi I, Sakuramoto S, Katai H, Sano T, Imamura H, Sasako M. Impact of expression of human epidermal growth factor receptors EGFR and ERBB2 on survival in stage II/III gastric cancer. Clin Cancer Res, 18:5992-6000, 2012
2. Shigematsu Y, Niwa T, Yamashita S, Taniguchi H, Kushima R, Katai H, Ito S, Tsukamoto T, Ichinose M, Ushijima T. Identification of a DNA methylation marker that detects the presence of lymph node metastases of gastric cancers. Oncol Lett, 4:268-274, 2012
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4. Ishida M, Morita S, Saka M, Fukagawa T, Taniguchi H, Katai H. Metachronous liver metastasis from early gastric cancer. J Gastrointest Surg, 16:837-841, 2012

# Department of Colorectal Surgery

**Yukihide Kanemitsu, Takayuki Akasu, Dai Shida, Seiichiro Yamamoto, Masashi Takawa**



## 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, multidisciplinary 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 preoperative treatment plans for patients about to undergo surgery.

## Routine activities

There are four staff surgeons, one chief resident, and four or five rotating residents. Every morning (8:00-8:30), we have a morning conference and rounds in wards 8B and 15A, B. A multidisciplinary team (MDT) meeting is held for cancer patients as a form of institutionalized communication every Tuesday morning (7:15-8:00), and a conference is held for the diagnosis of colorectal cancer: colorectal surgeons, endoscopists, and radiologists discuss the diagnosis for preoperative patients every Tuesday evening (18:30-19:30). Every Wednesday evening (17:00-18:30), a conference is held on the treatment of colorectal cancer: colorectal surgeons and medical oncologists discuss treatments for preoperative and postoperative patients. Ten to 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 trial (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. To evaluate the survival benefit and safety of primary resection plus chemotherapy compared to chemotherapy alone in asymptomatic stage IV colorectal cancer with synchronous unresectable metastatic disease, a randomized controlled trial comparing resection of the primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer (JCOG1007, iPACS) is ongoing. 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 2012, we published 4 papers, and the results of our research in 2012 are summarized as follows.

## Clinical research

To examine the technical and oncological feasibility of laparoscopic surgery for rectal cancer, we conducted a confirmatory phase II trial to evaluate laparoscopic surgery for preoperative clinical stage 0/I rectal cancer. In a prospective multicenter study of laparoscopic surgery in Japan, Lap ISR was feasible and safe for clinical stage 0/I rectal cancer

with a favorable short-term outcome.

Endoscopic submucosal dissection (ESD) is increasingly being used to resect early-stage colorectal carcinomas, despite the technical difficulties associated with the procedure. Laparoscopic-assisted colorectal surgery (LAC) is an alternative to open surgery for colorectal cancers, and ESD was recently introduced as another alternative. We compared ESD with LAC as minimally invasive treatments for early colorectal cancer. ESD was associated with a lower complication rate than LAC, with favorable en bloc and curative resection rates. The safety profile and possibility of curative treatment with colorectal ESD provide advantages for the treatment of early colorectal cancers with nul risk of lymph node metastasis.

A randomized controlled trial to confirm that the results of mesorectal excision alone are not inferior to those of mesorectal excision with lateral lymph node dissection was undertaken at 33 major hospitals in Japan. Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than mesorectal excision alone. The primary analysis will help to show whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

## Clinical trials

Our division plays a central role in conducting multi-institutional clinical trials in Japan. Y. Shimada is a representative of the Colorectal Cancer Group of the Japan Clinical Oncology Group (JCOG). Our 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.
7. JCOG1007: A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer (JCOG1007, iPACS) is ongoing.

**Table 1. Number of operative procedures**

| Operative Procedures | Number of patients | |
|---|---|---|
| | Open | Laparoscopic |
| Colectomy | 61 | 121 |
| High anterior resection | 3 | 7 |
| Low anterior resection | 54 | 43 |
| Abdomino-perineal resection | 20 | 4 |
| Hartmann's operation | 1 | |
| Intersphincteric resection | 2 | 10 |
| Total extirpation of large intestine | 1 | 1 |
| Total pelvic exenteration | 6 | |
| Total pelvic exenteration with sacrectomy | 1 | |
| Bypass | 2 | |
| Colostomy or ileostomy | 32 | |
| Local excision | 1 | |
| Other | 65 | |

## List of papers published in 2012
## Journal


1. Yamamoto S, Fujita S, Akasu T, Inada R, Moriya Y. Risk factors for anastomotic leakage after laparoscopic surgery for rectal cancer using a stapling technique. Surg Laparosc Endosc Percutan Tech, 22:239-243, 2012
2. Murata S, Koga Y, Moriya Y, Akasu T, Fujita S, Yamamoto S, Kakugawa Y, Ohtake Y, Saito N, Matsumura Y. Application of miRNA expression analysis on exfoliated colonocytes for diagnosis of colorectal cancer. Gastrointest Cancer: Targets and Therapy, 2:11-18, 2012
3. Fujii S, Yamamoto S, Ito M, Yamaguchi S, Sakamoto K, Kinugasa Y, Kokuba Y, Okuda J, Yoshimura K, Watanabe M. Short-term outcomes of laparoscopic intersphincteric resection from a phase II trial to evaluate laparoscopic surgery for stage 0/I rectal cancer: Japan Society of Laparoscopic Colorectal Surgery Lap RC. Surg Endosc, 26:3067-3076, 2012
4. Fujita S, Akasu T, Mizusawa J, Saito N, Kinugasa Y, Kanemitsu Y, Ohue M, Fujii S, Shiozawa M, Yamaguchi T, Moriya Y. Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial. Lancet Oncol, 13:616-621, 2012

# Department of Gastrointestinal Medical Oncology

**Yasuhiro Shimada, YasuhideYamada, Tetsuya Hamaguchi, Ken Kato, Satoru Iwasa, Yoshitaka Honma, Atsuo Takashima, Tsuyoshi Shirakawa**

## 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. A multi-kinase inhibitor, regorafenib, will be approved for colorectal cancer in 2013. For gastric cancer, an anti-HER2 monoclonal antibody, named trastuzumab, was also approved in 2011. 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 7 medical oncologists, 1 senior resident, 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 2012, we treated 2,208 hospitalized patients (524 of whom were newly diagnosed). Of these patients, 182 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 measured the gene mutations 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 RT-PCR assay. Some of these results on the correlation between gene mutation profile and cancer outcomes

led to the clinical development of novel molecular targeted drugs, for example an anti-FGF antibody or FGF kinase inhibitor for gastric cancer. We also collected serum of esophageal cancer patients who received neoadjuvant chemotherapy or chemoradiotherapy, and subjected it to a proteomics analysis. We detected some biomarkers which can predict the efficacy of the neoadjuvant treatment of esophageal cancer patients. We are going to confirm and validate these markers in the large phase III trial, JCOG1109.

## 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

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. We investigated the additive effect of ramucirumab, an anti-VEGFR2 receptor antibody, combined with FOLFIRI (5-FU/l-LV/Irinotecan) for colorectal cancer patients who failed to respond to first line treatment with FOLFOX or XELOX +bevacizumab. TAS-102, an oral novel fluoropyrimidine, was also compared to best supportive care in an international phase III trial for the salvage line of colorectal cancer patients.

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 the overseas strategies. A new adjuvant trial, JCOG0910, comparing S-1 with one of the standard regimens, capecitabine alone, started in March 2010. At the end of 2012, more than 1200 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 II part of JCOG0903, a phase I/II trial of chemoradiation with S-1/MMC for anal canal squamous carcinoma, continues to enroll patients.

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. A new pivotal phase III trial comparing S-1/CDDP(CS) to S-1/CDDP/Docetaxel(DCS) was started from April, 2012. 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. The AVAGAST trial which evaluated the additive effect of bevacizumab for fluoropyrimidine and cisplatin in first line treatment for metastatic gastric cancer was published in 2011.

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 has been completed, showing improved tolerability and preliminary favorable survival results.

Molecular-targeted drugs for advanced gastric cancer as well as colorectal cancer have been investigated. The result of the AVAGAST international phase III trial, showed no additive effect of bevacizumab to standard treatment. Cetuximab was also evaluated in an international phase III trial, the EXPAND trial, and the result was shown in the ASCO meeting 2012. No additive effect of cetuximab was shown, similar to the AVAGAST trial. RAD001 (an mTOR inhibitor) also showed a negative effect for gastric cancer. We have investigated some other molecular targeted drugs for example lapatinib (EGFR/HER2, a dual tyrosine kinase inhibitor), ramucirumab (anti-vascular monoclonal antibodies) or TKI258 (a receptor tyrosine-kinase inhibitor). 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

A phase III trial (JCOG0502) which compared surgery to chemoradiotherapy for stage I esophageal cancer patients started from 2006. At the end of 2012, more than 370 patients were enrolled for this study, and patient accrual was finished on January 2013.

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. The large pivotal trial JCOG1109 which compared standard preoperative FP to a DCF regimen (FP+Docetaxel) or an FP +radiation regimen just started from December 2012. A phase II study (JCOG0909) on the FP/RT (50.4 Gy) regimen plus salvage surgery with endoscopic resection in stage IB, II or III esophageal cancer is ongoing. A phase I/II study (JCOG0807) of triplet regimen (5-FU+CDDP+Dpcetaxel) has finished the final analysis and will be presented at the ASCO meeting 2013. Nimotuzumab is one of the anti-EGFR antibodies, which has shown activity for head and neck, gastric, and lung cancer. A phase I study of 5-FU+CDDP+Radiation with Nimotuzumab was finished and showed feasibility for stage IB/II/III/IVA esophageal cancer patients. A phase II study of cancer vaccine has finished patients accrual.

4. Other

A phase I study on 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 III study on AMN107 against gastrointestinal stromal tumors has also finished. An international phase III trial using regorafenib showed positive results compared to best supportive care in salvage treatment for gastrointestinal stromal tumors. An international phase III trial, RADIANT-4, which compared RAD001 to best supportive care in neuroendocrine tumor (NET) patients, is ongoing.

**Tables**

| Number of Patients Treated | Total no. of hospitalized pts | No. of newly diagnosed pts. | No. of pts. enrolled protocol |
|---|---|---|---|
| 1) Esophageal cancer | 791 | 171 | |
| Stage I FP+RT vs surgery JCOG0502 (phase III) | | | 11 |
| Stage I EMR+5FU/CDDP+RT JCOG0508 (phase II) | | | 1 |
| 5FU/CDDP+RT for Ce Esophageal Cancer (phase II) | | | 1 |
| Stage II/III EC-CRT+Salvage JCOG0909 (phase II) | | | 9 |
| S-488410 (phase I/II) | | | 4 |
| 5FU/CDDP+RT +DE766 (phase I) | | | 3 |
| NeoCFvsNeoDCFvsNeoCF-RT JCOG1109 (phase III) | | | 3 |
| 2) Gastric cancer | 810 | 154 | |
| S-1/oxaliplatin (SOX) vs S-1/cisplatin (SP) (phase III) | | | 7 |
| Paclitaxel ±I MC-1121B (ramucirumab/placebo) (phase III) | | | 7 |
| Neo S1/CDDP JCOG0501(phase III) | | | 3 |
| wPTX/Tmab (phase II) | | | 1 |
| Bevacizumab ± capecitabine/cisplatin AVAGAST (phaseIII) | | | 1 |
| Dovitinib (phase II) | | | 2 |
| AZD8931+paclitaxel (phase II) | | | 2 |
| S-1/cisplatin/trastuzumab (phase II) | | | 5 |
| S-1/CDDP(CS) vs Docetaxel+CS JCOG1013 (phase III) | | | 29 |
| 3) Colorectal cancer | 516 | 161 | |
| Adjuvant Capecitabine vs S-1 JCOG0910 (phase III) | | | 36 |
| FOLFOX+bevacizumab vs SOX+bevacizumab (phase III) | | | 5 |
| Observation vs FOLFOX JCOG0603 (phase II/III) | | | 2 |
| Stage II/III S-1/MMC JCOG0903 (phase I/II) | | | 3 |
| FOLFOX or FOLFIRI/Panitumumab Paff-J (phase II) | | | 5 |
| FOLFIRI ± MC-1121B (ramucirumab/placebo) (phase III) | | | 5 |
| CapeOX+bevacizumab vs SIRB TRICOLORE (phase III) | | | 6 |
| TAS-102 vs BSC (phase III) | | | 20 |
| Elderly patients 5-FU/l-LV vs FOLFOX JCOG1018 (phase III) | | | 1 |
| 4) Others | 91 | 38 | |
| AMN107 vs imatinib (GIST) (phase III) | | | 1 |
| Regorafenib vs BSC (GIST) (phase III) | | | 1 |
| RAD001 vs BSC (NET) (phase III) | | | 2 |
| Peptide vaccines (gastrointestinal cancer)(phase I) | | | 12 |
| AZD4547 (gastrointestinal cancer) (phase I) / pre screening | | | 4/88 |
| BYL719 (phase I) | | | 1 |
| Total | 2208 | 524 | 187 |

## List of papers published in 2012
## Journal


1. Kim HK, Choi IJ, Kim CG, Kim HS, Oshima A, Yamada Y, Arao T, Nishio K, Michalowski A, Green JE. Three-gene predictor of clinical outcome for gastric cancer patients treated with chemotherapy. Pharmacogenomics J, 12:119-127, 2012

2. Iwasa S, Nakajima TE, Nakamura K, Takashima A, Kato K, Hamaguchi T, Yamada Y, Shimada Y. First-line fluorouracil-based chemotherapy for patients with severe peritoneal disseminated gastric cancer. Gastric Cancer, 15:21-26, 2012

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4. Hirashima Y, Yamada Y, Tateishi U, Kato K, Miyake M, Horita Y, Akiyoshi K, Takashima A, Okita N, Takahari D, Nakajima T, Hamaguchi T, Shimada Y, Shirao K. Pharmacokinetic parameters from 3-Tesla DCE-MRI as surrogate biomarkers of antitumor effects of bevacizumab plus FOLFIRI in colorectal cancer with liver metastasis. Int J Cancer, 130:2359-2365, 2012

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11. Nakajima TE, Yoshida H, Okamoto N, Nagashima K, Taniguchi H, Yamada Y, Shimoda T, Masutomi K. Nucleostemin and TWIST as predictive markers for recurrence after neoadjuvant chemotherapy for esophageal carcinoma. Cancer Sci, 103:233-238, 2012

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# Department of Endoscopy, Gastrointestinal Endoscopy Division

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## Introduction

The Gastrointestinal Endoscopy Division and Bronchoscopy Division were unified again and became an independent unit under the name of the Endoscopy Center from July 2012. Now our Endoscopy Division is one of the most active Endoscopy Centers for both gastrointestinal imaging and bronchoscopy in the world.

The Gastrointestinal Endoscopy Division has eight staff physicians in the National Cancer Center Hospital (NCCH), three staff physicians in the Screening Technology and Development Division, three chief residents, five residents, four trainees and several rotating residents. The Bronchoscopy Division has welcomed three additional staff and resident doctors since 2010 and the total number of bronchoscopies and therapeutic procedures has dramatically increased.

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

## Routine activities in GI Endoscopy

Various diagnostic techniques including chromoendoscopy, magnifying endoscopy and endoscopic ultrasonography (EUS) are used to detect and evaluate early malignant lesions. Capsule endoscopy also has been accepted as being far less invasive. In our facility, small intestine capsule endoscopy has been performed since 2005. In order to obtain more accurate endoscopic diagnosis of gastrointestinal diseases, we routinely use the recently developed narrow-band imaging (NBI) system. A total of 11,190 (+2%), 3,231 (+8%), 392 (+5%), 69 (+6%), 41 and 16 (-43%) 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 2012.

Due to the increasing number of patients with superficial gastrointestinal neoplasms, the number of therapeutic endoscopy procedures is also increasing in this field. In 2012, 2,044 (+7%) endoscopic resections were carried out (pharynx 22 (+10%), esophagus 174 (-10%), stomach 361 (-1%) and colon 1,484 (+11%)). Among these, ESD, which was developed for large en-bloc resections with a low-risk of local recurrence, was performed for 61 (±0) superficial esophageal cancers, 330 (-4%) early gastric cancers and 125 (±0) superficial colorectal neoplasms. For colorectal ESDs and some esophageal ESDs, the newly developed ball-tip bipolar needle knife (B-knife) and IT-knife nano were used together with $CO_2$ insufflation. 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, 355 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.

**Table 1. Number of Procedures**

| | Performed in 2012 |
|---|---|
| Upper GI Endoscopy | 11,190 |
| Lower GI Endoscopy | 3,231 |
| Pharyngeal EMR/ESD | 22 |
| Esophageal EMR/ESD | 113/61 |
| Gastric EMR/ESD | 31/330 |
| Colorectal Polypectomy, EMR | 1,359 |
| Colorectal ESD | 125 |
| EUS/EUS-FNA/ERCP | 392/69/41 |
| Emergency Endoscopy | 355 |
| Capsule Endoscopy | 16 |

## Research activities in GI Endoscopy (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 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.

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 presented this paper at a Plenary Session of the American Society for Gastrointestinal Endoscopy (ASGE) in 2011 and this study was published in *Gastroenterology* in 2012 .

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 and the Japan Gastroenterological Endoscopy Society.

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.

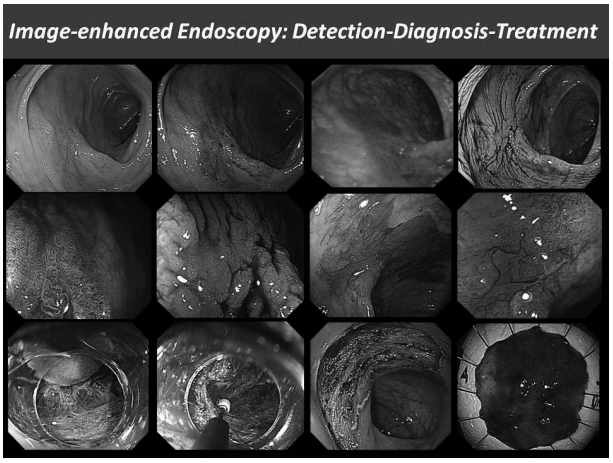


**Figure 1. Endoscopic diagnosis using image-enhanced endoscopy (high-resolution endoscopy, narrow-band imaging and autofluorescence imaging) and an endoscopic submucosal dissection (ESD) procedure for treating early colon cancer**

## Clinical trials in GI Endoscopy

A multicenter clinical trial is already 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).

A Japanese multicenter prospective cohort study is currently being conducted on EMR/ESD for early gastric cancer using a Web registry system developed to determine short-term and long-term outcomes based on the absolute and expanded indications (J-WEB/EGC). A total of 9,599 consecutive patients with 11,156 EGCs or suspected EGCs underwent EMR/ESD at the 41 participating institutions from July 2010 to June 2012 were enrolled in the study cohort using the Web registry system and each patient will be followed up a minimum of five years. The primary endpoint is the five-year overall survival with en-bloc resection, curative resection, complication, local recurrence, distant metastasis, metachronous EGC and recurrence-free survival being secondary endpoints in addition to the successful collection of long-term outcome data on enrolled patients utilizing the survey program.

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 was scheduled to continue until 2012 and ongoing analysis of the 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.

Little is known about the long-term outcomes of patients with submucosal invasive colorectal cancer who undergo endoscopic or surgical resection. We performed a retrospective analysis of the long-term outcomes of patients treated for submucosal colon and rectal cancer. We collected data from 549 patients with submucosal colon cancer and 209 with submucosal rectal cancer who underwent endoscopic or surgical resection at 6 institutions, over a median follow-up period of 60.5 months. We assessed recurrence rates, 5-year disease free survival, and 5-year overall survival. As a result, of patients treated with only endoscopic resection, the risk for local recurrence was significantly higher in high-risk patients with submucosal rectal cancer than patients with submucosal colon cancer. The addition of surgery is therefore recommended for patients with submucosal rectal cancer with pathology features indicating a high risk of tumor progression (*Gastroenterology* 2012, Dec. e-pub ahead of print). Considering this study result, we are now planning a prospective cohort study for the possibility of chemoradiotherapy for high-risk rectal submucosal cancer after endoscopic resections.

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## Journal

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# Department of Endoscopy, Respiratory Endoscopy Division

**Shinji Sasada, Takaaki Tsuchida, Yukiko Nakamura, Takehiro Izumo, Tomoyasu Mimori**

## 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 conference with CT imaging analysis and confirmation of the pathology results was held. Furthermore, we attended all clinical conferences in the Surgery, Oncology, Radiology and Pathology Divisions to discuss and decide upon treatment strategies. Seven hundred and five cases of transbronchial biopsy were performed. Endobronchial ultrasonography (EBUS) is used not only to evaluate mediastinal or hilar malignant lesions but also to evaluate whether the biopsy devices can be directed to the peripheral lung lesions. One-hundred sixty two cases of EBUS-TBNA (EBUS-trans bronchial needle aspiration) were performed as a less invasive procedure to improve the diagnosis for patients with mediastinal or hilar lymph node swelling. The EBUS-GS (guide sheath) method was performed in most of the peripheral pulmonary lesions.

Nineteen endobronchial stenosis patients were treated with airway stent placement (9 cases), endobronchial electrocautery ablation (5 cases), and tracheobronchial ballooning (5 cases). Five out of 19 intervention cases underwent procedures through the rigid bronchoscope under general anesthesia in the operation suite.

Medical thoracoscopy under local anesthesia in the operation suite was performed in 31 cases with unknown pleural effusion or a pleural tumor. Seven out of 31 cases underwent an electrocautery (IT knife) pleural biopsy because of pleural thickening.

In 2012, endobronchial photodynamic therapy was introduced, and was used in the treatment of 4 cases with squamous cell carcinoma (3 early stage, 1 advanced stage).

## Research activities

Our efforts have been focused on new diagnostic and therapeutic strategies including bronchoscopy, which involve CT-screening for lung cancer and lead to cure of, 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.

We also tried to improve the accuracy of a GGN (ground grass nodule) which had been impossible to visualize using a routine chest radiography or X-ray fluoroscopy. Chest tomosynthesis (the SONIALVISION safire radiography/fluoroscopy system, Shimadzu, Japan) is a term coined from "tomography" and "synthesis" and is a device that permits reconstruction of the coronal section image at a desired depth in a single session of photography. It is used mainly in the field of orthopedics currently, but there has been a report recently that it is excellent in visualizing chest nodules. Tomosynthesis could confirm the site of the lesion at a desired depth of the coronal section using chest tomosynthesis image mapping before bronchoscopic examination, and the lesion was diagnosed as an adenocarcinoma with a transbronchial biopsy.

## Clinical trials

We have started a clinical trial on detection of biomarker profiling using a small specimens obtained with bronchoscopy or thoracoscopy in patients with lung cancer.

**Table 1. Type of procedure**

| | |
|---|---|
| Diagnostic bronchoscopy under X-ray fluoroscopy | 551 |
| Diagnostic bronchoscopy without X-ray fluoroscopy | 195 |
| (Transbronchial biopsy) | (705) |
| Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) | 162 |
| Medical thoracoscopy | 31 |
| Airway stent placement | 9 |
| Electrocautery ablation | 5 |
| Balloon | 5 |
| Photodynamic therapy (PDT) | 4 |
| Endobronchial chemotherapy | 4 |
| Bronchial occlusion | 1 |
| Total | 967 |



## List of papers published in 2012
## Journal


1. Tamiya M, Tamiya A, Nakao K, Asami K, Okishio K, Satomu M, Shiroyama T, Morishita N, Suzuki H, Sasada S, Okamoto N, Kawaguchi T, Kobayashi M, Atagi S, Hirashima T, Kawase I. Efficacy of carboplatin and paclitaxel with bevacizumab as salvage chemotherapy for non-small cell lung cancer after failure of platinum-doublet chemotherapy. Anticancer Res, 32:3553-3557, 2012
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6. Kondo M, Nakata J, Arai N, Izumo T, Tagaya E, Takeyama K, Tamaoki J, Nagai A. Niflumic acid inhibits goblet cell degranulation in a guinea pig asthma model. Allergol Int, 61:133-142, 2012
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10. Shukuya T, Takahashi T, Harada H, Akamatsu H, Sakaguchi C, Imai H, Ono A, Nakamura Y, Tsuya A, Kenmotsu H, Naito T, Murakami H, Endo M, Takahashi K, Yamamoto N. Comparison of vinorelbine plus cisplatin and S-1 plus cisplatin in concurrent chemoradiotherapeutic regimens for unresectable stage III non-small cell lung cancer. Anticancer Res, 32:675-680, 2012
11. Naito T, Tanaka F, Ono A, Yoneda K, Takahashi T, Murakami H, Nakamura Y, Tsuya A, Kenmotsu H, Shukuya T, Kaira K, Koh Y, Endo M, Hasegawa S, Yamamoto N. Prognostic impact of circulating tumor cells in patients with small cell lung cancer. J Thorac Oncol, 7:512-519, 2012
12. Takahashi T, Boku N, Murakami H, Naito T, Tsuya A, Nakamura Y, Ono A, Machida N, Yamazaki K, Watanabe J, Ruiz-Garcia A, Imai K, Ohki E, Yamamoto N. Phase I and pharmacokinetic study of dacomitinib (PF-00299804), an oral irreversible, small molecule inhibitor of human epidermal growth factor receptor-1, -2, and -4 tyrosine kinases, in Japanese patients with advanced solid tumors. Invest New Drugs, 30:2352-2363, 2012
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# Department of Hepatobiliary and Pancreatic Surgery

**Kazuaki Shimada, Tomoo Kosuge, Minoru Esaki, Satoshi Nara, Yoji Kishi, Shutaro Hori**

## 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 and we perform around 300 surgeries each year, along with one chief resident and three or four residents. Occasionally, trainees from both Japan and overseas join our group.

*Operation and perioperative care*

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

**Table 1. Number of patients**

| | n |
|---|---|
| Invasive pancreatic cancer | 76 |
| Other pancreatic neoplasms | 24 |
| Hepatocellular carcinoma | 40 |
| Hepatic metastases | 53 |
| Intrahepatic cholangiocarcinoma | 13 |
| Bile duct cancer | 19 |
| Gallbladder cancer | 6 |
| Duodenal cancer | 15 |
| Others | 47 |
| Total | 293 |

**Table 2. Type of procedures**

| | n |
|---|---|
| Hepatectomy without biliary resection | 109 |
| Hepatectomy with biliary resection | 19 |
| Right hemihepatectomy and pancreaticoduodenectomy (HPD) | 1 |
| Classical Whipple (CW) | 22 |
| Pylorus-preserving pancreaticoduodenectomy (PPPD) | 45 |
| Distal pancreatectomy | 32 |
| Appleby operation | 1 |
| Medial pancreatectomy | 1 |
| Total pancreatectomy | 7 |
| Extended cholecystectomy | 8 |
| Other resections | 19 |
| No resection | 29 |
| Total | 293 |

**Table 3. Survival rates**

Invasive ductal carcinoma (2000-2009)

| Stages | n | 3-year survival rate (%) | 5-year survival rate (%) |
|---|---|---|---|
| I | 11 | 62 | 62 |
| II | 7 | 67 | 67 |
| III | 80 | 55 | 41 |
| IVa | 238 | 37 | 22 |
| IVb | 107 | 27 | 16 |
| Total | 443 | 39 | 26 |

Hepatocellular carcinoma (2000-2009)

| Stages | n | 3-year survival rate (%) | 5-year survival rate (%) |
|---|---|---|---|
| I | 37 | 89 | 73 |
| II | 158 | 89 | 82 |
| III | 227 | 68 | 54 |
| IV | 81 | 59 | 44 |
| Total | 503 | 74 | 62 |



## 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 analyzing "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 use of energy device during parenchyma transection of the liver: a multicenter randomized controlled trial (EPL-RCT)," and 3) "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 proceeding a study to evaluate the feasibility of laparoscopic hepatectomy in this hospital. These studies are supported by Grants-in-Aid for scientific research from the Ministry of Health, Labour and Welfare of Japan.

## List of papers published in 2012

### Journal


1. Yamamoto Y, Sakamoto Y, Ban D, Shimada K, Esaki M, Nara S, Kosuge T. Is celiac axis resection justified for T4 pancreatic body cancer? Surgery, 151:61-69, 2012
2. Hata S, Sakamoto Y, Yamamoto Y, Nara S, Esaki M, Shimada K, Kosuge T. Prognostic impact of postoperative serum CA 19-9 levels in patients with resectable pancreatic cancer. Ann Surg Oncol, 19:636-641, 2012
3. Nara S, Shimada K, Sakamoto Y, Esaki M, Kishi Y, Kosuge T, Ojima H. Prognostic impact of marginal resection for patients with solitary hepatocellular carcinoma: evidence from 570 hepatectomies. Surgery, 151:526-536, 2012
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5. Yamamoto Y, Shimada K, Takeuchi Y, Sofue K, Shibamoto K, Nara S, Esaki M, Sakamoto Y, Kosuge T, Hiraoka N. Assessment of the interface between retroperitoneal fat infiltration of pancreatic ductal carcinoma and the major artery by multidetector-row computed tomography: surgical outcomes and correlation with histopathological extension. World J Surg, 36:2192-2201, 2012
6. Kishi Y, Shimada K, Hata S, Oguro S, Sakamoto Y, Nara S, Esaki M, Hiraoka N, Kosuge T. Definition of T3/4 and regional lymph nodes in gallbladder cancer: which is more valid, the UICC or the Japanese staging system? Ann Surg Oncol, 19:3567-3573, 2012
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9. Beppu T, Sakamoto Y, Hasegawa K, Honda G, Tanaka K, Kotera Y, Nitta H, Yoshidome H, Hatano E, Ueno M, Takamura H, Baba H, Kosuge T, Kokudo N, Takahashi K, Endo I, Wakabayashi G, Miyazaki M, Uemoto S, Ohta T, Kikuchi K, Yamaue H, Yamamoto M, Takada T. A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci, 19:72-84, 2012
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11. Kamata T, Nara S. A case of peritoneal dissemination of high-grade small round cell sarcoma. Jpn J Clin Oncol, 42:1232, 2012

# Department of Hepatobiliary and Pancreatic Oncology

**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 multidisciplinary care given at the National Cancer Center Hospital (NCCH), 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

A phase I and randomized phase II study with Wilms tumor 1 (WT1) peptide vaccine plus gemcitabine and cisplatin (GC) for chemo-naïve patients with unresectable or recurrent biliary tract cancer was started, because the overexpression of WT1 is seen in the majority of patients with this disease, encouraging the potential of WT1-based immunotherapy. (Okusaka et al.). The aim of this trial is to evaluate the efficacy and safety of the regimen and to determine whether the regimen should be compared with the current standard regimen, GC, in a subsequent phase III trial for patients with unresectable or recurrent biliary tract cancer. This is the first randomized trial to evaluate the use of immunotherapy in patients with advanced biliary tract cancer.

As the level of circulating endothelial cells (CECs) is known to increase in response to various cancers, we investigated the predictive potential of CEC levels and the association of these levels with the expression of proangiogenic factors in pancreatic carcinoma patients (Kondo et al.). Pancreatic carcinoma patients receiving gemcitabine chemotherapy were prospectively assigned to this study. Baseline CEC levels were markedly higher in pancreatic carcinoma patients (n = 37) than in healthy volunteers (n = 53). Moreover, these high CEC levels were associated with decreased overall survival (median, 297 days versus 143 days, $P < 0.001$) and progression-free survival (median, 150 days versus 64 days, $P = 0.008$), as well as with high vascular endothelial growth factor, interleukin (IL)-8, and IL-10 expression in the pancreatic carcinoma patients. Several chemokines and proangiogenic factors correlate with the release of CECs, and the number of CECs detected may be a useful prognostic marker in pancreatic carcinoma patients undergoing gemcitabine chemotherapy.

We reviewed the medical records of 136 patients (41 with extrapulmonary neuroendocrine carcinoma [EP-NEC] and 95 with small-cell lung carcinoma [SCLC]) who were treated using a platinum-containing regimen for advanced disease between January 2000 and October 2008 at our hospital. (Terashima T, Morizane C et al.). The primary site of the EP-NEC was the gastrointestinal tract in 18 patients (GI tract group); the liver, biliary tract or

pancreas in 16 patients (HBP group), and other sites in 7 patients ('others' group). The response rate in the SCLC patients was 77.8%, and the response rate in the EP-NEC patients was 30.8% (37.5% in the GI tract group, 12.5% in the HBP group, and 57.1% in the 'others' group). The median survival time for the SCLC patients was 13.6 months, while that for the EP-NEC patients was 9.2 months (14.9 months in the GI tract group, 7.8 months in the HBP group, and 8.9 months in the 'others' group). A multivariate analysis demonstrated that a poor performance status, liver involvement, and the treatment regimen were independent unfavorable prognostic factors.

## Clinical trials

Thirty-two clinical trials are ongoing, including seven phase III trials, such as adjuvant chemotherapy versus placebo in HCC patients who had undergone hepatic resection or local ablation therapy, and adjuvant chemotherapy with a new regimen versus standard chemotherapy in pancreatic cancer patients after pancreatectomy. Two studies are collaboration trials with the Department of Diagnostic Radiology, and one with the Department of Radiation Oncology. Three trials are being conducted to evaluate cancer immunotherapy. Our studies are supported by National Cancer Center Research and Development Fund (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, No. H22-ganrinsho-ippan-022, No. H23-ganrinsho-ippan-006), and Health and Labour Sciences Research Grants, Clinical Research (Grant No. H21-rinshokenkyu-ippan-013, No. H23-jitsuyoka(gan)-ippan-002) from the Ministry of Health, Labour, and Welfare of Japan.



**Table 1. Number of patients**

| | No. of pts. |
|---|---|
| Pancreatic cancer | |
| Invasive ductal | 155 |
| Neuroendocrine | 23 |
| Others | 30 |
| Biliary tract cancer | |
| Extrahepatic bile duct | 9 |
| Gallbladder | 22 |
| Papilla of Vater | 5 |
| Liver cancer | |
| Hepatocellular | 230 |
| Intrahepatic cholangiocarcinoma | 36 |

**Table 2. Type of procedure**

| | No. of pts. |
|---|---|
| Pancreatic cancer | |
| Systemic chemotherapy | 111 |
| Chemoradiotherapy | 4 |
| Biliary tract cancer and Intrahepatic cholangiocarcinoma | |
| Systemic chemotherapy | 45 |
| Hepatocellular carcinoma | |
| Ethanol injection | 13 |
| Radiofrequency ablation | 32 |
| Transcatheter arterial (chemo)embolization | 129 |
| Intra-arterial chemotherapy | 36 |
| Systemic chemotherapy | 32 |
| Radiotherapy | 8 |

**Table 3. Survival rates**

| Diagnosis | No. of pts. | MST (mo) | Survival (%) |
|---|---|---|---|
| Pancreatic cancer | | | |
| Advanced | 392 | 10.2 | 1-yr: 42.3 |
| Biliary tract cancer and Intrahepatic cholangiocarcinoma | | | |
| Advanced | 184 | 11.6 | 1-yr: 47.3 |
| Hepatocellular carcinoma | | | |
| Radiofrequency ablation | 63 | 87.7 | 5-yr: 65.5 |
| Transcatheter arterial embolization | 263 | 40.4 | 3-yr: 55.4 |
| Systemic chemotherapy | 46 | 8.5 | 1-yr: 40.9 |

## List of papers published in 2012
## Journal


1. Okusaka T, Ueno M, Sato T, Heike Y. Possibility of immunotherapy for biliary tract cancer: how do we prove efficacy? Introduction to a current ongoing phase I and randomized phase II study to evaluate the efficacy and safety of adding Wilms tumor 1 peptide vaccine to gemcitabine and cisplatin for the treatment of advanced biliary tract cancer (WT-BT trial). J Hepatobiliary Pancreat Sci, 19:314-318, 2012

2. Okusaka T, Ueno H, Ikeda M, Takezako Y, Morizane C. Phase I study of TAC-101, an oral synthetic retinoid, in Japanese patients with advanced hepatocellular carcinoma. Cancer Sci, 103:1524-1530, 2012

3. Okusaka T, Kasugai H, Ishii H, Kudo M, Sata M, Tanaka K, Shioyama Y, Chayama K, Kumada H, Yoshikawa M, Seki T, Saito H, Hayashi N, Shiratori K, Okita K, Sakaida I, Honda M, Kusumoto Y, Tsutsumi T, Sakata K. A randomized phase II trial of intra-arterial chemotherapy using SM-11355 (Miriplatin) for hepatocellular carcinoma. Invest New Drugs, 30:2015-2025, 2012

4. Morizane C, Okusaka T, Ueno H, Kondo S, Ikeda M, Furuse J, Shinichi O, Nakachi K, Mitsunaga S, Kojima Y, Suzuki E, Ueno M, Yamaguchi T. Phase I/II study of gemcitabine as a fixed dose rate infusion and S-1 combination therapy (FGS) in gemcitabine-refractory pancreatic cancer patients. Cancer Chemother Pharmacol, 69:957-964, 2012

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8. Egawa S, Toma H, Ohigashi H, Okusaka T, Nakao A, Hatori T, Maguchi H, Yanagisawa A, Tanaka M. Japan Pancreatic Cancer Registry; 30th year anniversary: Japan Pancreas Society. Pancreas, 41:985-992, 2012

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10. Fujimoto A, Totoki Y, Abe T, Boroevich KA, Hosoda F, Nguyen HH, Aoki M, Hosono N, Kubo M, Miya F, Arai Y, Takahashi H, Shirakihara T, Nagasaki M, Shibuya T, Nakano K, Watanabe-Makino K, Tanaka H, Nakamura H, Kusuda J, Ojima H, Shimada K, Okusaka T, Ueno M, Shigekawa Y, Kawakami Y, Arihiro K, Ohdan H, Gotoh K, Ishikawa O, Ariizumi S-I, Yamamoto M, Yamada T, Chayama K, Kosuge T, Yamaue H, Kamatani N, Miyano S, Nakagama H, Nakamura Y, Tsunoda T, Shibata T, Nakagawa H. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. Nat Genet, 44:760-764, 2012

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# Department of Urology

**Hiroyuki Fujimoto, Motokiyo Komiyama, Hiroyuki Nakanishi, Tomohiko Hara, Takashi Kawahara**



## 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 five staff physicians and three 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 an 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 is indicated.
4. Testicular germ cell tumor (GCT). Stage I: careful observation regardless of a pathological element. Stage II or higher: EP (etoposide + CDDP) or BEP (BLM + etoposide + CDDP) chemotherapy as the 1st line. In nonseminomatous cases, 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 malignant urological tumors.

1. Renal cell carcinoma: Improvement of the treatment outcome in metastatic renal cell carcinoma remains a major problem. A phase II and III study using a VEGFR inhibitor (AG-013766) is also in progress.
2. Urothelial cancer: The effectiveness of a phase III study to confirm the efficacy of BCG instillation for high grade T1 bladder cancer (JCOG1019) is ongoing. For metastatic disease, a phase II study using a peptide vaccine (S288310) is in progress and a weekly CBDCA + PTX regimen has been indicated.
3. Prostate cancer: A phase II study to evaluate the efficacy of robotic assisted laparoscopic radical prostatectomy for low and intermediate risk prostate cancer is ongoing. A new operative method to achieve a complete surgical margin (extended radical prostatectomy) has been developed, and its efficacy in patients with specimen-confined disease has been evaluated without neoadjuvant endocrine therapy. To provide a more precise preoperative diagnosis, a new imaging strategy using 3.0 Tesla MRI has been developed. 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. 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 TAK700 has completed enrollment.

**Table 1. Patients statistics: Major treatment**

| | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|
| Radical/partial nephrectomy | 28 | 43 | 35 | 30 | 46 |
| Nephroureterectomy | 11 | 16 | 15 | 12 | 17 |
| Total cystectomy | 22 | 26 | 31 | 24 | 25 |
| TURBT | 161 | 163 | 130 | 140 | 130 |
| M-VAC | 31 | 42 | 62 | 50 | 62 |
| GC | | 50 | 71 | 84 | 83 |
| Radical prostatectomy | 105 | 111 | 98 | 111 | 87 (RALP 2) |
| Prostatic biopsy | 186 | 247 | 168 | 175 | 151 |
| High orchiectomy | 7 | 6 | 12 | 8 | 6 |
| Retroperitoneal lymphadenectomy | 10 | 7 | 8 | 13 | 6 |
| Chemotherapy for testicular cancer | 10 | 9 | 14 | 30 | 35 |
| Retroperitoneal tumor resection | 9 | 9 | 15 | 10 | 18 |

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 tumors, a second line TIP regimen has completed enrollment.

## Clinical trials

We are actively involved in the following ongoing protocol studies;

1. A phase II & III study: AG-013766 for metastatic renal cell carcinoma
2. A phase III study: BCG instillation for high grade T1 bladder cancer (JCOG1019)
3. A phase II study: Robotic assisted laparoscopic prostatectomy for low and intermediate risk prostate cancer
4. A phase III study: Salvage radiation vs hormone ablation for postoperative PSA failure in T1c-T2 prostate cancer (JCOG0401)
5. A phase II study:TAK700 for hormone-refractory prostate cancer
6. A phase II study: TIP for CDDP-refractory metastatic germ cell tumor.

## List of papers published in 2012
## Journal


1. Hashimoto K, Fujimoto H, Kouno T, Koseki M, Yonemori K, Hirata T, Yunokawa M, Shimizu C, Katsumata N, Tamura K, Ando M, Takeuchi M, Nakanishi H, Komiyama M, Nakagawa T, Fujiwara Y. The incidence and management of metachronous testicular germ cell tumors in patients with extragonadal germ cell tumors. Urol Oncol, 30:319-324, 2012
2. Hara T, Komiyama M. A case of left renal cell carcinoma with massive tumor thrombus extending into the inferior vena cava. Jpn J Clin Oncol, 42:658, 2012

# Department of Gynecology

**Takahiro Kasamatsu, Tomoyasu Kato, Shun-ichi Ikeda, Mitsuya Ishikawa, Satoshi Okada**



## 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 one resident 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 second Tuesday of each month.

1) Treatment strategy for uterine cervical cancer. Either conization or a 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 a radical hysterectomy and pelvic lymphadenectomy. Postoperative total pelvic irradiation following a radical hysterectomy is only considered for patients with metastasis to the pelvic nodes or parametrial tissue as confirmed by pathological examination. Furthermore, in 2012, intensity-modulated radiation therapy (IMRT) was employed for postoperative adjuvant radiotherapy. 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 a 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 adjuvant 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 (TC or dose dense TC). 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, patient numbers, and survival rates are shown in Tables 1, 2, and 3.

## Research activities

Serous adenocarcinoma originating from the cervix and endometrium is a rare and aggressive variant. Togami reported on the clinicopathological features of serous adenocarcinoma of the uterine cervix (1). Togami *et al.* also demonstrated that molecular biological prognostic factors, HER2 and HR, were related to RFS and/or OS in patients with

uterine papillary serous carcinoma (USPC) (2). Although UPSC is a rare tumor, it is mandatory to establish novel therapies, including chemotherapy, endocrine therapy and molecular-targeted drug therapy, based on the findings of the status of these molecular biological markers. Uehara et al analyzed the characteristics and prognosis of patients with uterine carcinosarcoma (USC) after breast cancer and hormone therapy, and concluded that a history of breast cancer and hormone therapy for breast cancer was a risk factor for developing UCS without obvious impacts on the characteristics of UCS (3). Both of these factors had statistically significant impacts on the prognosis of patients with UCS. Ikeda et al examined the correlations between the pretreatment values of four tumor markers (SCC, CEA, CA19-9, CA125) and postsurgical high-risk factors in patients with squamous cell carcinoma of the uterine cervix who underwent radical hysterectomy, and concluded that SCC, CEA, and CA19-9 ware useful for predicting the status of postsurgical high-risk factors.

## 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 and a phase II study on irinotecan and etoposide for patients with platinum-resistant taxan-pretreated ovarian cancer (JCOG 0503) are ongoing. A phase III trial of paclitaxel plus carboplatin (TC) versus paclitaxel plus cisplatin (TP) in stage IVB, persistent or recurrent cervical cancer was completed, and demonstrated that TC can be recommended as the new standard treatment for recurrent cervical cancer. A nonrandomized confirmatory trial of modified radical hysterectomy for patients with FIGO stage Ib1 (< 2 cm) uterine cervical cancer (JCOG1101) has been started. 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).

**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. Number of patients**

| | Stage | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|
| Cervical cancer | IA | 6 | 8 | 7 | 5 | 4 |
| | IB | 29 | 32 | 33 | 40 | 33 |
| | II | 18 | 13 | 13 | 5 | 4 |
| | III | 18 | 12 | 7 | 13 | 12 |
| | IV | 2 | 4 | 8 | 2 | 5 |
| | Total | 73 | 69 | 68 | 65 | 58 |
| Endometrial Cancer | I | 40 | 42 | 42 | 41 | 39 |
| | II | 7 | 5 | 6 | 4 | 8 |
| | III | 14 | 20 | 15 | 9 | 22 |
| | IV | 3 | 1 | 9 | 4 | 2 |
| | Total | 64 | 68 | 72 | 58 | 71 |
| Ovarian cancer | I | 15 | 15 | 13 | 16 | 9 |
| | II | 9 | 3 | 4 | 3 | 4 |
| | III | 8 | 11 | 18 | 13 | 11 |
| | IV | 7 | 2 | 5 | 3 | 2 |
| | NAC[a] | 8 | 9 | 5 | 8 | 9 |
| | Total | 47 | 40 | 45 | 43 | 39 |

[a] Neoadjuvant chemotherapy

**Table 3. Survival**

| FIGO Stage | Cervical cancer[a] | | Endometrial cancer[a] | | Ovarian cancer[b] | |
|---|---|---|---|---|---|---|
| | 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



## List of papers published in 2012
## Journal


1. Togami S, Kasamatsu T, Sasajima Y, Onda T, Ishikawa M, Ikeda S, Kato T, Tsuda H. Serous adenocarcinoma of the uterine cervix: a clinicopathological study of 12 cases and a review of the literature. Gynecol Obstet Invest, 73:26-31, 2012
2. Togami S, Sasajima Y, Oi T, Ishikawa M, Onda T, Ikeda S, Kato T, Tsuda H, Kasamatsu T. Clinicopathological and prognostic impact of human epidermal growth factor receptor type 2 (HER2) and hormone receptor expression in uterine papillary serous carcinoma. Cancer Sci, 103:926-932, 2012
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4. Ikeda S, Yoshimura K, Onda T, Kasamatsu T, Kato T, Ishikawa M, Sasajima Y, Tsuda H. Combination of squamous cell carcinoma-antigen, carcinoembryonic antigen, and carbohydrate antigen 19-9 predicts positive pelvic lymph nodes and parametrial involvement in early stage squamous cell carcinoma of the uterine cervix. J Obstet Gynaecol Res, 38:1260-1265, 2012
5. Ikeda S, Kato T. A case of pelvic actinomycosis unrelated to an intrauterine device. Jpn J Clin Oncol, 42:237-238, 2012
6. Eto T, Saito T, Kasamatsu T, Nakanishi T, Yokota H, Satoh T, Nogawa T, Yoshikawa H, Kamura T, Konishi I. Clinicopathological prognostic factors and the role of cytoreduction in surgical stage IVb endometrial cancer: a retrospective multi-institutional analysis of 248 patients in Japan. Gynecol Oncol, 127:338-344, 2012

# Department of Musculoskeletal Oncology and Rehabilitation

**Hirokazu Chuuman, Akira Kawai, Fumihiko Nakatani, Yoshikazu Tanzawa, Eisuke Kobayashi, Naofumi Asano, Koichi Ogura, Nokitaka Setsu, Tomohiro Fujiwara**

## 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 musculoskeletal oncology division of NCCH consists of 5 staff doctors (Drs. Hirokazu Chuman, Akira Kawai, Fumihiko Nakatani, Yoshikazu Tanzawa and Eisuke Kobayashi), 4 residents and 2 physiotherapists, 1 occupational therapist and 1 speech therapist. Occasionally, several fellows from Japan and overseas join our group. Outpatient consults are held every weekday. A constant number of about 30 patients are hospitalized for operation, chemotherapy or radiation therapy. Five or six major operations are routinely performed every week. In 2012, 299 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 35 reconstructive operations were conducted in collaboration with plastic surgeons to achieve adequate soft tissue coverage after the resection of malignant tumors of the trunk or limb-salvage operations for sarcomas of the extremities. As a result, almost 90% of the operations were performed with a limb-sparing approach. With regard to the patients' postoperative course, we have been collaborating with a physical therapist to rehabilitate the musculoskeletal system in cancer-bearing patients.

As for chemotherapy, we have been conducting 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 medical oncologists. We have been collaborating with pediatric oncologists for chemotherapeutic treatment of children and adolescents with sarcomas.

## Conferences

Monday (8:00 A.M-): Post-operative case conference
Tuesday (8:00 A.M-): Pre-operative case conference
Wednesday (8:30 A.M-): Rehabilitation conference
Thursday (7:30 A.M-): Journal club/ pediatrics and adolescence case conference

## 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 soft tissue sarcomas. Combined with each patient's clinical information, we have been establishing novel biomarkers for prediction of patients' prognoses or effects of the chemotherapeutic agents. Using the same method, we also have been searching for new genes or proteins for the molecular-targeted

treatment approach. Since 2009, we have also been focusing on the aberrant microRNA expressions in Ewing's sarcoma and osteosarcoma in order to develop novel molecular targeted therapies

## 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 adjuvant and second-line chemotherapy for bone and soft tissue sarcomas. Three multi-institutional clinical trials are active as follows:

1. Multi-institutional phase III clinical trial of multidrugs adjuvant chemotherapy for osteosarcomas (JCOG 0905) since 2010.
2. Multi-institutional phase 3 study of trabectedin for advanced soft tissue sarcoma since 2012.
3. Multi-institutional phase II study of Eribulin (an inhibitor of microtubule dynamics) for advanced soft tissue sarcoma since 2011.



**Table 1. Numbers treated in our division from 2010 -2012**

| Year | Benign STT | Malignant STT | Benign BT | Malignant BT | Total |
|---|---|---|---|---|---|
| 2010 | 86 | 146 | 44 | 44 | 320 |
| 2011 | 57 | 156 | 41 | 69 | 323 |
| 2012 | 53 | 195 | 22 | 78 | 348 |

STT, soft tissue tumor; BT, bone tumor

[Statistics]

| | Soft tissue sarcoma | Bone sarcoma | Benign bone and soft tissue Tumor | Spine or bone metastasis | Biopsy or others | Total |
|---|---|---|---|---|---|---|
| Surgeries performed in 2012 | 106 | 28 | 70 | 26 | 69 | 299 |

| | Soft tissue sarcoma | Bone sarcoma | Benign bone and soft tissue tumor | Bone metastasis | Total |
|---|---|---|---|---|---|
| New patients (2012) | 122 | 23 | 77 | 20 | 242 |

## List of papers published in 2012
## Journal

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2. Nakatani F, Ferracin M, Manara MC, Ventura S, Del Monaco V, Ferrari S, Alberghini M, Grilli A, Knuutila S, Schaefer K-L, Mattia G, Negrini M, Picci P, Serra M, Scotlandi K. miR-34a predicts survival of Ewing's sarcoma patients and directly influences cell chemo-sensitivity and malignancy. J Pathol, 226:796-805, 2012
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5. Kondo T, Kubota D, Kawai A. Application of proteomics to soft tissue sarcomas. Int J Proteomics, 2012:876401, 2012
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# Department of Dermatologic Oncology

**Naoya Yamazaki, Arata Tsutsumida, Ken-jiro Namikawa, Ryota Tanaka, Wataru Omata, Hironobu Eguchi, Kohei Ooashi**



## 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 1800 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. In particular, the numbers of patients with malignant melanoma were two hundred twenty eight, which was approximately twice the numbers 2 years ago. Most of the patients are examined and treated for skin cancer including malignant melanoma. Surgery is the main treatment modality for skin cancer, 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 Division has three staff dermatologic oncologists and four residents. We are also engaged in routine outpatient activities on Wednesdays and Thursdays in the National Cancer Center East.

In 2012, a total of 375 patients were examined for the first time in the dermatology department for a malignant skin tumor. The numbers of patients with malignant melanomas (228) and extramammary Paget's disease (18) were particularly large, and were approximately 10 times and 2 times, respectively, the numbers 15 years ago. There were also 6 cases of the rare cancer, angiosarcoma.

About 18 patients are hospitalized to undergo surgery, chemotherapy, or radiation therapy. In 2012, 265 operations were performed including 105 operations under general anesthesia. 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.

In addition to the above, we have treated patients with advanced cases of mucosal melanoma in the nasal cavity, genital lesions, perianal lesions, and uveal melanomas even though we are, from the beginning, "dermatologists ".

## Research activities

Malignant melanoma

The Department of Dermatologic Oncology has been 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.

In 2011 the JCOG Dermatologic Oncology Group was established to improve the standard treatment for Japanese skin cancer patients.

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 melanomas in Japanese, 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 are performed with the injection of technetium tin colloid, the blue dye plus fluorescence method (combination of indocyanine green and the Photodynamic Eye System). 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.

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 that 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) Postoperative natural interferon beta therapy in stage II and III cutaneous malignant melanomas.
(3) Phase I dose-escalation, safety/tolerability and preliminary efficacy study of intratumoral administration of GEN0101 in patients with advanced melanomas.

The clinical trials (industry-sponsored registration trials) are summarized in Table 3.
(1) We have conducted five kinds of industry-sponsored registration trials for malignant melanomas.
(2) We are carrying out some clinical trials in collaboration with the Investigational Drug Development and Hematology Divisions in our hospital.

**Table 1. Number of New Patients**

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

**Table 2. Operative Procedures (total number)**

| | |
|---|---|
| Wide local excision | 120 |
| Local excision | 78 |
| Sentinel node biopsy | 44 |
| Lymph node biopsy | 16 |
| Lymph node dissection | 32 |
| (neck) | 6 |
| (axilla) | 10 |
| (inguinal) | 12 |
| (groin) | 4 |
| (popliteal) | 0 |
| (epitrochlear) | 0 |
| Skin graft | 40 |
| Local flap | 8 |
| Free flap | 1 |
| Amputation | 14 |
| Others (biopsy/debridement) | 5 |

**Table 3. New Agent Studies in 2011**

| Agent | Eligible Cancer Type | Trial Phase |
|---|---|---|
| ONO-4538 | Melanomas | II |
| ONO-4538 | Solid Tumors | I |
| MAGE-A3 | Melanomas | III |
| BCX1777 | T/NK-Cell Lymphomas | I |
| E7777 | Peripheral/Cutaneous T Cell Lymphomas | I/II |
| Lenalidomide | ATL, Peripheral T Cell Lymphomas | I |
| KW0761 | ATL,T/NK-Cell Lymphomas | II |
| Romidepsin | Peripheral/Cutaneous T Cell Lymphomas | I/II |
| Vemurafenib | Melanomas | I/II |
| Ipilimumab | Melanomas | II |
| SCH54031 | Melanomas | I |
| Dabrafenib | Solid Tumors | I |
| BYL719 | Solid Tumors | I |
| RO4987655 | Solid Tumors | I |
| WT4869 | Solid Tumors | I |
| AZD8931 | Gastric Cancer | II |
| PF-00299804 | Lung Cancer | III |
| Lenalidomide | ATL | II |
| SyB-1717 | Radiotherapy-Induced Nausea and Vomiting | II |

## List of papers published in 2012
## Journal


1. Oshita C, Takikawa M, Kume A, Miyata H, Ashizawa T, Iizuka A, Kiyohara Y, Yoshikawa S, Tanosaki R, Yamazaki N, Yamamoto A, Takesako K, Yamaguchi K, Akiyama Y. Dendritic cell-based vaccination in metastatic melanoma patients: phase II clinical trial. Oncol Rep, 28:1131-1138, 2012

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# Department of Hematology

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

## Introduction

The Hematology Division is united with the Hematopoietic Stem Cell Transplantation (HSCT) Division, and the research and clinical activity in the Hematology Division are devoted to the diagnosis and treatment of hematologic malignancies. In the past, our Division introduced new disease entities, including adult T-cell leukemia-lymphoma (ATL) (JCO 2009;27:453) and angioimmunoblastic T-cell lymphoma (Blood 1988;72:1000). 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 inpatient 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 and pathologists 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 cytologic examinations, flowcytometric and molecular-genetic analyses. Five staff physicians, two chief residents, and two 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 (PCR) and fluorescence in-situ hybridization (FISH) techniques for the detection of t(8;14), t(14;18), t(11;18), t(9;22), t(8;21), t(15;17), and so on. Our recent research has focused on indolent B-cell non-Hodgkin lymphoma (B-NHL). Clinical as well as molecular genetic analysis of ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma cases led to the discovery of a tumor suppressor gene deleted at 6q23; we identified the A20 gene as a new tumor suppressor gene in various B-cell malignancies (Nature 2009;459:712). We have shown that the mutations and/or deletions are common in Japanese Hodgkin lymphoma cases (Ref 5) and are now extending the study to find other mutated genes.

From January 2012 to December 2012, we authored or coauthored 21 original articles concerning hematologic malignancies. Among them, discussions concerning the origin of epithelial tumors developing after allogeneic HSCT contributed to our understanding of the stem cells of solid tumors (Ref 6).

## Clinical trials

In 2012, we conducted 32 new-agent studies, including 9 international studies, and 7 cooperative group studies (Tables 2 and 3). The numbers are still increasing including domestic ones. Almost all the new agents that are developed against hematologic malignancies in Japan have been evaluated in our

**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 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acute myelocytic leukemia (AML) | 12 | 18 | 10 | 8 | 8 | 9 | 8 | 9 | 10 | 6 | 10 | 8 | 13 | 12 |
| Acute lymphocytic leukemia (ALL) | 6 | 3 | 8 | 3 | 2 | 1 | 2 | 4 | 9 | 8 | 2 | 2 | 1 | 1 |
| Chronic myelocytic leukemia (CML) | 15 | 9 | 24 | 11 | 7 | 5 | 6 | 10 | 11 | 3 | 3 | 2 | 2 | 2 |
| Myelodysplastic syndrome (MDS) | 9 | 9 | 8 | 5 | 6 | 5 | 3 | 3 | 9 | 8 | 20 | 9 | 3 | 3 |
| Hodgkin lymphoma (HL) | 10 | 10 | 14 | 15 | 16 | 9 | 13 | 21 | 11 | 12 | 7 | 11 | 16 | 15 |
| Non-Hodgkin lymphoma (NHL) | 133 | 204 | 215 | 268 | 291 | 299 | 278 | 265 | 210 | 208 | 151 | 185 | 243 | 172 |
| Adult T-cell leukemia-lymphoma (ATL) | 3 | 4 | 5 | 4 | 5 | 4 | 6 | 6 | 4 | 5 | 5 | 3 | 6 | 6 |
| Chronic lymphocytic leukemia (CLL) | 1 | 2 | 3 | 3 | 2 | 4 | 5 | 4 | 5 | 6 | 4 | 2 | 1 | 4 |
| Multiple myeloma (MM) | 7 | 7 | 8 | 6 | 9 | 19 | 14 | 9 | 8 | 10 | 12 | 9 | 10 | 7 |
| Waldenström macroglobulinemia (WM) | 3 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 3 | 1 | 2 | 2 | 1 |
| Total | 199 | 267 | 295 | 324 | 347 | 356 | 335 | 331 | 279 | 269 | 215 | 233 | 297 | 223 |

Division, and many of them have been approved by the Ministry of Health, Labour and Welfare (MHLW).

For ATL, based on the published results of a phase III study, JCOG9801 (JCO 2007;25:5458) and a phase I study on mogamulizumab, a humanized anti-CCR4 (CC chemokine receptor 4) antibody (JCO 2010;28:1591), we completed patient enrolment to a randomized phase II study comparing the intensified chemotherapy regimen (mLSG15) with or without mogamulizumab. We have conducted a pivotal phase II study on mogamulizumab monotherapy against relapsed ATL (Ref 15), and the agent was approved by the MHLW in March 2012. The agent is now being applied to treat other types of T-cell malignancies, and has shown promising activity against peripheral T-cell lymphoma (ASH 2012, #795).

A phase I study of oligopeptide vaccine OCV-501 against WT1 protein in AML cells to maintain cases in complete remission, is continuing. The agent was developed in Japan, and the study is the first vaccine study against hematologic malignancies aiming at approval by the MHLW.

For treatment of B-cell malignancies, a phase III trial for newly diagnosed diffuse large B-cell lymphoma (JCOG0601) is ongoing. In that trial, a dose-intense schedule of rituximab is being compared with that of a standard 3-week regimen, in combination with the administration of Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisolone (CHOP regimen).

In June 2012, we completed patient enrolment into a phase II study on a rituximab-incorporating dose-intensified chemotherapy with autologous HSCT for untreated mantle cell lymphoma (JCOG0406).



**Table 2. Clinical trials for new agent development**

| Disease | Agents | Phase | Enrolled Patients in 2012 | Enrolled Patients in Total |
|---|---|---|---|---|
| CML | Nilotinib | III | 0 | 1 |
| | Bosutinib | I/II | 1 | 3 |
| | Ponatinib | I | 1 | 1 |
| MDS | Panobinostat + Azacitidine | Ib | 0 | 0 |
| | Rigosertib | I | 0 | 0 |
| AML | WT1 vaccine | I | 2 | 3 |
| | WT1 (maintenance) | I | 2 | 2 |
| | Volasertib (BI6727) | I | 1 | 1 |
| ALL | Inotuzumab ozogamicin (CMC-544) | I | 0 | 0 |
| MM | Bendamustine + PSL | II | 1 | 1 |
| | Carfilzomib | I | 2 | 3 |
| | Siltuximab | I | 1 | 1 |
| | Anti-BAFF Ab (LY2127399) | I | 0 | 0 |
| | Perifosine | I | 0 | 0 |
| | Pomalidomide | I | 0 | 0 |
| | Lenalidomide | II | 0 | 0 |
| PTCL | Forodesine | I | 0 | 2 |
| | Mogamulizumab (KW-0761) | II | 0 | 2 |
| | Romidepsin | I/II | 6 | 6 |
| | Denileukin diftitox (E7777) | I | 1 | 2 |
| | Darinaparsin | I | 1 | 1 |
| | Lenalidomide | II | 1 | 1 |
| CD30+ lymphoma | Brentuximab vedotin (SGN-35) | I | 6 | 7 |
| B-CLL | Ofatumumab + Chlorambucil | I/II | 0 | 0 |
| FL | Obinutuzumab (GA101) | III | 8 | 11 |
| | Inotuzumab ozogamicin + R-CVP | I | 0 | 8 |
| | Everolimus (RAD001) | I | 4 | 4 |
| | Ofatumumab vs. Rituximab | III | 17 | 27 |
| | Ofatumumab +/- Bendamustine | III | 2 | 2 |
| | Rituximab + Bendamustine | II | 6 | 6 |
| | Forodesine | I | 0 | 2 |
| MCL | R-CHP +/- Bortezomib | III | 0 | 2 |
| DLBCL | Enzastaurin | III | 0 | 7 |
| | Ofatumumab | III | 1 | 1 |
| | Everolimus | III | 0 | 1 |
| | Inotuzumab ozogamicin | III | 4 | 7 |
| B-NHL | Ibrutinib (PCI-32765) | I | 1 | 1 |
| ML | Alisertib (MLN8237) | I | 3 | 3 |
| | Vorinostat (SAHA) | I | 10 | 10 |
| AML, ML, MM | OPB-51602 | I | 0 | 1 |

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

To develop new effective treatments for B-cell malignancies, we have investigated an anti-CD22 antibody drug conjugate (inotuzumab ozogamicin) (Ref 14), as well as new generation anti-CD20 antibodies (Ref 3). In addition, we initiated a phase I study on the Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765), which has shown significant efficacy against various B-cell malignancies.

For CD30-expressing lymphomas such as Hodgkin lymphoma and anaplastic large cell lymphoma, we have been conducting a phase I/II study on brentuximab vedotin (SGN-35), an anti-CD30 antibody drug conjugate, which has shown remarkable efficacy against relapsed or refractory patients.

**Table 3. Cooperative group studies**

| Disease / Protocol | Phase | Year | No. of pts (a) | %CR (b) | OS (b) |
|---|---|---|---|---|---|
| AML | | | | | |
| JALSG-AML 97 | III | (98-01) | 15 | 79% | 47% (5-yr) |
| JALSG-AML 201 | III | (02-06) | 13 | 78% | 57% (5-yr) |
| JALSG-APL 97 | III | (98-02) | 2 | 95% | 86% (4-yr) |
| JALSG-APL 204 | III | (04-11) | 2 | 94.50% | 89.1% (5-yr) |
| JALSG-AML209 | IV | (11-) | 9 | 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-) | 36 | NA | NA |
| JCOG 0406 | III | (08-) | 5 | NA | NA |
| JCOG 0908 | III | (10-) | 11 | NA | NA |
| Indolent B-cell lymphoma | | | | | |
| JCOG 0203 | II/III | (02-07) | 52 | 77% | 88% (6-yr) |
| Adult T-cell leukemia-lymphoma | | | | | |
| JCOG 9303 | II | (94-97) | 6 | 36% | 31% (2-yr) |
| JCOG 9801 | III | (98-03) | 6 | 33% | 19% (3-yr) |
| JCOG 0907 | II | (10-) | 0 | NA | NA |
| Nasal NK/T-lymphoma | | | | | |
| JCOG 0211-DI | I/II | (03-07) | 8 | 77% | 78% (2-yr) |
| Multiple myeloma | | | | | |
| JCOG 9301 | III | (93-98) | 10 | 50% (d) | 50% (4-yr) |
| JCOG 0112 | III | (02-05) | 9 | 46% (d) | 63% (2-yr) |
| JCOG 0904 | II(c) | (10-) | 5 | 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 enrolled patients in the JCOG or JALSG trials is shown here.

(c) randomized phase II study

(d) CR + PR rate. Abbreviations: JCOG, Japan Clinical Oncology Group; JALSG, Japan Adult Leukemia Study Group; LSG, Lymphoma Study Group; OS, overall survival; NA, not available

## List of papers published in 2012
## Journal


1. Tsukasaki K, Tobinai K. Clinical Trials and Treatment of ATL. Leuk Res Treatment, 2012:101754, 2012
2. Tobinai K. Guest editorial: Management of malignant lymphoma is continuously improving. Int J Hematol, 96:533-534, 2012
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# Department of Hematopoietic Stem Cell Transplantation

**Takahiro Fukuda, Yuji Heike, Takuya Yamashita, Sung-Won Kim, Saiko Kurosawa, Shigeo Fuji**

## 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, which are filtered by a central high-efficiency particulate air filtration system, are solely dedicated to our Transplant Unit.

## Routine activities

Six staff physicians (Drs. Heike, Yamashita, Kim, Kurosawa, Fuji, and Fukuda) and 2 chief residents (Drs. Hayashi and Ito) participate in the transplant program. Children who have undergone HSCT are managed in collaboration with Dr. Makimoto, the Chief of the Pediatric Oncology Division, and transplant team. In 2012, a total of 97 transplantations were performed at the 12B and 12A transplant units. The numbers of each type of HCST and those who underwent HSCT between 2008 and 2012 are shown in Tables 1 and 2, respectively. At the weekly conference on Monday afternoons, in collaboration with doctors of the Hematology Divisions, about 30 hospitalized HSCT patients and those who have been referred for HSCT, are reviewed for clinical management and a decision regarding their eligibility for HSCT. The transplant unit is staffed by 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 the principal investigators for Government-supported grant projects. Dr. Heike has organized a cell processing facility on the adjoining $12^{th}$ floor and a facility on the $11^{th}$ floor specializing in gene therapy in compliance with good manufacturing procedures (GMP). One clinical trial of gene therapy using the HSV-TK suicide gene for T-cell add-back following haploidentical HSCT is ongoing. 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 in Japan. In the Division, 11 clinical trials are ongoing, and 11 trials have completed patient accrual. A nationwide large survey of quality of life (QOL) was conducted for patients with acute leukemia who received chemotherapy or HSCT. In 2012, we have published 19 articles in peer-reviewed international journals and 8 manuscripts have been accepted for E-pub before print or are in press for publication.

**Table 1. Number of each type of HSCT**

| | Year | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|
| Allogeneic | | 77 | 93 | 90 | 76 | 72 |
| Unrelated | Bone marrow transplantation | 48 | 59 | 60 | 54 | 46 |
| | Peripheral blood stem cell transplantation | 1 | 0 | 0 | 0 | 3 |
| | Cord blood transplantation | 1 | 5 | 1 | 4 | 8 |
| Related | Bone marrow transplantation | 5 | 2 | 5 | 2 | 0 |
| | Peripheral blood stem cell transplantation | 22 | 27 | 24 | 16 | 15 |
| Autologous | | 8 | 18 | 19 | 25 | 25 |
| Total | | 85 | 111 | 109 | 101 | 97 |

**Table 2. Number of patients who underwent HSCT between 2008 and 2012**

| Diagnosis | Allogeneic | Autologous |
|---|---|---|
| Acute myeloid leukemia | 165 | 1 |
| Myelodysplastic syndrome | 32 | 0 |
| Acute lymphocytic leukemia | 58 | 0 |
| Malignant Lymphoma (including ATL) | 143 | 56 |
| Multiple Myeloma | 0 | 20 |
| Solid tumors | 2 | 18 |
| Others | 8 | 0 |
| Total | 408 | 95 |

## List of papers published in 2012
## Journal


1. Tada K, Kim SW, Asakura Y, Hiramoto N, Yakushijin K, Kurosawa S, Tajima K, Mori S, Heike Y, Tanosaki R, Maeshima AM, Taniguchi H, Furuta K, Kagami Y, Matsuno Y, Tobinai K, Takaue Y, Fukuda T. Comparison of outcomes after allogeneic hematopoietic stem cell transplantation in patients with follicular lymphoma, diffuse large B-cell lymphoma associated with follicular lymphoma, or de novo diffuse large B-cell lymphoma. Am J Hematol, 87:770-775, 2012
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5. Ishida T, Hishizawa M, Kato K, Tanosaki R, Fukuda T, Taniguchi S, Eto T, Takatsuka Y, Miyazaki Y, Moriuchi Y, Hidaka M, Akashi K, Uike N, Sakamaki H, Morishima Y, Suzuki R, Nishiyama T, Utsunomiya A. Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study. Blood, 120:1734-1741, 2012
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9. Fuji S, Nakamura F, Hatanaka K, Taniguchi S, Sato M, Mori S, Sakamaki H, Yabe H, Miyamoto T, Kanamori H, Ueda Y, Kawa K, Kato K, Suzuki R, Atsuta Y, Tamaki T, Kanda Y. Peripheral blood as a preferable source of stem cells for salvage transplantation in patients with graft failure after cord blood transplantation: a retrospective analysis of the registry data of the Japanese Society for Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant, 18:1407-1414, 2012
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# Department of Blood Transfusion and Cellular Therapy

**Ryuji Tanosaki**



## Introduction

The Department of Blood Transfusion and Cellular Therapy was formerly a division of the Department of Pathology and Clinical Laboratories. It just started in July 2012, to enable us to focus more on the management of patients with hematologic malignancies in collaboration with the Departments of Hematology-Oncology, Hematopoietic Stem Cell Transplantation, and Pediatrics. Our missions include not an only in-hospital transfusion service but also to provide support for the hematology and stem cell transplantation team in respect of blood transfusion and cellular therapy. In common with the Department of Pathology and Clinical Laboratories, our blood transfusion examination laboratory received ISO 15189 accreditation, which certifies the quality and competence of a medical laboratory with regard to quality management and technique, developed by the International Organization for Standardization Technical Committee 212 (ISO/TC 212). Our hospital is also accredited by the Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT). The chief doctor (R.T.) also supervises the phlebotomy section of the outpatient clinics.

## Routine activities

Currently, our staff members consist of 1 JSTMCT-accredited medical doctor and 4 specifically-engaged medical technologists (including 1 JSTMCT-accredited technologist) who come to us from the Department of Pathology and Clinical Laboratories consisting of 49 full-time and 9 part-time medical technologists and 4 assistants. Most activities in our department are undertaken in collaboration with the Department of Pathology and Clinical Laboratories. The Transfusion Medicine Committee is held every month, the members of which consist of the deputy director in charge of safety management, chief doctors of this department and clinical departments of surgery and internal medicine, chief of Department of Pharmacy, vice-chief of the Nursing Division, and a secretary. An administrative meeting is also held weekly, the attendees consisting of two chief doctors and three head doctors of this Department and the Department of Pathology and Clinical Laboratories, and the head and vice-head medical technologists. An all-staff meeting is held once a month.

As an in-hospital transfusion service section, we purchase blood products, which are required and ordered by clinicians, from the Red Cross, and examine and confirm the ABO blood type, and provide them for clinical use without any delay. Last year, the total units of red cell concentrates (RCC), platelet concentrates (PC) and fresh frozen plasma (FFP), which were consumed in our hospital, were 8793, 32445 and 4212, respectively. We employ the Type & Screen and computer cross-match system, but special attention is paid to blood typing, because about 100 cases of hematopoietic stem cell transplantation (SCT) are performed in our hospital every year including many ABO-mismatched donor-recipient pairs. To avoid any mistake of transfusions going to the incorrect recipients, we have established a firm safety system; a check sheet in which the appropriate or permissive ABO-blood types for the particular patient are described is always placed on the bedside of each patient undergoing allogeneic SCT and the attending doctor, nurses, and the patient double check this list with each other on every occasion of blood transfusion. When ordering blood products, protection is in place to prevent changing of the ABO-blood type, and some special process is required before any blood product of a type other than the patient's original blood type can be ordered. The unique computer program of the transfusion service section also protects inappropriate blood-type orders. The blood transfusion service also uses a check and identify system for those patients who need ABO-mismatched blood product. Bar codes are used to match the patient and his or her designated blood product at each process during transfusion.

About 90% of platelet concentrates (PC) are consumed by hematology-oncology patients. Once an order for PC is made, the blood transfusion service staff checks the patient's morning platelet counts, and, when it is 20,000/μL or more, the staff calls and asks the attending physician if the order is really necessary. In a review we previously performed, we revealed that the platelet counts were below 20,000/μL in more than 80% of patients who underwent PC transfusion in our hospital. In 2012, the wastage of total blood products was 0.6%; RCC 1.6%, PC 0.2%, FFP 1.1%. Thanks to the Tokyo Red Cross and the convenient location of our hospital, blood products are available within 1 hour almost every time when

they are needed in an emergency.

All transfusion procedures in our hospital are performed under a strict hemo-vigilant system which employs electronic medical records managed by the computer system at the blood transfusion service. Any adverse events must be recorded by the attending nurse at 5 min, 20 min, and at the end of transfusion and these data are gathered in the computer at the blood transfusion service. Adverse events are observed associated with transfusions, especially in the case of PC (about 5%). Reduction of supernatant from a PC pack is performed in patients who have experienced repetitive or severe transfusion-associated reactions. Severe adverse events must be reported to the Red Cross and to the Ministry of Health, Labour and Welfare of Japan, and a further analysis of the causative agents is then performed by the Red Cross laboratory.

The chief doctor is also involved in the management of transplant patients both as inpatients and in the outpatient clinic as a staff member of the hematopoietic stem cell transplantation team. He attends a daily morning round, a weekly transplantation conference, a weekend check-out meeting, and a weekly journal club. These activities facilitate and promote inter-departmental collaboration.

## List of papers published in 2012

### Journal

1. Kanda J, Hishizawa M, Utsunomiya A, Taniguchi S, Eto T, Moriuchi Y, Tanosaki R, Kawano F, Miyazaki Y, Masuda M, Nagafuji K, Hara M, Takanashi M, Kai S, Atsuta Y, Suzuki R, Kawase T, Matsuo K, Nagamura-Inoue T, Kato S, Sakamaki H, Morishima Y, Okamura J, Ichinohe T, Uchiyama T. Impact of graft-versus-host disease on outcomes after allogeneic hematopoietic cell transplantation for adult T-cell leukemia: a retrospective cohort study. Blood, 119:2141-2148, 2012

## Research activities and clinical trials

One of the Department's research projects is to develop a new enumeration technique of hematopoietic stem cells using an automated hematology analyzer, which started in 2006, in collaboration with a medical diagnostic company. Another project is to establish the nation-wide infrastructure of processing and management of cellular products used for hematopoietic stem cell transplantation as a committee member of the corresponding academic societies. We also participated in multi-center evaluation studies for the standardization of CD34-positive cell enumeration.

The chief doctor also contributes to transplantation activities, especially for adult T-cell leukemia-lymphoma in collaboration with the Department of Hematopoietic Stem Cell Transplantation with the support of a grant for an Anti-Cancer Project from the Ministry of Health, Labour and Welfare of Japan, and as a member of the National Marrow Bank.

# Department of Pediatric Oncology

**Atsushi Makimoto, Hiroshi Kawamoto, Chika Tanaka, Yuko Araki, Hide Kaneda**



## 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 pediatricians, two pediatric surgeons and one resident. This division handles about 60 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 a "risk-adapted therapy" method 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 Division's 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, the DC is managing 5 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.

**Table 1. Number of patients**

| Diagnosis | Newly diagnosed | Pretreated |
|---|---|---|
| Rhabdomyosarcoma | 5 | 3 |
| Ewing sarcoma family | 4 | 1 |
| Osteosarcoma | 2 | 2 |
| Neuroblastoma | 1 | 1 |
| Retinoblastoma* | 2 | 3 |
| Germ cell tumor | 2 | 0 |
| Hepatoblastoma | 1 | 2 |
| Other solid tumors | 15 | 4 |
| Acute lymphoblastic leukemia | 3 | 0 |
| Acute myeloid leukemia | 1 | 0 |
| Non-Hodgkin lymphoma | 2 | 0 |
| Other hematologic diseases | 1 | 0 |
| Total | 39 | 16 |

*; extended case only

(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 or unapproved drugs. One of the objectives of the following trials is gathering data on, and assessing the safety and efficacy data of, such off-label or unapproved drugs. The two trials (4 and 5 below) are investigator-initiated registration-directed clinical trials conducted under the Pharmaceutical Affairs Law.

(1) A phase I-II trial of the combination of topotecan and ifosfamide for recurrent pediatric solid tumors.
(2) A randomized phase II study on 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) A phase I trial of immunotherapy using HLA-A2- and A24-restricted glypican-3 peptide vaccine for pediatric tumors.
(4) Phase II trial of glucarpidase for patients who were treated with high-dose methotrexate resulting in slow excretion.
(5) A feasibility trial of ch14.18 combined with IL-2 and various colony-stimulating factors for recurrent neuroblastomas.

## List of papers published in 2012

### Journal

1. Yamamoto Y, Makimoto A. A case of stage IV neuroblastoma treated with aggressive surgery following intensive neoadjuvant chemotherapy with autologous stem cell transplantation. Jpn J Clin Oncol, 42:359, 2012

# Department of General Internal Medicine

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



## Introduction

The increasing number of cancer patients who visit the National Cancer Center Hospital have a wide range of non-cancer related medical problems such as diabetes, hypertension, heart diseases, and kidney diseases. Cancer or its treatment can aggravate the pre-existing medical conditions and sometimes can cause these problems. These medical issues must be addressed and managed along with the cancer itself so that our patients can go through optimal cancer therapies and have a better outcome. The Department of General Internal Medicine was reorganized in October 2010 to better serve these diverse needs of cancer patients and provide more comprehensive, patient-centered care. Our staff members have experience and expertise in their respective fields and provide comprehensive management of these issues.

## Routine activities

We see cancer patients on both an inpatient and outpatient basis in consultation upon the request of NCCH cancer specialists. Reasons for consultation include preoperative assessment of surgical risks, assessment of ischemic heart disease, management of hyperglycemia, treatment of heart and renal failure, management of infections, and other medical disorders. When necessary, we also offer appropriate referral to other health care facilities for further evaluation or treatment. In addition, patients seen in consultation may be followed after discharge as outpatients for the duration of their care at NCCH. Since April of 2011, we have expanded our diabetes consultation service into NCC Hospital East, improving the quality of diabetes care there.

Cardiology:

Cardiologists take charge of ECG and echocardiography sessions, in-hospital consultation, and outpatient clinic. Consultations include preoperative assessment of surgical risks, assessment of ischemic heart disease, management of arrhythmia, management of heart failure, and management of other cardiological problems. The number of consultations is about 2000 a year. When an emergency procedure is necessary, we consider transferring the patient to other facilities which have specialists. Recently, the number of clinical trials for cancer that require echocardiography assessment is increasing so that we make every effort to practice the test more efficiently.

Diabetology:

We have provided more than 400 diabetes consultations in 2012, which include perioperative management of diabetes, treatment of steroid-induced hyperglycemia during chemotherapy, and so on. In many cases, initiation of insulin is the treatment of choice. We also offer close follow-up on an outpatient basis for those who have diabetes during their cancer treatment at NCCH.

Infectious diseases:

Our main job is to provide infection-related medical care for cancer patients. We receive about 30 consultations monthly, such as surgical site infection, febrile neutropenia, catheter related infection, nosocomial pneumonia and so on. We additionally monitor and manage infection control.

Nephrology:

To reply to consultations from NCCH cancer specialists is the main work (213 consultations per year in 2012). The details of consultations are as follows: assessment and treatment of acute kidney injury (AKI), management of chronic kidney disease (CKD) (including assessment of the optimal drug dose for CKD patients), treatment of electrolyte imbalance (hyponatremia, hypernatremia, hyperkalemia, hypokalemia, hypercalcemia, hypocalcemia, hypomagnesemia), assessment of polyuria (diabetes insipidus, salt wasting syndrome [SWS], diabetes mellitus and so on), assessment of edema, management of hypertension (including refractory hypertension, like renovascular hypertension), assessment and treatment of nephrotic syndrome especially after the hematopoietic stem cell transplantation, and so on. In case of the necessity for further evaluation of a patient, we work in cooperation with the Department of Internal Medicine, Keio University Hospital. An apparatus for hemodialysis was acquired in October, 2012, so that hemodialysis patients have been able to receive cancer treatment at NCCH.

## Research activities

The evaluation of hyponatremia in cancer patients was performed. The article under the title of "Hyponatremia in cancer patients " was published in *The Japanese Journal of Nephrology*.

# Department of Dentistry

**Takao Ueno**



## Introduction

Oral complications are common in cancer patients, especially those receiving chemotherapy or undergoing radiation therapy of the head and neck. Various oral complications in cancer patients can disturb eating and the deglutition of the patient and thus cause a hypoalimentation state and dehydration, while also leading to the onset of infections such as aspiration-related pneumonia.

The Division of Dentistry provides oral hearth care for cancer patients in cooperation with various medical departments in order to reduce the risk of complications. It is necessary for dentists and dental hygienists to support a patient to allow for the successful performance of appropriate cancer treatment. To prevent and treat oral complications associated with 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.

Furthermore, in 2008 the Division established a medical cooperation system to provide dental treatment to cancer patients at local dental clinics in cooperation with the Japan Dental Association. Dentists attended a lecture on the basic knowledge necessary for treatment of cancer patients, and such participating dental clinics were then registered as "cancer cooperation dental clinics". This cooperation is divided into three phases, with three different lectures depending on the stage of the cooperation.

There were 2,019 "cancer cooperation dental clinics" in stage 1, and 1,494 people in stage 2, as of December 2012. The first stage of the cooperation was started at the end of January, 2011, and 570 patients had consulted by the end of December 2012. The second stage of the cooperation was started in March 2012, and 32 patients were introduced to dental clinics within the medical cooperation system. The medical-dental cooperative system for cancer patients is now expected to spread throughout Japan in the future. A local dentist that becomes a member of the cancer treatment team will thus be provided with support to "maintain the function of the oral cavity " in cancer patients.

## Routine activities

1) Management of oral complications associated with high-dose chemotherapy and/or stem cell transplantation 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, pharyngeal and esophageal surgery
4) Making prostheses for restoration of postoperative facial defects
5) Prevention and treatment of bisphosphonate-associated osteonecrosis
6) Establishing the cooperative system between medical departments and dental clinics 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 the medical-dental cooperative system are under study.
2) A prospective study about the onset frequency of pneumonia after operations for esophageal cancer
3) A prospective study on the taste disorder in the stomach cancer adjuvant postoperative treatment

**Table1. Number of patients**

| | Number of patients |
|---|---|
| Dental check up and oral health care before operation (Introduction to the cooperation dental clinic) | 338 (246) |
| Dental check up and oral care before chemotherapy | 81 |
| Dental check up and oral care before stem cell transplant | 78 |
| Dental check up and oral care before Radiation therapy to the head and neck cancer | 54 |
| Oral care and treatment of oral complications ( mucositis or oral infection ) During canter therapy | 188 |
| Dental treatment relevant to bisphosphonate or denosumab | 168 |
| General dental treatment, others | 115 |
| Total | 1026 |

# Department of Genetic Counseling

**Teruhiko Yoshida, Kokichi Sugano**

## Introduction

Most of the common diseases arise through a complex interplay among life style/ environmental factors, genetic predisposition and aging. Cancer is among such multi-factorial diseases, and nowadays, as many as half of the Japanese population develop some form of malignancy during their life time. Although it is no longer rare to have some relatives with cancer, most of the cases are considered polygenic and have no obvious family history (such as 3 or more patients with the same or related cancer types within the 2nd-degree relatives). 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 Genetic Counseling Division in a daily practice is to provide cancer genetic counseling in a broad sense, and we respond to 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 active participation of a nurse with an interest and training in clinical genetics is critical for the counseling sessions. Genetic risk for the possible hereditary cancer syndromes will be assessed for each client, based on a family history, age at diagnosis, type and pattern of cancer development such as multiple primaries, other accompanying signs and symptoms. The availability of a genetic testing session will be then explained, if applicable, with careful consideration of risk, benefit and limitation. Both pre- and post-genetic test counseling is essential to make the genetic testing useful to the clients and their family members in the long run. A flowchart of the outpatient clinic genetic counseling process is shown in Figure 1.

## Research activities

Genetic diagnosis in the Division has been performed in close collaboration with the Division of Genetics of the National Cancer Center Research Institute, especially in the genetic testing for hereditary retinoblastoma, familial adenomatous

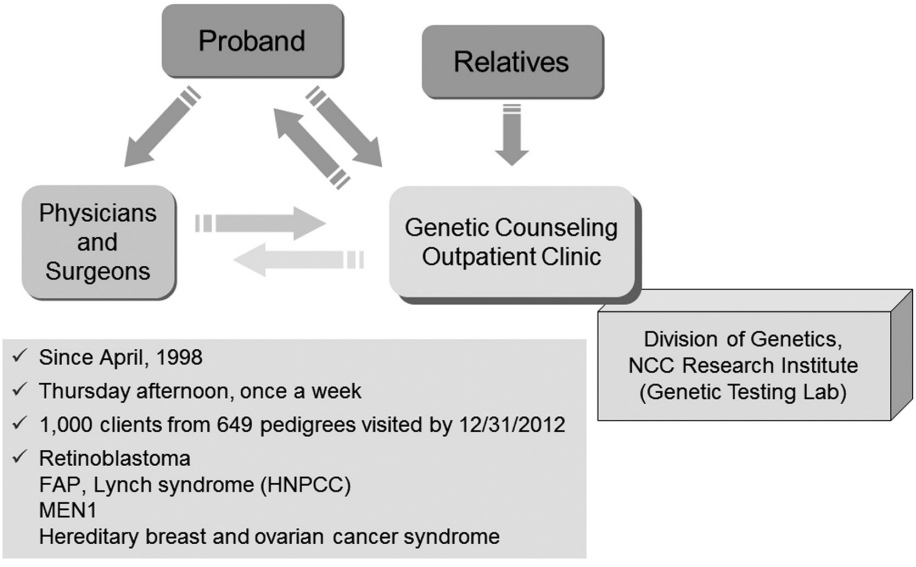


**Figure 1. An outline of genetic counseling clinic at NCC hospital**

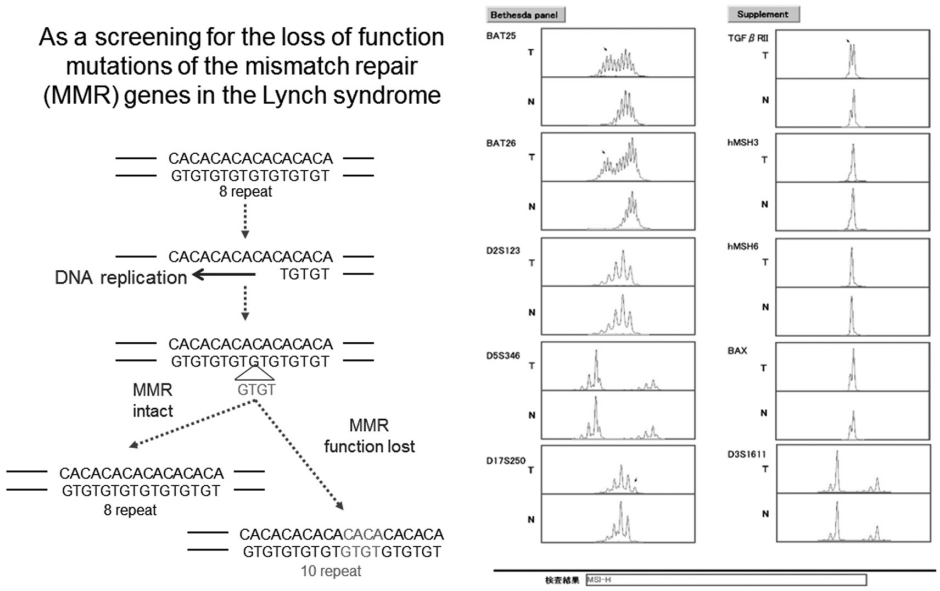


**Figure 2. Principle of MSI and an example of the MSI test report at the NCC hospital.**

**Table 1. Number of patients**

| | Proband | Relative | Total |
|---|---|---|---|
| Lynch syndrome (Hereditary Non-Polyposis Colon Cancer; HNPCC) | 17 | 10 | 27 |
| Familial Adenomatous Polyposis (FAP) | 2 | 8 | 10 |
| Retinoblastoma | 8 | 7 | 15 |
| Hereditary Breast and Ovarian Cancer Syndrome (HBOC) | 20 | 6 | 26 |
| MEN I (Multiple Endocrine Neoplasia Type I) | 0 | 0 | 0 |
| Other diseases | 12 | 1 | 13 |
| Counseling only | 0 | 0 | 0 |
| Total | 59 | 32 | 91 |

polyposis and Lynch syndrome. In 2012, the genetic testing was included as a part of the Core Facility activity of the Research Institute and has been continued by the staff of the Division of Genetics. For Lynch syndrome, microsatellite instability (MSI) testing has been performed on formalin-fixed paraffin-embedded histological sections as an initial screening of the candidates for the sequencing analyses of the mismatch repair (MMR) genes. The MSI test is now covered by the health insurance system in Japan, but immunohistochemical detection of the loss of an MMR protein expression has been shown to be as sensitive and specific as the MSI test. A collaborative study supported by the National Cancer Center Research and Development Fund and led by the doctors in the Gastrointestinal Endoscopy Division and Department of Pathology and Clinical Laboratories is now underway to compare MSI and MMR immunohistochemistry and to find the optimum criteria to identify those patients in whom the Lynch syndrome screenings are recommended.

## List of papers published in 2012

Publication list of the Genetic Counseling Division is included in that of the Division of Genetics, National Cancer Center Research Institute.

## Clinical trials

No clinical trial was performed in 2012.

# Department of Anesthesia and Intensive Care

**Tetsufumi Sato, Yoko Kinoshita, Tsukasa Satake, Nobuko Yokokawa, Rie Suzuki, Minako Arai, Moritoki Egi, Yosuke Kawaguchi, Shinji Sugita, Yuya Uyama, Jun Hozumi, Takayuki Sugai, Takuya Oohata**



## Introduction

Our Department provides anesthesia and intensive care. Anesthetic services are provided for 15 main operating theatres and sessions in endoscopy. There are about 4,000 operations per year. The Intensive Care Unit has 8 beds and provides care for all specialties including general medical and general surgical cases. There are over 400 admissions annually and the ICU is also responsible for resuscitation services within the hospital.

## Routine activities

The Department of Anesthesia and Intensive Care at the National Cancer Research Center Central Hospital is comprised of 13 staff anesthetists who are involved in critical care, education and research. Our Department provides perioperative care to the all patients requiring general anesthesia and spinal analgesia. Our operation theater performs approximately 4,000 surgical procedures per year, which include neurosurgical, orthopedic, plastics, ophthalmologic, gynecologic, urologic, and general surgery (Table 1). We also provide care to patients undergoing procedures in locations outside the main operating room such as sessions in endoscopy. In addition, many patients are seen in the Anesthesia Consult Clinic, which runs every weekday. Many staff members also have other clinical appointments including attendance in the ICU (the 8-bed Medical/Surgical Unit) and providing acute pain management. Some members of the Department are actively involved in research at the clinical levels and supervise post doctorate, doctorate, postgraduate and undergraduate students.

Our ICU is certificated by the Japanese Society of Intensive Care Medicine. It provides care for all specialties including general medical, general surgical and neurosurgical cases. It is managed as a closed-system ICU, supported by two certificated intensivists and a trainee. There are 8 operational ICU beds and over 400 admissions annually (41.4 patients per month) ( Figure 1). The length of stay in the ICU is 3.9 days on average (Figure 2). The ICU is also responsible for resuscitation services within the hospital.

A weekly conference is held with all anesthesiologists and Intensives for updating the current world standard of acute medicine. A weekly lecture is also held for education of intensive care nurses. Occasionally, a mortality and morbidity conference is held with doctors of other departments.

## Clinical trials

One of the Department members is on the faculty of the clinical trial group in Japanese Society of Intensive Care Medicine. To understand the incidence and risk factors of severe adverse event in post-operative patients, epidemiological analyses have been performed. To improve current care for perioperative patients, prospective studies are being conducted.

**Table 1. Case for anesthetic management**

| | |
|---|---|
| Thoracic surgery | 604 |
| Breast surgery | 484 |
| Gastric surgery | 464 |
| Colon surgery | 443 |
| Urologic surgery | 354 |
| Ophthalmologic surgery | 301 |
| Orthopedic surgery | 286 |
| Hepato-Biliary-Pancreatic surgery | 245 |
| Gynecologic surgery | 205 |
| Esophageal surgery | 139 |
| Head-neck surgery | 122 |
| Neuro-surgery | 117 |
| Skin surgery | 101 |
| Plastics surgery | 82 |
| Other | 86 |
| Total | 4033 |

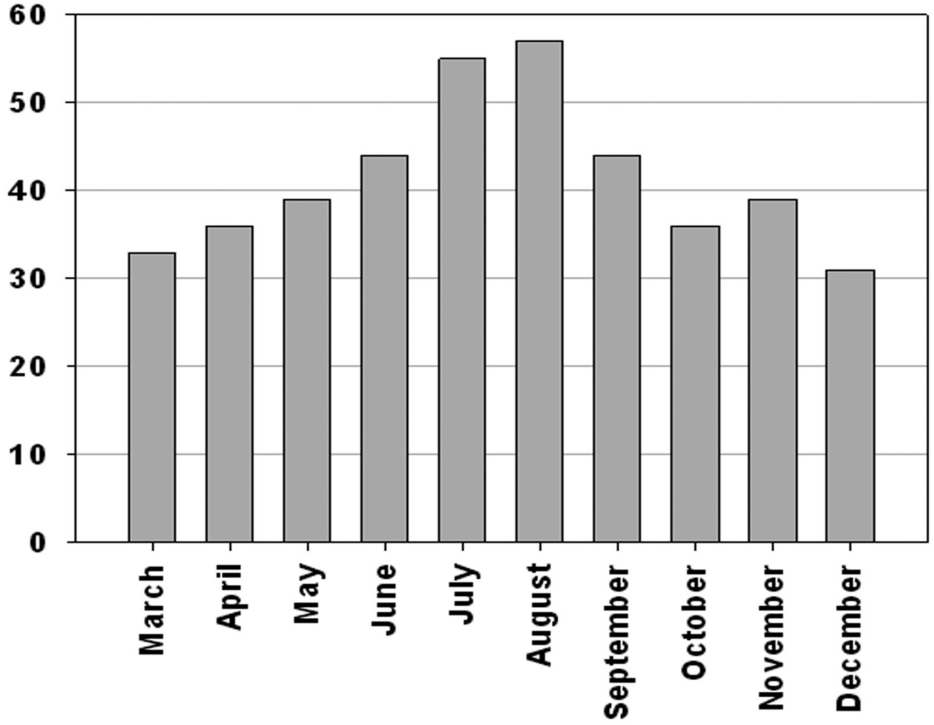


**Figure 1. Number of patients admitted to the ICU.**

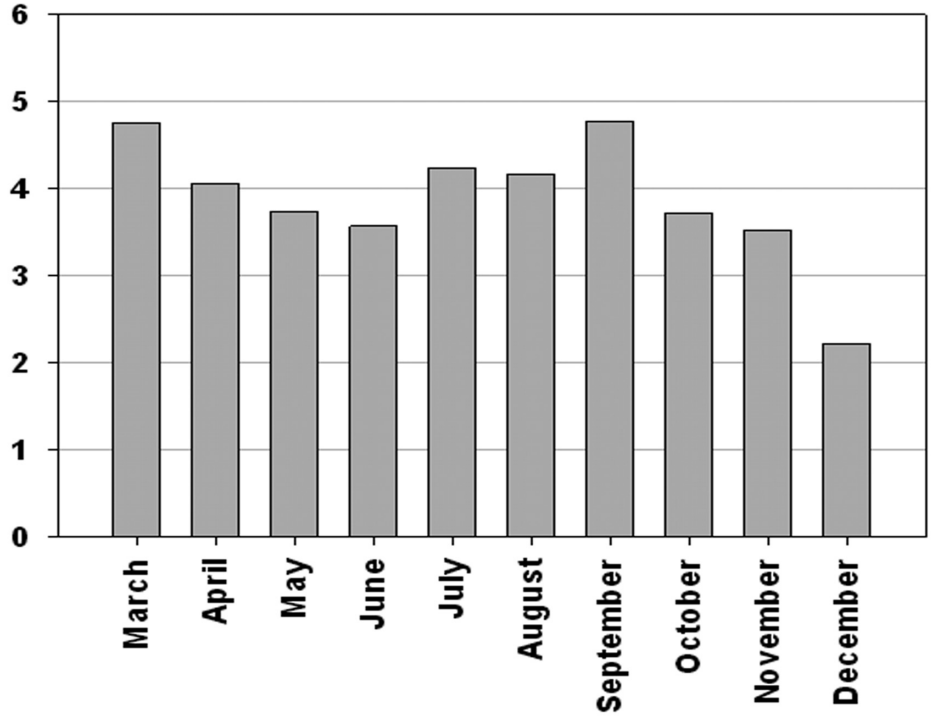


**Figure 2. Length of stay in the ICU**

# Department of Palliative Care

**Motohiro Matoba, Osamu Saito, Chio Shuto, Hironori Mawatari**



## Introduction

It was in June, 1999, when 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 (NCCH). 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, child care 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 instill 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 a day. 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 purpose 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, 26 residents trained with our team during 2012. 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.

## Research activities

In particular, our division has focused on basic to clinical, and clinical to basic translational interactive collaboration with the Division of Cancer Pathophysiology in National Cancer Center Research Institute.

Our collaborative studies are focused on the aspect of the improvement of pain treatment for severe and intolerable cancer pain. One is abdominal pain of patients with peritoneal carcinomatosis, most of which are refractory to morphine. In collaboration with the Division of Cancer Pathophysiology, we demonstrated that abdominal pain associated with peritoneal carcinomatosis is accompanied by decreased expression of the m-opioid receptors (ref). Second is pain induced by oral mucositis of cancer patients receiving radiation and/or anticancer drugs. In such cancer patients, to date no appropriate analgesic has been found which does not affect the senses of taste and food texture. Our division is developing such an innovative and unique analgesic. With experiments using a cell culture system and an animal mucositis model, we found that cell membrane-impermeable local anesthetic QX-572 could be a candidate. Based on the preclinical studies, we are going to try a Phase I/II study with oral mucositis patients.

In addition, establishment of a pain management monitoring system and improving opioid consumption has started at Aomori Prefectural Central Hospital. Also, construction is underway of a supporting system for children and their families whose father/mother is suffering and dying from advanced cancer.

**Table 1. Number of patients**

| | |
|---|---|
| Lung cancer | 37 |
| Sarcoma | 30 |
| Breast cancer | 26 |
| Rectal cancer | 23 |
| Esophageal cancer | 20 |
| Primary unknown cancer | 20 |
| Bladder cancer | 18 |
| Uterine cancer | 16 |
| Leukemia | 14 |
| Gastric cancer | 11 |
| Skin cancer | 11 |
| Pancreatic cancer | 9 |
| Malignant melanoma | 9 |
| Renal cancer | 8 |
| Prostate cancer | 8 |
| Malignant lymphoma | 7 |
| Colon cancer | 6 |
| Head and Neck cancer | 6 |
| Urethral cancer | 6 |
| Bile duct cancer | 5 |
| Multiple myeloma | 4 |
| Liver cancer | 4 |
| Malignant mesothelioma | 3 |
| Others | 27 |
| Total | 328 |

**Table 2. Type of procedure**

| | |
|---|---|
| Adjustment of non-opioid analgesics | 118 |
| Commencement of opioid analgesics | 61 |
| Adjustment of opioid analgesics | 104 |
| Opioid rotation | 51 |
| Adjustment of adjuvant analgesics | 41 |
| Nerve block | 2 |
| Management of side effect of analgesics | 80 |
| Others | 23 |

## List of papers published in 2012
## Journal


1. Saito O, Akagi T, Tatsuno M, Miura K, Shuto C, Kudo N, Murakami S, Matoba M. A small amount of katamine with oxycodone induced an acute hyperactive delirium due to voriconazole, a CYP3A4 inhibitor, in a case of multiple myeloma with cancer pain. Palliat Care Res, 7:506-509, 2012
2. Shuto C. Activation of in-hospital palliative care – from the palliative care team approach. Symptom Management in Cancer Patients, 23:151-157, 2012
3. Suzuki M, Narita M, Hasegawa M, Furuta S, Kawamata T, Ashikawa M, Miyano K, Yanagihara K, Chiwaki F, Ochiya T, Suzuki T, Matoba M, Sasaki H, Uezono Y. Sensation of abdominal pain induced by peritoneal carcinomatosis is accompanied by changes in the expression of substance P and mu-opioid receptors in the spinal cord of mice. Anesthesiology, 117:847-856, 2012
4. Suzuki M, Narita M, Ashikawa M, Furuta S, Matoba M, Sasaki H, Yanagihara K, Terawaki K, Suzuki T, Uezono Y. Changes in the melanocortin receptors in the hypothalamus of a rat model of cancer cachexia. Synapse, 66:747-751, 2012
5. Higashi T, Yoshimoto T, Matoba M. Prevalence of analgesic prescriptions among patients with cancer in Japan: an analysis of health insurance claims data. Glob J Health Sci, 4:197-203, 2012
6. Yamaguchi T, Narita M, Morita T, Kizawa Y, Matoba M. Recent developments in the management of cancer pain in Japan: education, clinical guidelines and basic research. Jpn J Clin Oncol, 42:1120-1127, 2012
7. Kokubun H, Ebinuma K, Matoba M, Takayanagi R, Yamada Y, Yago K. Population pharmacokinetics of transdermal fentanyl in patients with cancer-related pain. J Pain Palliat Care Pharmacother, 26:98-104, 2012
8. Akiyama M, Takebayashi T, Morita T, Miyashita M, Hirai K, Matoba M, Akizuki N, Shirahige Y, Yamagishi A, Eguchi K. Knowledge, beliefs, and concerns about opioids, palliative care, and homecare of advanced cancer patients: a nationwide survey in Japan. Support Care Cancer, 20:923-931, 2012
9. Torigoe K, Nakahara K, Rahmadi M, Yoshizawa K, Horiuchi H, Hirayama S, Imai S, Kuzumaki N, Itoh T, Yamashita A, Shakunaga K, Yamasaki M, Nagase H, Matoba M, Suzuki T, Narita M. Usefulness of olanzapine as an adjunct to opioid treatment and for the treatment of neuropathic pain. Anesthesiology, 116:159-169, 2012
10. Morita T, Miyashita M, Yamagishi A, Akizuki N, Kizawa Y, Shirahige Y, Akiyama M, Hirai K, Matoba M, Yamada M, Matsumoto T, Yamaguchi T, Eguchi K. A region-based palliative care intervention trial using the mixed-method approach: Japan OPTIM study. BMC Palliat Care, 11:2, 2012

# Department of Psycho-Oncology

**Ken Shimizu, Yoshio Oshima, Masashi Kato, Tomomi Takahashi**



## Introduction

The Psycho-Oncology Division was reestablished in September 1995, together with the 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 the distress of patients, patients' families and our staff. Research activity is focused on studying the psychosocial influence of cancer on the quality of life of patients, their families, and oncology staff members.

## Routine activities

The Psychiatry Division consists of two full time staff psychiatrists and one part time psychiatrist, and one chief resident. One staff psychotherapist and 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.

A range of psychiatric diagnosis is based on the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) shown in the Table. In 2012, a total of 757 patients were referred for psychiatric consultation. The mean age was 52.8 years old and 16.6% percent of the referrals were outpatients. Three-hundred and sixty (47.6%) of the total number of referred patients were males. The most common psychiatric diagnosis was Adjustment Disorders (20.5%), followed by Delirium (19.6%), and major depression (8.7%), while 17.4% 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 (14.9%), followed by lung cancer (8.7%), stomach cancer (8.7%), esophageal cancer (7.5%) and breast cancer (6.9%).

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 planned 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 its feasibility and usefulness.

**Table 1. Patient demographics**

| | | | |
|---|---|---|---|
| Patients | Total number | 757 | |
| | Age | 52.8 years | |
| | Male | 360 | 47.6% |
| | Inpatients | 631 | 83.4% |

**Table 2. Number of cancers by site**

| | | | |
|---|---|---|---|
| Cancer site | Lung | 66 | 8.7% |
| | Breast | 52 | 6.9% |
| | Hematological | 113 | 14.9% |
| | Esophageal | 57 | 7.5% |
| | Stomach | 66 | 8.7% |

**Table 3. Breakdown of diagnoses**

| | | | |
|---|---|---|---|
| Diagnosis | Adustment Disorders | 155 | 20.5% |
| | Delirium | 148 | 19.6% |
| | Major Depression | 66 | 8.7% |
| | No Diagnosis. | 132 | 17.4% |

## List of papers published in 2012
## Journal


1. Asai M, Akizuki N, Fujimori M, Matsui Y, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Psychological states and coping strategies after bereavement among spouses of cancer patients: a quantitative study in Japan. Support Care Cancer, 20:3189-3203, 2012
2. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Yamada Y, Fujimori M, Ogawa A, Fujisawa D, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Clinical biopsychosocial risk factors for depression in lung cancer patients: a comprehensive analysis using data from the Lung Cancer Database Project. Ann Oncol, 23:1973-1979, 2012
3. Ogawa A, Nouno J, Shirai Y, Shibayama O, Kondo K, Yokoo M, Takei H, Koga H, Fujisawa D, Shimizu K, Uchitomi Y. Availability of psychiatric consultation-liaison services as an integral component of palliative care programs at Japanese cancer hospitals. Jpn J Clin Oncol, 42:42-52, 2012

# Department of Diagnostic Radiology

**Yasuaki Arai, Masahiko Kusumoto, Yoshito Takeuchi, Kenichi Takayasu, Yasunori Mizuguchi, Gen Iinuma, Miyuki Sone, Hiroaki Kurihara, Hirokazu Watanabe, Tomoko Manabe, Kentaro Shibamoto, Mototaka Miyake, Shunsuke Sugawara, Hirotaka Tomimatu, Hiroaki Onaya**



## Introduction

The Department of Diagnostic Radiology provides a wide range of modalities, including interventional radiology (IR), general radiology, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, mammography and nuclear medicine. We seek individuals with outstanding leadership capabilities, proven academic and administrative experiences, 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 | 38,683 |
| 2 | MRI | 7,721 |
| 3 | IR | 3,606 |
| 4 | RI | 4,347 |
| 5 | Ultrasound | 13,165 |
| 6 | Radiograph | 78,561 |
| 7 | Gastrointestinal study | 2,071 |

## Research activities

CT colonography (CTC) has been covered by medical insurance for a diagnostic tool in colorectal diagnosis since last year. In our center, CTC has been successfully introduced into the colorectal screening program, and 1200 candidates have been examined since 2010. Electronic cleansing with fecal barium tagging and CO2 gas insufflation systems have been developed for effective CTC preparation in formal NCC collaboration studies with the associated companies. Furthermore, we are now planning a multi-center trial to establish an evidence of CTC for colorectal screening system in Japan.

Small hypovascular hepatocellular carcinoma (HCC) is frequently found but the biological behavior still remains unclear. The 4,474 patients who met solitary HCC <=3cm, histopathologically proven and Child Pugh A or B were studied. Of them, 802 (18%) were hypovascular. Logistic regression analysis revealed five independent predictors for hypovascular HCC; tumor size <1.5 cm, alpha-fetoprotein <200 ng/ml, des-γ-carboxy prothrombin < 40 mAU/ml, well differentiated grade, and positivity for hepatitis C virus antibody. These results could help in determining a diagnostic and treatment algorithm for small hypovascular HCC.

To clarify the characteristics of ovarian endometrial tumors of borderline malignancy, MR imaging findings and histopathological findings were correlated. The relationship between extracapsular extension of prostate cancer and ADC values was evaluated using 3.0 T MR imaging.

To establish the CT classification of lung adenocarcinoma corresponding to the new IASLC/ATS/ERS pathological classification and to build the database of small adenocarcinomas with both volumetric thin-section CT images and continuous histological sections, a multicenter study has started in collaboration with the Japanese Society of Thoracic Radiology.

The Japan Response Evaluation Criteria in Solid Tumors (RECIST) working group has developed a tumor response evaluation computer system, which is capable of semiautomatic RECIST evaluation and is compliant with DICOM (Digital Imaging and Communications in Medicine) data. Moreover, two tumor response evaluation criteria, RECIST version 1.1 and modified RECIST for hepatocellular carcinoma (HCC) treated using transcatheter arterial chemoembolization (TACE), were compared. From the viewpoint of the high inter- and intra-observer reproducibility, we concluded that the modified RECIST approach was more suitable for tumor response criteria in clinical trials of TACE for HCC.

A multi tracer consisting of [18F]FDG, [18F]FBPA, anti-[18F]FACBC, [11C]choline, [11C]methionine and [64Cu]DOTA-antibody PET imaging has been studied for cancer patients to improve the sensitivity and specificity of detecting tumor sites or tumor characteristics. [18F]FDG dynamic PET sampling with Patrak-plot analysis allows us to calculate the glucose metabolic rate of the tumor site. [18F]FBPA PET/CT, known as an evaluator for BNCT, has been conducted in 25 cancer patients in this year. Anti-[18F]FACBC PET/CT has been carried out in prostate cancer patients as a phase II clinical trial. [11C]choline and [11C]methionine PET/CT examinations have been performed routinely one

day per week. As for [64Cu]DOTA-antibody PET imaging, [64Cu]DOTA-trastuzumab PET/CT has been conducted in HER-2 positive breast cancer patients. Furthermore, [64Cu]DOTA-cetuximab, an anti-EGFR-1 imaging agent, has been synthesized successfully in the hospital and we are waiting for the institutional review board (IRB) approval for clinical use. 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.

## Clinical trials

In addition to a number of company-oriented clinical trials, investigator-oriented clinical trials on interventional radiology are ongoing at NCC. We led a multi-institutional cooperative study group of interventional radiology (JIVROSG: Japan Interventional Radiology in Oncology Study Group) as the flagship hospital and recruited patients for 8 ongoing trials: a phase I/II study of RFA for intrapelvic malignant tumors (JIVROSG-0204); 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 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 stenosis (JIVROSG-0806); a phase III study evaluating the efficacy of stenting for SVC/IVC syndrome (JIVROSG-0807) and a phase II study evaluating the efficacy of arterial infusion chemotherapy and radiotherapy for unresectable maxillary carcinoma (JIVROSG-0808).

## List of papers published in 2012
### Journal


1. Morishita H, Yamagami T, Takeuchi Y, Matsumoto T, Asai S, Masui K, Sato H, Taniguchi F, Sato O, Nishimura T. A new flow control technique using diluted epinephrine in the N-butyl-2-cyanoacrylate embolization of visceral artery pseudoaneurysms secondary to chronic pancreatitis. Cardiovasc Intervent Radiol, 35:932-937, 2012
2. Akahane A, Sone M, Ehara S, Kato K, Suzuki M, Tanaka R, Suwabe A, Itabashi T, Masahiro K. Central venous port-related infection in patients with malignant tumors: an observational study. Ups J Med Sci, 117:300-308, 2012
3. Arai Y. Clinical trials of interventional oncology. Int J Clin Oncol, 17:301-305, 2012
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# Department of Radiation Oncology

**Jun Itami, Minako Sumi, Yoshinori Ito, Hiroshi Mayahara, Madoka Morota, Naoya Murakami, Koichi Inaba, Kotaro Yoshio**

## Introduction

The role of the Department is to provide state of art radiation therapy to all the relevant patients, to educate and develop the expertise of radiation oncologists, radiation technologists, and medical physicists, and to lead new developments in radiation oncology in Japan as well as worldwide. All Departmental Activities are dedicated to Cancer Patients. In this year, a new building for the hospital-based boron neutron capture therapy (BNCT) using an accelerator was launched, and will be finished in November 2013. 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 of 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. 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 December 2011, gold markers have been implanted to improve geometric precision of radiation field reproducibility.

Brachytherapy is also performed very intensively to obtain local control and many patients are referred to our Department from all over Japan. 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 using 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 and choroidal melanomas. LDR interstitial implants are carried out by radiation oncologists using Au-198 grains and Ir-192 thin wires for the management of head and neck tumors and gynecological malignancies.

## Research activities

Clinical research is an indispensable part of the daily activities of the Department. The primary interests of the research activities of the Department are 1) an optimal fractionation regimen for the pain palliation of bone metastasis; 2) the safety and feasibility of 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 difference between intratherapeutic tumor and normal tissue. These studies are financially supported by grants from the Ministry of Health, Labour and Welfare (MHLW), Japan.

The Division staff is 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: 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: 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 to hepatocellular carcinoma.

F-BPA PET/CT: A feasibility study of F-BPA PET/CT in detecting malignancies in comparison to FDG PET/CT.

Development of an Adaptive Radiation Therapy System

**Table 1. Number of Radiation Treatment Plans**

| Primary Sites | No. of All Treatment Plans | | | | | |
|---|---|---|---|---|---|---|
| | 2007 | 2008 | 2009 | 2010 | 2011 | **2012** |
| Head & neck | 111 | 115 | 95 | 128 | 166 | **158** |
| Brain | 90 | 117 | 99 | 113 | 97 | **77** |
| Lung | 357 | 397 | 431 | 429 | 348 | **430** |
| Breast | 523 | 549 | 452 | 487 | 503 | **485** |
| Esophagus | 276 | 220 | 213 | 265 | 237 | **268** |
| Stomach | 30 | 34 | 29 | 25 | 15 | **35** |
| Colorectal | 101 | 86 | 78 | 66 | 119 | **113** |
| Pancreas and hepatobiliary | 60 | 38 | 48 | 69 | 68 | **64** |
| Gynecological | 154* | 255 | 331 | 274 | 328 | **418** |
| Genitourinary | 118 | 128 | 159 | 192 | 169 | **172** |
| Bone & soft tissue | 64 | 75 | 69 | 103 | 92 | **86** |
| Skin | 19 | 16 | 26 | 58 | 71 | **58** |
| Pediatric | 25 | 22 | 32 | 25 | 66 | **49** |
| Hematological | 145 | 137 | 220 | 159 | 157 | **202** |
| Other | 35 | 47 | 52 | 19 | 14 | **39** |
| Total | 2108 | 2236 | 2334 | 2412 | 2450 | **2654** |

*: No. of Cases

**Table 2. Purpose of Radiation Therapy**

| | No. of All Treated Patients | | | | | |
|---|---|---|---|---|---|---|
| | 2007 | 2008 | 2009 | 2010 | 2011 | **2012** |
| No. of Treatment Plans | 2108 | 2236 | 2334 | 2412 | 2450 | **2654** |
| Curative Intent | 1393 | 1535 | 1500 | 1587 | 1662 | **1858** |
| Palliative Treatment | 715 | 701 | 834 | 825 | 788 | **796** |
| Curative/Palliative | 1.95 | 2.19 | 1.80 | 1.92 | 2.11 | **2.33** |
| New Patients | 1234 | 1181 | 1210 | 1277 | 1288 | **1271** |

**Table 3. Special Radiation Therapy**

| | No. of Treated Patients | | | |
|---|---|---|---|---|
| | 2009 | 2010 | 2011 | **2012** |
| IORT | 0 | 0 | 1 | **0** |
| TBI | 38 | 41 | 52 | **51** |
| SRT-Brain | 6 | 3 | 2 | **6** |
| SRT-Body | 20 | 33 | 45 | **37** |
| IMRT-Brain | 1 | 7 | 11 | **12** |
| IMRT-H&N | 27 | 34 | 45 | **62** |
| IMRT-Thorax | 0 | 1 | 3 | **6** |
| IMRT-Gyne | 0 | 6 | 14 | **23** |
| IMRT-Prostate | 47 | 46 | 55 | **56** |
| IMRT-Others | 7 | 11 | 9 | **13** |
| Intracavitary RT 192Ir-HDR | 41 | 50 | 49 | **40** |
| Intracavitary RT 192Ir-LDR | 0 | 0 | 0 | **0** |
| Interstitial RT 192Ir-HDR | 22 | 6 | 25 | **37** |
| Interstitial RT 192Ir-LDR | 0 | 0 | 0 | **1** |
| Interstitial RT 198Au-LDR | 6 | 6 | 4 | **7** |
| Interstitial RT 125I-LDR | 16 | 26 | 16 | **28** |
| Interstitial RT 106Ru-LDR | 7 | 10 | 13 | **23** |
| Non-Sealed Radionuclide Therapy 89Sr | 3 | 5 | 12 | **4** |
| Non-Sealed Radionuclide Therapy 131I | 1 | 14 | 21 | **24** |

IORT; intraoperative radiotherapy
TBI; total body irradiation

## List of papers published in 2012
## Journal


1. Mayahara H, Ito Y, Morizane C, Ueno H, Okusaka T, Kondo S, Murakami N, Morota M, Sumi M, Itami J. Salvage chemoradiotherapy after primary chemotherapy for locally advanced pancreatic cancer: a single-institution retrospective analysis. BMC Cancer, 12:609, 2012
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# Department of Pathology

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



## Introduction

In the Pathology Division the practice, education and research of diagnostic and anatomic pathology are carried out. Diagnostic pathology practice comprises all issues concerning the processing of cell and tissue specimens obtained from patients, preparation of tissue blocks and pathology slides, and histological and cytopathological diagnoses of diseases. The practice of anatomic pathology consists of the autopsy, and post-mortem systemic gross and microscopic examination of patients. Case conferences with each clinical division were held periodically this year. Residents and trainees were accepted for training in diagnostic pathology on a rotating basis. To provide more accurate and informative diagnosis in the future, the staff members have conducted basic, clinical, or translational research by themselves or in collaboration with other divisions or institutions.

## Routine activities

In 2012, a total of 14 board-certified pathologists, 7 residents and 11 medical technologists, including 11 cytotechnologists, cooperatively performed routine histological and cytopathological diagnosis of specimens obtained from patients at the National Cancer Center Hospital (NCCH) and the Research Center for Cancer Prevention and Screening (RCCPS), and education of the residents. Seven pathologists working exclusively in the NCCH also shared management of the division. Another 7 pathologists were concurrently on the staff of NCC Research Institute (NCCRI). In September, in parallel with Clinical Laboratories Division, this Pathology Division obtained certification of ISO15189.

1. Surgical pathology

A total of 19,834 histological diagnoses were provided consisting of 16,085 biopsy specimens including 1,913 intraoperative frozen sections and 3,749 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 1,006 sentinel lymph nodes n the intraoperative assessment of metastasis.

2. Cytopathology

Cytopathological diagnoses were provided for a total of 11,335 patients including 404 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-four 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. Outpatient clinic for pathology consultation (second opinion)

To the 191 patients, we provided histopathological/cytopathological diagnosis as a second opinion.

5. 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, NCC East, and trimonthly multi-institutional pathology TV conferences.

## Research activities

1. Gastrointestinal pathology

Clinicopathological and molecular characteristics of premalignant lesions and initial carcinomas of the stomach and colon were studied.

The histological status of gastritis surrounding carcinomas at the esophagogastric junction was studied.

2. Hematopathology

Prognostic factors in patients with diffuse large B-cell lymphomas treated with rituximab-containing chemotherapy were studied.

3. Pulmonary and mediastinal pathology

The clinical significance of c-Met, phosphor-Met expressions, MET gene copy alterations, cathepsin D expression, and metastasis limited to segmental and/or subsegmental lymph nodes were studied in lung adenocarcinoma. Molecular alterations were examined in thymomas and thymic carcinomas. Development of the assay system to detect rearrangements of ALK, ROS, and RET by fluorescence in situ hybridization and immunohistochemistry is ongoing in collaboration with the NCCRI and other divisions in NCCH.

4. Soft tissue pathology

MDM2 and CDK4 co-expression was shown to be correlated with dedifferentiated-type osteosarcoma. NKX2.2 expression was shown to be a marker for Ewing's sarcoma.

5. Neuropathology

A case of unclassified high-grade glioma with polar spongioblastoma pattern was reported.

6. Breast and gynecological pathology

The intensity of tumor-infiltrating lymphocytes was shown to be a significant predictive factor of the response to neoadjuvant chemotherapy in triple-negative breast cancer. The gene protein assay, in which both HER2 protein expression and gene amplification are seen simultaneously, was developed and applied to breast cancer specimens.

7. Digital pathology

We continued the establishment of digital pathology and intelligence database system in collaboration with a Japanese company using a high-speed, high-resolution, and high-fidelity scanner and PlayStation™-based viewers.

8. Quality assessment and central pathology review

A study of nationwide external quality assessment with regard to immunohistochemistry of hormone receptors and HER2 was conducted in collaboration with the Japanese Society of Pathology. A central pathology review in clinical trials was performed for cancers of various organs.

**Table 1. Numbers of Histopathological Specimens Diagnosed in the Pathology Division in 2012**

| Field | Number of specimens |
|---|---|
| | Total |
| Gastrointestinal tracts | 8105 |
| Breast | 2384 |
| Respiratory organs | 2063 |
| Gynecology | 1267 |
| Hematology | 1032 |
| Urology | 894 |
| Hepatobiliary and pancreas | 670 |
| Head and neck | 635 |
| Dermatology | 596 |
| Orthopedics | 518 |
| Others | 1182 |
| Research Center for Cancer Prevention and Screening | 488 |
| Total | 19834 |

**Table 2. Numbers of Cytopathological Specimens Diagnosed in the Pathology Division in 2012**

| Field | Number of specimens |
|---|---|
| | Total |
| Gynecology | 4034 |
| Urology | 2988 |
| Respiratory organs | 1863 |
| Gastrointestinal tracts | 733 |
| Breast | 435 |
| Hepatobiliary and pancreas | 426 |
| Radiation oncology | 188 |
| Head and neck | 177 |
| Hematology | 116 |
| Others | 375 |
| Research Center for Cancer Prevention and Screening | 812 |
| Total | 12147 |

**Table 3. Numbers of Autopsies Performed in the Pathology Section in 2012**

| Department/Division | Number |
|---|---|
| Thoracic Oncology | 9 |
| Hematology and Hematopoietic Stem Cell Transplantation | 7 |
| Breast and Medical Oncology | 5 |
| Gastrointestinal Oncology | 3 |
| Neurosurgery | 3 |
| Hepatobiliary and Pancreatic Oncology | 2 |
| Radiation Oncology | 2 |
| Dermatology | 1 |
| Thoracic Surgery | 1 |
| Urology | 1 |
| Total | 34 |



## List of papers published in 2012
## Journal


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. Multicenter study for optimal categorization of extramural tumor deposits for colorectal cancer staging. Ann Surg, 255:739-746, 2012
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5. Kang KJ, Kim KM, Kim JJ, Rhee PL, Lee JH, Min BH, Rhee JC, Kushima R, Lauwers GY. Gastric extremely well-differentiated intestinal-type adenocarcinoma: a challenging lesion to achieve complete endoscopic resection. Endoscopy, 44:949-952, 2012
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11. Mimae T, Tsuta K, Maeshima AM, Okada M, Asamura H, Kondo T, Tsuda H. Cathepsin D as a potential prognostic marker for lung adenocarcinoma. Pathol Res Pract, 208:534-540, 2012
12. Tsuta K, Kozu Y, Mimae T, Yoshida A, Kohno T, Sekine I, Tamura T, Asamura H, Furuta K, Tsuda H. c-MET/phospho-MET protein expression and MET gene copy number in non-small cell lung carcinomas. J Thorac Oncol, 7:331-339, 2012
13. Tsuta K, Wistuba II, Moran CA. Differential expression of somatostatin receptors 1-5 in neuroendocrine carcinoma of the lung. Pathol Res Pract, 208:470-474, 2012
14. Yoshida A, Sekine S, Tsuta K, Fukayama M, Furuta K, Tsuda H. NKX2.2 is a useful immunohistochemical marker for Ewing sarcoma. Am J Surg Pathol, 36:993-999, 2012
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16. Sone M, Nishikawa Y, Nagahama Y, Kumagai E, Doi Y, Omori Y, Yoshioka T, Tokairin T, Yoshida M, Sugiyama T, Enomoto K. Recovery of mature hepatocytic phenotype following bile ductular transdifferentiation of rat hepatocytes in vitro. Am J Pathol, 181:2094-2104, 2012
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33. Kashimoto K, Komatsu S, Ichikawa D, Arita T, Konishi H, Nagata H, Takeshita H, Nishimura Y, Hirajima S, Kawaguchi T, Shiozaki A, Fujiwara H, Okamoto K, Tsuda H, Otsuji E. Overexpression of TRIM44 contributes to malignant outcome in gastric carcinoma. Cancer Sci, 103:2021-2026, 2012

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## Book

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# Department of Clinical Laboratories

**Hitoshi Tsuda, Koh Furuta, Takao Miura**



## Introduction

The Clinical Laboratories Division provides an important service as an in-hospital diagnostic unit by examining laboratory specimens and screening for disorders. All laboratory data are provided for clinicians under strict internal and external quality control. After a nearly one-year preparation, the laboratories in this Department acquired the accreditation of ISO 15189, which certifies the quality and competence of a medical laboratory with regard to quality management and technique, developed by the International Organization for Standardization's Technical Committee 212 (ISO/TC 212). The staff of the Clinical Laboratories Division will continuously work to improve the quality and quantity of laboratory services.

## Routine activities

Forty-nine full-time and 9 part-time medical technologists, and 4 assistants provide services. These staff work in the sections of 1) general laboratory medicine and hematology; 2) biochemistry; 3) endocrinology, immunology, and tumor markers; 4) bacteriology; 5) genetic diagnostics, 6) transfusion, 7) phlebotomy, 8) physiological examination, and 9) pathology in the National Cancer Center Hospital (NCCH); and in the sections of phlebotomy and physiological examination in the Research Center for Cancer Prevention and Screening (RCCPS). The sections of 1) to 5) are to be supervised by Dr. Koh Furuta. The pathology section staff are supervised by the doctors in the Pathology Division, and the transfusion and phlebotomy staff are supervised by a doctor of the Department of Transfusion Therapy. In addition, the physiological examination staff are directly supervised by Dr. Yasunori Mizuguchi, Department of Diagnostic Radiology, and Dr. Masaaki Shoji and Dr. Takeshi Iwasa, the General Internal Medicine Division. The bacteriology staff are members of the Infection Control Team (ICT) and participate in the activities of infection management in collaboration with the staff physicians.

An administrative meeting is held weekly, attending members of which consist of two chief doctors and three head doctors of this Department and the Department of Transfusion Therapy, and the head and vice-head medical technologists. The quality control meeting is regularly held twice a month, and an all-staff meeting is held once a month. The division also participates in several domestic and international programs for inter-laboratory standardization and external quality control including the College of American Pathologists (CAP) Survey. The actual number of laboratory tests performed in this Division in 2012 is shown in Table 1.

## Research activities

An in-hospital bio-bank, which was established in 2002, has been maintained for use by various researchers, and more than 700,000 post clinical test blood samples have been cryo-preserved at -20 °C as of the end of 2012.

Three sections, general laboratory medicine and hematology, biochemistry, and endocrinology, immunology and tumor markers, participated in the external quality control program endorsed by the Japanese Society of Laboratory Medicine. In this particular program, the precise degradation processes of routine clinical specimens were investigated with other eight domestic university hospitals.

Using the Metafer system (an automated image analysis-assisted fluorescence in situ hybridization [FISH] system), the technique to evaluate the FISH imaging of HER2 gene amplification was established. Furthermore, using the Metafer system, we tried to establish a method to evaluate FISH images of ALK-rearranged, ROS-rearranged, and RET-rearranged lung cancers.

The molecular pathology laboratory has been set up, FISH of epidermal growth factor receptor (EGFR) in stomach cancer was performed, and data are under acquisition. Many case reports with important ultrasound findings were presented in scientific meetings by the staff of the physiology section.

Under the education committee in the ISO15189 scheme, a monthly seminar by the staff was started from this year for the purpose of promoting research activity in the Division.

**Table 1. Number of laboratory tests examined in the Clinical Laboratories Division (2012)**

| Section | Number |
|---|---|
| General laboratory medicine | 499,152 |
| Hematology | 1,296,880 |
| Biochemistry | 2,851,195 |
| Endocrinology, immunology and tumor markers | 353,591 |
| Bacteriology | 52,305 |
| Physiology | 83,158 |
| Genetic diagnostics | 760 |
| Total | 5,137,041 |

## List of papers published in 2012

### Journal


1. Furuta K, Matsuhita K, Goto Y, Miyagi Y, Sawabe M, Shirakashi R, Takeuchi T, Masui T, Aoki I, Nakagawara A. An attempt to establish a network of bioresource facilities in Japan. Biopreserv Biobank, 10: 6, 2012
2. Wakai S, Yokozawa K, Nakamura A, Adegawa Y, Furuta K. Long term storage of fluorescent in situ hybridization (FISH) slides. Biopreserv Biobank, 10: 23, 2012
3. Wakai S, Yokozawa K, Nakamura S, Miura T, Furuta K, Tanosaki R, Tsuda H. HER2 amplification testing using automated image analysis-assisted fluorescence in situ hybridization. Jpn J Med Technol, 61:562-566, 2012

# Consultation, Counseling and Support Service Center

**Masashi Kato, Yukiko Higuchi, Mariko Suda, Ryuta Suyama, Natsuko Moroi, Kayoko Miyata, Noriko Saito, Kyoko Shima, Yuko Ogo, Keiko Nozawa, Tomoko Takayama, Chikako Yamaki, Maiko Fujimori, Eri Hirayama, Miyako Momiyama**



## Introduction

The staff members called "Cancer Counseling and Support Specialists" work mainly at the Consultation, Counseling and Support Service Center of the National Cancer Center Hospital (NCCH). The staff cope with various problems of cancer patients and their families with the ultimate aim of helping patients feel relieved and to help them receive medical care. By putting ourselves in the patients' position, we can make real efforts to solve their problems.

## Routine activities

1 Consultation, Counseling and Support Services
  (1) Consultation and counseling face to face
  (2) Consultation and counseling on the telephone

We provide consultation, counseling and support to help the cancer patients, their families and ordinary citizens solve their psychosocial problems through various social work skills, social recourses and cancer information. We also counsel on the telephone in the hope that patients can see the benefit of the information in the books and websites, and make use of this information by themselves.

By August 2012, we also provided consultation for the clients of the "Kanja-Hikkei Support Center" by means of the booklets published by the Cancer Control and Information Services (CIS). Since September 2012, the operation of the "Kanja-Hikkei Support Center" was transferred to the CIS section.

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

We hold the following support groups and programs for the patients and their families
- The pancreatic cancer and biliary tract cancer class
- The class for women before undergoing breast cancer surgery
- The support group for families of brain tumor patients
- The support group for families of pancreatic cancer and biliary tract cancer patients
- CLIMB (Children's Lives Include Moments of Bravery) Support Program
- 1st year anniversary program of the support group for families of brain tumor patients

In the hospital, we discuss the patients with the doctors and medical staff. We are participating in the medical meetings of five specialties.

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 where required and helped patients to change hospitals.

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 the NCCH

5 Activities related to NCCH committees

6 Activities related to the 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 regarding counseling and support for cancer patients and their families.

1. Yukiko H, Kayoko M. New support class to understand changes in body image for women with breast cancer. In The 20th Annual Meeting of the Japanese Breast Cancer Society in Kumamoto city Japan. June 28-30, 2012.

2. Yukiko H, Ryuta S, Kayoko M. The background about the consultation about the treatment choice in a consultation, counseling and support service center. In The Japan Society of Clinical Oncology in Pacifico Yokohama, Kanagawa Japan. October 25-27, 2012.

3. Yukiko H, Mariko S, Natsuko M. Psychosocial support for family members of a malignant brain tumor patient by support group. In The 30th Annual Meeting of the Japan Society for Neuro-Oncology in Grand Prince Hotel Hiroshima, Hiroshima Japan. November 25-27, 2012.

4. Yukiko H, Kayoko M, Natsuko M, Mizuho Information and Research Institute. 2012 Entrustment Project of Ministry of Health, Labour and Welfare. Development of assistance procedure for the compatibility of medical care and occupational life: Occupational cancer and other malignant neoplasms.

**Table 1. The number of cases**

| | | |
|---|---|---|
| 1 | Total | 9,201 (Per month: 767) |
| 2 | New cases | 5,368 |
| | New cases from NCCH | 2,138 |
| | New cases from Other hospitals | 3,230 |

**Table 2. Achievements of support groups and programs**

| | | Number of times meetings were held | Number of participants |
|---|---|---|---|
| 1 | The pancreatic cancer and biliary tract cancer cundergoinglass | 46 | 207 (Patients: 131, Families: 76) |
| 2 | The class for women before receiving breast cancer surgery | 11 | 61 (Patient: 50, Families: 11) |
| 3 | The support group for families of brain tumor patients | 12 | 50 (Spouses: 28, Children: 12, Parents: 1, Siblings: 9) |
| 4 | The support group for families of pancreatic cancer and biliary tract cancer | 1 | 11 |
| 5 | CLIMB (Children's Lives Include Moments of Bravery) Support Program | 2 | 3 |
| 6 | 1st year anniversary program of the support group for families of brain tumor patients | 1 | 72 (Families: 50, Medical personnel: 16, Mass media: 6) |

# 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. Plastic Surgery and Pediatric Surgery Groups have newly joined this year.

## Routine activities

During 2012, the Surgical Center supported more than 4,700 surgical cases and more than 4,100 general anesthesia surgical cases, a 4.8% increase in the number of cases and a 4.9% increase in the general anesthesia cases over 2011. 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 Da Vinci robotic surgical system has been introduced to provide less invasive surgery to the patients.

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 50 foreign doctors have visited our surgical center.

**Table 1. Total number of operations**

| | Jan. | Feb. | March | Apr. | May | June | July | Aug. | Sep. | Oct. | Nov. | Dec. | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Anesthesia | | | | | | | | | | | | | |
| General | 132 | 147 | 125 | 129 | 143 | 131 | 133 | 165 | 129 | 134 | 133 | 129 | 1630 |
| General and epidural | 201 | 227 | 222 | 179 | 201 | 188 | 205 | 207 | 208 | 244 | 209 | 211 | 2502 |
| Epidural and lumbar | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 1 | 1 | 3 | 0 | 1 | 9 |
| Epidural and lumbar | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 4 |
| Lumbar | 17 | 15 | 14 | 8 | 11 | 15 | 12 | 7 | 5 | 4 | 7 | 4 | 119 |
| Local | 31 | 40 | 32 | 38 | 34 | 39 | 53 | 40 | 27 | 49 | 31 | 36 | 456 |
| Others | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 33 | 5 | 6 | 8 | 27 |
| Total | 381 | 430 | 393 | 356 | 390 | 374 | 404 | 420 | 382 | 440 | 387 | 390 | 4747 |

**Table 2. Number of general anesthesia cases**

| | Jan. | Feb. | March | Apr. | May | June | July | Aug. | Sep. | Oct. | Nov. | Dec. | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Neurosurgery | 10 | 12 | 11 | 13 | 11 | 6 | 9 | 14 | 9 | 7 | 8 | 12 | 122 |
| Ophthalmology | 26 | 29 | 26 | 26 | 26 | 32 | 27 | 25 | 26 | 29 | 26 | 21 | 319 |
| Head & Neck Surgery | 12 | 14 | 13 | 13 | 16 | 18 | 17 | 22 | 16 | 13 | 16 | 12 | 182 |
| Breast Surgery | 43 | 40 | 37 | 29 | 29 | 39 | 44 | 55 | 43 | 43 | 44 | 47 | 501 |
| Thoracic Surgery | 51 | 53 | 56 | 48 | 48 | 51 | 51 | 50 | 60 | 68 | 52 | 59 | 657 |
| Esophageal Surgery | 11 | 11 | 13 | 11 | 11 | 11 | 16 | 13 | 11 | 14 | 8 | 13 | 141 |
| Gastric Surgery | 37 | 37 | 45 | 30 | 30 | 40 | 46 | 43 | 44 | 51 | 33 | 41 | 482 |
| Colorectal Surgery | 43 | 60 | 38 | 32 | 32 | 27 | 28 | 34 | 39 | 45 | 44 | 35 | 464 |
| Hepatobiliary & Pancreatic Surgery | 19 | 27 | 23 | 23 | 23 | 23 | 18 | 22 | 17 | 23 | 25 | 24 | 267 |
| Gynecology | 15 | 20 | 20 | 17 | 17 | 13 | 17 | 20 | 18 | 19 | 19 | 11 | 207 |
| Urology | 20 | 18 | 27 | 21 | 21 | 16 | 20 | 24 | 21 | 27 | 20 | 21 | 251 |
| Dermatology | 9 | 9 | 5 | 9 | 9 | 8 | 10 | 7 | 7 | 10 | 12 | 12 | 108 |
| Orthopedic Surgery | 21 | 26 | 17 | 27 | 27 | 21 | 19 | 25 | 16 | 19 | 18 | 20 | 262 |
| Others | 16 | 18 | 16 | 9 | 9 | 14 | 16 | 18 | 10 | 10 | 17 | 12 | 169 |
| Total | 333 | 330 | 347 | 308 | 308 | 319 | 338 | 372 | 337 | 378 | 342 | 340 | 4132 |

# 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 4 divisions (the Clinical Trial Coordination Division, the Physician-initiated Registration-directed Clinical Trials Support Division, Clinical Trial Site Management 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 as well as the physician-initiated registration directed clinical trials. 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 192 registration-directed clinical trials including 6 physician-initiated registration directed clinical trials in 2012 (Table 1). The Clinical Data Management Division supports 17 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 the National Cancer Center Hospital (NCCH), all members of this Office will work together to contribute to reinforcing the clinical research capabilities of the NCCH and to making this Office a valuable unit for all members of our hospital.

**Table 1. Registration-directed Clinical Trials including Investigator-initiated Registration-directed Clinical Trials**

| Department | Eligible Cancer Type | Trial Phase | number of trials |
|---|---|---|---|
| Department of Neurosurgery and Neuro-Oncology | | | 2 |
| | Glioma | Phase III | 1 |
| | Glioblastoma | Phase III | 1 |
| Department of Breast Surgery | | | 1 |
| | Breast cancer | Phase III | 1 |
| Department of Breast and Medical Oncology | | | 26 |
| | Breast cancer | Phase I | 1 |
| | | Phase I/II | 1 |
| | | Phase II | 3 |
| | | Phase III | 7 |
| | | Post-marketing | 1 |
| | Ovarian cancer and others | Phase I | 1 |
| | | Phase II | 2 |
| | | Phase III | 2 |
| | Cervical cancer | Phase III | 1 |
| | Uterine corpus cancer | Phase II | 1 |
| | Endometrial cancer | Phase II | 1 |
| | Solid tumors | Phase I | 3 |
| | Malignant tumor | Phase I/II | 1 |
| | | Post-marketing | 1 |
| Department of Thoracic Surgery | | | 1 |
| | Lung cancer | Phase III | 1 |
| Department of Thoracic Oncology | | | 33 |
| | Solid tumors | Phase I | 12 |
| | Lung cancer | Phase I | 3 |
| | | Phase I/II | 2 |
| | | Phase II | 4 |
| | | Phase III | 8 |
| | | Post-marketing | 4 |

| | | | |
|---|---|---|---|
| Department of Colorectal Surgery | | | 1 |
| | Colon cancer | medical device | 1 |
| Department of Gastrointestinal Medical Oncology Division | | | 24 |
| | Colon cancer | Phase I/II | 1 |
| | | Phase III | 3 |
| | | Post-marketing | 1 |
| | Gastric cancer | Phase II | 3 |
| | | Phase III | 6 |
| | Esophageal cancer | Phase I | 1 |
| | | Phase I/II | 2 |
| | | Phase II | 1 |
| | GIST | Phase III | 2 |
| | Neuroendocrine tumor | Phase III | 1 |
| | Solid tumors | Phase I | 3 |
| Department of Endoscopy | | | 1 |
| | Colon cancer | medical device | 1 |
| Department of Hepatobiliary and Pancreatic Oncology | | | 28 |
| | Hepatocellular cancer | Phase I | 4 |
| | | Phase I/II | 3 |
| | | Phase II | 1 |
| | | Phase III | 8 |
| | Pancreatic cancer | Phase I/II | 1 |
| | | Phase II | 3 |
| | | Phase III | 2 |
| | Pancreatic endocrine tumors | Phase II | 1 |
| | | Phase III | 1 |
| | Neuroendocrine tumor | Phase I/II | 1 |
| | | In vitro diagnostic | 1 |
| | Solid tumors | Phase I | 2 |
| Department of Urology | | | 8 |
| | Renal cell cancer | Phase II | 2 |
| | | Phase III | 1 |
| | Prostatic cancer | Phase I/II | 2 |
| | | Phase II | 1 |
| | | Phase III | 2 |
| Department of Orthopedic Surgery | | | 5 |
| | Soft tissue sarcoma | Phase II | 3 |
| | | Phase III | 1 |
| | Soft tissue tumors, Bone tumors | Phase II | 1 |
| Department of Dermatologic Oncology | | | 5 |
| | Malignant melanoma | Phase I | 1 |
| | | Phase I/II | 1 |
| | | Phase II | 2 |
| | | Phase III | 1 |
| Department of Hematology Division | | | 47 |
| | Malignant lymphoma | Phase I | 10 |
| | | Phase I/II | 2 |
| | | Phase II | 6 |
| | | Phase III | 9 |
| | Leukemia | Phase I | 3 |
| | | Phase I/II | 3 |
| | | Phase II | 1 |
| | | Phase III | 2 |
| | Multiple myeloma | Phase I | 4 |
| | | Phase I/II | 1 |
| | | Phase II | 2 |
| | MDS | Phase I | 2 |
| | Hematopoietic organ tumor | Phase I | 2 |
| Department of Hematopoietic Stem Cell Transplantation | | | 2 |
| | Allogenic stem cell transplant | Phase I | 1 |
| | GVHD | PhaseII/III | 1 |
| Department of Pediatric Oncology | | | 4 |
| | Nausea/Vomiting | Phase III | 1 |
| | Candidiasis, Aspergillosis | Phase II | 1 |
| | Malignant tumor | Phase I | 1 |
| | | Phase II | 1 |
| Department of Diagnostic Radiology | | | 3 |
| | Hepatocellular cancer | Phase III | 2 |
| | Hypervascular cancer | medical device | 1 |
| Department of Radiation Oncology | | | 1 |
| | Nausea/Vomiting | Phase II | 1 |
| Total | | | 192 |

As of December 2012

# Nutrition Management Office

**Setsuko Kuwahara, Masahiro Sunaga, Hiroki Matsubara, Hiroko Takashima, Yasuko Muramatsu, Noriko Aoki**



## Introduction

2012 was a year for enhancing the organization of the Nutritional Management Office. We organized our resources so as to enhance the activity of the Nutrition Support Team (NST) to promote patient support through having and more than one specialized and full-time service in the NST, and we were happy to obtain approval for the inclusion of two registered dietitians.

Our research project was to promote the continuation of last year's research plan "Towards the development of supportive therapy, to improve taste disorders" During cancer treatment, many patients have experienced a decrease in appetite and QOL, and it is believed that improving their appetite could improve successful treatment rates.

Other activity. Six 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 their post-surgical status following, for example, esophageal surgery and hepatobiliary-pancreatic surgery.

In addition, we have also supported treatment which focuses on the provision of meal planning. In the August 2012 survey, 50% of the total patient are using individual comments meal.

## Routine activities

Dietary meals totaled 435,209 in 2012, and we gave nutrition-related dietary advice to 1,992 persons. There have been 809 requests for consultation to the NST, 67 per month on average, and this aspect of the Office has shown strong growth by 35% annually. (Table 1)

We created a booklet "Tips for meals in troubled times"and sent out 200,000 copies to cancer facilities nationwide. This was done in cooperation with the Foundation for Cancer Research, and the booklet has been utilized by many patients and medical staff . At the same time, we also focused on food service.

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. 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) In Kobe, we have held 31 study groups on nutritional management in cancer patients, with educational lectures and research reports as the contents of the program.
2) The Hospital Group for Disease Prevention Study Group of Japan, under the slogan "A Beneficial 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, Saitama , Nagano, Yamanashi, Osaka)
4) Research project
   ① Survey of dysgeusia
   ② Studies on nutrition in the surgical treatment of esophageal cancer
   ③ 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 2012**

| Clinical Departments | Jan | Feb | Mar | Apr | May | Jun | July | Aug | Sept | Oct | Nov | Dec | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Esophageal Surgery | 1 | 6 | 1 | 2 | 3 | 2 | 6 | 3 | 3 | | 3 | 6 | 36 |
| Head and Neck Surgery | | | | 1 | 4 | 3 | 5 | 3 | 1 | 1 | 7 | 2 | 27 |
| Gastrointestinal Medical Oncology | 9 | 7 | 12 | 23 | 14 | 15 | 17 | 16 | 10 | 21 | 24 | 18 | 186 |
| Hematopoietic Stem Cell Transplantation | 9 | 8 | 11 | 9 | 14 | 9 | 16 | 12 | 13 | 14 | 14 | 7 | 136 |
| Thoracic Oncology | 2 | 3 | 4 | 1 | 3 | | 4 | 2 | 5 | 3 | 6 | 4 | 37 |
| Thoracic Surgery | | 1 | | | 6 | 2 | | 2 | | 1 | | 2 | 14 |
| Hepatobiliary and Pancreatic Oncology | 2 | 4 | 2 | 1 | 4 | 3 | 5 | 4 | 2 | 6 | 3 | 2 | 38 |
| Hepatobiliary and Pancreatic Surgery | 2 | 4 | 1 | 3 | | 4 | | 1 | 2 | 2 | 4 | 6 | 29 |
| Breast Oncology and Medical Oncology | 6 | 7 | 4 | 9 | 7 | 16 | 5 | 3 | 12 | 6 | 13 | 4 | 92 |
| Gynecology | 3 | 2 | 2 | 2 | 4 | 1 | 1 | 2 | 1 | 5 | | 3 | 26 |
| Neurosurgery and Neuro-Oncology | | | 1 | 1 | | 1 | | | 1 | | | | 4 |
| Gastric Surgery | 1 | 2 | 3 | 1 | | 2 | 1 | 4 | 3 | 10 | 6 | 12 | 45 |
| Colorectal Surgery | | 1 | | | 2 | 3 | 3 | 8 | 5 | 2 | 1 | 1 | 26 |
| Urology | 4 | 3 | 3 | 2 | 1 | 2 | 3 | 2 | 6 | 3 | 1 | 1 | 31 |
| Pediatric Oncology | | 1 | 1 | | 2 | 2 | 1 | | 1 | | | 1 | 9 |
| Orthopedic Surgery | | | | | | | | 2 | 1 | 1 | | 2 | 6 |
| Dermatologic Oncology | 1 | 1 | 2 | | 1 | 1 | 4 | 2 | 2 | 2 | | 1 | 17 |
| Hematology | 1 | 2 | 2 | 1 | 3 | 4 | 2 | 4 | 1 | | 6 | 6 | 32 |
| Radiation Oncology | 1 | | 4 | 2 | | 1 | 1 | 1 | | 2 | 1 | 1 | 14 |
| Diagnostic Radiology | | | | | | | 1 | | | | 1 | | 2 |
| Breast Surgery | | | | | 1 | | | | | | | | 1 |
| Respiratory Endoscopy | | | | | | | | | 1 | | | | 1 |
| Total | 42 | 52 | 53 | 58 | 69 | 71 | 75 | 71 | 70 | 79 | 90 | 79 | 809 |
| | | | | | | | | | | | | mean | 67 |

# Department of Pharmacy

**Yoshikazu Hayashi**



## 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 toward the hospital's goal of envisaging the highest quality of medical care, practice and research. A state-of-the-art computerized system and other pharmacy-related equipment ensure quality control and inventory management, promote the proper use of drugs, and enhance the efficiency and quality of our services.

## Routine activities

As part of the fundamental function of the hospital, the 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 for patients has been widely acknowledged. Clinical pharmacists visit inpatients and give advice on taking medicine, focusing especially on pain control with opioids, and participate in the palliative-care support team. The Pharmacy also provides outpatients with guidance on 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, instructions and explanations, which are easy to understand by patients, for the proper use of drugs, such as those regarding efficacy and effectiveness, precautions, and guidance concerning symptoms at the early stage of adverse reactions, are automatically printed out for patients when a prescription is ordered.

The injection order is directly linked to an automatic "picking system" device, and this linkage ensures that injections are made properly and efficiently. This injection-ordering system contains an additional function, a regimen-ordering system for anti-cancer drugs which makes it possible to check the dose as well as the interval of chemotherapy. The Pharmacy has 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 and journals.

## Information services

The mission of the Pharmacy Information Services is to provide an evidence-based foundation for safe and effective drug therapy for cancer patients. The internal online pharmacy journal is published monthly. Current safety information, newly adopted drugs, questions-and-answers, and topic of approvals are available for medical staff on the in-hospital computer network. The 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 attaches the most importance to technical aspects of cancer care. In the second year, through required rotations in a variety of focused hematology/oncology services, the resident refines 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 2011 | FY 2010 |
|---|---|---|
| 1) Oral and topical preparations | | |
| Prepared in the hospital pharmacy | 136,594 | 141,536 |
| Inpatients | 123,594 | 128,566 |
| Outpatients | 13,000 | 12,970 |
| Taken to outside pharmacies | 67,346 | 66,080 |
| (% of prescription filled outside) | 83.8 | 83.6 |
| 2) Injections | | |
| Inpatients | 268,631 | 289,568 |
| Outpatients | 36,372 | 34,697 |

**Table2. Amounts of Drugs Consumed**

| | FY 2011 (including sales tax) | (%) | FY 2010 (including sales tax) | (%) |
|---|---|---|---|---|
| Total | 4,663,916 | 100.0 | 4,564,239 | 100.0 |
| Internal medicines | 398,595 | 8.5 | 407,375 | 8.9 |
| External | 50,001 | 1.1 | 33,747 | 0.7 |
| Injection | 3,352,939 | 71.9 | 3,129,818 | 68.6 |
| Narcotics | 166,877 | 3.6 | 154,469 | 3.4 |
| Blood | 357,681 | 7.7 | 430,021 | 9.4 |
| X-ray imaging | 240,041 | 5.1 | 249,640 | 5.5 |
| RI | 58,537 | 1.3 | 108,945 | 2.4 |
| Others | 39,245 | 0.8 | 50,223 | 1.1 |

Unit:1000 yen

**Table 3. Aseptic Preparation of Injectable Drugs**

| | FY 2011 | FY 2010 |
|---|---|---|
| Anticancer Drugs | 35,154 | 49,552 |
| Others | 32,489 | 32,112 |

**Table 4. House Preparations**

| | FY 2011 | FY 2010 |
|---|---|---|
| Sterilized | 108 | 103 |
| Non-sterilized | 172 | 138 |

**Table 5. Investigational Drugs**

| | FY 2011 | FY 2010 |
|---|---|---|
| Newly registered | 41 | 46 |
| Ongoing study | 123 | 109 |
| Total | 164 | 155 |

## List of papers published in 2012

### Journal


1. Makino Y, Yamamoto N, Sato H, Ando R, Goto Y, Tanai C, Asahina H, Nokihara H, Sekine I, Kunitoh H, Ohe Y, Sugiyama E, Yokote N, Tamura T, Yamamoto H. Pharmacokinetic and pharmacodynamic study on amrubicin and amrubicinol in Japanese patients with lung cancer. Cancer Chemother Pharmacol, 69:861-869, 2012
2. Yonemori K, Hirakawa A, Ryushima Y, Saito M, Yamamoto H, Hirata T, Ando M, Kodaira M, Yunokawa M, Shimizu C, Tamura K, Yamamoto H, Fujiwara Y. An analysis of guidance for proper usage documents for oncology drugs in Japan. Pharmaceut Med, 26:165-170, 2012
3. Azuma Y, Hata K, Sai K, Udagawa R, Hirakawa A, Tohkin M, Ryushima Y, Makino Y, Yokote N, Morikawa N, Fujiwara Y, Saito Y, Yamamoto H. Significant association between hand-foot syndrome and efficacy of capecitabine in patients with metastatic breast cancer. Biol Pharm Bull, 35:717-724, 2012

# Department of Nursing

**Kazuko Nasu**



## Introduction

The Nursing Division bears responsibility for team healthcare at the National Cancer Center Hospital (NCCH), the core institution for national cancer treatment and control in Japan. The responsibility of the Nursing 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.

## Routine activities

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 Division is working to provide safe and reliable nursing in response to advances in medicine with a conscientious approach and responsibility as a nurse in the NCCH.

We adopted the two-shift nursing system in 11 units, comprising an 8-hour day shift and a 16-hour night shift. Inpatient unit nurses work together more closely than nurses in an outpatient clinic. Moreover, we have strengthened the support for the patient discharge process so that patients can return earlier to their own home or area.

We are accepting and meeting the challenge to provide 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 stage required for actual cancer care by carrying out practical nursing training. During the first month, we provided training courses on 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 a non-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 developing and improving 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 10 specialized nurse training courses: Cancer chemotherapy nursing I and II; Clinical trial nursing; Palliative care nursing I and II; Lymphedema care; Wound and skin care; Pressure ulcer care; Dysphagia nursing; and Radiotherapy and IVR nursing. A total of 212 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, 8 certified nurse specialists and 27 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 the educational program by giving lectures and practice training for the curricula of Certified Nurse Specialists or Certified Nurses.

### Research activities

We presented 13 studies on nursing at some annual conferences in 2012. Last 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 are making effort to improve the quality of nursing research through getting support from some physicians and statisticians. We expect our nurses from the NCCH to create and develop cancer nursing to even higher levels of proficiency and expertise.

# Hospital East

# Preface

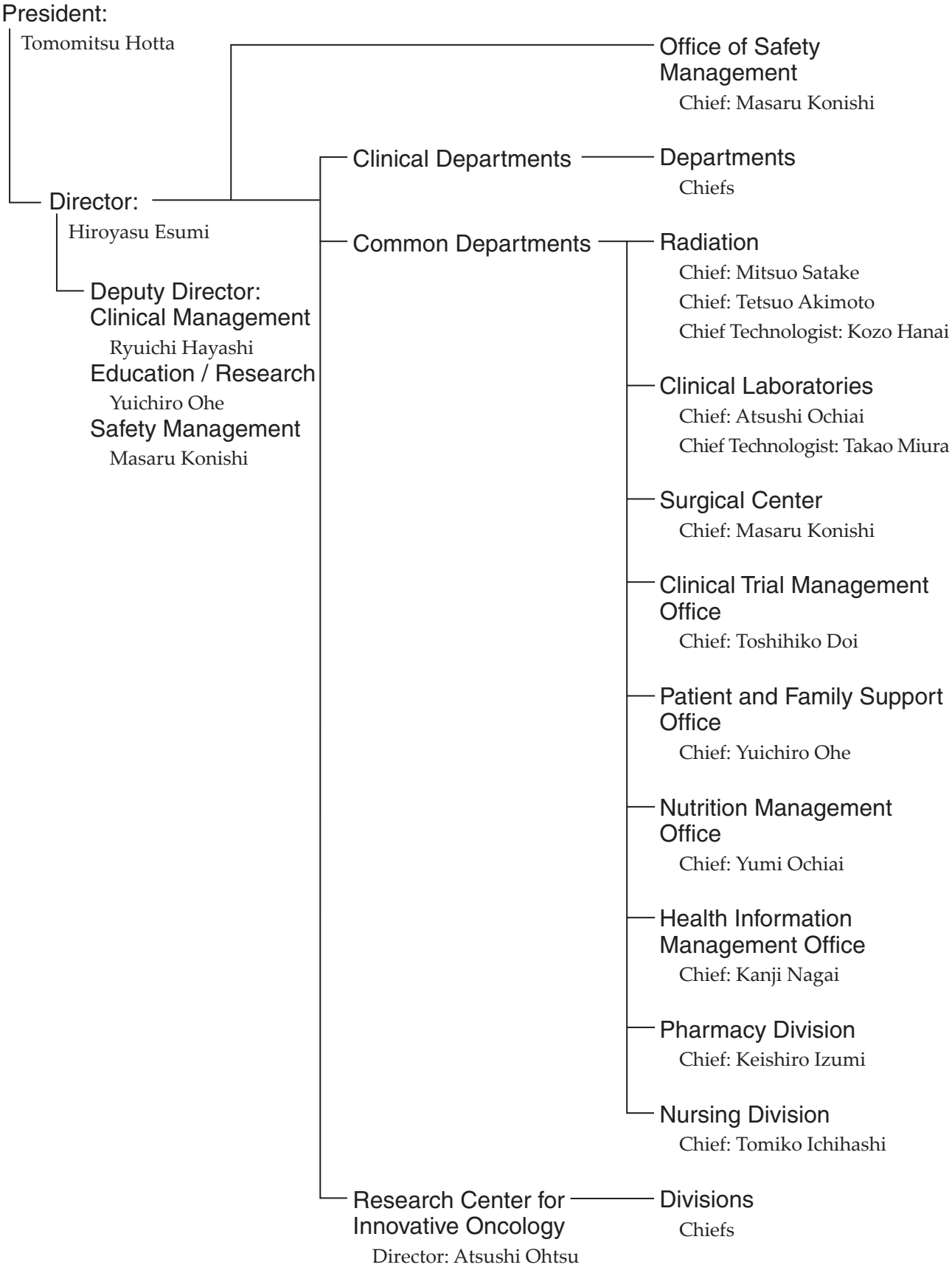
The number of patients with cancer in Japan has been steadily increasing over the last 10 years, although the age-adjusted incidence of gastric, lung, liver and cervical cancers has decreased. This has been mainly caused by the shift in the Japanese population. It is estimated that one in four people in Japan will be over 65 years old in 2015 and this country will be a super-aging society in the coming 10-20 years. Accordingly, the number of newly diagnosed cancer patients is anticipated to be almost 900,000 annually. Substantial changes in medical technology and systems for providing medical care are mandatory. The NCC Hospital East started to reorganize its activities in a timely fashion to meet these requirements by establishing the Research Center for Innovative Oncology about 10 years ago. The Research Center, together with the clinical departments of the Hospital East, is engaged in developing new cancer diagnostics, therapeutics and models of medical and care systems. Innovative endoscopy including hypoxia imaging using the differential spectrum of hemoglobin, and 3D reconstruction of endoscopic images with optical coherence tomography (OCT) technology are examples of devices developed in our Institute. New drug delivery systems using micelle technology and novel anticancer drugs based on completely new ideas, which have been developed in our Institute, are under clinical evaluation. Several investigator initiated trials, including first in human trials, have been are successfully conducted in our hospital, and others are ongoing.

In addition to the early stages of the clinical development of drugs and equipment, our activity has been extended to support the home healthcare of cancer patients that will be a keystone of the structure of the Japanese healthcare system in the coming decades. In point of fact, the number of outpatients has increased steadily every year and the number has obviously exceeded the structural limitations of our hospital outpatient clinic. Expansion of the outpatient clinic and the operating theater is now underway to fulfill the ever-increasing demand.

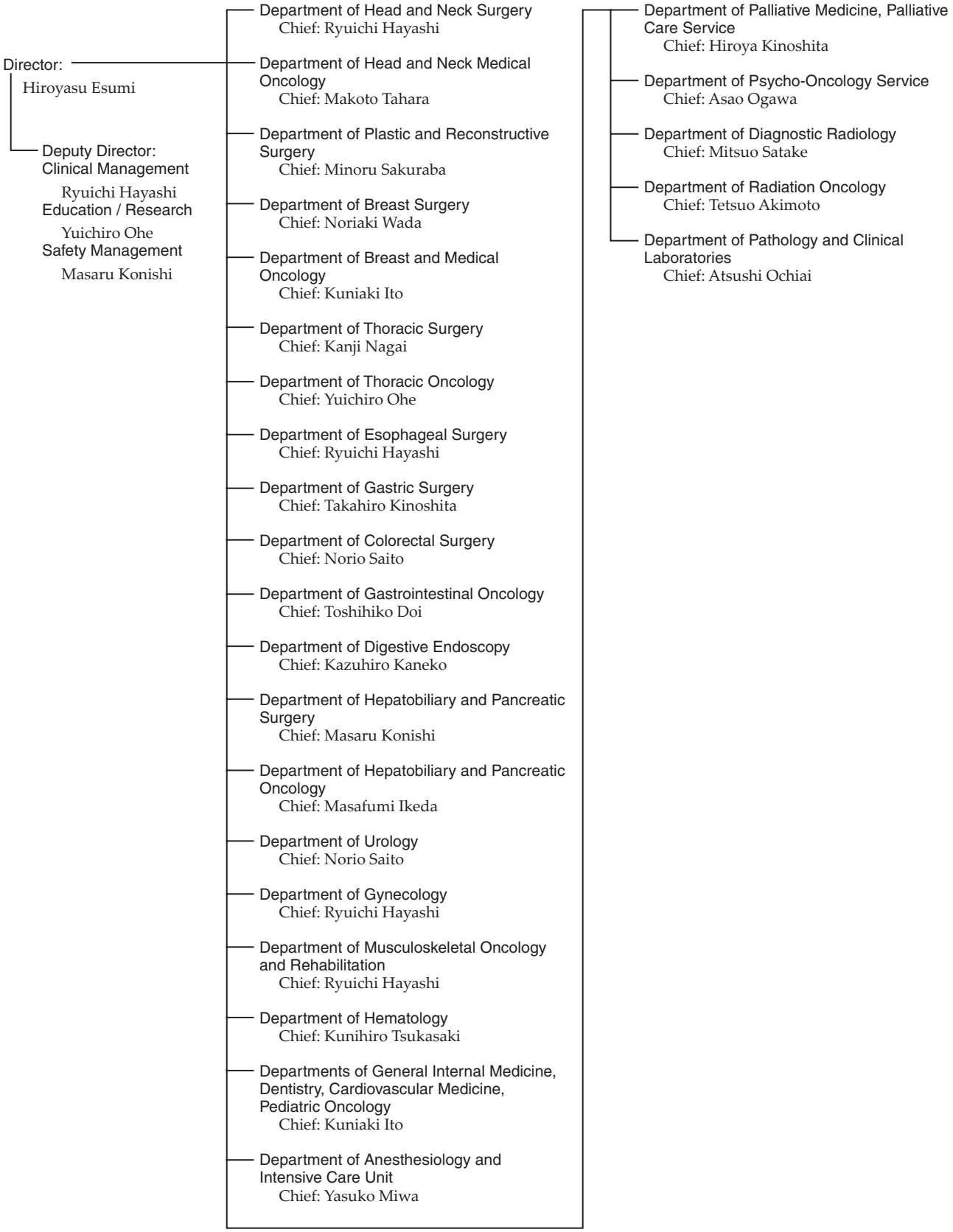
As noted above, by 2015, the 65-and-over age group will account for some 25% of the total Japanese population, and the number of people in advanced old age, above the age of 80 years, will also have grown significantly. This will make Japan a super-aging society, which is a situation that no country has ever experienced before, and we at the NCC Hospital East are already taking the requisite steps to be able to meet the unique challenges posed by such a super-aging society.

Hiroyasu Esumi M.D., Ph.D.
Director, National Cancer Center Hospital East

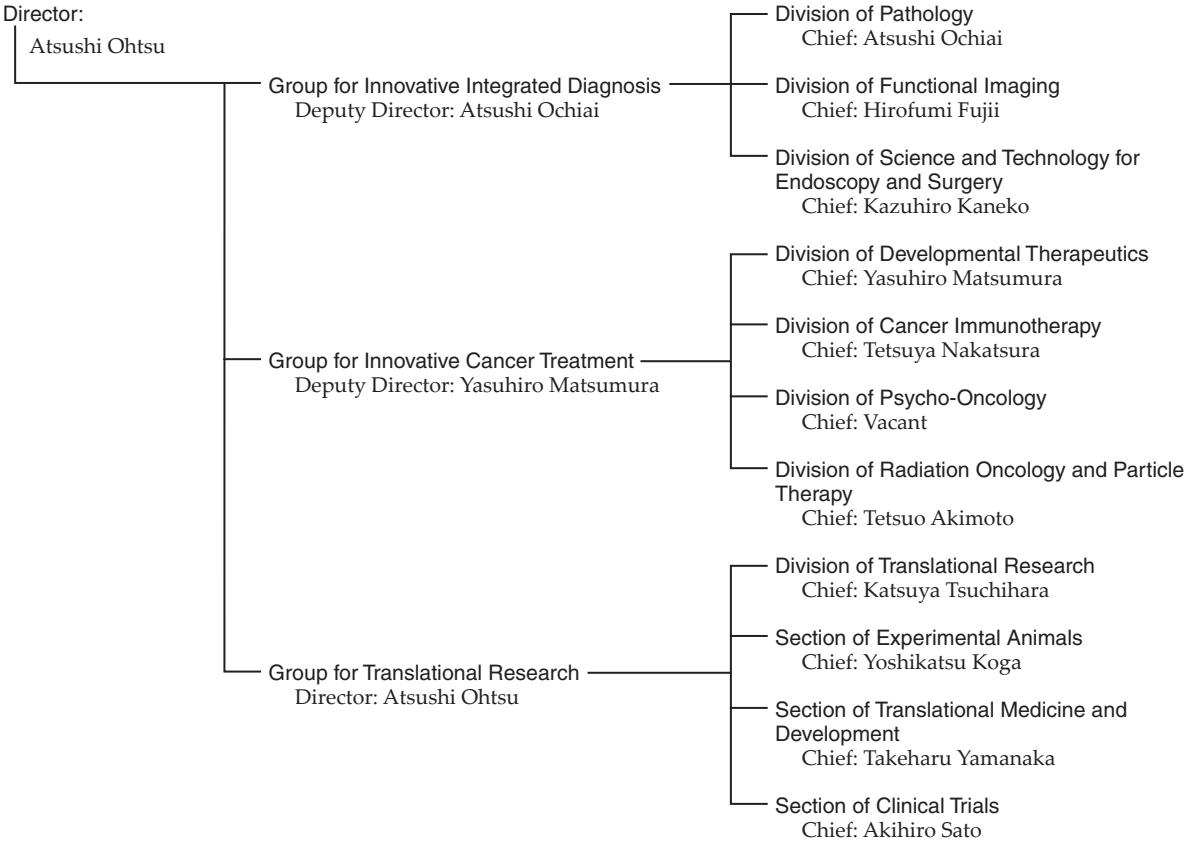
## Organization



# Clinical Departments



# Research Center for Innovative Oncology



# Activities of the Departments

# Department of Head and Neck Surgery

**Masakazu Miyazaki, Ryuichi Hayashi, Takeshi Shinozaki, Toshifumi Tomioka, Shinya Jinnouchi, Takao Hamamoto**

## 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 the microsurgical transfer of various flaps.

## Routine activities

The current treatment policy for head and neck cancer is multimodal therapy. To effectively implement available therapeutic modalities, 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 2012, 280 new patients were treated: 452 patients underwent surgery under general anesthesia and 31 patients under local anesthesia. 101 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 and salvage surgery after chemoradiation, 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 with a laser microdissection system. The levels of expression of MMP2, LOXL2, IL7R, NTRK2, GPR161 and GPR116 were higher in the cancerous tissues than in the noncancerous tissues. The p53 mutation was found in 33% of 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, participate somehow in the progression of carcinogenesis.

2. Narrow band imaging endoscopy for unknown primary tumor sites of the neck

Examinations used to search for unknown primary tumors of squamous cell carcinomas of the neck include CT, MRI, laryngoscopy, gastrointestinal endoscopy, and positron-emission tomography (PET). Narrow band imaging (NBI) endoscopy in which an optical color-separation filter is used to narrow the spectral transmittance bandwidth is also used. Twenty-eight patients in whom primary squamous cell carcinomas could not be detected with conventional white light laryngoscopy underwent NBI endoscopy and PET. Primary lesions were

**Table 1. Number of new patients**

| | |
|---|---|
| Tongue | 46 |
| Oral cavity excluding tongue | 48 |
| Oropharynx | 39 |
| Hypopharynx | 47 |
| Cervical esophagus | 10 |
| Larynx | 18 |
| Nasal cavity and paranasal sinuses | 8 |
| Thyroid gland | 37 |
| Major salivary gland | 17 |
| Cancer Unknown Primary | 7 |
| Others | 3 |
| Total | 280 |

**Table 2. Type of procedure**

| | |
|---|---|
| Glossectomy | 61 |
| Resection of oral cavity | 62 |
| Oropharyngectomy | 46 |
| Hypopharyngectomy | 31 |
| Cervical esophagectomy | 4 |
| Laryngectomy | 25 |
| Resection of the nasal and/or paranasal sinuses | 11 |
| Thyroidectomy | 52 |
| Parotidectomy | 20 |
| Submandibulectomy | 13 |
| Endoscopic resection | 47 |
| Neck dissection | 69 |
| Others | 11 |
| Total | 452 |

**Table 3. Survival rates**

| Diagnosis | Treatment | No.ofPts. | 5-yrsurvival(%) | 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

detected with NBI endoscopy in 3 patients, but no primary lesions were detected with PET. However, PET was used to detect a lower gingival cancer and a palatine tonsillar cancer. Both PET and NBI endoscopy are effective for detecting unknown primary tumors of squamous cell carcinomas of the neck.

## Clinical trials

1. Multicenter study to establish the indication of paratracheal lymph node dissection for hypopharyngeal carcinoma

A retrospective study was conducted and 286 cases were enrolled in this study from 9 hospitals. Bilateral paratracheal lymph node metastasis was found in 38% of the patients with esophageal invasion, but on the other hand it was also found in 15% of the patients without esophageal invasion. Bilateral lymph node dissection and total thyroidectomy are needed for the patients with esophageal invasion, but preserving thyroid function is possible in those patients without esophageal invasion.

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 planned number of cases is 100 and 80 patients have been enrolled for this study.

## List of papers published in 2012

### Journal

1. Shinozaki T, Hayashi R, Ebihara M, Miyazaki M, Daiko H, Saikawa M, Ebihara S. Narrow band imaging endoscopy for unknown primary tumor sites of the neck. Head Neck, 34:826-829, 2012

# Department of Head and Neck Medical Oncology

**Makoto Tahara, Hiroto Ishiki, Tomoko Yamazaki, Tomohiro Enokida**

## Introduction

The Head and Neck Medical Oncology Division is engaged in the clinical management of patients with head and neck cancer (HNC), and research into anticancer drugs for the treatment of HNC.

Our missions are to: 1) provide the best evidence-based treatment; 2) promote the importance of supportive care in the treatment of patients with HNC; 3) facilitate the timely approval of new drugs by active participation in global clinical trials to eliminate the drug lag; 4) develop cutting-edge treatments; and 5) train experts in head and neck medical oncology.

## Routine activities

Our division consists of two physicians, one senior resident and one resident. We manage the treatment of HNC patients who receive chemotherapy, including concurrent chemoradiotherapy, induction chemotherapy and palliative chemotherapy. An estimated 60% of HNC patients will present with locally advanced disease (stage III/IV) and require a multidisciplinary approach, including surgery, radiotherapy, and chemotherapy. Furthermore, HNC patients are at risk of injury and impairment of vital organs, including the eyes, ears, nose, mouth, pharynx, and larynx, both from the cancer itself and from the series of treatments provided to cure it. In treating patients, we therefore carefully assess both the curability of the condition and possible subsequent complications, such as swallowing dysfunction and cosmetic changes. Given the increasing complexity of the management of HNC, recommended treatment for patients who are referred to our institution is decided at weekly head and neck cancer conferences attended by a multidisciplinary team, which includes head and neck surgeons, radiation oncologists, plastic surgeons, dentists, pharmacists, and medical oncologists.

A total of 218 patients were treated in the inpatient clinic of our division from January 2012 to December (Table 1). Although induction chemotherapy is not yet standard therapy, 40 patients who had high-risk distant metastasis, including N2c or N3, or who had T4 in the nasal cavity, received induction chemotherapy followed by concurrent chemoradiotherapy.

The outpatient service of our division is available from Monday to Friday.

We carefully follow patients during and after treatment and provide palliative chemotherapy as an outpatient service.

## Research activities

Our research activity has focused on two areas, the development of new treatments in clinical trials for HNC and biomarker analysis in HNC.

1) Development of new treatments

Based on the results of our previously reported phase I trial (Tahara M, et. al, Cancer Science 2011), a multicenter phase II trial of concurrent chemoradiotherapy with S-1 and CDDP in patients with unresectable locally advanced squamous cell carcinoma (JCOG0706) was conducted under the JCOG. Results were reported at the last ASCO meeting. Randomized trial of concurrent chemoradiotherapy with S-1 and CDDP compared with concurrent chemoradiotherapy with CDDP is now planning.

Based on the results of our previously reported feasibility study (Kiyota N, Tahara M, et. al, JJCO 2012), a multicenter phase II/III trial of postoperative concurrent chemoradiotherapy with weekly CDDP compared with postoperative concurrent chemoradiotherapy with 3-weekly CDDP for high risk squamous cell carcinoma of the head and neck (JCOG 1008) is now ongoing. Furthermore, this trial will be an intergroup study between JCOG and EORTC group.

2) Biomarker analysis

An analysis of gene expression profiles in head and neck cancer is being carried out to determine the biomarker that can predict treatment outcomes. Recently, the existence of circulating microRNAs (miRNAs) in the blood of cancer patients has raised the possibility that miRNAs may serve as a novel diagnostic marker. Therefore, we are now conducting a prospective study to compare the miRNA expression patterns before and after disease recurrence in head and neck cancer patients.

**Table 1. Number of patients**

| Primary site | No. of patients (N=218) |
|---|---|
| Nasal cavity | 19 |
| Nasopharynx | 20 |
| Oropharynx | 28 |
| Hypopharynx | 47 |
| Oral cavity | 51 |
| Larynx | 18 |
| Salivary | 14 |
| Thyroid | 16 |
| Primary unknown | 4 |
| Other | 1 |

**Table 2. Type of procedure**

| | No. of patients (N=218) |
|---|---|
| Induction chemotherapy followed by CRT | 40 |
| Definitive CRT | 40 |
| Postoperative adjuvant CRT | 18 |
| Palliative chemotherapy | 23 |
| RT | 24 |
| Hormone therapy | 3 |
| BSC | 14 |
| Others | 36 |

**Table 3. Survival rates**

| Diagnosis | No.of pts | MST (mo) | 5-yr survival (%) |
|---|---|---|---|
| Unresectable locally advanced SCCHN | 32 | 65 | 53 |
| High risk SCCHN receiving adjuvant CRT | 25 | n.v. | 60 (3-yr) |
| Recurrent and Metastatic SCCHN | 30 | 9.8 | n.v. |
| T4b Nasal and Sinonasal cancer | 13 | n.v. | 75.5 |

n.v. : not verified



## Clinical trials

A feasibility study of the combination with docetaxel, cisplatin and 5-FU (TPF) as an induction chemotherapy for locally advanced SCCHN is ongoing.

To establish adequate dose modification of S-1 for patients who require dose reductions due to toxicity, a prospective study comparing the pharmacokinetics of S-1 at the initial dosage with that at a reduced dosage is ongoing.

To facilitate the timely approval of new drugs and eliminate the drug lag, we are also participating in the following global trials: 1) a randomized, open-label, phase III study to evaluate the efficacy and safety of oral afatinib (BIBW 2992) versus intravenous methotrexate in patients with R/M-SCCHN who have progressed after platinum-based therapy; 2) a randomized, double-blinded, placebo-controlled, phase III study to evaluate the efficacy and safety of oral afatinib (BIBW 2992) as adjuvant therapy after chemoradiotherapy in patients with primary unresected SCCHN; 3) a double-blinded, randomized phase III study evaluating the efficacy and safety of sorafenib compared to a placebo in patients with locally advanced/metastatic RAI-refractory differentiated thyroid cancer; and 4) a double-blinded, randomized phase III study evaluating the efficacy and safety of Lenvatinib(E7080) compared to a placebo in patients with locally advanced/metastatic RAI-refractory differentiated thyroid cancer.

## List of papers published in 2012
## Journal

1. Kiyota N, Tahara M, Okano S, Kawashima M, Matsuura K, Onozawa Y, Nibu K, Hayashi R, Yoshimura K, Ohtsu A. Phase II feasibility trial of adjuvant chemoradiotherapy with 3-weekly cisplatin for Japanese patients with post-operative high-risk squamous cell carcinoma of the head and neck. Jpn J Clin Oncol, 42:927-933, 2012

2. Okano S, Tahara M, Zenda S, Fuse N, Yoshino T, Doi T, Kawashima M, Ogino T, Hayashi R, Ohtsu A. Induction chemotherapy with docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin in patients with T4b nasal and sinonasal malignancies. Jpn J Clin Oncol, 42:691-696, 2012

# Department of Plastic and Reconstructive Surgery

**Minoru Sakuraba, Shogo Nagamatsu, Azusa Oshima, Masahide Fujiki, Junichi Nakao, Yutaka Fukunaga**

## Introduction

The Plastic and Reconstructive Surgery Division has mainly focused on surgical reconstruction following cancer resection. 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 a pedicled flap, local flap, skin graft, etc, are used for reconstructive surgery. The objectives of reconstructive surgery are not only the morphological reconstruction, but also the restoration of postoperative function after resective surgery. The quality of life (QOL) of the patient can be improved with the functional and morphological reconstruction.

## Routine activities

Five plastic surgeons cover reconstructive operations both in the National Cancer Center Hospital East (NCCH-E) 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 and so on. In the NCCH-E, head and neck reconstruction is the most frequently performed operation accounting for 65% of reconstructive surgical regions. In the head and neck region, the free jejunal graft and the rectus abdominis musculocutaneous flap are the most frequently used procedures. A weekly conference is held with doctors of the Department of Head and Neck surgery, Radiation Oncology, and Head and Neck Oncology. Breast reconstruction using autologous tissue transfer was employed in 2005, and since then, the patient need for breast reconstruction has continued to increase. 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. A multi-institutional analysis of postoperative complications and swallowing function after a total pharyngo-laryngo-esophagectomy and reconstruction with a free jejunal graft was performed continuously. 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. Another multi-institutional analysis of postoperative complications after microsurgical head and neck reconstruction was started to clarify the risk factor of postoperative vascular thrombosis.

## Clinical trials

A clinical trial of LAT-AGN192024 eyelashes was carried out throughout 2012. LAT-AGN 192024 ophthalmic solution 0.03% was administered in patients with hypotrichosis of the eyelashes due to their anticancer drug treatment. The efficiency and safety were evaluated with a randomized and double blinded multi-institutional clinical trial. Patient registration has closed and the data are now under analysis.

**Table1. Cooperation with other divisions**

| NCCH East | No. of patients |
|---|---|
| Head & Neck surgery | 119 |
| Orthopedic surgery | 1 |
| Esophageal surgery | 11 |
| Breast surgery | 49 |
| Dermatology | ---- |
| Urologic surgery | 2 |
| HB&P surgery | 0 |
| Ophthalmic surgery | ---- |
| Colorectal surgery | 12 |
| Gastric surgery | 0 |
| Thoracic surgery | 2 |
| Gynecology | ---- |
| Plastic & Reconstructive | 2 |
| Total | 198 |

**Table2. Operative Procedures**

| NCCH East | No. of patients |
|---|---|
| Microvascular free flap | 112 |
| Jejunum | 34 |
| RAMC or DIEP | 36 |
| Anterolateral thigh | 18 |
| Fibula bone | 7 |
| Latissimus Dorsi | 1 |
| Radial Forearm | 0 |
| Other flaps | 7 |
| Other Microsurgery | 2 |
| Supercharge | 1 |
| Nerve Graft | 0 |
| Limb Salvage | 0 |
| Hepatic Artery | 0 |
| Others | 1 |
| Subtotal | 114 |
| Pedicled flaps | 28 |
| PMMC | 7 |
| Latissimus Dorsi | 8 |
| RAMC | 0 |
| Other flaps | 13 |
| Other Procedures | 57 |
| Total | 199 |

## List of papers published in 2012
## Journal


1. Sakuraba M, Miyamoto S, Nagamatsu S, Kayano S, Taji M, Kinoshita T, Kosuge T, Kimata Y. Hepatic artery reconstruction following ablative surgery for hepatobiliary and pancreatic malignancies. Eur J Surg Oncol, 38:580-585, 2012

# Department of Breast Surgery

**Noriaki Wada, Kimiyasu Yoneyama**

## 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 for 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 on Monday evenings 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, individual cases are presented to a team of highly trained cancer specialists, including radiologists, breast surgeons, pathologists, radiation oncologists, and medical oncologists. Indeed, our multidisciplinary team approach to breast cancer treatment sets the quality of care we provide for our patients well apart from the norm.

Changes in the annual number of patients with breast cancer who underwent surgery are shown in Table 1. A total of 300 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, 76 (25%) underwent primary systemic therapy. The types and number of operative procedures performed in 2012 are shown in Table 2. The rate of breast-conserving surgeries (including two radiofrequency ablation alone cases) was 74% (223/300). Sentinel node biopsy was performed in 226 patients, and 184 patients were spared from ALND.

## Clinical and research activities (Trials)

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

   A phase II study on RFA without resection was performed for T=<1.0 cm, N0 breast cancer patients with no extensive intraductal components using a Cool-tip electrode system. Moreover, a new phase II trial of RFA for breast cancer with T =<1.5 cm 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.

**Table 1. Number of primary breast cancer patients operated on during 2003-2012**

| Clinical stage | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|
| Stage 0 | 18 | 14 | 29 | 34 | 27 | 23 | 38 | 39 | 43 | 28 |
| Stage I | 97 | 100 | 89 | 79 | 94 | 84 | 86 | 80 | 86 | 91 |
| Stage II | 104 | 97 | 94 | 103 | 87 | 87 | 122 | 137 | 112 | 128 |
| Stage III | 33 | 24 | 35 | 34 | 25 | 33 | 42 | 32 | 43 | 49 |
| Stage IV, unknown | 1 | 2 | 2 | 1 | 4 | 0 | 3 | 1 | 1 | 4 |
| Total | 253 | 237 | 249 | 251 | 237 | 227 | 291 | 289 | 285 | 300 |

**Table 2. Types of operative procedures performed in 2012 for primary breast cancer**

| Type of operation | N |
|---|---|
| BT+SNB | 29 |
| BT+SNB→ALND | 12 |
| BT+ALND | 32 |
| BT alone | 1 |
| BP+SNB | 153 |
| BP+SNB→ALND | 30 |
| BP+ALND | 33 |
| BP alone | 8 |
| RFA+SNB | 2 |
| Total | 300 |

Total mastectomy with immediate breast reconstruction was performed in 16 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 by stage**
**OP year: Jan 1993- Dec 2006**

| Clinical stage | N | 5 yr. OS | 10 yr. OS |
|---|---|---|---|
| Stage 0 | 159 | 99% | 95% |
| Stage I | 792 | 96% | 93% |
| Stage II | 1355 | 90% | 80% |
| Stage III | 287 | 68% | 55% |
| Stage IV, unknown | 30 | 33% | 10% |
| Total | 2623 | 89% | 81% |

Median follow up period: 98 months [0-230]

# Department of Breast and Medical Oncology

**Nobuaki Matsubara, Hirofumi Mukai, Kuniaki Itoh, Yoichi Naito, Ako Hosono, Masaoki Sasaki**

## Introduction

Patients with different types of cancer, including those with breast and genitourinary tract cancers, are treated with standard chemotherapy and/or managed in clinical trials in daily medical practice at the Division of Breast/Medical Oncology. 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, developmental therapeutics of new anticancer agents sponsored by pharmaceutical companies and development of combination chemotherapy involving newly developed drugs or new combinations of currently available drugs.

## Routine activities

The major and specific target disease of the Division comprised breast cancer. Eligible patients were invited to participate in large phase II/III studies. The Division also treated cancers of the genitourinary tract, cancer of unknown primary origin, soft tissue sarcomas and gynecological cancers including uterine and ovarian cancers. For patients with diseases treated with established standard chemotherapeutic regimens, standard chemotherapy was administered in routine medical practice. Patients in whom standard chemotherapy had failed and those with cancers for which standard chemotherapy was unavailable were invited to participate in clinical studies on experimental drugs and regimens. In 2012, 597 patients with different types of cancer 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 oncology 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. Morning case conferences on inpatient care are held on every day, and a weekly case conference on new patients visiting the clinics at the Division is held on Thursday evenings in collaboration with the Division of hematology. A weekly educational review on oncology and hematology is also conducted on Tuesday evenings. Moreover, a biweekly joint conference is held on Wednesday evenings and on Monday evenings with breast surgeons and with urologists, respectively. Morning journal clubs also meet on Mondays and Fridays at the Division in collaboration with the Division of 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. Combination phase I studies of the following anticancer agents were conducted: BIBW2992 (afatinib, an oral inhibitor of tyrosine kinases) and weekly vinorelbine for patients unresponsive to chemotherapy and those with cancers for which standard chemotherapy was unavailable, and E7389 (elibuline, a synthetic analog of Halichondrin B) and trastuzumab for patients with advanced or recurrent breast cancer in whom HER-2 was overexpressed. A phase II study of E7389 for treated patients with soft tissue sarcomas is also ongoing. Phase I studies of the following anticancer agents were conducted: cabazitaxel (a new taxane derivative) for patients with hormone refractory prostate cancer, JNJ212082 (abiraterone acetate, a CYP17 inhibitor for androgen antagonist) for patients with castration-resistant prostate cancer who have not received chemotherapeutic agents, and NK105 (paclitaxel-incorporating micellar nanoparticle formulation) for patients with advanced or metastatic cancer for which standard chemotherapy was unavailable.

In addition, many phase III studies are being conducted as follows: a randomised, open-label, phase III study on taxane based chemotherapy with lapatinib or tarastuzumab as first-line therapy for woman with HER2 positive metastatic breast cancer; a randomised placebo controlled trial of RAD001 (everolimus, mTOR inhibitor) combined with paclitaxel and trastuzumab for patients with HER-2 positive metastatic and/or locally advanced breast cancer as a primary treatment; a randomised double-blind placebo-controlled trial of neratinib (an erbB1/2/4 inhibitor) after trastuzumab in women

**Table 1. Number of new patients in 2012**

| | |
|---|---|
| Breast cancer | 285 |
| Genitourinary cancers | 181 |
| Gynecological cancers | 31 |
| Cancer of unknown primary | 42 |
| Others | 58 |
| Total | 597 |

with early-stage HER-2 overexpressed/amplified breast cancer; a randomised, open-label, phase III study on adjuvant lapatinib versus trastuzumab versus both lapatinib and trastuzumab treatment in patients with HER-2 overexpressed primary breast cancer (ALTTO: Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation); a randomised multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer (APHINITY: Adjuvant Pertuzumab and Herceptin IN Initial Therapy); a randomised phase III study on NK105 versus paclitaxel in patients with recurrent or metastatic breast cancer; and a randomised phase III study on lapatinib, trastuzumab, and both lapatinib and trastuzumab, combined with aromatase inhibitor in patients with HER-2 overexpressed breast cancer who received neo-/adjuvant therapy with trastuzumab and endocrine therapy.



## List of papers published in 2012
### Journal


1. Matsubara N, Itoh K, Mukai H, Nagai S. Long-term outcome of pleurodesis with OK-432 in metastatic breast cancer: a new risk model for success from an analysis of 75 cases. Int J Clin Oncol, 17:470-476, 2012
2. Yamaguchi T, Mukai H. Ki-67 index guided selection of preoperative chemotherapy for HER2-positive breast cancer: a randomized phase II trial. Jpn J Clin Oncol, 42:1211-1214, 2012
3. Ishihara M, Mukai H, Nagai S, Onozawa M, Nihei K, Shimada T, Wada N. Retrospective analysis of risk factors for central nervous system metastases in operable breast cancer: effects of biologic subtype and Ki67 overexpression on survival. Oncology, 84:135-140, 2012

# Department of Thoracic Surgery

**Kanji Nagai, Junji Yoshida, Tomoyuki Hishida, Keijyu Aokage, Tomohiro Haruki, Yuki Matsumura**

## 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 (NCCH-E) 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 13 scientific papers published in English, and 2 in Japanese, the Division made 50 presentations: 8 international, 32 national, and 10 regional.

## Routine activities

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 tumor is attempted based on modified Thomfold's criteria after consultation with the patient. The majority of these cases are metastases from colorectal carcinomas, while most of the mediastinal tumors are thymic epithelial tumors.

The surgical procedures of the 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 have become 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 normal. This year, 30-day operative mortality occurred in 3 (0.9%) patients undergoing surgery for primary lung cancer.

## Research activities and 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 | 335 |
| Metastatic lung tumor | 55 |
| Mediastinal tumor | 26 |
| Others | 58 |
| Total | 474 |

**Table 2. Type of procedure –Primary lung cancer**

| | |
|---|---|
| Pneumonectomy | 18 |
| Lobectomy | 264 |
| (Bronchoplasty) | (11) |
| Limited resection | 45 |
| Exploratory thoracotomy | 8 |
| Total | 335 |

**Table 3. Overall Survival rates for resected primary lung cancer(as of 2012)**

| Pathologic stage | Number of patients | MST(month) | 5-yr survival rate(%) |
|---|---|---|---|
| IA | 1115 | NR | 86.6 |
| IB | 459 | NR | 67.0 |
| IIA | 283 | NR | 54.3 |
| IIB | 191 | 42.8 | 44.4 |
| IIIA | 395 | 36.1 | 35.1 |

Surgery between 2000 and 2009, Stages according to TNM Classification 7th edition: NR:Not reached

## List of papers published in 2012
## Journal

1. Kawase A, Yoshida J, Ishii G, Nakao M, Aokage K, Hishida T, Nishimura M, Nagai K. Differences between squamous cell carcinoma and adenocarcinoma of the lung: are adenocarcinoma and squamous cell carcinoma prognostically equal? Jpn J Clin Oncol, 42:189-195, 2012
2. Nakao M, Hishida T, Ishii G, Yoshida J, Nishimura M, Nagai K. Malignant granular cell tumor of the posterior mediastinum with dissemination. Asian Cardiovasc Thorac Ann, 20:71-73, 2012
3. Shimada Y, Niho S, Ishii G, Hishida T, Yoshida J, Nishimura M, Yoh K, Goto K, Ohmatsu H, Ohe Y, Nagai K. Clinical features of unresectable high-grade lung neuroendocrine carcinoma diagnosed using biopsy specimens. Lung Cancer, 75:368-373, 2012
4. Matsumura Y, Ishii G, Aokage K, Kuwata T, Hishida T, Yoshida J, Nishimura M, Nagai K, Ochiai A. Morphophenotypic characteristics of intralymphatic cancer and stromal cells susceptible to lymphogenic metastasis. Cancer Sci, 103:1342-1347, 2012
5. Asai M, Akizuki N, Fujimori M, Matsui Y, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Psychological states and coping strategies after bereavement among spouses of cancer patients: a quantitative study in Japan. Support Care Cancer, 20:3189-3203, 2012
6. Takuwa T, Ishii G, Nagai K, Yoshida J, Nishimura M, Hishida T, Neri S, Hasegawa S, Ochiai A. Characteristic immunophenotype of solid subtype component in lung adenocarcinoma. Ann Surg Oncol, 19:3943-3952, 2012
7. Neri S, Ishii G, Taira T, Hishida T, Yoshida J, Nishimura M, Nagai K, Ochiai A. Recruitment of podoplanin positive cancer-associated fibroblasts in metastatic lymph nodes predicts poor prognosis in pathological N2 stage III lung adenocarcinoma. Ann Surg Oncol, 19:3953-3962, 2012
8. Maeda R, Ishii G, Ito M, Hishida T, Yoshida J, Nishimura M, Haga H, Nagai K, Ochiai A. Number of circulating endothelial progenitor cells and intratumoral microvessel density in non-small cell lung cancer patients: differences in angiogenic status between adenocarcinoma histologic subtypes. J Thorac Oncol, 7:503-511, 2012
9. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Influence of cigarette smoking on survival and tumor invasiveness in clinical stage IA lung adenocarcinoma. Ann Thorac Surg, 93:1626-1632, 2012
10. Nakao M, Yoshida J, Goto K, Ishii G, Kawase A, Aokage K, Hishida T, Nishimura M, Nagai K. Long-term outcomes of 50 cases of limited-resection trial for pulmonary ground-glass opacity nodules. J Thorac Oncol, 7:1563-1566, 2012
11. Matsumura Y, Hishida T, Yoshida J, Aokage K, Ishii G, Nagai K. Reasonable extent of lymph node dissection in intentional segmentectomy for small-sized peripheral non-small-cell lung cancer: from the clinicopathological findings of patients who underwent lobectomy with systematic lymph node dissection. J Thorac Oncol, 7:1691-1697, 2012
12. Kinoshita T, Yoshida J, Ishii G, Aokage K, Hishida T, Nagai K. Pulmonary metastasis from encapsulated cervical ectopic type a thymoma. Ann Thorac Surg, 94:e141-142, 2012
13. Shimada Y, Yoshida J, Hishida T, Nishimura M, Ishii G, Nagai K. Predictive factors of pathologically proven noninvasive tumor characteristics in T1aN0M0 peripheral non-small cell lung cancer. Chest, 141:1003-1009, 2012

# Department of Thoracic Oncology

**Yuichiro Ohe, Hironobu Ohmatsu, Koichi Goto, Seiji Niho, Kiyotaka Yoh, Shigeki Umemura, Shingo Matsumoto, Yuji Matsumoto, Masahiro Morise**



## 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, 5A 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 and residents are teaching methods of reading chest X-ray and CT imaging films.

## Research activities

Our research activities are focused on four areas: 1) development of new and effective diagnosis and treatment modalities; 2) detection, diagnosis, and treatment of peripheral-type minute lung cancers that are not visible in plain chest X-rays; 3) collaborative studies with the Research Center for Innovative Oncology in the following areas: correlation between gene abnormalities and clinical characteristics; precancerous lesions; atypical adenomatous hyperplasia; and 4) translational research from bench to bed-side or from bed-side to bench for the development of innovative treatment strategies.

Whole genome analysis of small cell cancer to detect new driver mutations and establishment of diagnosis methods for KIF5B-RET fusion gene which is a newly discovered driver gene of adenocarcinoma of the lung are under particular 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, the usefulness of continuation and switch maintenance chemotherapy using pemetrexed for non-squamous non-small cell lung cancer (NSCLC) has been established. An in house feasibility study of maintenance chemotherapy of TS-1 for stage IV 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. More than two-thirds of the target number of patients have already entered in this study.

CH5424802 is a newly developed selective ALK inhibitor and very effective for ALK fusion positive NSCLC, although 4-5% of NSCLC are positive for EML4-ALK fusion protein. A phase I /II study of CH5424802 demonstrated durable response and a response rate higher than 90% without severe toxicity.

JCOG0605 is a randomized phase 3 study

**Table 1. Number of patients in 2012**

| | | |
|---|---|---|
| Lung Cancer | | 381 |
| | Small cell lung cancer | 68 |
| | Adenocarcinoma | 193 |
| | Squamous cell carcinoma | 69 |
| | Large cell carcinoma | 2 |
| | NSCLC NOS | 40 |
| | Others | 9 |
| Thymic cancer | | 7 |
| Thymoma | | 0 |
| Malignant pleural mesothelioma | | 7 |
| Primary unknown | | 1 |

**Table 2. Initial treatment of lung cancer in 2012**

| | |
|---|---|
| Chemotherapy | 221 |
| Chemoradiotherapy | 55 |
| Surgery followed by chemotherapy | 31 |
| Radiotherapy | 12 |
| Palliative care | 55 |
| Others | 7 |

**Table 3. Survival of lung cancer patients treated in 2005-2009**

| Disease | Stage | Treatment | N | Survival rate (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 1y | 2y | 3y | 4y | 5y |
| NSCLC | III | Chemoradiotherapy | 240 | 78 | 48 | 37 | 31 | 23 |
| NSCLC | IIIB-IV | Chemotherapy | 832 | 48 | 26 | 15 | 8 | 4 |
| SCLC | LD | Chemoradiotherapy | 106 | 83 | 40 | 28 | 19 | 19 |
| SCLC | ED | Chemotherapy | 180 | 39 | 7 | 2 | 1 | 0 |

comparing nogitecan vs weekly cisplatin, irinotecan and etoposide for previously treated SCLC. Patient accrual of JCOG0605 has been completed this year.

JCOG1011 is a randomized phase 2 study for LD-SCLC comparing cisplatin and amrubicin with CODE regimen (weekly cisplatin, vincristine, Adriamycin, etoposide) after induction chemoradiotherapy with cisplatin and etoposide, and has started.

An investigator initiated clinical trial of vandetanib, which is inhibitor of RET, VEGFR and EGFR for KIF5B-RET fusion gene positive NSCLC is under preparation and will start soon.

## List of papers published in 2012
### Journal


1. Goto K, Satouchi M, Ishii G, Nishio K, Hagiwara K, Mitsudomi T, Whiteley J, Donald E, McCormack R, Todo T. An evaluation study of EGFR mutation tests utilized for non-small-cell lung cancer in the diagnostic setting. Ann Oncol, 23:2914-2919, 2012
2. Yoh K, Kubota K, Ohmatsu H, Goto K, Niho S, Ohe Y. Feasibility study of zoledronic acid plus cisplatin-docetaxel as first-line treatment for advanced non-small cell lung cancer with bone metastases. Anticancer Res, 32:4131-4135, 2012
3. Niho S, Ohe Y, Ishikura S, Atagi S, Yokoyama A, Ichinose Y, Okamoto H, Takeda K, Shibata T, Tamura T, Saijo N, Fukuoka M. Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: a multicenter feasibility study (JCOG 0402). Ann Oncol, 23:2253-2258, 2012
4. Niho S, Kunitoh H, Nokihara H, Horai T, Ichinose Y, Hida T, Yamamoto N, Kawahara M, Shinkai T, Nakagawa K, Matsui K, Negoro S, Yokoyama A, Kudoh S, Kiura K, Mori K, Okamoto H, Sakai H, Takeda K, Yokota S, Saijo N, Fukuoka M. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer, 76:362-367, 2012
5. Ito M, Niho S, Nihei K, Yoh K, Ohmatsu H, Ohe Y. Risk factors associated with fatal pulmonary hemorrhage in locally advanced non-small cell lung cancer treated with chemoradiotherapy. BMC Cancer, 12:27, 2012
6. Goto K, Ichinose Y, Ohe Y, Yamamoto N, Negoro S, Nishio K, Itoh Y, Jiang H, Duffield E, McCormack R, Saijo N, Mok T, Fukuoka M. Epidermal growth factor receptor mutation status in circulating free DNA in serum: from IPASS, a phase III study of gefitinib or carboplatin/paclitaxel in non-small cell lung cancer. J Thorac Oncol, 7:115-121, 2012
7. Kawata Y, Niki N, Ohmatsu H, Kusumoto M, Tsuchida T, Eguchi K, Kaneko M, Moriyama N. Quantitative classification based on CT histogram analysis of non-small cell lung cancer: correlation with histopathological characteristics and recurrence-free survival. Med Phys, 39:988-1000, 2012

# Department of Esophageal Surgery

**Hiroyuki Daiko, Takeo Fujita**

## Introduction

The Esophageal Surgery Division deals with neoplasms arising from the esophagus. The surgical management of esophageal cancer has been the main clinical as well as research activity of this Division. In particular, the Division is striving to establish minimally invasive surgery which consists of neoadjuvant treatment followed by minimally invasive esophagectomy. The Division is conducting a study to define the role of surgery in the multimodal approach to the treatment of esophageal cancer, with the aim that thoracolaparoscopic esophagectomy, consisting of thoracoscopic esophagectomy and laparoscopic reconstruction, should become a standard surgical procedure.

## Routine activities

The Esophageal Surgery Division consists of 2 staff surgeons 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 4 patients are operated upon every week. In 2012, 145 patients underwent esophagectomy. Transthoracic esophagectomy with extended lymph node dissection was performed on 65 nontreated cases or with neoadjuvant chemotherapy before surgery, and modified transthoracic esophagectomy was performed as a salvage procedure in 9 patients in whom other therapeutic modalities had failed. Thoracoscopic esophagectomy in the prone position with radical lymph node dissection was undertaken in 69 cases and transhiatal esophagectomy without thoracotomy was performed in 11 cases. Postoperatively, within 30 days, 1 patient died due to complications after a salvage operation.

## Clinical activities

Currently, the Division is examining the role of thoracolaparoscopic esophagectomy as a minimally invasive esophagectomy comprising thoracoscopic esophagectomy and laparoscopic reconstruction. For patients without lymph node metastasis in the thoracic inlet, thoracoscopic esophagectomy in the prone position with radical lymph node dissection and laparoscopic reconstruction after esophagectomy for patients without history of laparotomy are being performed in an attempt to establish them as standard surgical procedures for esophageal cancer.

For the treatment of patients aged over 80 years and at high risk, a two-stage surgical procedure divided into resection and reconstruction is being attempted.

A randomized controlled phase III study comparing Cisplatin and 5-fluorouracil versus Cisplatin and 5-fluorouracil plus Docetaxel versus Cisplatin and 5-fluorouracil concurrent radiation as neoadjuvant treatment for locally advanced esophageal cancer is ongoing.

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

Since 2000, the Division has started to perform salvage surgery for patients in whom definitive chemoradiotherapy has failed. The operative procedures and postoperative management have been refined gradually. The Division is also studying the role and efficacy of salvage surgery in the multimodal treatment of esophageal cancer.

**Table 1. Type of Procedure**

| | |
|---|---|
| 1 stage operation | 131 |
| 2 stage operation | 14 |
| | |
| Rt-Transthoracic Esophagectomy | 65 |
| Thoracoscopic Esophagectomy | 69 |
| Lt-Transthoracic Esophagectomy | 0 |
| Salvage Esophagectomy | 9 |
| Transhiatal Esophagectomy | 11 |
| Thoracoscopic enucleation for GIST | 1 |
| Emergency Operation | 12 |
| Others | 8 |
| Total | 177 |

## List of papers published in 2012
## Journal


1. Daiko H, Nishimura M. A pilot study of the technical and oncologic feasibility of thoracoscopic esophagectomy with extended lymph node dissection in the prone position for clinical stage I thoracic esophageal carcinoma. Surg Endose, 26:673-680, 2012
2. Daiko H, Fujita T, Matsumura Y, Nishimura M. A new approach for posterior mediastinal tumors: thoracoscopic resection in the prone position. Asian J Endosc Surg, 5:138-140, 2012
3. Fujita T, Daiko H, Nishimura M. Early enteral nutrition reduces the rate of life-threatening complications after thoracic esophagectomy in patients with esophageal cancer. Eur Surg Res, 48:79-84, 2012
4. Hosokawa Y, Kinoshita T, Konishi M, Takahashi S, Gotohda N, Kato Y, Daiko H, Nishimura M, Katsumata K, Sugiyama Y, Kinoshita T. Clinicopathological features and prognostic factors of adenocarcinoma of the esophagogastric junction according to Siewert classification: experiences at a single institution in Japan. Ann Surg Oncol, 19:677-683, 2012

# Department of Gastric Surgery

**Takahiro Kinoshita, Hidehito Shibasaki, Masaru Konishi, Shinichiro Takahashi, Naoto Gotohda, Yuichiro Kato, Taira Kinoshita, Kenji Sakai**



## 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 ten resident surgeons. The gastric tumors we manage to include not only common gastric adenocarcinomas but also adenocarcinomas of the esophagogastric junction (AEG), which are increasing recently, probably due to reduction of *Helicobacter pylori* (HP)-infection rates, and gastric submucosal tumors (GIST etc.). Annually 260-300 patients are operated on either with a conventional laparotomy or laparoscopic surgery. Laparoscopic gastrectomy with radical lymph node (LN) dissection was introduced in 2010 to pursue minimal invasiveness and better quality of life (QOL) for the patients. Recent high-definition laparoscopic imaging enables more meticulous and accurate maneuvers. In 2012, about 60% of gastrectomies were performed under laparoscopy. The basis of our surgery is radical extirpation of cancer lesions, but at the same time organ functions and a 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) by surgery combined with recent advanced chemotherapy regimens, including molecular-targeting drugs (Trastuzumab).

## Routine activities

Usually 16-18 patients are hospitalized and 5-7 patients undergo operations per week. A weekly film conference is held every Monday from 17:00 with doctors of 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 via laparoscopic surgery with nodal dissection based on the pathological findings of specimens obtained with ESD. In other patients with c-stage I gastric cancer, laparoscopic surgery with nodal dissection is indicated as initial interventions. Not only distal gastrectomy but also total gastrectomy or function preserving procedures (pylorus-preserving gastrectomy or proximal gastrectomy) are performed laparoscopically. Basically, all of the procedures, mobilization, lymphadenectomy and reconstruction, are carried out under laparoscopy, and are referred to as total laparoscopic procedures. Currently D2 radical dissection is also performed under laparoscopy with much less blood loss, therefore this indication may be expanded. In patients with c-stage II or III gastric cancer open gastrectomy is basically indicated. When the tumor has infiltrated adjacent organs (liver, pancreas, etc.), extended radical operations (pancreaticoduodenectomy, plus hepatectomy) are chosen. For AEGs, when the tumor involves the distal esophagus for a length greater than 3 cm, the left thoracoabdominal approach is selected. Otherwise, the abdominal approach is chosen according to the results of JCOG 9502, and recently the transhiatal approach can be also employed laparoscopically with a better surgical view. When patients are diagnosed as having p-stage II or III in the final pathological findings after operation, postoperative adjuvant chemotherapy with S-I is recommended to them according to the Gastric Cancer Treatment Guidelines, but now its duration for p-stage II is being estimated in a phase III JCOG trial, and the feasibility of XELOX therapy is under a phase II trial.

We place importance on education of the gastric surgeons, including those from other institutions, as well as hands-on training for resident surgeons in our hospital. Surgeons from domestic or foreign hospitals have visited our division to study 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, if eligible for the

**Table 1. Number of patients**

| | |
|---|---|
| Gastric cancer | 284 |
| Others (GIST etc.) | 31 |

**Table 2. Type of procedure**

| | |
|---|---|
| Open gastrectomy | 92 |
| Distal Gastrectomy | 33 |
| Pylorus-preserving Gastrectomy | 1 |
| Proximal Gastrectomy | 1 |
| Total Gastrectomy | 43 |
| Pancreaticoduodenectomy | 2 |
| Partial Gastrectomy | 3 |
| Others (bypass, exploration, etc.) | 9 |
| Laparoscopic Surgery | 194 |
| Distal Gastrectomy | 117 |
| Pylorus-preserving Gastrectomy | 5 |
| Proximal Gastrectomy | 26 |
| Total Gastrectomy | 15 |
| Partial Gastrectomy | 14 |
| Others (bypass, exploration, etc.) | 17 |

**Table 3. Survival rates of gastric cancer patients shown by stage**

| 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.); Pts, patients

respective study, are 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 appearances of large-sized type 3 or type 4 lesions. In this trial, a neoadjuvant chemotherapy arm is compared to a surgery preceding 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, a palliative gastrectomy arm is compared to Ba chemotherapy arm.
3. JCOG 0912 A phase III randomized study on 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 on 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 on ESD for an expand indication in the treatment of early gastric cancer of the undifferentiated type
7. JCOG 1104 A phase II trial to define the optimal period of adjuvant S-1 chemotherapy for pathological stage II gastric cancer patients who have undertgone a D2 gastrectomy

## List of papers published in 2012

### Journal


1. Kinoshita T, Gotohda N, Kato Y, Takahashi S, Konishi M, Okazumi S, Katoh R, Kinoshita T. Laparoscopic transhiatal resection for Siewert type II adenocarcinoma of the esophagogastric junction: operative technique and initial results. Surg Laparosc Endosc Percutan Tech, 22:e199-203, 2012
2. Fujita T, Gotohda N, Kato Y, Kinoshita T, Takahashi S, Konishi M, Daiko H, Nishimura M, Kuwata T, Ochiai A, Kinoshita T. Clinicopathological features of stomach cancer with invasive micropapillary component. Gastric Cancer, 15:179-187, 2012

# Department of Colorectal Surgery

**Norio Saito, Masanori Sugito, Masaaki Ito, Akihiro Kobayashi, Yusuke Nishizawa, Nobuhiro Sugano, Hideaki Nishigori**



## Introduction

The Colorectal and Pelvic Surgery Division was established 14 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 a 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 350 patients with very low rectal tumors and has resulted in cure, preservation of anal function, and a better QOL.

## Research activities

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 from the anal verge. However, permanent colostomy causes severe impairment of patient 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 preoperatively regarding the potential functional adverse effects after ISR. 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 34 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 postoperatively the feasibility and the oncologic outcome of local therapy for T1 and a part of T2 rectal cancer without lymph node metastases. In this study, 32 patients have been registered. This study is currently in progress.

## Clinical trials

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)
- A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer (JCOG1007)
- Randomized Phase III study of mFOLFOX7 or CAPOX plus bevacizumab versus 5-fluorouracil/leucovorin or capecitabine plus bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer (JCOG1018)
- A randomized controlled trial comparing laparoscopic surgery with open surgery in palliative resection of primary tumor in incurable Stage IV colorectal cancer (JCOG1107)
- A Phase II/III randomized multicenter trial of intersphincteric resection (ISR) with or without preoperative chemotherapy for very low-lying rectal cancer.

**Table 1. Number of patients (2012.1-2012.12)**

| Colorectal cases | | | Other cases | | Total |
|---|---|---|---|---|---|
| Colon | Rectum | Sub-total | Gastro-intestinal | Others | |
| 148 | 180 | 328 | 5 | 112 | 445 |

**Table 2. Type of procedure**
**Operative Procedures (2012.1-2012.12)**

| Colon N=148<br>Laparoscopic (LAP) : 119, Open : 29 | | |
|---|---|---|
| Sigmoidectomy | 41 | (LAP:36) |
| Right (hemi) colectomy | 43 | (LAP:36) |
| Ileocecal resection | 20 | (LAP:19) |
| Limited colectomy | 27 | (LAP:23) |
| Hartmann procedure | 0 | |
| High anterior resection | 0 | |
| Low anterior resection | 3 | (LAP:1) |
| Left (hemi) colectomy | 4 | (LAP:3) |
| Stoma | 0 | |
| Other | 10 | |

| Rectum N=180<br>Laparoscopic (LAP) :103, Open : 93 | | |
|---|---|---|
| Low anterior resection | 71 | (LAP:50) |
| *Abdominoanal resection(AAR) | 50 | (LAP:22) |
| High anterior resection | 17 | (LAP:11) |
| Abdominoperineal resection (APR) | 18 | |
| Hartmann procedure | 4 | |
| Local excision | 4 | |
| Total pelvic exenteration | 2 | |
| Stoma | 7 | |
| Others | 7 | |

* Conventional coloanal anastomosis:5
Partial intersphincteric resection (ISR) :17
Subtotal ISR:23
Total ISR:4
Partial external sphincter resection (ESR):1

**Table 3. Survival rates**

| Stage | Colon | | | Rectum | | |
|---|---|---|---|---|---|---|
| | No. of pts | 5-yr survival (%) | | No. of pts | 5-yr survival (%) | |
| | | overall | cancer specific | | Overall | cancer specific |
| Stage 0 | 7 | 100 | 100 | 10 | 100 | 100 |
| Stage I | 155 | 96 | 100 | 119 | 94.9 | 99.1 |
| Stage II | 239 | 91.8 | 95.5 | 158 | 84.6 | 89.9 |
| Stage III | 158 | 83.9 | 87.5 | 132 | 81.3 | 83.4 |
| Stage IIIb | 50 | 66.1 | 66.1 | 89 | 60.8 | 63.6 |
| Stage IV | 133 | 21.1 | 22.5 | 77 | 25.3 | 25.7 |

Op:1999.1-2005.12

## List of papers published in 2012
## Journal


1. Nishizawa Y, Kobayashi A, Saito N, Nagai K, Sugito M, Ito M, Nishizawa Y. Surgical management of small bowel metastases from primary carcinoma of the lung. Surg Today, 42:233-237, 2012
2. Nishigori H, Ito M, Nishizawa Y, Koyama A, Koda T, Nakajima K, Minagawa N, Nishizawa Y, Kobayashi A, Sugito M, Saito N. Postoperative chylous ascites after colorectal cancer surgery. Surg Today, 42:724-728, 2012
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# Department of Gastrointestinal Oncology

**Toshihiko Doi, Takayuki Yoshino, Nozomu Fuse, Takashi Kojima, Kohei Shitara**

## Introduction

In 2012, approximately 500 patients were treated by 5 medical oncologists and 5 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, approximately 1361 patients are hospitalized under normal circumstances and the hospital stay with chemotherapy or palliative therapy was short. Our activities for each type of GI cancer in 2012 are shown in Table 1 (Number), Table 2 (Treatment), and Table 3 (efficacy). In clinical trials, both 62 sponsored initiated trials which consisted of 31 phase I trials including first-in-human, first-in-class drugs in a global fashion and 31 phase2/3 global trials to approve investigational new drugs (INDs) were conducted.

## Research activities

Phase I

Our Division has focused more on the early stage clinical development of investigational agents. Over 100 patients have been registered in phase I trials annually. We organize a weekly phase I trials meeting to share the updated information and to allocate patients to adequate phase I trials. Several results of phase I trials, such as studies on a cMET+VEGFR-2 inhibitor (golvatinib, E7050), an angiopoietin-1/2 antagonist (trebananib, AMG 386), an IGF-1R inhibitor (ganitumab, AMG 479) and a histone deacetylase inhibitor (vorinostat) for GI cancer, were presented at international meetings and published. Recently, the number of first-in-human trials and trials around the same time as Western countries is increasing. Our retrospective analysis of 368 patients treated in 47 phase I trials in the recent 3 years showed that the frequency of severe adverse events in these early 14 phase I trials were not higher than that of other 34 phase I trials conducting after completion of phase I trials in Western countries (3.3% vs. 8.5%).

Esophageal Cancer (EC)

The result of a multicenter phase II trial of neo-adjuvant chemo radiotherapy (CRT) in stage II or III EC was presented at the ASCO-GI meeting, 2012. A multicenter phase II trial of combined treatment with endoscopic mucosal resection and chemoradiotherapy for clinical Stage I EC (JCOG0508) has been completed. The enrollment in of a multicenter phase II trial of S-488410 (vaccination with multiple peptides) in stage IV EC has been completed.

Gastric Cancer (GC)

The results of a global randomized phase III trial comparing everolimus to placebo (GRANITE) was presented at the 2012 Gastrointestinal Cancers Symposium and the results of a global randomized phase III trial comparing capecitabine plus cisplatin (XP) with cetuximab to XP (EXPAND) was presented at the ESMO 2012 Congress. They failed to show any survival benefit for everolimus and cetuximab in GC patients. We investigated the relationship between serum HER2 levels and the histologic HER2 status in patients with advanced/recurrent gastric cancer and presented the results at the 2012 Gastrointestinal Cancers Symposium.

Colorectal Cancer (CRC)

Based on our promising results from a randomized phase II trial comparing TAS-102 with BSC (best supportive care) published in *Lancet Oncology*, an international phase III trial, called the *RECOUSE* trial, to confirm the clinical benefit of TAS-102 is ongoing as a company-sponsored trial. We reported the results of the *CORRECT* trial to show the clinical benefit of regorafenib published in *the Lancet*, which has just been approved by the US FDA and will be approved in Japan soon. We have developed a consortium of 7 cancer centers to collect more than 100 strictly selected archived samples as the first-step in the trial called the BREAC trial (*Biomarker Research for Anti-EGFR Monoclonal Antibodies by Comprehensive Cancer*

*Genomics*), from colorectal cancer patients who had received anti-EGFR therapy; the selection of more than 50 super-responder and non-responder cases. We have started whole exon mutation analyses to find the specific gene candidates potentially related to the efficacy of anti-EGFR therapy. As the second step to validate the specific gene candidates, we will investigate the association between the specific gene candidates and the efficacy for another consecutive 250 colorectal cancer patients who had received anti-EGFR therapy. Our BREAC trial is built upon a "disruptive paradigm" that brings together the best attributes of both academia and industry by creating cross-functional professional teams working in a goal-oriented, milestone-driven manner to convert knowledge into tests, devices, drugs and policies that can benefit patients as quickly as possible.

**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 chemo radiotherapy (CRT) in stage II or III EC (JCOG0909) are ongoing. A multicenter phase II trial of adjuvant chemotherapy with IMF-001 (vaccination with multiple peptides) in stage II/III EC is going as investigator initiated trial.

Gastric Cancer (GC)

In a phase II trial of TAS-102, which was the first investigator-initiated trial using an unapproved agent for us, a multicenter global phase II/III trial comparing trastuzumab emtansine to taxane in HER2-positive GC patients (GATSBY) and a multicenter phase III trial comparing docetaxel with cisplatin plus S-1 (DCS) to cisplatin plus S-1 (CS; JCOG 1013), a multicenter phase II trial comparing 12 months of S-1 to 6 months of S-1 as an adjuvant chemotherapy (JCOG 1104), a multicenter phase II trial of AUY922 and trastuzumab in HER2-positive GC patients, and a multicenter phase II trial of dovitinib in scirrhous GC patients, enrollment has been opened.

The enrollment for a multicenter global phase III trial comparing paclitaxel plus ramucirumab to paclitaxel plus placebo (RAINBOW), a multicenter phase II trial of cetuximab with CS, a multicenter randomized phase II trial of S-1 plus leucovorin (SL), oxaliplatin with SL and CS has been completed and the follow-up is ongoing. The enrollment for a multicenter phase II trial of neoadjuvant chemotherapy with DCS (JCOG 1002) is ongoing. The follow-up of a multicenter phase III trial (G-SOX) comparing S-1 plus oxaliplatin to CS is ongoing.

Colorectal Cancer (CRC)

An international randomized phase III trial comparing ramucirumab with a placebo in combination with FOLFIRI in the second-line setting is ongoing. Similarly, an international phase III trial called the *RECOUSE* trial, to confirm the clinical benefit of TAS-102 with a placebo in a salvage setting is ongoing. We have conducted a randomized, multicenter, phase III study called the *ACHIEVE* trial, to compare 6 months of either mFOLFOX6 or XELOX with 3 months of the same regimen as adjuvant chemotherapy in patients with completely resected stage III colon cancer, together with 6 other nations' collaborative groups in the US, UK/Australia, Italy, Greece and France. We also have conducted a confirmatory study, called the *SUNRISE* trial, on an Onco*type* DX Colon Cancer assay to assess the relationship between continuous recurrence score and the likelihood of recurrence in patients with resected stage II and stage III colon cancer. In order to achieve personalized medicine, we are conducting an *Analysis of Biopsy samples for Cancer genomics* called *ABC* study, using target sequencing from pre-treatment biopsy samples for advanced solid tumors including CRCs.

**Table 1. Number of patients**

| Tumor Type | Number of new patients | Number of hospitalized patients |
|---|---|---|
| Esophageal | 219 | 128 |
| Gastric | 246 | 118 |
| Colorectal | 395 | 47 |
| Other type of tumors | 80 | 13 |
| Total | 940 | 306 |

**Table 2. Treatment**

| Tumor Type | Treatment | Number of patients |
|---|---|---|
| Esophageal Cancer | Chemotherapy (include CRT*) | 130 |
| Gastric Cancer | Chemotherapy | 158 |
| Colorectal Cancer | Chemotherapy | 218 |

*chemoradiation

**Table 3. 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% |

## List of papers published in 2012
## Journal


1. Doi T, Ohtsu A, Yoshino T, Boku N, Onozawa Y, Fukutomi A, Hironaka S, Koizumi W, Sasaki T. Phase I study of TAS-102 treatment in Japanese patients with advanced solid tumours. Br J Cancer, 107:429-434, 2012
2. Doi T, Takiuchi H, Ohtsu A, Fuse N, Goto M, Yoshida M, Dote N, Kuze Y, Jinno F, Fujimoto M, Takubo T, Nakayama N, Tsutsumi R. Phase I first-in-human study of TAK-285, a novel investigational dual HER2/EGFR inhibitor, in cancer patients. Br J Cancer, 106:666-672, 2012
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9. Moriwaki T, Bando H, Takashima A, Yamazaki K, Esaki T, Yamashita K, Fukunaga M, Miyake Y, Katsumata K, Kato S, Satoh T, Ozeki M, Baba E, Yoshida S, Boku N, Hyodo I. Bevacizumab in combination with irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) in patients with metastatic colorectal cancer who were previously treated with oxaliplatin-containing regimens: a multicenter observational cohort study (TCTG 2nd-BV study). Med Oncol, 29:2842-2848, 2012
10. Murakami H, Doi T, Yamamoto N, Watanabe J, Boku N, Fuse N, Yoshino T, Ohtsu A, Otani S, Shibayama K, Takubo T, Loh E. Phase 1 study of ganitumab (AMG 479), a fully human monoclonal antibody against the insulin-like growth factor receptor type I (IGF1R), in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 70:407-414, 2012
11. Tada M, Ishii-Watabe A, Maekawa K, Fukushima-Uesaka H, Kurose K, Suzuki T, Kaniwa N, Sawada J, Kawasaki N, Nakajima TE, Kato K, Yamada Y, Shimada Y, Yoshida T, Ura T, Saito M, Muro K, Doi T, Fuse N, Yoshino T, Ohtsu A, Saijo N, Okuda H, Hamaguchi T, Saito Y, Matsumura Y. Genetic polymorphisms of FCGR2A encoding Fcgamma receptor IIa in a Japanese population and functional analysis of the L273P variant. Immunogenetics, 64:869-877, 2012
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# Department of Digestive Endoscopy

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



## Introduction

The Digestive Endoscopy Division covers the fields of the gastrointestinal (GI) tract and head and neck regions. In 2012, a total of 11,815 examinations were performed. A narrow band imaging (NBI) system using the LUCERA spectrum (Olympus Optical Co., Ltd.) has been included for routine examination in 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 tissue samples of patients in order to examine strategies to enable the early detection, prevention, or prediction of the prognosis for treatment. These projects are conducted in collaboration with not only commercial companies but also the Faculties of Technology and Science of 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

In addition to the above, molecular biological analysis of cancers of the esophagus, head and neck, stomach, and colorectum is underway. Importantly, analysis of 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

**Table 1. Number of Patients Examined in 2008-2012**

| Section | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|
| Upper gastrointestinal endoscopy | 5154 | 5545 | 5720 | 6350 | 6647 |
| Endoscopic ultrasonography | 110 | 86 | 78 | 70 | 54 |
| Endoscopic mucosal resection (esophagus) | 111 | 130 | 145 | 181 | 168 |
| Endoscopic mucosal resection (stomach) | 196 | 231 | 211 | 205 | 215 |
| Endoscopic balloon dilation | 1073 | 866 | 613 | 644 | 711 |
| Percutaneous endoscopic gastrostomy | 146 | 173 | 218 | 215 | 171 |
| Photodynamic therapy (esophagus) | 36 | 23 | 47 | 48 | 39 |
| Colonoscopy | 2071 | 2027 | 2250 | 1550 | 2302 |
| Polypectomy/EMR | 731 | 791 | 744 | 800 | 912 |
| Narrow Band Imaging (head and neck) | 193 | 194 | 147 | 95 | 106 |
| Endoscopic mucosal resection (head and neck) | 31 | 21 | 41 | 41 | 46 |

EMR, Endoscopic mucosal resection, including ESD. ERCP, Endoscopic retrograde cholangio-pancreatography

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. Hypoxia imaging is applied in the detection of 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 a 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 an InGaAs CCD imaging system has been developed, since nanoparticles of rare earth act as fluorescent agents. With a low-temperature atmospheric pressure plasma system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnosis system using photosensitizing agents, such as hypericin and 5ALA, has been constructed. Moreover, 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: hypoxia imaging for neoplasia of alimentary tract in a single unit; a phase II clinical trial for specific stent implantation for benign esophageal stricture; a clinical trial for photodynamic diagnosis using 5ALA; multicenter clinical trials of a follow-up study after EMR of m1-3 esophageal cancers; a phase I/II study of PDT using Laserphyrin in residual/recurrent cases followed by chemoradiation for esophageal cancers; a phase III randomized trial regarding the efficacy of a proton pump inhibitor followed by EMR for esophageal cancer; a phase II trial for combined treatment of endoscopic mucosal resection and chemoradiotherapy for clinical stage I esophageal carcinoma (JCOG0508); a multicenter clinical study on early gastric cancer following endoscopic treatment using a web-based enrollment system; 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.

**Table 2. Endoscopic procedures in 2012**

| | | 2011 | 2012 |
|---|---|---|---|
| Esophagus | EMR | 100 | 89 |
| | ESD | 45 | 79 |
| Stomach | EMR | 9 | 3 |
| | ESD | 202 | 212 |
| Colon and rectum | EMR* | 744 | 834 |
| | ESD | 17 | 78 |
| Head and neck | EMR | 6 | 7 |
| | ESD | 35 | 33 |

EMR , endoscopic mucosal resection; ESD, endoscopic submucosal dissection; *, including polypectomy

## List of papers published in 2012
### Journal


1. Ikematsu H, Saito Y, Tanaka S, Uraoka T, Sano Y, Horimatsu T, Matsuda T, Oka S, Higashi R, Ishikawa H, Kaneko K. The impact of narrow band imaging for colon polyp detection: a multicenter randomized controlled trial by tandem colonoscopy. J Gastroenterol, 47:1099-1107, 2012
2. Yano T, Muto M, Minashi K, Iwasaki J, Kojima T, Fuse N, Doi T, Kaneko K, Ohtsu A. Photodynamic therapy as salvage treatment for local failure after chemoradiotherapy in patients with esophageal squamous cell carcinoma: a phase II study. Int J Cancer, 131:1228-1234, 2012
3. Yano T, Muto M, Yoshimura K, Niimi M, Ezoe Y, Yoda Y, Yamamoto Y, Nishisaki H, Higashino K, Iishi H. Phase I study of photodynamic therapy using talaporfin sodium and diode laser for local failure after chemoradiotherapy for esophageal cancer. Radiat Oncol, 7:113, 2012
4. Yoda Y, Yano T, Kaneko K, Tsuruta S, Oono Y, Kojima T, Minashi K, Ikematsu H, Ohtsu A. Endoscopic balloon dilatation for benign fibrotic strictures after curative nonsurgical treatment for esophageal cancer. Surg Endosc, 26:2877-2883, 2012
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6. Hotta K, Saito Y, Fujishiro M, Ikehara H, Ikematsu H, Kobayashi N, Sakamoto N, Takeuchi Y, Uraoka T, Yamaguchi Y. Impact of endoscopic submucosal dissection for the therapeutic strategy of large colorectal tumors. J Gastroenterol Hepatol, 27:510-515, 2012
7. Muto M, Ezoe Y, Yano T, Aoyama I, Yoda Y, Minashi K, Morita S, Horimatsu T, Miyamoto S, Ohtsu A, Chiba T. Usefulness of endoscopic radial incision and cutting method for refractory esophagogastric anastomotic stricture (with video). Gastrointest Endosc, 75:965-972, 2012
8. Nakajima Y, Zenda S, Minashi K, Yano T, Tahara M, Doi T, Onozawa M, Nihei K, Fujii S, Ohtsu A. Non-surgical approach to small cell carcinoma of the esophagus: does this rare disease have the same tumor behavior as SCLC? Int J Clin Oncol, 17:610-615, 2012
9. Saraya T, Ikematsu H, Fu KI, Tsunoda C, Yoda Y, Oono Y, Kojima T, Yano T, Horimatsu T, Sano Y, Kaneko K. Evaluation of complications related to therapeutic colonoscopy using the bipolar snare. Surg Endosc, 26:533-540, 2012

# Department of Hepatobiliary and Pancreatic Surgery

**Masaru Konishi, Shinichiro Takahashi, Takahiro Kinoshita, Hidehito Sibasaki, Naoto Gotohda, Yuichiro Kato, Motokazu Sugimoto, Takahiro Toda, Kenji Sakai, Eiji Higaki**



## 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 surgery is a safe alternative for selected patients with hepatobiliary pancreatic neoplasms, and has fulfilled its indications. In our division, laparoscopic hepatectomy has been performed since 2002, and laparoscopic distal pancreatectomy since 2011.

## Routine activities

In the National Cancer Center Hospital East (NCCH-E), 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 2012, 209 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. The results of the primary endpoint will be opened in 2013.

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 complete and follow-up is on-going.

JASPAC-05 is a phase II study on neoadjuvant S-1 and concurrent radiotherapy for patients with borderline resectable pancreatic cancer. Recruitment started in 2012.

Prep02/JSAP05 is a randomized phase III study on neoadjuvant chemotherapy using combination therapy with gemcitabine and S-1 vs. surgery first in patients with resected pancreatic cancer. This study is now under preparation.

Pancreatic fistula represent a major complication after pancreatoduodenectomy (PD). Mortality after PD is mostly due to pancreatic fistula formation. We are engaged in exploratory studies to investigate the innovative techniques or management for reducing pancreatic fistula formation after PD. Furthermore, perfusion CT analysis is underway to quantify the preoperative risk of the formation of pancreatic fistulae.

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.

JCOG1202 is a phase III study to compare S-1 with surgery alone as adjuvant chemotherapy for patients with curatively resected extrahepatic bile duct cancer. This study is now under preparation.

**Table 1. Number of patients**

| | |
|---|---|
| Invasive pancreatic cancer | 33 |
| Other pancreatic neoplasms | 19 |
| Hepatocellular carcinoma | 30 |
| Hepatic metastases | 63 |
| Intrahepatic cholangiocarcinoma | 5 |
| Bile duct cancer | 24 |
| Gallbladder cancer | 6 |

**Table 2. Type of procedure**

| | |
|---|---|
| Pancreaticoduodenectomy | 53 |
| Distal pancreatectomy | 11 |
| Total pancreatectomy | 4 |
| Laparoscopic distal pancreatectomy | 4 |
| Hepatectomy with biliary reconstruction | 4 |
| Hepatectomy without biliary reconstruction | 74 |
| Laparoscopic hepatectomy | 22 |
| Other procedures | 37 |
| Total | 209 |

**Table 3. Survival rates**

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

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 (HCC). Follow-up is on-going.

Recruitment in a phase II trial on adjuvant immunotherapy with Glypican-3, and in a phase III trial on adjuvant chemoprevention with Peretionin for HCC patients 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 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.

## List of papers published in 2012
### Journal


1. Konishi M. Adjuvant chemotherapy for resectable biliary tract cancer: current status and future direction. J Hepatobiliary Pancreat Sci, 19:301-305, 2012
2. Shirakawa H, Kinoshita T, Gotohda N, Takahashi S, Nakagohri T, Konishi M. Compliance with and effects of preoperative immunonutrition in patients undergoing pancreaticoduodenectomy. J Hepatobiliary Pancreat Sci, 19:249-258, 2012
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4. Gotohda N, Konishi M, Takahashi S, Kinoshita T, Kato Y, Kinoshita T. Surgical outcome of liver transection by the crush-clamping technique combined with Harmonic FOCUS. World J Surg, 36:2156-2160, 2012

# Department of Hepatobiliary and Pancreatic Oncology

**Masafumi Ikeda, Shuichi Mitsunaga, Satoshi Shimizu, Izumi Ohno, Hideaki Takahashi**



## Introduction

The Hepatobiliary and Pancreatic Oncology Division is responsible for the treatment and management of patients with hepatic, biliary, and pancreatic cancers. Our goal is to provide high-quality cancer treatment with adequate palliative care, and to develop novel and effective treatments through well-designed clinical trial and research.

## Routine activities

Our Division is composed of 5 staff oncologists and 2 residents, with 35-45 beds in the hospital and we conduct clinical rounds for admitted patients every morning and evening. Most new patients with unresectable hepatobiliary and pancreatic tumors are hospitalized for tumor diagnosis and treatment. Individual patient treatment strategies are discussed in weekly tumor board conferences attended by medical oncologists, surgeons, radiologists, radiation oncologists, and pharmacologists.

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. Recently, endoscopic ultrasonographic examinations or endoscopic ultrasound-guided fine needle aspiration have also begun to be frequently performed for biliary and pancreatic tumors. Furthermore, endoscopic or percutaneous transhepatic biliary drainage and stenting are performed for obstructive jaundice.

## Research activities

A medical team, "Team Nexavar", composed of medical oncologists, pharmacologists and nurses, provides supportive care for the toxicities of sorafenib. The results of our medical team are superior in terms of the percentage of cases discontinuing treatment on account of adverse events, including the hand-foot syndrome, as compared to previous reports, and the significance of team medication has been clarified. The predictive factors of tumor response and survival, the usefulness of urea-containing ointments for the prevention of hand-foot syndrome and the efficacy and safety for Child Pugh B cases have been also investigated in advanced hepatocellular carcinoma (HCC) patients treated with sorafenib.

Pancreatic cancer

Arctigenin, which is contained in abundance in the seeds of Arctium lappa, exerts favorable antitumor activity by attenuating the tolerance of cancer cells to glucose starvation, as demonstrated in mouse xenograft models. A phase I trial was conducted to investigate the recommended dose of this agent in patients with gemcitabine-resistant metastatic pancreatic cancer, and favorable clinical responses were obtained. A multicenter phase II trial is being planned to evaluate the efficacy and safety of this substance.

For advanced pancreatic cancer, the current research focus is investigation of the mechanism of cancer cachexia to facilitate development of innovative therapies. Our data indicate that the causes of cachexia are 'Neural invasion' and 'Inflammation'. We have shown that neural invasion induces cachexia via astrocytic activation of the neural route, termed neuroinflammation, in patients with pancreatic cancer. In addition, we have investigated the impact of tumor-associated macrophages on invasive ductal carcinoma of the pancreatic head, the clinical significance of des-acyl ghrelin levels as a predictor of gastrointestinal toxicities, and the symptomatic changes to predict disease control by chemotherapy.

Hepatitis B viral (HBV) reactivation following chemotherapy

HBV reactivation has often been reported in patients undergoing chemotherapy for the treatment of malignant disease. Prospective studies to clarify the present status of HBV reactivation following chemotherapy for solid tumors are being conducted.

## Clinical trials

Forty one clinical trials (sponsored: 26 trials, investigator-initiated: 15 trials) are ongoing, and 11 clinical trials (sponsored: 6 trials, investigator-initiated: 6 trials) are being planned for the upcoming year.

**Table 1. Number of patients**

| | |
|---|---|
| Hepatocellular carcinoma | 119 |
| Biliary tract cancer | |
| Intrahepatic cholangiocarcinoma | 20 |
| Extrahepatic cholangiocarcinoma | 8 |
| Gallbladder cancer | 23 |
| Papilla of vater carcinoma | 2 |
| Pancreatic cancer | |
| Locally advanced disease | 56 |
| Metastatic disease | 116 |
| Other | 25 |
| Total | 369 |

**Table 2. Type of procedure**

| | Number of patients |
|---|---|
| Hepatocellular carcinoma | |
| Radiofrequency ablation | 87 |
| Transarterial chemoembolization | 192 |
| Intra-arterial chemotherapy | 59 |
| Systemic chemotherapy | 70 |
| Proton beam radiotherapy | 13 |
| Biliary tract cancer | |
| Systemic chemotherapy | 55 |
| Radiotherapy | 4 |
| Pancreatic cancer | |
| Systemic chemotherapy | 239 |
| Chemoradiotherapy | 13 |
| Total | 732 |

**Table 3. Survival rates**

| Diagnosis | | | |
|---|---|---|---|
| Hepatocellular carcinoma | No. of pts | MST(mo) | 2-yr survival(%) |
| Radiofrequency ablation | 191 | 57.2 | 83.0 |
| Transcatheter 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 | No. of pts | MST(mo) | 2-yr survival(%) |
| Systemic chemotherapy | 385 | 6.5 | 7.2% |
| Period: | 1992/11-2012/12 | | |
| Pancreatic cancer | No. of pts | MST(mo) | 1-yr survival(%) |
| Locally advanced disease | 115 | 8.9 | 35.9 |
| Metastatic disease | 833 | 6.9 | 26.1 |
| Period: | 1992/11-2012/12 | | |

Hepatocellular carcinoma

To elucidate the survival benefit of intra-arterial chemotherapy, a randomized controlled trial comparing the combined administration of sorafenib with intra-arterial cisplatin with sorafenib alone for highly advanced HCC is underway.

Among sponsored trials, the enrollments for some phase III trials of brivanib vs. placebo in combination with TACE, of brivanib vs. sorafenib as a first-line chemotherapy, and of brivanib vs. placebo, S-1 vs. placebo, everolimus vs. placebo as second-line chemotherapy have already been completed. Some phase III trials of peretinoin vs. placebo in the adjuvant setting after resection or ablation, and of orantinib vs. placebo in combination with TACE are underway. Two randomized phase II trials comparing dovitinib vs. sorafenib as a first-line chemotherapy, and GC33 vs. placebo in the second-line setting are also underway. Enrollments for phase I trials of an ALK-1 inhibitor (PF-03446962) and a PDGFR-$\alpha$ antagonist (MEDI-575) have been completed, and phase I trials of nintedanib, pimasertib, a STAT3 inhibitor (OPB-31121), a c-MET inhibitor (ARQ197) and a peptide vaccine including glypican-3, etc. (ONO-7268MX1) are ongoing.

Biliary tract cancer

A phase I investigators-initiated trial of combined gemcitabine, cisplatin and S-1 therapy is ongoing to determine the recommended doses for subsequent trials. The role of adjuvant therapy in resectable biliary tract cancer is still uncertain, and no recommended standard exists. A randomized trial comparing adjuvant S-1 with observation is being planned to determine whether adjuvant chemotherapy with S-1 might improves the outcomes of patients with resected biliary tract cancer.

Pancreatic cancer

A multicenter phase II trial of neoadjuvant S-1 and concurrent radiotherapy for borderline resectable pancreatic cancer (JASPAC05), and a randomized phase II trial of S-1 and concurrent radiotherapy with versus without induction chemotherapy for locally advanced pancreatic cancer (JCOG1106) are ongoing. As sponsored trials, enrollments for a phase III trial of gemcitabine and an IGF-1R antagonist (AMG479) with gemcitabine and a placebo for untreated metastatic pancreatic cancer have been completed. In this trial, the number of enrolled cases was the highest in the world. As for Japanese multicenter trials, a phase II trial of FOLFIRINOX has been completed, while enrollments for a phase III trial of a peptide vaccine (OCV-C01) and a phase II trial of gemcitabine and nab-paclitaxel are now ongoing.

## List of papers published in 2012
## Journal


1. Hagiwara S, Sakurai T, Nishina S, Tanaka K, Ikeda M, Ueshima K, Minami Y, Inoue T, Yada N, Kitai S, Takita M, Nagai T, Hayaishi S, Arizumi T, Park AM, Munakata H, Nishida N, Kudo M. Characteristic Pattern of Reactivation of Hepatitis B Virus during Chemotherapy for Solid Cancers. Dig Dis, 30:541-546, 2012
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3. Imoto A, Mitsunaga S, Inagaki M, Aoyagi K, Sasaki H, Ikeda M, Nakachi K, Higuchi K, Ochiai A. Neural invasion induces cachexia via astrocytic activation of neural route in pancreatic cancer. Int J Cancer, 131:2795-2807, 2012
4. Yoshikawa K, Mitsunaga S, Kinoshita T, Konishi M, Takahashi S, Gotohda N, Kato Y, Aizawa M, Ochiai A. Impact of tumor-associated macrophages on invasive ductal carcinoma of the pancreas head. Cancer Sci, 103:2012-2020, 2012

# 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 (NCCH-E) 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-seven patients newly received ureteral stents and 15 underwent nephrostomy for obstructive uropathy.

Inpatient activities: A daily conference is held with doctors of the Department of Pelvic Surgery on diagnosis and treatment of the patients with colorectal and urological cancer. We performed 38 combination surgeries with colorectal surgeons. In the Department of Urology, 104 general anaesthesia surgeries, 78 spinal anesthesia surgeries and 56 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

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 function. 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.

**Table 1. Number of patients**

| | |
|---|---|
| Renal cell carcinoma | 33 |
| Upper urinary tract urothelial cell carcinoma | 19 |
| Bladder cancer | 48 |
| Prostate cancer | 28 |
| Testicular cancer | 9 |

**Table 2. Type of procedure**

| | |
|---|---|
| Radical nephrectomy | 17 |
| Partial nephrectomy | 16 |
| Nephroureterectomy | 19 |
| Radical cystectomy | 15 |
| TURBT | 68 |
| Radical prostatectomy | 28 |

**Table 3. Survival rates**

| Diagnosis | No.of pts | 5-yr survival(%) |
|---|---|---|
| Renal cell carcinoma | 218 | 88 |
| Upper urinary tract urothelial cell carcinoma | 65 | 69 |
| Bladder cancer (muscle - invasive) | 77 | 72 |
| Prostate cancer | 258 | 96.3 |



## List of papers published in 2012
## Journal

1. Waseda Y, Komai Y, Yano A, Fujii Y, Noguchi N, Kihara K. Pathological complete response and two-year disease-free survival in a primary gastric choriocarcinoma patient with advanced liver metastases treated with germ cell tumor-based chemotherapy: a case report. Jpn J Clin Oncol, 42:1197-1201, 2012

# Department of Musculoskeletal Oncology and Rehabilitation

**Umio Yamaguchi, Takuro Sakurai**

## Introduction

The Department of Musculoskeletal Oncology and Rehabilitation is a team consisting of a panel of orthopedic surgeons and rehabilitation professionals. We strive to provide expert interdisciplinary care for a variety of benign and malignant bone and soft tissue tumors and tumor-like conditions, and we also provide comprehensive medical rehabilitation services, for both outpatient and inpatient care. The Department of Musculoskeletal Oncology and Rehabilitation started its service in 1992, but it followed a meandering course. In the last 10 years, outpatient and rehabilitation services were provided by medical staff working concurrently with the National Cancer Center Hospital (NCCH), but in the case of surgical or chemotherapeutic treatment, the patients were referred to the NCCH. This year, our department reinstated its inpatient care services including those pertaining to surgical treatment. Currently, we have one orthopedic surgeon and one rehabilitation staff member engaging with patients and staff in daily activities. As always, our services are consistently supported by the concurrent involvement of medical staff from the NCCH. We have planned to increase the number of medical personnel in an effort to meet increasing patient needs.

## Routine activities

Our outpatient service is open for three days a week to treat new patients and to provide follow-up treatment to patients who have completed intensive treatment. We also see patients on both an outpatient and inpatient basis in consultation upon the request of other cancer specialists. The reasons for consultation include patients who have developed metastatic disease of the bone and soft tissue, those who need rehabilitation, and those who have any orthopedic problems. Every week, 2-3 operations under general or local anesthesia are performed in our Department. The operation is consistently supported by medical staff from NCCH. In cases where patients need a multidisciplinary approach to treatment, we offer appropriate referral to NCCH for further treatment.

Our rehabilitation services focus on cancer rehabilitation, and aim to reduce the common side effects of cancer and its treatment, including fatigue, weakness, poor endurance, pain, nausea, anxiety, depression and loss of confidence. Exercise increases strength and endurance, restores confidence and is an important part of rehabilitation. Every Monday and Friday, both outpatient and inpatient rehabilitation are performed by a senior occupational therapist. One of the characteristic of our rehabilitation service is an active involvement of the nurses in supporting the rehabilitation. In an effort to provide the best possible prosthetic and orthotic care for our patients in a timely and efficient manner, a special outpatient service is also opened every Monday.

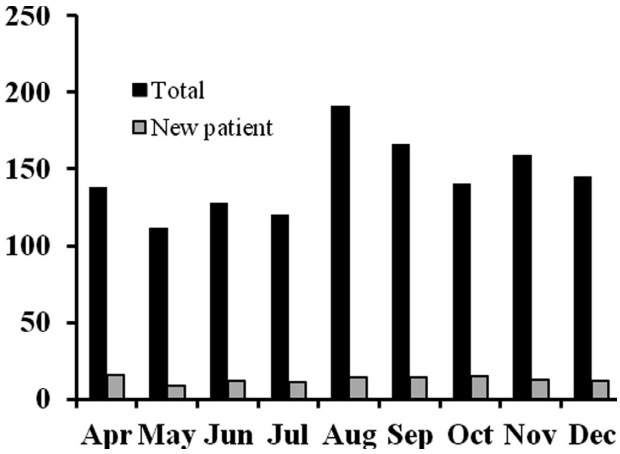


**Figure 1. Number of patients treated at the outpatient clinic (2012).**

**Table 1. Characteristics and number of patients enrolled for rehabilitation.**

| Clinical department | 2011 | 2012 |
|---|---|---|
| Hematology oncology | 29 | 39 |
| Thoracic oncology | 24 | 35 |
| Thoracic surgery | 18 | 29 |
| Head and neck oncology | 12 | 21 |
| Gastrointestinal oncology | 12 | 21 |
| Esophageal surgery | 18 | 19 |
| Musculoskeletal oncology | 2 | 17 |
| Palliative medicine | 9 | 15 |
| Colorectinal surgery | 8 | 13 |
| Hepatobiliary and pancreatic oncology | 7 | 12 |
| Others | 7 | 24 |
| Total | 146 | 245 |

# Department of Hematology

**Kunihiro Tsukasaki, Masahiko Nezu, Kuniaki Itoh, Hiromi Yuasa**



## Introduction

The Department of Hematology works in cooperation with the Department of Breast and Medical Oncology. The staff physicians of both Departments collaborate regarding outpatient care and education of residents as a medical oncology team. The staff physicians and residents of this Department carry out clinical and research activities related to the multi-disciplinary treatment of patients with hematological malignancies which consist of more than 100 disease entities under the WHO classification (version 2008). Our Department focuses on early and late phases of clinical trials in collaboration with the Research Center for Innovative Oncology and Japan Clinical Oncology Group (JCOG), respectively, especially studies on lymphoid malignancies.

## Routine activities

The number of patients with newly diagnosed hematologic malignancies in our Department is increasing, and approximately 220 patients with newly diagnosed hematological malignancies including non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, macroglobulinemia, acute leukemia, myelodysplastic syndrome and chronic leukemia were cared this year (Table 1). The Department is currently providing routine chemotherapy as an outpatient service to an increasing number of relatively aged patients with hematological malignancies. All patients undergoing intensive chemotherapy and autologous peripheral blood hematopoietic stem cell transplantation (APBSCT) (Table 2) are managed in laminar airflow rooms in the designated ward on the eighth floor. Besides managing patients, the Department also provides consultation on hematological abnormalities detected in the Department of Clinical Laboratories. A morning case conference on inpatient care of our Department is held from Monday to Friday, and a weekly case conference on new patients visiting the clinics at our Department and Breast and the Medical Oncology Department is held on Thursday evenings. A weekly conference, including an educational review on hematology, is conducted on Tuesday evenings. On Wednesday evenings, a weekly joint conference on lymphoid malignancies with expert pathologists and an educational cytology conference are held. A joint morning journal club for both or Department of ours and the Breast and Medical Oncology Department is held on Mondays and Fridays.

## Research activities

Ancillary studies associated with retrospective case series and clinical trials at this Department have been consecutively conducted focusing on several kinds of hematological malignancies and their complications. Recently, a nation-wide survey of human T-lymphotropic virus type I (HTLV-1) associated adult T-cell leukemia-lymphoma (ATL) is in preparation under a grant for Cancer Research from the Ministry of Health, Labour and Welfare to elucidate the pathophysiology including geographical findings as compared to those surveys in the 1980s and 1990s.

## Clinical trials

Clinical trials on hematological malignancies performed by our Department comprise protocols prepared in-house and participation in the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG-LSG), the Japan Adult Leukemia Study Group (JALSG) and others. The Department participated in pharmaceutical company-sponsored new-agent trials including international ones for hematological malignancies. The following JCOG clinical trials are ongoing: a randomized phase III trial of rituximab administered weekly or tri-weekly with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in patients with newly diagnosed CD20+ diffuse large B cell lymphoma (DLBCL) (JCOG0601) in which a dose-intense schedule of rituximab is evaluated; a randomized phase II trial comparing biweekly rituximab-CHOP or biweekly rituximab-CHOP/cyclophosphamide, cytarabine, dexamethasone, etoposide and rituximab (CHASER) followed by high dose melphalan, cyclophosphamide, etoposide and dexamethasone (LEED) with APBSCT in patients with newly diagnosed poor risk CD20+ DLBCL (JCOG0908);

**Table 1. Number of patients**

| | |
|---|---|
| Non-Hodgkin's lymphoma | 153 |
| Hodgkin's lymphoma | 6 |
| Multiple myeloma | 15 |
| Acute leukemia | 6 |
| Chronic leukemia | 3 |
| Others | 32 |
| Total | 215 |

**Table 2. Type of procedure**

| | |
|---|---|
| PBSCT for non-Hodgkin's lymphoma in relapse | 3 |
| PBSCT for myeloma in remission | 2 |
| Total | 5 |

a phase II trial comparing 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); a randomized phase II trial comparing dexamethasone with bortezomib or thalidomide in patients with relapsed/refractory multiple myeloma in relapse (JCOG0904); and a phase II study of mLSG15 chemotherapy followed by allo-HSCT, comparing the results with historical controls in JCOG9801 to evaluate the promising efficacy of allo-HSCT, possibly associated with a graft-versus-ATL effect, especially in view of a comparison with intensive chemotherapy. A phase III study evaluating the efficacy of the combination of interferon-alpha (IFN) and zidovudine (AZT) as compared to watchful-waiting for indolent ATL is to be initiated (JCOG PC908) under a highly advanced medical technology assessment system because IFN and AZT are not covered for ATL by the National Health Insurance in Japan.

## List of papers published in 2012

### Journal


1. Tsukasaki K, Tobinai K, Hotta T, Shimoyama M. Lymphoma study group of JCOG. Jpn J Clin Oncol, 42:85-95, 2012
2. Yamaguchi M, Tobinai K, Oguchi M, Ishizuka N, Kobayashi Y, Isobe Y, Ishizawa K, Maseki N, Itoh K, Usui N, Wasada I, Kinoshita T, Hotta T, Tsukasaki K, Oshimi K. Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211. J Clin Oncol, 30:4044-4046, 2012
3. Kagami Y, Itoh K, Tobinai K, Fukuda H, Mukai K, Chou T, Mikuni C, Kinoshita T, Fukushima N, Kiyama Y, Suzuki T, Sasaki T, Watanabe Y, Tsukasaki K, Hotta T, Shimoyama M, Ogura M. Phase II study of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) therapy for newly diagnosed patients with low- and low-intermediate risk, aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG9508. Int J Hematol, 96:74-83, 2012
4. Azuma T, Tobinai K, Takeyama K, Shibata T, Hidaka M, Kurosawa M, Kasai M, Chou T, Fukushima N, Mukai K, Tsukasaki K, Shimoyama M. Phase II study of intensive post-remission chemotherapy and stem cell transplantation for adult acute lymphoblastic leukemia and lymphoblastic lymphoma: Japan Clinical Oncology Group Study, JCOG9402. Jpn J Clin Oncol, 42:394-404, 2012

# Department of Pediatric Oncology

**Ako Hosono, Kuniaki Itoh**

## Introduction

The Pediatric Oncology Division was established in December 2011 to provide treatment of pediatric cancers including a wide variety of diseases such as hematologic malignancies comprising leukemia and lymphoma, embryonal tumors comprising neuroblastomas, nephroblastomas and hepatoblastomas, and mesenchymal tumors comprising Ewing sarcomas, rhabdomyosarcomas and osteosarcomas. Although they usually occur in children under age of 15, they occasionally occur in adolescents and young adults (AYA). Most of the pediatric cancers are highly chemosensitive as well as radiosensitive. They are possibly curable in a certain situation where the intensity of multidisciplinary treatment and disease characteristics are balanced well. However, there are absolutely refractory cases who need new treatments other than standard chemotherapy. Moreover, long-term survivors of pediatric cancers often suffer from complications secondary to chemotherapy and radiotherapy. There are three major missions in the Pediatric Oncology Division in NCCE as follows: (1) To provide a state-of-the-art treatment for AYA patients in collaboration with the Medical Oncology group. (2) To develop new treatments for pediatric cancer by sharing agents and knowledge with the Clinical Development Center. and (3) To provide less toxic proton-beam radiation therapy as one of the three proton centers for children in Japan. All three activities are currently in process and several projects have already started (refer to "Research activities and clinical trials").

## Routine activities

The pediatric outpatients service is open for three days a week, Monday, Wednesday and Friday, to treat newly diagnosed patients, patients who received chemotherapy in the outpatient setting and to provide follow-up treatment to patients who have completed an intensive treatment course. Also, the care of children receiving palliative treatment is carried out with the Palliative care and Psycho-Oncology group. Daily rounds and a conference are held every morning with the Medical Oncology group, where we hold discussions about patients among various experts. We also join the conference with the Orthopedic Surgery, Thoracic Surgery and Urology Divisions at any time.

## Research activities and clinical trials

As written above, several projects which are expected to achieve our missions are ongoing. Proton-beam radiation therapy is currently provided as an Investigational Medical Care (Sensin-iryo). However, the medical cost related to the treatment with this system could possibly financially overburden patients and their families. To pursue the possibility of getting this technique approved under the Japanese Health Insurance system, we plan a clinical trial to gather data on safety in pediatric patients. Other projects include treatment development using relatively new off-label drugs as well as experimental agents such as peptide vaccines. One of the objectives of the following trials is gathering data on, and assessing the safety and efficacy data of, such off-label drugs and eventually getting them approved by the Ministry of Health, Labour and Welfare.

Two clinical trials described below are currently active.

(1) A randomized phase II study on 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.
(2) A phase I trial of immunotherapy using HLA-A2 and A24-restricted glypican-3 peptide vaccine for pediatric tumors.

One pediatric clinical trial using a cocktail of three peptide vaccines is about to start as an investigator-initiated registration-directed clinical trial.

## List of papers published in 2012
### Journal

1. Kanegane H, Yang X, Zhao M, Yamato K, Inoue M, Hamamoto K, Kobayashi C, Hosono A, Ito Y, Nakazawa Y, Terui K, Kogawa K, Ishii E, Sumazaki R, Miyawaki T. Clinical features and outcome of X-linked lymphoproliferative syndrome type 1 (SAP deficiency) in Japan identified by the combination of flow cytometric assay and genetic analysis. Pediatr Allergy Immunol, 23:488-493, 2012

# Department of Anesthesiology and Intensive Care Unit

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

## Introduction

The Department of Anesthesiology and Intensive Care Unit (ICU) consists of 5 staff members, including 4 JSA (Japan Society of Anesthesiologists) board certified anesthesiologists and 3 rotating residents. Each year, we provide more than 2,000 anesthesia services in 8 operating rooms and over 1200 patients are admitted to the ICU. A large number of operations in the head and neck surgery division and procedures involving a thoracotomy for lung and esophageal cancer are one of the features of this hospital. Accordingly a special anesthesia induction method for difficult airway and use of the one-lung ventilation technique are often necessary for anesthesiologists.

Currently, our ICU admits mainly postsurgical patients that have undergone major abdominal, thoracic and complex surgical procedures, as well as patients who have suffered from serious preoperative complications. Increasingly complex procedures are being performed on more seriously ill patients with coronary disease, chronic obstructive pulmonary disease (COPD), neurological disorders and so on. Accordingly, the ICU needs to play a more and more important role in postsurgical care for such patients.

The goals of The Department of Anesthesiology and Intensive Care Unit are to provide anesthetic and perioperative care to patients, with their safety being the highest priority.

## Routine activities

Five staff members (4 full-time and one visiting anesthesiologists) and 9 part-time anesthesiologists cover 8 operating rooms. A preanesthesia case presentation is held every morning to examine the case of the day and discuss the anesthesia strategy for patients with various complications. A Journal club is also held once a week. We provided 2,542 anesthesia services in 2012 and annual number of patients admitted to the ICU was 1412.

## Research activities

Dr. Miwa presented "A Combination of treatments between Kampo Medicine and Neuronal Blockade for Post-herpetic Neuralgia" at the 15th World Congress of Pain Clinicians of WSPC (The World Society of Pain Clinicians) and "The exploitation of a transdermal system (TDS) of ketamine: a pharmacokinetic assessment" at the 14th World Congress on Pain of IASP (International Association for the Study of Pain).

**Table 1. Number of Anesthesia Cases**

| Type of Surgery | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|
| Head and Neck | 458 | 474 | 515 | 424 | 454 |
| Thoracic | 472 | 503 | 488 | 466 | 473 |
| Esophageal | - | - | 137 | 126 | 182 |
| Gastric, Hepatobiliary, Pancreatic | 508 | 566 | 542 | - | - |
| Hepatobiliary and Pancreatic | - | - | - | 269 | 231 |
| Gastric | - | - | - | 286 | 308 |
| Colorectal | 453 | 418 | 491 | 426 | 453 |
| Urologic | 59 | 79 | 88 | 78 | 107 |
| Orthopedic | - | - | - | - | 22 |
| Breast | 233 | 282 | 297 | 291 | 309 |
| Plastic and Reconstructive | - | - | - | - | 3 |
| Total | 2183 | 2322 | 2558 | 2366 | 2542 |

**Table 2. Number of Patients Admitted to the ICU**

| | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|
| Number of Patients | 1163 | 1167 | 1435 | 1228 | 1412 |

# Department of Palliative Medicine, Palliative Care Service

**Hiroya Kinoshita, Yoshihisa Matsumoto, Mieko Fukui, Kazuaki Hiraga**

## Introduction

The National Cancer Center Hospital East (NCCH-E) opened the palliative care unit in 1992 for the purpose of providing only palliative care services. 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 main 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 and the mortality rate in this unit were reduced to approximately 5 days and approximately 70%, respectively.

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 is actively studying the construction of a regional palliative care model prepared for large scale disasters and a feasibility study on early palliative care. In addition, 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 late phase II study on S-297995 for opioid-induced constipation is ongoing.

**Table1. New referrals to the outpatient clinic (n=385, January - December 2012)**

| | | N (%) |
|---|---|---|
| Age | Mean ± SD (median, range) (yr) | 67.8±11.4 (70, 13-91) |
| Gender | (male/female) | 220/165 |
| Survivors or receiving anticancer therapy | | 78 (20.3) |
| Cancer site | Lung | 108 (28.1) |
| | Breast | 41 (10.6) |
| | Head and Neck | 37 (9.6) |
| | Colorectal | 34 (8.8) |
| | Pancreas | 28 (7.3) |
| | Stomach | 24 (6.2) |
| | Kidney/Bladder | 20 (5.2) |
| | Others | 93 (24.2) |

**Table2. Admission to the palliative care unit (n=363, January - December 2012)**

| | | N (%) |
|---|---|---|
| Age | Mean ± SD (median, range) (yr) | 67.1±10.6 (67, 36-92) |
| Gender | (male/female) | 223/140 |
| Cancer site | Lung | 107 (29.5) |
| | Colorectal | 43 (11.8) |
| | Pancreas | 33 (9.1) |
| | Stomach | 31 (8.5) |
| | Head and Neck | 29 (8.0) |
| | Breast | 28 (7.7) |
| | Esophagus | 12 (3.3) |
| | Others | 80 (22.0) |
| Waiting time for admission | Mean ± SD (median, range) (days) | 4.1±5.0 (2, 0-32) |

# Department of Psycho-Oncology Service

**Asao Ogawa, Daisuke Fujisawa, Hiroyuki Takei, Kensuke Higa, Tomohiko Mitsutsuka, Junko Ueda, 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, adjunctive with the Psycho-oncology Division of the Research Center for Innovative Oncology, also aims to study the influence of psychosocial issues upon quality of life and survival of cancer patients. Management of elderly patients with cancer, who are frequently comorbid with cognitive impairment or dementia, is another focus of interest.

## Routine activities

The Psycho-Oncology Division is composed of 2 attending psychiatrists, 2 clinical psychologists, and 3 psychiatry residents. The clinical activities include psychiatric consultation, involving comprehensive assessment and addressing of psychiatric problems of cancer patients. The patients are either self-referred or referred by their oncologists in charge. The consultation data are shown in the Table. Psychiatric diagnosis is based on the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria. Consultation data also includes individuals who are family members of cancer patients.

A conference with the Supportive Care Team is held on Wednesdays, and a multicenter joint clinical teleconference involving 6 cancer center hospitals and 3 university hospitals 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 and clinical trials

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

**Table1. Psychiatric consultation data (n=1111; January-December, 2012)**

| Section | | N (%) |
|---|---|---|
| Age | Mean ± SD (median, range) (yr) | 65.8±11.7 (67, 23-93) |
| Gender | (male/female) | 670 (60.3%) / 441 (39.7%) |
| Inpatient / Outpatient | | 741 (66.7%) / 370 (33.3%) |
| Cancer patient / Family member | | 1066 (95.9%) / 45 (4.1%) |
| Cancer site | Lung | 231 (20.8%) |
| | Head and Neck | 198 (17.8%) |
| | Colon | 114 (10.3%) |
| Stage | Recurrent or metastatic | 767 (69.0%) |
| PS | 0/1, 2/3, 4 | 378 (34.0%) / 465 (41.9%) / 268(24.1%) |
| Pain | Present | 241 (21.7%) |
| Psychiatric diagnosis | Delirium | 312 (28.1%) |
| | Adjustment disorders | 109 (9.8%) |
| | Major depression | 54 (4.9%) |
| | Dementia | 86 (7.7%) |
| | No diagnosis | 247 (22.2%) |

## List of papers published in 2012
## Journal

1. Giasuddin NA, Chowdhury NF, Hashimoto N, Fujisawa D, Waheed S. Pathways to psychiatric care in Bangladesh. Soc Psychiatry Psychiatr Epidemiol, 47:129-136, 2012
2. Kato TA, Tateno M, Shinfuku N, Fujisawa D, Teo AR, Sartorius N, Akiyama T, Ishida T, Choi TY, Balhara YP, Matsumoto R, Umene-Nakano W, Fujimura Y, Wand A, Chang JP, Chang RY, Shadloo B, Ahmed HU, Lerthattasilp T, Kanba S. Does the 'hikikomori' syndrome of social withdrawal exist outside Japan? A preliminary international investigation. Soc Psychiatry Psychiatr Epidemiol, 47:1061-1075, 2012
3. Shirai Y, Fujimori M, Ogawa A, Yamada Y, Nishiwaki Y, Ohtsu A, Uchitomi Y. Patients' perception of the usefulness of a question prompt sheet for advanced cancer patients when deciding the initial treatment: a randomized, controlled trial. Psychooncology, 21:706-713, 2012
4. Inoue T, Honda M, Kawamura K, Tsuchiya K, Suzuki T, Ito K, Matsubara R, Shinohara K, Ishikane T, Sasaki K, Boku S, Fujisawa D, Ono Y, Koyama T. Sertraline treatment of patients with major depressive disorder who failed initial treatment with paroxetine or fluvoxamine. Prog Neuropsychopharmacol Biol Psychiatry, 38:223-227, 2012
5. Ito M, Nakajima S, Fujisawa D, Miyashita M, Kim Y, Shear MK, Ghesquiere A, Wall MM. Brief measure for screening complicated grief: reliability and discriminant validity. PLoS One, 7:e31209, 2012
6. Ogawa A, Nouno J, Shirai Y, Shibayama O, Kondo K, Yokoo M, Takei H, Koga H, Fujisawa D, Shimizu K, Uchitomi Y. Availability of psychiatric consultation-liaison services as an integral component of palliative care programs at Japanese cancer hospitals. Jpn J Clin Oncol, 42:42-52, 2012
7. Kagami M, Maruyama T, Koizumi T, Miyazaki K, Nishikawa-Uchida S, Oda H, Uchida H, Fujisawa D, Ozawa N, Schmidt L, Yoshimura Y. Psychological adjustment and psychosocial stress among Japanese couples with a history of recurrent pregnancy loss. Hum Reprod, 27:787-794, 2012
8. Takeuchi M, Takeuchi H, Fujisawa D, Miyajima K, Yoshimura K, Hashiguchi S, Ozawa S, Ando N, Shirahase J, Kitagawa Y, Mimura M. Incidence and risk factors of postoperative delirium in patients with esophageal cancer. Ann Surg Oncol, 19:3963-3970, 2012
9. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Yamada Y, Fujimori M, Ogawa A, Fujisawa D, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Clinical biopsychosocial risk factors for depression in lung cancer patients: a comprehensive analysis using data from the Lung Cancer Database Project. Ann Oncol, 23:1973-1979, 2012

# Supportive Care Team

**Hiroya Kinoshita, Asao Ogawa, Daisuke Fujisawa, Yoshihisa Matsumoto, Hiroyuki Takei, Yoichiro Higashi, Tomofumi Miura, Kensuke Higa, Yasuhiro Hirano, Junko Nouno, Harumi Koga, Yuko Tanaka, Chiyuki Terada, Kumi Nakamura, Yasuhiko Ichida, Shinya Motonaga, Asuka Iwamoto, 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, certified nurse specialists, certified nurses, clinical psychologists, pharmacy practitioners, registered dietitians and social workers. The SCT keeps regular contact with clinician-teams in charge, discusses patients' needs, and refers patients and families to the appropriate services. Interdisciplinary team conferences and SCT rounds are held on Wednesdays. The SCT consultation data are shown in the table.

## Research activities and clinical trials

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

**Table1. Supportive Care Team consultation data (n = 936; January-December, 2012)**

| | | N (%) |
|---|---|---|
| Age | Mean ± SD (range) (yr) | 66.1 ± 11.7 (23-93) |
| Gender | (male/female) | 619 (66%) / 317 (34%) |
| Service | Palliative care/ Psycho-oncology | 195 / 741 |
| Cancer site | Lung | 235 (25%) |
| | Head and Neck | 177 (19%) |
| | Colon | 100 (11%) |
| | Stomach | 78 (8%) |
| | Esophagus | 73 (8%) |
| | Pancreas | 71 (8%) |
| Stage | I / II / III / IV | 93 (10%) / 68 (7%) / 98 (10%) / 398 (43%) |
| | / recurrence / unknown / others | / 217 (23%) / 23 (2%) / 38 (4%) |
| Performance status | 0/ 1/ 2/ 3/ 4 | 173 (19%) / 166 (18%) / 218 (23%) / 245 (26%) / 134 (14%) |
| Physical symptoms | Pain | 367 (39%) |
| (moderate - severe) | Appetite loss | 241 (26%) |
| | Fatigue | 135 (14%) |
| | Respiratory distress | 129 (14%) |
| Psychiatric diagnosis | Delirium | 292 (39%) |
| (primary diagnosis) | Adjustment disorders | 33 (4%) |
| | Dementia | 49 (7%) |
| | Major Depressive Disorder | 24 (3%) |
| Outcome | Discharge/ Hospital transfer | 607 (65%) / 55 (6%) |

## List of papers published in 2012
## Journal

Please refer to the "Psycho-Oncology Service" sections.

# Department of Diagnostic Radiology

**Mitsuo Satake, Ryoko Iwata, 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 multi-slice CT scanners, including one area detector CT scanner and one Dual Source CT, two MRI systems (1.5 T and 3 T) one interventional radiology (IVR) CT system, one multi-axis c-arm CT system, two gamma cameras with the capacity for single photon emission CT (SPECT), two digital radiographic (DR) systems for fluoroscopy, two mammography and four computed radiographic (CR) systems. Our IVR-CT systems use digital subtraction angiography with multi-detector 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 imaging systems enhance the efficacy of routine examinations.

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

Small interfering RNAs (siRNAs) were 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 was 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 reveals 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.

**Table1. Number of Cases Examined**

| | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|
| Plain X-ray examination | 33,913 | 33,841 | 34,330 | 35,032 | 39,128 |
| Mammography (MMG) | 2,272 | 2,388 | 2,595 | 2,434 | 2,380 |
| Fluoroscopic Imaging (GI-series, etc.) | 3,387 | 3,781 | 3,478 | 3,903 | 4,029 |
| CT | 18,014 | 19,543 | 21,128 | 21,967 | 24,101 |
| MRI | 5,053 | 5,723 | 5,830 | 5,708 | 5,619 |
| RI | 1,693 | 1,718 | 1,676 | 1,582 | 1,586 |
| PET | 1,585 | 1,670 | 2,048 | 2,239 | 2,284 |
| Angiography | 766 | 711 | 728 | 656 | 742 |
| Total | 66,683 | 69,375 | 71,813 | 73,521 | 79,869 |

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.

## List of papers published in 2012

### Journal

1. Kuno H, Onaya H, Iwata R, Kobayashi T, Fujii S, Hayashi R, Otani K, Ojiri H, Yamanaka T, Satake M. Evaluation of cartilage invasion by laryngeal and hypopharyngeal squamous cell carcinoma with dual-energy CT. Radiology, 265:488-496, 2012

# Department of Radiation Oncology

**Tetsuo Akimoto, Mitsuhiko Kawashima, Sadatomo Zenda, Masakatsu Onozawa, Satoko Arahira, Masamichi Toshima, Atsushi Motegi**

## Introduction

Radiotherapy (RT) plays an essential role in the management of cancer patients. It is used (1) as a curative treatment for many patients with loco-regional localized malignant disease; (2) as integrated therapy combined with chemotherapy and/or surgery; and (3) as 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, whereas the dose to the surrounding normal tissues should be kept as low as possible in order to contain the severity of radiation-related complications within an acceptable level.

The primary aim of the Radiation Oncology Division is to develop high precision RT such as intensity modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT) , stereotactic RT and proton beam therapy (PBT) and establish the definitive role of RT in cancer treatment. Another important goal is to establish standard treatments for various cancers and optimal irradiation techniques including total dose, fractionation and radiation fields.

## Routine activities

At present, the staff of the Radiation Oncology Division consists of 7 consultant physicians (radiation oncologists), 15 radiation technologists, 3 medical physicists, 1 nurse, and 1 clerk. We have more than 1,000 thousand new cases for conventional RT and 200 new patients for proton beam therapy every in every year. The quality assurance of 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 is performes 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.

The selection of the treatment approaches is determined through clinical conferences between a radiation oncologist, surgical oncologists and medical oncologists. More than 30 clinical trials involving RT as the sole or a combined treatment modality for various cancers are in progress.

The section is responsible for conventional (photon-electron) RT, the systems for which comprise t 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 section is also responsible for PBT managed by a team that is composed of 6 operating staff members and 1 technician for setting up the compensator and aperture; the latter is sent from the system manufacturers and works in collaboration with the other staff members of the Division. PBT is managed in 2 treatment rooms and both rooms are routinely used for rotational gantry treatment. The Division ensures quality assurance and regular maintenance of the PBT machines for precise dose delivery and safe treatment.

## Research activities

In the Radiation oncology division, the following research activities are in progress.

1) Establishment of optimal combined approaches including RT and chemotherapy for locally advanced head and neck cancer, non-small cell lung cancer and esophageal cancer.
2) Establishment of the clinical usefulness of IMRT for head and neck cancer and localized prostate 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 and locally advanced esophageal cancer.
6) PBT for pediatric malignancies.
7) The role of gene polymorphism in the development of acute and late radiation-related complications.

**Table1. The changes in the number of patients treated with RT**

Number of patients treated with radiotherapy during 2007-2011

| | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|
| New patients | 1097 | 1084 | 1080 | 1616 | 1440 |
| New treatments | 1363 | 1388 | 1385 | 1388 | 1388 |
| Head and neck cancers | 249 | 289 | 281 | 320 | 223 |
| Lung and mediastinal cancers | 391 | 390 | 370 | 411 | 329 |
| Breast cancers | 296 | 264 | 297 | 406 | 325 |
| Gastrointestinal cancers | 202 | 221 | 202 | 228 | 176 |
| Hepatobiliary tract cancers | 63 | 47 | 46 | 54 | 38 |
| Urological cancers | 114 | 112 | 120 | 151 | 100 |
| Bone and soft tissue cancers | 8 | 8 | 6 | 15 | 2 |
| Hematological cancers | 25 | 33 | 27 | 6 | 19 |
| Others | 15 | 24 | 35 | 20 | 19 |
| Proton therapy | 76 | 75 | 81 | 90 | 56 |
| IMRT | | 6 | 4 | 31 | 83 |

## 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 cell carcinoma of the cervical esophagus.

## List of papers published in 2012
## Journal


1. Hojo H, Zenda S, Akimoto T, Kohno R, Kawashima M, Arahira S, Nishio T, Tahara M, Hayashi R, Sasai K. Impact of early radiological response evaluation on radiotherapeutic outcomes in the patients with nasal cavity and paranasal sinus malignancies. J Radiat Res, 53:704-709, 2012
2. Nakamura K, Akimoto T, Mizowaki T, Hatano K, Kodaira T, Nakamura N, Kozuka T, Shikama N, Kagami Y. Patterns of practice in intensity-modulated radiation therapy and image-guided radiation therapy for prostate cancer in Japan. Jpn J Clin Oncol, 42:53-57, 2012
3. Okamoto M, Ishikawa H, Ebara T, Kato H, Tamaki T, Akimoto T, Ito K, Miyakubo M, Yamamoto T, Suzuki K, Takahashi T, Nakano T. Rectal bleeding after high-dose-rate brachytherapy combined with hypofractionated external-beam radiotherapy for localized prostate cancer: the relationship between dose-volume histogram parameters and the occurrence rate. Int J Radiat Oncol Biol Phys, 82:e211-e217, 2012
4. Kawashima M, Hayashi R, Tahara M, Arahira S, Miyazaki M, Sakuraba M, Zenda S, Ogino T. Prospective trial of chemotherapy-enhanced accelerated radiotherapy for larynx preservation in patients with intermediate-volume hypopharyngeal cancer. Head Neck, 34:1363-1368, 2012

# Department of Pathology and Clinical Laboratories

**Atsushi Ochiai, Takahiro Hasebe, 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 at the National Cancer Center Hospital East (NCCH-E).

Seven pathologists, including 6 pathologists who are board-certified by the Japanese Society of Pathology, are assigned to the PD. Two are full-time staff, with the another being part-time. The others originally belong to the Pathology Division at the Research Center for Innovative Oncology (RCIO) and concurrently work at the DPCL. Also working in the division are 4 clinical laboratory technicians. Two doctors and 2 technicians, cytology experts and cytoscreeners, respectively, are all 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 13 clinical laboratory technicians (11 full-time and 2 part-time) and 1 secretary work at the CLD.

## Routine activities

The primary routine activity at the PD is surgical pathology. In 2012, 8,886 biopsy specimens, including 798 frozen sections and 919 review cases, and 2,281 surgical 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) and Digestive Endoscopy Division (Tuesday) and Thoracic Surgery (Friday). Five thousand two hundred and thirty three (5,233) cytology specimens were evaluated (Table 2). Seven cases of autopsies were performed, and all cases were, or are to be presented and discussed in clinico-pathological conferences. Conference-style training sessions are open every Thursday morning for the residents.

The CLD provides accurate and reliable data to help understand each patient's conditions and support prompt decision making for all clinicians working at NCCH-E. Most of the essential laboratory test services are available on a round-the-clock basis. Most of the general laboratory tests for hematology, biochemistry, serology and urinalysis are automatically performed by an automated analyzer, which enables the Division

**Table 1. Number of pathology samples examined at Pathology Division in 2012**

| Origin | Biopsy | Surgical | Autopsy |
|---|---|---|---|
| Gastrointestinal Oncology | 2887 | | |
| Digestive Endoscopy | 1617 | | |
| Head and Neck Surgery | 695 | 396 | 1 |
| Thoracic Surgery | 535 | 449 | 2 |
| Hematology and Medical Oncology | 507 | | 2 |
| Breast Surgery | 488 | 304 | |
| Thoracic Oncology | 378 | | 1 |
| Colorectal Surgery | 364 | 425 | |
| Gastrointestinal Oncology | 341 | | 1 |
| Gastric, Hepatobiliary and Pancreatic Surgery | 248 | 465 | |
| Ambulant Treatment Center | 224 | | |
| Urology | 210 | 14 | |
| Radiation Oncology | 182 | | |
| Esophageal Surgery | 83 | 172 | |
| Orthopedic Surgery | 25 | 19 | |
| Obstetrics and Gynecology | 23 | | |
| Dermatology | 7 | | |
| Anesthesiology | 4 | 2 | |
| Plastic and Reconstructive Surgery | 4 | 14 | |
| Dental Division | 3 | | |
| Others | 61 | 21 | |
| Total | 8886 | 2281 | 7 |

**Table 2. Number of cytology samples examined by the Pathology Division in 2012**

| Origin | |
|---|---|
| Thoracic Surgery | 1275 |
| Thoracic Oncology | 1228 |
| Urology | 714 |
| Obstetric and Gynecology | 602 |
| Head and Neck Surgery | 405 |
| Hepatobiliary and Pancreatic Oncology | 329 |
| Gastric, Hepatobiliary and Pancreatic Surgery | 202 |
| Hematology and Medical Oncology | 136 |
| Breast Surgery | 114 |
| Colorectal Surgery | 108 |
| Gastrointestinal Oncology | 60 |
| Diagnostic Radiology | 12 |
| Ambulant Treatment Center | 12 |
| Esophageal Surgery | 12 |
| Palliative Medicine | 7 |
| Radiation Oncology | 3 |
| Orthopedic Surgery | 2 |
| Anesthesiology | 2 |
| Others | 10 |
| Total | 5233 |

to provide results within one hour after sample 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 Table 3 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 counts, 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 assays are performed by an automated analyzer. The section also performs immunological assays for several tumor markers.
iv) The physiology section performs electrocardiography, the respiratory function test, 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 the intramural infection control team at NCCH-E.
vi) The blood transfusion section consolidates any usages of blood preparation/products in NCCH-E. The section is also responsible for collecting and advertising all up-to-date information related to the safe usage of blood preparations/products. Daily routine activities for each blood transfusion case include blood typing, irregular antibodies screening and cross-matching.

## Research activities

All of the pathologists are involved in research activities in 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.

All the technicians working in 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

The CLD actively participated in almost all of clinical trials carried out at NCCHE through the provision of laboratory data. The PD participated in 34 new trials in 2012.

## List of papers published in 2012

### Journal

Please refer to the section for the Division of Pathology at the Research Center for Innovative Oncology

**Table 3. Number of laboratory tests performed in the Clinical Laboratory Division in 2008-2012**

| Section | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|
| General laboratory medicine | 196,233 | 230,610 | 265,517 | 264,452 | 282,716 |
| Hematology | 527,567 | 560,110 | 589,144 | 622,666 | 676,889 |
| Biochemistry | 1,424,263 | 1,493,858 | 1,569,963 | 1,648,755 | 1,811,244 |
| Serology | 125,409 | 136,127 | 139,759 | 146,104 | 141,224 |
| Bacteriology | 21,822 | 22,466 | 21,978 | 21,657 | 25,112 |
| Blood transfusion | 21,378 | 24,181 | 22,441 | 21,895 | 20,550 |
| Physiology | 34,258 | 39,232 | 43,215 | 43,275 | 45,408 |
| Total | 2,211,641 | 2,506,584 | 2,652,017 | 2,768,804 | 3,003,143 |

# Clinical Trial Management Office

**Toshihiko Doi**

## Introduction

The mission of the Clinical Trials Management Office (CTMO) is to facilitate the conducting of quality clinical trials at NCCHE, especially those which are all conducted as a sponsored initiated trial, to achieve registration. The CTMO will also assist investigators with infrastructure support, including Institutional Review Board (IRB) and initial regulatory guidance. A total of 30 staff members support the CTMO: 8 Clinical Research Coordinators (CRCs) (5 nurses and 3 pharmacologists), 10 data managers, 5 medical technologists, 1 free nurse and 7 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 or investigators 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 process data using a range of computer applications and database systems to support collection, cleaning up 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 the 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.

## Daily 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 the 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) Preparation 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 the administration of the CTMO increased in 2011, as in previous years. The CTMO has conducted and supported in excess of 130 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 (`first in man' clinical trial and multinational simultaneous phase 1 trial). In 2012, we managed Japanese phase 1 clinical trials and multinational simultaneous phase 1 trials as

early clinical trial development, such as a first in man trial of inhibitor MET/VEGFR. We have also participated in the clinical trials on rare cancer. We have the largest number of enrolled patients in the world part of the international collaborative trial thyroid, prostate, and pancreatic cancer. For clinical trials on colorectal cancer, we have played a central role in the world.

Our task is also to cooperate with more investigator initiated clinical trials (IITs) as phase 1 units than last year. The Japanese Government will provide support to the NCCH & NCCH-E with plans to establish an infrastructure enabling early-stage and exploratory clinical trials of new drugs and medical devices sponsored by industry and research institutions. The Phase 1 team has been started in collaboration with oncology experts to share updated trial information, to hold phase 1 meetings for patient recruitment, and brief meetings for information sharing. As a result of these meetings, we can achieve high-quality trial content with efficient recruitment of patients. Drug development is a costly and risky affair and involves a great deal of money and time. The CTMO will challenge newer and more advanced trials such as unapproved multi-drug combination trials and biomarker-driven trials. Furthermore, we will contribute to the worldwide network system for phase 1 trials to establish the acceleration of the pre-clinical and clinical development of investigational anti-cancer agents.



**Table 1. The number of trials which CTMO supported**

| | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|
| Phase1 | 17 | 14 | 25 | 31 | 35 |
| Phase1/2 | 6 | 5 | 4 | 5 | 7 |
| Phase2 | 21 | 22 | 18 | 21 | 31 |
| Phase3 | 15 | 20 | 43 | 46 | 56 |
| PMS[#1] | 9 | 7 | 6 | 5 | 4 |
| Total | 68 | 68 | 96 | 108 | 133 |

#1 Post-marketing Study

**Table 2. Proportion of clinial trials involved by CTMO**

| | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|
| Proportion of clinial trials involved by CTMO (%) | 88.0 | 87.3 | 91.7 | 92.4 | 91.9 |

**Table 3. The number of domestic and global clinical trials**

| Trial type | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|
| Domestic | 56 | 49 | 53 | 58 | 76 |
| Global or multi-nation | 13 | 20 | 45 | 51 | 60 |
| Total | 69 | 69 | 98 | 109 | 136 |

# Pharmacy Division

**Keishiro Izumi, Yasuhiko Ichida, Akio Hiroi, Takashi Uemura, Reiko Matsui, Masahito Yonemura, Sonoko Kobayashi, Hiromi Shinano, Hideki Funazaki, Hiroko Ouchi, Shinya Suzuki, Ikuyo Ueda, Shinya Motonaga, Tomoko Ogawa, Mai Itagaki, Tomoka Hagihara, Kenji Kawasumi, Aya Ikeuchi, Takeshi Koike, Misaki Kobayashi**

## Introduction

The main objectives of our Pharmacy Division are: (1) To promote clinical studies to obtain new empirical data; (2) To provide chemotherapy based on the most recent empirical data; and (3) To pursue patient-centered pharmaceutical care.

Our residents' training program started in 2006. In 2012, six residents joined our Division. Presently, our Division has a total of eighteen residents. In addition, our Division has accepted 7 trainees from other institutions for our oncology-pharmacist training programs.Through this year, 3 terms of the training courses, we have educated 15 pharmacy students and 2 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. In inpatient care, the Division assigns pharmacists to provide medication counseling and drug information for healthcare providers and patients, to pursue effective pharmaceutical care. In outpatient care, the Division provides a pharmacy outpatient service in which pharmacists check patients for adverse reactions and doses of antineoplastic agents, especially in the case of oral anticancer medications. We then assess the necessity of supportive-care medications and suggest them to physicians. The pharmacy outpatient service also reviews the drugs taken by all patients to evaluate when patients have to stop their anticoagulants before their operation or when they have to stop metformin before examinations with iodinated-contrast material. Pharmacists are on duty at the Outpatient Chemotherapy Center as dedicated staff members. The pharmacists provide a Chemotherapy Hotline Service, which is a direct line for our outpatients who have any problems concerning their chemotherapy treatment. In the Outpatient Chemotherapy Center, pharmacists are always available to provide drug information for healthcare providers and patients. We also manage investigational drugs.

## New developments

Over the years, the services of our Division have been under continuous expansion and development. Last year, the Division started assigning a pharmacist as a dedicated member in ward (6B), but in addition, since June 2012, we have assigned three pharmacists as dedicated staff members in three wards (4B, 6B, PCU) since June 2012. These dedicated pharmacists have started evaluating high risk medications, drug interactions, and drug compatibilities in the wards and have monitored prescriptions and suggested medications through medical conferences or by attending medical team rounds. The Division has started assigned a pharmacist to the operation room for narcotic and muscle relaxant control for 4.5 hours each day.

**Table 1.**

| | 2010 | 2011 | 2012 |
|---|---|---|---|
| Number of Prescriptions | | | |
| Prepared in hospital pharmacy | | | |
| Total | 84,492 | 86,643 | 90,392 |
| Inpatients | 78,327 | 80,837 | 84,800 |
| Outpatients | 6,165 | 5,806 | 5,592 |
| Taken to outside pharmacies | 50,731 | 55,826 | 59,722 |
| (% of prescription filled outside) | (89.2%) | (90.6%) | (91.4%) |
| Injections | | | |
| Total | 157,958 | 159,730 | 160,105 |
| Inpatients | 132,407 | 132,969 | 126,428 |
| Outpatients | 25,551 | 26,761 | 33,677 |
| Number of Prescriptions | | | |
| (Investigational new Drugs) | 4,435 | 4,676 | 4,584 |
| Aseptic Preparation of Injection Mixture | | | |
| Anticancer drugs | 32,007 | 35,386 | 38,663 |
| Others | 4,689 | 3,320 | 3,994 |
| Number of medication counseling sessions (for inpatients) | | | |
| Patients | 5,063 | 5,067 | 6,418 |
| Counseling sessions which earned a counseling fee | 6,522 | 6,645 | 7,139 |
| Number of medication counseling sessions (for outpatients) | | | |
| in the Outpatient Chemotherapy Center | 5,705 | 6,701 | 8,965 |
| in the pharmacy outpatient service | 479 | 738 | 1,782 |
| in the 'Nexavar' outpatient service | 416 | 583 | 381 |
| Number of calls on the Chemotherapy Hotline | 980 | 1,468 | 1,665 |
| Number of home medication checks | 5,422 | 5,364 | 6,017 |

# Nursing Division

**Tomiko Ichihashi**

## Introduction

Recently, giving better treatment to cancer patients, residential care and treatment have become an integral part of patients' recovery and maintaining 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 let those discharged return home without facing problems medically and physically.

To provide the continuity of care for the patient and their family, we started the integration of an outpatient clinic and ward nursing. We have prepared an educational course for the palliative care certified nurse in 2013, because of the improvement of patients' QOL and nursing skills in cancer nursing.

This has further led to increased patient awareness of their diet-related problems diet. We have also set up an outpatient section since September, 2010, which offers guidance to patients on a list of all kinds of cancer surgery like esophageal, epigastrial, abdominal, respiratory, head and neck and urinary cancer. Patients will be given a lecture about prevention of complications after surgery. We work together with other sections to reduce patient uneasiness and anxiety arising from the pre- and post-surgical situations, and to support the patients' decision about their treatment. As for nurses, all wards introduced a two-working-shift system in September, 2009. Furthermore, 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 children whose parents have to start working early in the morning.

We set these goals below for the purpose of clarifying our mission and raising the quality of care.

To shine with learning and act full of life.

1. To practice nursing with respect for the patient's preference and hope, to practical nursing skills.
2. To try to make our hospital a bright and rewarding work environment to increase the satisfaction of our staff.
3. To bring out each individual nurse's ability to work with each other to provide safe and comfortable care services.
4. To prepare for the educational course on palliative care certified nurse starting in 2013, for human resource development in the field of cancer nursing.
5. To take part in the hospital's administration in order to implement strategic hospital management.

## Routine activities

In 2012, of the current 319 nurses, 42 are newly employed. The average number of outpatients per day was 777.3, while that of inpatients was 349.7. The average hospitalization term was 14.8 days. The number of chemotherapy treatments in The Medical Treatment Center per day was 89.7 and the number of operations conducted was 2571. We provided educational services for patients undergoing chemotherapy on how to deal with the side effects, and also provide telephone-follow-up services and hot-line-telephone services to solve patient problems and relieve anxiety once they have returned home.

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.

In April, 2011, we established the post of head nurse in charge of nursing education to help nurses to study and to support their mental health.

There are 5expert nurses, 1 psychiatric mental health nurse and 21 certified expert nurses specializing in wound ostomy care (4), cancer pain (6), cancer chemotherapy (6), palliative care (1), infection control (2), breast care (2), swallowing and eating (2) and radiation (2). They are in charge of the specialized cancer nursing course education programs.

We have subsequently accepted trainees participating in the expert nurse course and certified expert nurse course.

As for nursing-related research projects, not only expert nurses and certified nurses, but also registered nurses in our hospital have both participated and attended external training programs. We gave 19 presentations at academic conferences in 2012.

**Table1. The number of trainee (< 1 week)**

| | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|
| Postgraduate Nurse | 6 | 14 | 6 | 5 |
| Certified Expert Nurse | 13 | 12 | 17 | 25 |
| Expert Nurse | 5 | 4 | 3 | 3 |
| Others | 1 | 0 | 0 | 0 |
| Total | 25 | 30 | 26 | 33 |
| Nursing Student | 172 | 156 | 141 | 139 |

## Preface

The Research Center for Innovative Oncology (RCIO) was originally funded as a branch of the National Cancer Center Research Institute in 1994 at the Kashiwa campus. In order to focus more on translational research projects (TR) and mutual collaborative efforts between basic and clinical researchers, the National Cancer Center Kashiwa campus was reorganized in 2005, as a result of which the RCIO became part of the Hospital East. Originally, the RCIO consisted of five divisions: the Pathology, Investigational Treatment, Functional Imaging, Psycho-oncology, and Particle Therapy divisions and conducted numerous studies in collaboration with other academic institutions and industries. The RCIO have developed new endoscopic instruments such as narrow band imaging (NBI) in collaboration with Hospital East, which has already become one of the standard procedure in the world. Several new drug-delivery system (DDS) agents based on cutting-edge nanotechnology have originally been developed in RCIO and one of them is now under evaluation in an international phase III trial. We are also pioneers of proton-beam therapy, new imaging instruments such as super-MRI, and psycho-oncology, in which our researchers are leading these fields. In 2008, we organized the Clinical Trial section in order to manage and support investigator-initiated trials for facilitating more translational researches and early clinical trials. In 2011, the National Cancer Center Hospital East was selected as "a designated center for early and exploratory clinical trials" by the government and our RCIO has been playing a central role. For this purpose, we not only reorganized the RCIO through expanding to eight divisions and three support sections but also organized the Exploratory Oncology Research & Clinical Trial Center (NCC-EPOC) together with the Tsukiji campus. Detailed information of NCC-EPOC is available in another section. In 2012, our hospital was also selected as "a designated center for new endoscopic instrument development" and several exploratory studies with new diagnostic instruments/devices have been initiated. The number of the patients who received proton-beam irradiation has been rapidly increasing in recent years and this approach has achieved significant benefit in head and neck and prostate cancer. A supportive care center with a collaboration of psycho-oncology, palliative care, nursing, pharmacy, and social worker divisions is also being organized to provide a variety of support options for patients. With these activities we are actively establishing a top innovative cancer center with the best amenities for cancer patients in the world.

Atsushi Ohtsu, MD PhD
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National Cancer Center Hospital East

# Division of Pathology

**Atsushi Ochiai, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Takeshi Kuwata, Takahiro Hasebe, Chisako Yamauchi, Syuichi Mitsunaga**



## Introduction

The contribution of the members of the Division of Pathology to both the Research Center for Innovative Oncology (RCIO) and the National Cancer Center Hospital (East) [NCCH-E] comprises 4 major activities: 1) Pathological diagnoses for the NCCH-E; l. 2) Clinical resident training for diagnosis and translational research (TR); 3) Basic and translational research into cancer; and 4) Establishment and maintenance of the NCCH-E tissue bank (Biobank) system.

## Routine activities

The staff members of the Division of Pathology are responsible for all routine pathological and cytological diagnosis for NCCH-E with the collaboration of the staff pathologists of the Department of Pathology and NCCH-E Clinical Laboratories. The Division also participates in the training of clinical residents in pathological diagnosis and translational research using clinical samples from NCCH-E, in addition to participating in clinicopathological meetings and research conferences between the NCCH-E and the RCIO.

## Research activities

The research activities of the Division of Pathology currently focus on the application of the morphological study of cancer tissue to the clinical course of the patient. These activities aim I) to elucidate new biological roles for cancer epigenetics and cancer-stromal interaction; II) to develop a new cancer treatment strategy (Preclinical study); and III) to design and perform experimental and clinicopathological studies on cancer. Prognostic factors and clinicopathological characteristics of various cancers have also been investigated in collaboration with the NCCH-E Diagnostic Pathology Section and other institutions.

I) Elucidate new biological roles for cancer epigenetics and cancer-stromal interaction: The neoplastic transformation by mutant *RAS* is thought to require remodeling of the expression of an entire set of genes. We investigated and elucidated the oncogenic role of EZH2, a histone modifier protein that is induced by oncogenic mutant *RAS*, through the Elk-1 signaling pathway using pancreatic cancers in a transgenic rat model. MEK-inhibition or *EZH2*-knockdown restored expression of a tumor suppressor, *RUNX3* and inhibition of the cancer cell growth. This is the first report on the epigenetic regulation of tumor suppressors including RUNX3 by oncogenic RAS signaling in pancreatic carcinogenesis (1). We previously reported that podoplanin (PDPN) expressed on stromal fibroblasts is the functional protein responsible for the promotion of tumor formation in mouse subcutaneous tissue. To elucidate the underlying molecular mechanism, we co-injected both the human lung adenocarcinoma cell line and human fibroblasts (hFbs) overexpressing wild-type podoplanin (WT-PDPN) and found that the activation state of RhoA in hFbs expressing WT-PDPN was high and the constitutive active RhoA enhanced tumor formation. These data indicated that the enhanced RhoA activity in hFbs expressing PDPN may be one of the mechanisms resulting in the promotion of tumor formation, suggesting that biomechanical remodeling of the microenvironment by stromal fibroblasts may play important roles in tumor progression (2).

II) Development of a new cancer treatment strategy (Preclinical study): We established a novel murine model of cancer cachexia using N-inv of human pancreatic cancer cells. Mice with N-inv showed a loss of body weight, skeletal muscle and fat mass without appetite loss, which are compatible with an animal model of cancer cachexia. Activation of astrocytes in the spinal cord connected with N-inv was observed in our model. Experimental cachexia was suppressed by disrupting neural routes or inhibiting the activation of astrocytes. These data provided the first evidence that N-inv induces cachexia *via* astrocytic activation of the neural route in pancreatic cancer (3).

III) Experimental and clinicopathological studies on cancer: The histological predictive and prognostic factors for in various histological types of lung cancers (4-10), gastrointestinal tract cancers (11-13), pancreatic tumors (14) and other tumors (15) are

also being investigated and reported in collaboration with the clinical divisions of the NCCH-E and other institutions. We have also participated in multicenter trials on pathological studies (16-20).

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# Division of Functional Imaging

**Hirofumi Fujii, Izumi O Umeda, Masayuki Yamaguchi, Mitsuyoshi Yoshimoto**

## Introduction

The Division of Functional Imaging actively investigates mainly 2 kinds of imaging modalities, namely, radionuclide imaging and magnetic resonance (MR) imaging, to establish therapeutic strategies for minimally invasive and personalized cancer treatments. For radionuclide imaging, some experimental studies were performed using a single photon emission computed tomography (SPECT) scanner in a small animal model to visualize heterogeneous tumor interiors. For MR imaging, some experimental studies were done using both a 9.4 T scanner dedicated to small animal imaging and a 3.0 T whole-body scanner.

## Research activities

*In vivo* visualization of intratumoral heterogeneity would be an innovation that could contribute to improved cancer therapy. To date, however, conventional nuclear medicine tests have failed to visualize heterogeneity *in vivo* because of limited spatial resolution. Recently, newly-developed SPECT scanners dedicated to small animal imaging have been able to obtain excellent spatial resolution of <1 mm, but few studies have focused on the evaluation of intratumoral heterogeneity. We investigated the optimal conditions of acquisition and reconstruction to achieve *in vivo* SPECT visualization of intratumoral heterogeneity under the limited conditions of actual small animal imaging.

The acquisition for 30 min with pinhole apertures of 1.4 mm-diameter, but not 1.0 mm, and optimizing the reconstruction parameters could yield the best spatial resolution of 1.3 mm. The minimal radioactivity concentration for visualization of heterogeneous tumor interiors was estimated to be as high as 0.2–0.5 MBq/mL. By administering liposomes containing $^{111}$In to tumor-bearing mice, SPECT imaging successfully showed heterogeneous intratumoral $^{111}$In distribution *in vivo* (1).

We also tried to clearly visualize the heterogeneous distribution of hypoxia inducible factor 1$\alpha$ (HIF) activity in tumor tissues *in vivo*. We synthesized $^{125}$I-IPOS, an $^{125}$I labeled chimeric protein probe that was designed to visualize HIF activity. $^{125}$I-IPOS accumulated well in FM3A tumors and high resolution SPECT/CT fusion images successfully demonstrated the heterogeneity of $^{125}$I-IPOS intratumoral distribution. SPECT-MRI fusion images could provide more detailed information about the intratumoral distribution of $^{125}$I-IPOS (2). High resolution SPECT images successfully demonstrated heterogeneous intratumoral distribution of $^{125}$I-IPOS. SPECT/CT fusion images, or SPECT-MRI fusion images, would be useful to understand the features of heterogeneous intratumoral expression of HIF activity *in vivo*.

Pancreatic cancers highly express $\alpha_v\beta_3$ integrin. We previously demonstrated that SPECT with $^{111}$In-DOTA-c(RGDfK) successfully detected pancreatic cancers in a hamster carcinogenesis model (3). We synthesized RGD-liposomes loaded with ferrioxamine B (Fe-deferoxamine) as MR contrast agents. The RGD-liposomes also showed high affinity to $\alpha_v\beta_3$ integrin. In PANC-1 bearing nude mice, MR studies revealed that RGD-liposomes loaded with ferrioxamine B enhanced the T/M signal ratio on T1 images by 40% compared with RKG-liposomes as a control. Therefore, RGD-liposomes might be possible candidates for *in vivo* MR imaging of pancreatic cancer.

Magnetic resonance (MR) imaging can provide anatomical images of experimental animals with high spatial resolution and high tissue contrast. Taking advantage of these high resolutions, we visualized the interiors of small lymph nodes of mice using an MR lymphography (MRL) technique. In MRL, superparamagnetic iron oxide (SPIO) is used as contrast media to reduce signals from normal lymphatic tissues and, in contrast, highlight small metastatic foci. This MRL technique is anticipated to become a valuable diagnostic imaging tool for sentinel lymph node (SLN) metastasis in breast cancer as well as esophageal cancer. We found that this MRL technique can highlight not only metastatic foci, but also hyperplastic lymphatic tissues which are frequently seen in inflammatory lymph nodes. This finding suggests that the metastatic foci in lymph nodes cannot precisely be differentiated from hyperplastic lymphatic tissue by means of MR lymphography, and this should draw the attention of the radiologist to the pitfalls of the MRL technique in SLN diagnosis (4).

Since 2011, we have been developing multiple-animal MR imaging techniques to increase the throughput of preclinical MRI research. This year, we developed a new multi-animal hepatic MR imaging system which is less susceptible to motion artifacts.

In addition, a new post-processing technique was developed to promote precise interpretation of multiple-animal MR images.

### Clinical trials

Clinical trials of hypoxia PET tests are 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 the clinical and pathological features of tumors with high avidity to these radiopharmaceuticals. The effects of systemic chemotherapy on the cerebral metabolism and cognitive function in breast cancer patients were evaluated with MR spectroscopy.

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# Division of Science and Technology for Endoscopy and Surgery

**Kazuhiro Kaneko, Masaaki Ito**

## Introduction

Approximately 50 years have passed since the gastrofiberscope came into existence, and the associated diagnostic technique has progressed rapidly. Up to the present, endoscopy has been widely used for the screening for, diagnosis and treatment of early cancer in the aero-digestive tract including the pharynx, esophagus, stomach, and colorectum. With conventional endoscopy, observations are made using white light to illuminate the mucosal surface with a special attention being paid to the appearance of reddish and irregular portion compared to adjacent areas. Thus, detection of suspicious early cancerous lesions has been largely based on the macroscopic characteristics of the lesions.

One of the characteristic natures of early-stage cancer is the growth of blood vessels (neovascularity). Using two narrow wavebands of light (blue, 390-445 nm; and green, 530-550 nm) that have excellent absorption characteristics in circulating hemoglobin, narrow band imaging (NBI) endoscopy may provide better images of the capillaries in the mucosal surface.

Another characteristic nature of the tumor is hypoxia. As a tumor grows, it rapidly outgrows its blood supply, leaving portions of the tumor with regions where the oxygen concentration is significantly lower than in healthy tissues. Thus, there have been attempts to visualize the spatial distribution of tumor hypoxia, such as fluorescent labeling techniques or hemoglobin absorption-based techniques. However, these methods are limited because of low spatiotemporal resolution of current imaging techniques. We have developed an imaging technology that can derive the oxygen saturation ($StO_2$) images from only a few wavelength measurements. Thus, the next generation novel endoscopy should be able to visualize specific functions in cancerous tissue. To allow further development of the technology, illumination sources based on laser and near-infrared energy will be required.

## Routine activities

The present research activities mainly focus on the development of new instruments for endoscopic diagnosis and new endoscopic treatment modalities. Since posing a problem in the present condition is required in development research regarding endoscopy, our division collaborates with Endoscopy division. Therefore, endoscopic diagnosis are routinely performed for cancer patients, endoscopic treatment, such as EMR or ESD, are performed in patients with early GI tract cancers. We perform lectures to resident doctors regarding individual projects. Furthermore, meeting is constantly conducted with the faculties including students from the Faculties of Technology and Science of University.

## Research activities

Research studies have been conducted in various fields for cancer patients using endoscopy in the GI tract and head and neck to establish strategies for prevention, or endoscopic diagnosis and treatment. In addition, ongoing studies have been designed to develop new devices or procedures in innovative and less invasive laparoscopic surgery for gastrointestinal malignancies. These projects are being conducted as prospective clinical studies and preclinical studies in collaboration with not only commercial manufacturers but also University, Faculties of Technology and Science.

Developing research into novel endoscopy systems is being performed. Hypoxia imaging is being used to detect neoplastic lesions of the head and neck and alimentary tracts, with two types of visualized images, such as pseudocolour $StO_2$ imaging with an $StO_2$ overlay image. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and rare earth nanoparticles, doped yttrium oxide. This system is capable of penetrating through the gastrointestinal wall and obtaining images. With a low-temperature atmospheric pressure plasma system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnostic system using photosensitizing agents, such as hypericin, has been constructed. A novel tattooing system under endoscopy has been developed, for which a patent is currently being applied. Ongoing projects are to develop needle graspers for a needle ultrasonic coagulator in the surgical field.

## Clinical trials

A first in human clinical trial of hypoxia imaging is ongoing on the endoscopic diagnosis of neoplasia of the esophagus, stomach, and colorectum. We conducted a proof-of-the-concept trial for 40 patients with neoplastic lesions in the esophagus including the pharynx, stomach and colorectum. In this first in human trial (UMIN 000004983), two types of $StO_2$ images were used. One was a pseudocolour $StO_2$ image that showed $StO_2$ levels as different hues, and the other was an $StO_2$ overlay image that overlapped the $StO_2$ levels in blue on a white light illumination image to detect the background mucosa. In a system using near-infrared light with nanoparticles, nanoparticles of rare earth act as fluorescent agents. Nanoparticles are attached to a probe, and when the probe is attracted to the surface of cancer cells, irradiation of the nanoparticles with near-infrared light causes them to fluoresce, outlining the tumorous lesion. Molecular imaging endoscopy using of this system with an InGaAs CCD imaging device has currently been developed in collaboration with the Faculty of Technology of University. Preclinical studies, such as the use of a low-temperature atmospheric pressure plasma system and photodynamic diagnosis (PDD) with hypericin, are being performed using appropriate animal models.

## List of papers published in 2012

### Journal


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# Division of Developmental Therapeutics

**Masahiro Yasunaga**



## Drug delivery system in cancer chemotherapy

Tumor-targeted delivery of therapeutic agents is a longstanding pharmacological goal to improve the treatment selectivity and therapeutic index. Most scientists have sought to use 'active' receptor-mediated tumor-targeting systems. However, the 'passive' targeting afforded by the "Enhanced Permeability and Retention (EPR) effect" provides a versatile and non-saturable approach for tumor-selective delivery. Polymeric micelles are ideally suited to exploit the EPR effect, and have been used for the delivery of a range of anticancer drugs in preclinical and clinical studies.

A phase 3 study of NK-105, a paclitaxel incorporating micelle, is now underway in Japan, Taiwan, and Korea in patients with metastatic breast cancer. Phase 2 trials of NC-6004, a cisplatin incorporating micelle, and NK012, an SN-38 incorporating micelle, are underway in Japan and other countries. A Phase 1 study of K-912, an epirubicin incorporating micelle will begin soon. In addition to clinical trials, an anticancer incorporating micelle conjugated with a monoclonal antibody (mAb) is being developed.

## Cancer stromal targeting (CAST) therapy

In spite of the recent success of monoclonal antibody (mAb) drug conjugate (ADC) therapy in patients with hypervascular and special tumors recognized by a particular mAb, there are several issues to be solved before ADC can be recognized as a universal therapy for any type of cancer. In particular, most human solid tumors possess abundant stroma that hinders the distribution of ADC. To overcome these drawbacks, we developed a unique strategy involving cancer-stromal targeting (CAST) therapy using a cytotoxic immunoconjugate bound to the collagen 4 or fibrin network in the tumor stroma from which the payload can be released gradually and distributed throughout the tumor, resulting in the arrest of tumor growth due to induced damage to tumor cells and tumor vessels. Our findings have also suggested that the conjugate-design, in parallel with the choice of targeting antibodies, should be selected to maximize the therapeutic effect depending on the distinct stromal structure of each individual tumor (1).

## Noninvasive diagnostic test for colorectal cancer

Several methods for the early detection of colorectal cancer (CRC) to reduce its mortality rate have been reported. The potential of a fecal miRNA test has therefore been investigated for the early detection of CRC. CRC patients (n=299) and healthy volunteers (n=116) with no abnormalities detected by screening colonoscopy were enrolled in this case control study. The value of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve using miR-17, -18a, -19a, -19b, -20a, -92a, -106a, -135b, and -146a was greater than than 0.7. The overall sensitivity and specificity in the validation study were 67.5% (170/252) and 75.3% (61/81), respectively. Further comparative study of this test for CRC screening is needed (2).

## Pharmacogenomics study

Fcγ receptor IIa (FcγRIIa) plays an important role in antibody-dependent cellular cytotoxicity (ADCC) and inflammation. A pharmacogenomics study in Japanese population suggested that L273P could have functional significance in ADCC responses through FcγRIIa (3).

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## Journal

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# Division of Cancer Immunotherapy

**Tetsuya Nakatsura**

## Introduction

Our Division aims to investigate evidenced-based cancer immunotherapy, repeating basic research and translational research. This Division is focused on developing not only more effective immunotherapeutic strategies, but also immunological methods for the suppression of recurrence or for cancer prevention.

## Research activities

RFA for HCC induces GPC3 peptide-specific CTLs

Glypican-3 (GPC3), a carcinoembryonic antigen, is an ideal target for anticancer immunotherapy against hepatocellular carcinoma (HCC). We attempted to compare the induction of the GPC3-specific T-cell-mediated immune response after locoregional therapies in HCC patients and tumor-bearing mice. Twenty-seven HCC patients treated with locoregional therapies, including radiofrequency ablation (RFA), surgical resection and transcatheter arterial chemoembolization (TACE), were prospectively enrolled in this study. Additionally, we performed RFA experiments using a mouse model. The GPC3-specific T-cell response was investigated pre-treatment and post-treatment by an interferon-γ enzyme-linked immunospot assay using peripheral blood mononuclear cells from HCC patients and lymph node cells from tumor-bearing mice. Circulating GPC3-specific cytotoxic T lymphocytes (CTLs) increased in 5 of 9 patients after RFA and in 4 of 9 patients after 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 brought about by RFA compared with surgical resection for HCC patients and tumor-bearing mice. The combination treatment with RFA and immunotherapy is a reasonable strategy against HCC (1).

GPC3-derived peptide vaccine against HCC

We conducted a phase I clinical trial using this GPC3-derived peptide vaccine in patients with advanced HCC, which has recently been concluded. In this study, 33 patients with advanced HCC received GPC3 peptide vaccination with dose-escalation. Peptides were emulsified with IFA and administered in liquid form by intradermal injection on days 1, 15 and 29. The $GPC3_{298–306}$ peptide was used in HLA-A24-positive patients and the $GPC3_{144–152}$ peptide in HLA-A2-positive patients. In this trial, we collected evidence of immune responses, demonstrated antitumor effects, and demonstrated the safety of our GPC3-derived peptide vaccine. One patient manifested a partial response (PR) and 4 out of 19 patients with stable disease (SD) exhibit tumor necrosis or regression that did not meet the criteria for PRs. Two months after initiation of treatment, the disease control rate (PR+SD) was 60.6%. When we analyzed the frequency of GPC3-specific CTLs *ex vivo* with interferon γ (IFNγ) enzyme-linked immunospot (ELISPOT) assays, we could detect GPC3 peptide-specific CTLs in the peripheral blood of most patients. In parallel with this, we established several $GPC3_{144–152}$ peptide-specific CTL clones from peripheral blood mononuclear cells (PBMCs) of patients vaccinated in this trial. Tumor biopsies were performed in seven patients and the infiltration of $CD8^+$ T cells was assesses with immunohistochemistry. In five cases, we observed a marked intratumoral infiltration of $CD8^+$ T cells upon vaccination. A correlation between immunological and clinical responses is nowadays a required as proof for the clinical efficacy of immunotherapy. The frequency of GPC3 peptide-specific CTLs in the peripheral blood correlated with overall survival in HCC patients who received the peptide vaccination. In a multivariate analysis, the frequency of GPC3-peptide-specific CTLs constitute the only predictive factor for overall survival in this trial. Analysis of all 33 patients showed a median overall survival of 12.2 mo (95% CI, 6.5–18.0) in patients with a high frequency of GPC3-specific CTLs, compared with 8.5 mo (95% CI, 3.7–13.1) in individuals with a low GPC3-specific CTL frequency ($p = 0.033$). These observations suggest that GPC3-derived peptide vaccines represent a novel immunotherapeutic strategy for patients with HCC, with a potential to improve overall survival. We subsequently conducted a phase II

study of the GPC3-derived peptide vaccine as an adjuvant therapy for patients with HCC (UMIN-CTR: 000002614). Forty patients with HCC who had undergone surgery or radiofrequency ablation were enrolled in this phase II, open-label, single-arm trial. Ten vaccinations were performed over 1 y after curative treatment. Primary endpoints were the 1- and 2-y recurrence rates, while secondary endpoints were immunological responses, as measured with an IFNγ ELISPOT assay. The correlation between the time of recurrence and immunological responses is currently being analyzed. In the phase I trial, we did not confirm whether the tumor-infiltrating lymphocytes detected after vaccination were GPC3 peptide-specific. To address this issue, we are initiating a pilot study of liver biopsies performed before and after GPC3 peptide vaccination for advanced HCC (UMIN-CTR: 000005093). GPC3 is overexpressed in several malignant tumors, including ovarian clear cell carcinoma (CCC), which is normally characterized by a poor prognosis due to low sensitivity to conventional chemotherapy. We confirmed that a $GPC3_{144–152}$ peptide-specific CTL clone can recognize HLA-A2-positive and GPC3-positive ovarian CCC cell lines using an IFNγ ELISPOT assay, and that is can kill ovarian CCC cell lines. We are currently conducting a phase II study with a GPC3-derived peptide vaccine in ovarian CCC patients (UMIN-CTR: 000003696). We expect that the results of these trials will provide a rationale for larger randomized clinical trials that will determine the efficacy of GPC3-derived peptide vaccines. In addition, as the antitumor effect of the peptide vaccine alone is not dramatic in advanced cancer patients, we aim to develop combinational approaches or strong antigen-specific immunotherapeutic strategies, including adoptive cell transfer approaches following lymphodepletion. Finally, clinical trials of the adoptive cell transfer of GPC3-specific CTLs in patients with HCC in Japan are planned. Well-designed clinical trials using an innovative immunotherapeutic approaches will lead to the development of efficient new therapies for the treatment of GPC3-expressing tumors (2, 3).

## 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 for evaluating immunological efficacy of GPC3 peptide vaccine in patients with advanced HCC. We are also currently conducting a phase II study with a GPC3 peptide vaccine in ovarian CCC patients and a phase I study with a GPC3 peptide vaccine in pediatric cancer patients.

## List of papers published in 2012
### Journal


1. Nobuoka D, Motomura Y, Shirakawa H, Yoshikawa T, Kuronuma T, Takahashi M, Nakachi K, Ishii H, Furuse J, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Kinoshita T, Komori H, Baba H, Fujiwara T, Nakatsura T. Radiofrequency ablation for hepatocellular carcinoma induces glypican-3 peptide-specific cytotoxic T lymphocytes. Int J Oncol, 40:63-70, 2012
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# Psycho-Oncology Division

**Asao Ogawa, Daisuke Fujisawa, Hiroya Kinoshita**

## 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

Risk Factors for Depression in Cancer Patients

Various risk factors for depression in cancer patients have been suggested but have been examined separately in studies with relatively small sample sizes. We designed and executed a study which examined the risk factors of depression in lung cancer patients, using the largest consecutive sampling.

A total of 1334 consecutively recruited lung cancer patients were selected, and data on cancer-related variables, personal characteristics, health behaviors, physical symptoms, and psychological factors were obtained. The participants were divided into groups with or without depression using the Hospital Anxiety and Depression Scale. Among the recruited patients, 165 (12.4%) manifested depression. The results of a binary logistic regression analysis were significant (overall R2, 36.5%), and a greater risk for depression was strongly associated with psychological factors, such as personality characteristics (neuroticism) and the coping style (low fighting spirit, helplessness/hopelessness, and anxious preoccupation). Although the contributions of cancer-related variables, personal characteristics, health behaviors, and clinical state were relatively low, significant correlations were also seen for cancer stage, cancer type, sex, and age. Depression was most strongly linked with personality traits and the coping style, and preventive interventions using screening instruments to identify these risk factors may be useful.

Research into, 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, the national medical insurance system 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 ¼ < 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.

## List of papers published in 2012
## Journal


1. Giasuddin NA, Chowdhury NF, Hashimoto N, Fujisawa D, Waheed S. Pathways to psychiatric care in Bangladesh. Soc Psychiatry Psychiatr Epidemiol, 47:129-136, 2012
2. Kato TA, Tateno M, Shinfuku N, Fujisawa D, Teo AR, Sartorius N, Akiyama T, Ishida T, Choi TY, Balhara YP, Matsumoto R, Umene-Nakano W, Fujimura Y, Wand A, Chang JP, Chang RY, Shadloo B, Ahmed HU, Lerthattasilp T, Kanba S. Does the 'hikikomori' syndrome of social withdrawal exist outside Japan? A preliminary international investigation. Soc Psychiatry Psychiatr Epidemiol, 47:1061-1075, 2012
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9. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Yamada Y, Fujimori M, Ogawa A, Fujisawa D, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Clinical biopsychosocial risk factors for depression in lung cancer patients: a comprehensive analysis using data from the Lung Cancer Database Project. Ann Oncol, 23:1973-1979, 2012

# Division of Radiation Oncology and Particle Therapy

**Tetsuo Akimoto, Mitsuhiko Kawashima, Sadatomo Zenda, Teiji Nishio, Ryosuke Kohno**

## Introduction

The aim of research in the Radiation Oncology and Particle Therapy Division is to develop innovative treatment techniques and conduct clinical trials for proton beam therapy (PBT) with or without chemotherapy for various cancers to establish the definitive role of PBT in cancer treatment. Another important goal is to establish standard treatments for various cancers and optimal irradiation techniques including total dose, fractionation and radiation fields of PBT.

## Routine activities

The staff of the Radiation Oncology and Particle Therapy Division consists of 7 consultant physicians (radiation oncologist) and 3 medical physicists. We have had more than 200 new patients for proton beam therapy. PBT quality assurance is regularly 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. PBT is routinely based on three-dimensional radiation therapy planning, and uses RT-dedicated multi-detector-row helical computed tomography (CT) scanning in order to confirm the precise radiation dose delivered to the targeted tumors. Respiratory-gating has been applied especially in the patients with lung, esophagus and liver cancers. The selection of treatment approaches is determined through clinical conferences between the radiation oncologist, surgical oncologists and medical oncologists.

The PBT team is composed of 6 operating staff members and 1 technician who sets up the compensator and aperture; the technicians are sent from the system manufacturers and work in collaboration with the other staff members of the Division. There are 2 treatment rooms for PBT and both rooms are routinely used for rotational gantry treatment.

## Research activities

In the Radiation Oncology and Particle Therapy Division, the following research activities are under progress.

1) Evaluation of the feasibility of PBT combined with chemotherapy for inoperable locally advanced non-small cell lung cancer and locally advanced esophageal cancer.
2) Proton dose distribution measurements using a MOSFET detector with a simple dose-weighted correction method for LET effects.
3) Hypofractionated PBT for localized prostate cancer.
4) PBT for pediatric malignancies.
5) Development and clinical applicability of linear scanning treatment using a pencil beam.
6) Development of an algorithm for pencil beam activity 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 for clinical application.
7) Dose-volume histogram analysis of the safety of proton beam therapy for unresectable hepatocellular carcinoma.
8) A feasibility study of a molecular-based patient setup verification method using a parallel-plane PET system.

## Clinical trials

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

1) A phase II study of PBT for malignant melanoma of the nasal cavity.
2) A phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.

**Table 1. Number of patients treated with radiotherapy during 2007-2011**

| | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|
| New patients | 78 | 52 | 57 | 107 | 200 |
| Head and neck cancers | 22 | 13 | 24 | 39 | 49 |
| Lung and mediastinal cancers | 17 | 22 | 13 | 12 | 24 |
| Hepatocellular carcinoma | 6 | 6 | 6 | 12 | 27 |
| Prostate cancer | 31 | 11 | 14 | 42 | 93 |
| Others | 2 | 0 | 0 | 2 | 7 |

The changes in the number of patients treated with PBT

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3. Okamoto M, Ishikawa H, Ebara T, Kato H, Tamaki T, Akimoto T, Ito K, Miyakubo M, Yamamoto T, Suzuki K, Takahashi T, Nakano T. Rectal bleeding after high-dose-rate brachytherapy combined with hypofractionated external-beam radiotherapy for localized prostate cancer: the relationship between dose-volume histogram parameters and the occurrence rate. Int J Radiat Oncol Biol Phys, 82:e211-217, 2012
4. Kohno R, Hotta K, Matsubara K, Nishioka S, Matsuura T, Kawashima M. In vivo proton dosimetry using a MOSFET detector in an anthropomorphic phantom with tissue inhomogeneity. J Appl Clin Med Phys, 13:3699, 2012

# Division of Translational Research

**Katsuya Tsuchihara, Sachiyo Mimaki, Hideki Makinoshima, Shingo Matsumoto, Hiroyasu Esumi, Takayuki Yoshino, Atsushi Watanabe, Tomomitsu Nasuno**



## 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 Division of Translational Research 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 the therapeutic effects of anti-cancer treatment strategies. The final goal of the project is the application of these findings to the development of the rationale underlying anti-cancer strategies.

## Routine activities

A weekly conference and journal club is held with all the researchers, technical staff, visiting scientists, and graduate students. Lab members are strongly encouraged to participate and chair the basic and translational research conferences held in Research Center for Innovative Oncology.

## Research activities

Development of Anti-austeric Drugs

Cancer cells in solid tumors frequently encounter a hypoxic and nutrient-deficient 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) is one of the anti-austerity compounds identified in this division. Preclinical studies revealed that a crude extract of *Arctium lappa* possessed equivalent anti-austeric abilities. With the aim of the clinical application of *Arctium lappa*, a phase I clinical trial recruiting advanced pancreatic cancer patients was done. According to the determined appropriate dose, an investigator-initiated phase II clinical trial has been started.

Implication of biomarkers for cancer therapy

To explore more effective genomic biomarkers in anti-EGFR antibody treatment for advanced colorectal cancer, a multi-centered retrospective study combined with whole exon sequencing and copy number variation analyses (BREAC study) is being conducted. More than 100 characteristically anti-EGFR antibody-sensitive and –resistant cases have been enrolled. To clarify the effectiveness and feasibility of multiplex trans-organ pan-cancer genomic biomarker testing, an intramural expert panel has been organized and an ABC study (Analyses of Biopsy samples for Cancer genomics) has been started. More than 100 cases were enrolled in the first 7 months.

Molecular epidemiology of lung adenocarcinoma

Whole exon sequencing was adopted to clarify the mutation profiles of Japanese lung cancer. Somatic mutations of 97 cases of archived lung adenocarcinoma and of 55 cases of small cell lung cancer specimens were identified. Largely diverse mutation patterns of individual tumors were exhibited.

## List of papers published in 2012
## Journal


1. Bando H, Yoshino T, Yuki S, Shinozaki E, Nishina T, Kadowaki S, Yamazaki K, Kajiura S, Tsuchihara K, Fujii S, Yamanaka T, Ohtsu A. Clinical outcome of Japanese metastatic colorectal cancer patients harbouring the KRAS p.G13D mutation treated with cetuximab + irinotecan. Jpn J Clin Oncol, 42:1146-1151, 2012
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5. Magolan J, Adams NBP, Onozuka H, Hungerford NL, Esumi H, Coster MJ. Synthesis and evaluation of anticancer natural product analogues based on angelmarin: targeting the tolerance towards nutrient deprivation. ChemMedChem, 7:766-770, 2012
6. Inazuka F, Sugiyama N, Tomita M, Abe T, Shioi G, Esumi H. Muscle-specific knock-out of NUAK family SNF1-like kinase 1 (NUAK1) prevents high fat diet-induced glucose intolerance. J Biol Chem, 287:16379-16389, 2012
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# Section of Translational Medicine and Development

**Takeharu Yamanaka, Izumi Miki, Yuko Kineri, Rika Kojima**

## Introduction

Established in April 2012, our Section provides a multifaceted support to accelerate the development of translational research. The emerging field of "personalized medicine" holds great promise in the fight against cancer but achieving this goal will require massive amounts of genomic and clinical data and a sophisticated infrastructure to manage and analyze the data. Our team has now completed a step in building this infrastructure. Currently, we have established a data repository for the National Cancer Center East (NCCE) genome research as well as a routine biostatistics/bioinformatics support which is available to help the planning and design stages of a variety of projects.

Another upfront requirement toward personalized medicine includes the arrangement of environment for developing companion diagnostic genetic tests. With such devices, physicians can modify regimens to reflect pharmacogenetic differences among patients. We are tackling problems which are associated with the "E" part in the well-known ACCE criteria for evaluating a genetic test (Analytic validity, Clinical validity, Clinical utility, and associated Ethical, legal and social implications; See www.cdc.gov/genomics/gtesting/ACCE/). Especially with regard to handling the "legal" aspect, our section now takes the role in the office of technology licensing which catalyzes commercial and non-commercial applications of the NCC's innovations through stewardship of the intellectual property.

## Routine activities

Translational Research Center
- data management for genomic data from clinical studies
- comprehensive support for biostatistics/bioinformatics aspects

Design and Analysis of Clinical Trials
- biostatisticians support the design and analysis aspects of clinical trials, especially with biomarkers. Several international or nationwide phase III trials are currently under support.

Center for Collaborative Research
- office of technology licensing for strategic management of the intellectual property of NCCE
- platform for linking up NCCE with industrial partners regionally and internationally.

Regulatory Affairs
- members of several expert panels for regulatory affairs led by PMDA and MHLW

Office of Communications and Public Relations
- best source for up-to-date and accurate information about the NCCE Research Center for Innovative Oncology

## List of papers published in 2012
## Journal

1. Kuno H, Onaya H, Iwata R, Kobayashi T, Fujii S, Hayashi R, Otani K, Ojiri H, Yamanaka T, Satake M. Evaluation of cartilage invasion by laryngeal and hypopharyngeal squamous cell carcinoma with dual-energy CT. Radiology, 265:488-496, 2012
2. Takeda M, Okamoto I, Yamanaka T, Nakagawa K, Nakanishi Y. Impact of treatment with bevacizumab beyond disease progression: a randomized phase II study of docetaxel with or without bevacizumab after platinum-based chemotherapy plus bevacizumab in patients with advanced nonsquamous non-small cell lung cancer (WJOG 5910L). BMC Cancer, 12:327, 2012
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# Clinical Trial Section

**Akihiro Sato, Hiromi Hasegawa, Yoshihiro Aoyagi, Tomohisa Sudo, Kaori Tobayama, Miki Fukutani, Kayo Toyosaki, Noriko Suzuki, Takako Tomisawa, Kayoko Ohsumi, Satoru Ueno, Shogo Nomura, Yasutaka Watanabe, Mie Yamada, Mai Kikuchi, Natsuko Takagi, Hiroko Tahara, Yukie Hayashi, Yasuko Nishikubo, Minako Honda, Harumi Nakazima, Rie Ehara, Kyoko Kaneko, Tomoko Watanabe, Akiko Nakayama, Yukiko Abe, Yumi Nakatani, Miho Takanashi, Kazushi Endo**

## Introduction

Established in 2008, the Clinical Trial Section supports Investigator Initiated Clinical Trials (IITs) Programs at the National Cancer Center Hospital East (NCCH-E) through the Clinical Data / Coordinating Center. Our section consults on development strategy, and supports project management and protocol development. The Section consists of 6 groups (IRB office, CRC for IITs, Research Concierge, Data Management, Clinical Trial Management, and Statistics).

## Routine activities

Data management group
- Data base and CRF form design
- Data management
- Central monitoring
- System administration

Clinical Trial management group
- Project management
- Study management
- Site visit monitoring
- Medical writing

Statistical group
- Study design
- Statistical analysis
- Consultation

CRC Group
- Support IITs that are conducted in NCCH-E

Research Concierge group
- Support for informed consent for genetic research
- Support trans rational research using genome information

IRB Office
- Oversees all IRB activities

## Research activities and clinical trials

CRC Office for IITs
- CRCs, in 2011 supported 48 IITs including a Sponsor Investigator IND trial. A total of 497 patients participated in the IITs.

Data Management, Clinical Trial Management, Statistical Groups
- Seven clinical studies, a medical device and a new anticancer drug study, and first-in- man phase 0 study, are active as of 2011
- Started the consultation for statistics design and analysis for IITs by our biostatistician

Research Concierge Group
- RCs supported about 3,000 informed consents in 2011

We focused research activities on clinical trial methodology. We are developing a new EDC system, sampling source document verification (SDV) method and comprehensive information sharing infrastructure for early clinical trials.

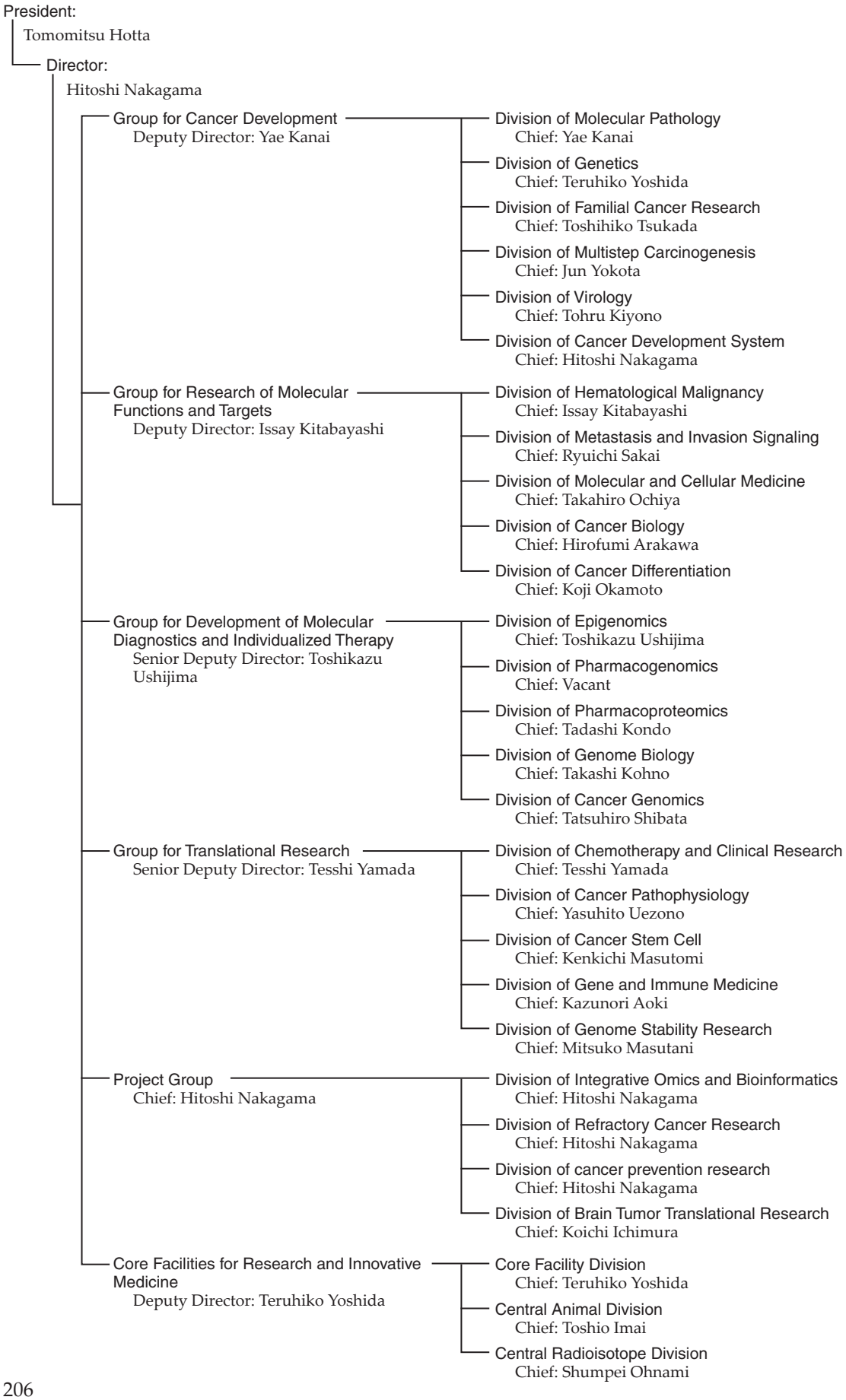
# Research Institute

# 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 more than 50 years. The NCCRI is now internationally recognized for its 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 Hospitals to further encourage and facilitate the development of translational-type studies in our Institute. The NCCRI currently has approximately 90 research staff, around 90 postdoctoral fellows, and more than 180 supporting staff. Foreign scientists and research fellows are also welcomed on a regular basis. The "Annual Report 2012" 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.

## Multilayer-omics analysis during multistage carcinogenesis

To clarify the significance of DNA methylation alterations during carcinogenesis, a methylome analysis using a single CpG resolution Infinium array was performed. Non-cancerous renal tissue samples obtained from patients with renal cell carcinomas were already at precancerous stages associated with the accumulation of DNA methylation alterations. An unsupervised hierarchical clustering analysis based on DNA methylation levels at the CpG sites, where DNA methylation alterations had occurred in precancerous stages and were inherited by and strengthened in tumorous tissue samples, identified CpG islands methylator phenotype (CIMP)-positive renal cell carcinomas (1). Clinicopathologically aggressive tumors accumulated in the CIMP-positive cluster which was characterized by the accumulation of DNA hypermethylation on CpG islands. The cancer-free and overall survival rates of patients with CIMP-positive renal cell carcinomas were significantly lower than those of patients with CIMP-negative renal cell carcinomas. DNA hypermethylation of the *FAM150A*, *GRM6*, *ZNF540*, *ZFP42*, *ZNF154*, *RIMS4*, *PCDHAC1*, *KHDRBS2*, *ASCL2*, *KCNQ1*, *PRAC*, *WNT3A*, *TRH*, *FAM78A*, *ZNF671*, *SLC13A5* and *NKX6-2* genes became hallmarks of CIMP in renal cell carcinomas (1). We have applied for patents regarding prognostication using CIMP-marker genes and are now attempting to make such prognostication techniques clinically applicable. We are now performing whole-exome, transcriptome, proteome analyses to identify molecular targets in CIMP-positive and -negative patients with renal cell carcinomas.

Whole-exome analysis of renal cell carcinomas identified frequent somatic non-synonymous mutations of *GCN1L1*, *MED12* and *CCNC*, which are members of the *CDK8* mediator complex directly regulating β-catenin-driven transcription. Mutations of *MACF1*, which functions in the Wnt/β-catenin signaling pathway, were also identified in renal cell carcinomas. A combination of methylome and transcriptome analyses further highlighted the significant role of the Wnt/β-catenin signaling pathway in renal carcinogenesis. Genetic aberrations and reduced expression of *ERC2* and *ABCA13* were frequent in renal cell carcinomas, and *MTOR* mutations were identified as one of the major disrupters of cell signaling during renal carcinogenesis. Our results confirm that a multilayer-omics analysis can be a powerful tool for revealing pathways that play a significant role in carcinogenesis.

The Infinium assay revealed that non-cancerous lung tissue obtained from patients with lung adenocarcinomas was at precancerous stages with DNA methylation alterations. The DNA methylation status of specific genes at precancerous stages significantly correlated with recurrence after establishment of lung adenocarcinomas. DNA hypermethylation of such recurrence-related genes, *ADCY5*, *EVX1*, *GFRA1*, *PDE9A* and *TBX20* genes, resulted in reduced mRNA expression in tumorous tissue samples. 5-Aza-2′-deoxycytidine treatment of lung cancer cell lines restored the mRNA expression levels of these genes. Reduced mRNA expression in tumorous tissue samples of these genes significantly correlated with tumor aggressiveness. DNA methylation alterations at precancerous stages can therefore determine tumor aggressiveness and outcome through silencing of specific genes (20).

## Activiries in the international human epigenome consortium (IHEC)

The IHEC has been established by researchers and founding agencies from Canada, South Korea, the EU, Italy, Germany, Japan and the USA to comprehensively characterize the standard epigenome profiles of multiple normal cell lineages from different human populations (http://www.ihec-epigenomes.org/). We are now one of several Japanese member teams of the IHEC supported by the Core Research for Evolutional Science and Technology (CREST) division of the Japan Science and Technology (JST) Agency. We are now performing whole-genome bisulfite sequencing using the post-bisulfite adaptor-tagging method,

chromatin immunoprecipitation sequencing and RNA sequencing of purified target cells, i.e. hepatocytes, oval cells and Kupffer cells from the liver, foveolar epithelial cells, mucosal neck cells and fundic gland mucosal cells from the stomach, and foveolar epithelial cells from both the ascending and descending colon. Accurate epigenome profiling of normal cells will allow the identification of disease-specific epigenome profiles, thus facilitating a potential breakthrough in the prevention, diagnosis and therapy of diseases.

### Antitumor immune responses

The host immune reaction is one of the leading players in the tumor microenvironment that is characterized by anti-tumor and pro-tumor. Tumor-infiltrating M2 macrophages, neutrophils, or the prevalence of Tregs were independent prognosticators of a worse outcome in patients with pancreatic cancers, whereas $CD4^+$ T cells, $CD8^+$ T cells, or the prevalence of $HLA\text{-}DR^+CD68^+$ M1 macrophages were independent prognosticators. We then connected the apparently related factors, and two variables emerged: tumor-infiltrating $CD4^+T^{high}$/ $CD8^+T^{high}$/$\%Treg^{low}$ and tumor-infiltrating $\%M1^{high}$/ $M2^{low}$. These are independent prognosticators useful for evaluating the immune microenvironment of pancreas cancer.

### Role of β-catenin in hepatocarcinogenesis

*CTNNB1*, encoding β-catenin, is one of the most frequently mutated oncogenes in hepatocellular carcinomas. However, it remains unclear how active β-catenin signaling confers growth advantage to hepatocytes during tumorigenesis. Our previous analyses identified several genes induced by active β-catenin signaling in hepatocellular carcinomas. To clarify the functional significance of these β-catenin-regulated genes *in vivo*, we have introduced a transposon-based model of hepatocarcinogenesis. Now, we are analyzing the roles of hepatocellular carcinoma-related genes, including those regulated by β-catenin, as well as their functional interactions in the development of hepatocellular carcinomas.

### Clinicopathological studies

From surgically resected materials of biliary tract cancers, the establishment of cancer cell lines and mouse xenograft models is routinely performed. Using originally-established cell lines and xenograft models, the efficacy of newly developed anti-cancer drugs was examined *in vitro* and *in vivo* (2). Based on such preclinical data, clinical trials of the examined drugs have recently been launched.

Widely scattered nuclear 'dot-like' focal immunoreactivity for DNA methyltransferase (DNMT) 3B in testicular seminomas reflects the potential for differentiation to embryonal carcinomas and other non-seminomatous testicular germ cell tumors: patients with stage I seminomas showing focal DNMT3B expression are at increased high risk of relapse, and should be subject to careful surveillance (3). The existence of arginase II -expressing cancer-associated fibroblasts is an indicator of a poor prognosis, as well as hypoxia, in pancreatic ductal carcinoma tissue. The histopathological examination of consecutive patients with pancreatic ductal carcinomas revealed that pancreatic intraglandular metastasis predicts a poorer outcome in postoperative patients. The presence of activating *GNAS* mutations is a characteristic genetic feature of colorectal villous adenoma (4) and pyloric gland adenomas of the stomach and duodenum. Multivariate analyses identified the independent risk factors for lymphatic and venous involvement, such as a larger tumor size, deeper invasion, and the presence of an undifferentiated-type adenocarcinoma component, in endoscopically resected gastric cancers. Other clinicopathological studies were also conducted to further the understanding of the pathogenesis and promote the diagnosis and treatment of various tumors (5-9).

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# Division of Genetics

**Teruhiko Yoshida, Hiromi Sakamoto, Fumiaki Koizumi, Hiroki Sasaki, Hitoshi Ichikawa, Norihisa Saeki, Kazuhiko Aoyagi, Yasuo Kodera, Kazuyoshi Yanagihara, Takao Nishimura, Takeshi Sawada, Jun Hashimoto, Shinji Nakamichi, Sumiko Ohnami, Mineko Ushiama, Yoko Odaka, Misuzu Okuyama, Rie Komatsuzaki, Fumiko Chiwaki, Sachiyo Mitani, Akiko Takahashi, Masumi Shimizu, Mika Shioya, Sayaka Mito, Mayumi Akitaya, Yuka Kitamura, Yukiko Ito, Rumi Koyama, Hiroo Takahashi, Aya Kuchiba, Takayuki Sasaki, Akio Ashida, Hiroe Sakuyama, Nozomi Nakata, Masashi Tamaoki**

## Introduction

In 2012, the three major research areas of the Division of Genetics were 1) molecular understanding of cancer susceptibility; 2) transcriptome analyses of cancers and leukemia; and 3) development of personalized cancer diagnosis and treatment. We have also maintained our participation in the biobanking project of the Tsukiji campus of NCC, particularly for the peripheral blood samples.

## Genetic susceptibility to cancers

We continued an investigation of prostate stem cell antigen (*PSCA*), a gene related to susceptibility to diffuse-type gastric cancer, which was identified by our previous genome-wide association study (GWAS). *PSCA* is overexpressed in many types of cancers such as prostate cancer, in which the gene has been considered to have a cancer-promoting function. However, we found that *PSCA* is down-regulated in gastric cancer and has a cell-proliferation inhibition activity in a gastric cancer cell line, suggesting its role in tumor suppression at least in the case of gastric carcinogenesis. We investigated the PSCA expression status in several cancers and found that PSCA is also down-regulated in gallbladder cancer, and functional analyses revealed a cell-proliferation inhibition activity in gallbladder cancer-derived cell lines (3). These findings indicate the *PSCA* could have a tumor-suppressive function depending on the context of the cancer type. We also reported *PSCA* expression in the islet of the normal human pancreas (4).

Clinical genetic testing on hereditary cancer syndromes has been continued as a long-standing collaborative effort with the Genetic Counseling Division of the National Cancer Center Hospital to support its genetic diagnosis.

## Transcriptome analyses of cancers and leukemia

The Division has been involved in the NiBio Integrated Disease Omics Project, which is a multi-center collaborative work to identify the therapeutic molecular targets for 11 major diseases including adult solid tumors through multi-layered omics analyses. We have provided genome and transcriptome analysis core activities. This year, through an RNA sequencing analysis of 30 lung adenocarcinomas, a *KIF5B-RET* fusion gene was identified as a novel therapeutic target in a collaborative work with the researchers in the Division of Genome Biology and the National Center for Global Health and Medicine. Other collaborative research included a gene expression profiling analysis of leukemic and normal hematopoietic cells to understand the molecular pathways leading to leukemia and to develop their clinical applications (17, 18).

## Development of personalized diagnosis and treatment for cancer

Five major research projects are underway in this category: First, we developed and validated mini DNA chips containing 6 marker (9) and 3 control genes for predicting gastric cancer recurrence from peritoneal washing samples with 189 first cohort and 250 second cohort samples. We have also established peritoneal metastasis model mice and 41 new gastric cancer cell lines, and identified the biological features of peritoneal metastasis-associated gastric CSCs. Second, we successfully identified 4 intrinsic subtypes (B, C1, D, F3) of ESCCs through the gene expression-based unsupervised clustering of four independent sets of 85, 72, 40, and 77 biopsy samples. The subtype D included merely 20-25% 5-year survivors treated with definitive CRT but subtype B contained 65-70%, which was clearly higher than the cases treated with neoadjuvant chemotherapy (55%, JCOG9907).

In both types, the main transcriptional pathways were identified. The third project is on everolimus, an oral mTOR inhibitor, which effectively inhibited cell growth at concentrations under 100 nM ($IC_{50}$) in five of nine triple-negative breast cancer (TNBC) cell lines. All five sensitive cell lines were categorized as a basal-like subtype positive for either epidermal growth factor receptor (EGFR) or CK5/6, whereas the resistant cell lines were not of this subtype. *In vivo* assays demonstrated antitumor activity in a mouse xenograft model of basal-like breast cancer but not in the non-basal breast cancer. These results suggested that everolimus had a preferential activity against the basal-like subtypes of TNBCs (5). The forth project is the development of a novel flow-cytometry-based detection and sorting system, On-Chip Sort, for circulating tumor cells (CTCs) independent of EpCAM expression of tumor cells. The spiked tumor cells count was linear over a range of 10 to 1000 cells, with a recovery rate of ≥ 90%. A significantly higher recovery rate was observed with our system (90 - 102%) than CellSearch (0%) when EpCAM-negative PC-14 cells were spiked, suggesting the superior sensitivity of our system especially in capturing the EpCAM-negative tumor cells. The fifth project has focused on the large difference in the clinical outcomes among patients with the HER2-positive type of breast cancer, which remains a key issue for trastuzumab treatment. We demonstrated that the inter-individual differences in the trastuzumab-mediated ADCC activities of the PBMC were consistent and reproducible. An *ex vivo* gene expression analysis has been developed to measure changes in the mRNA expression quantitatively after exposure to IgG. Using this technology, we found that the increased expressions of TNFSF15, IL6 and CXCL3 were significantly correlated with the ADCC activity. The association was apparently replicated in a prospective evaluation of the patients who were receiving trastuzumab-based neoadjuvant chemotherapy.

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### Journal


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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. A new diagnostic DNA test for multiple endocrine neoplasia type 1 (MEN1) was evaluated for clinical usefulness. Drug resistance of prolactinoma and pharmacological actions of rikkunshito, a traditional Japanese herbal medicine, were also investigated.

## Research activities

DNA diagnosis of MEN1

MEN1 is a familial cancer syndrome characterized by the multiple occurrences of endocrine tumors in the pituitary, parathyroid, and enteropancreatic endocrine tissues. MEN1 is caused by heterozygous germline mutations of the causative gene *MEN1*, which encodes a tumor suppressor protein named menin. Because the optimal therapies for MEN1-associated tumors, especially for multicentric parathyroid and pancreatic tumors, are different from those for sporadic, non-hereditary endocrine tumors, accurate differential diagnoses are mandatory before planning treatment. Germline mutation analysis of the *MEN1* gene 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 found that mutant menin proteins associated with MEN1 were unstable and were rapidly degraded by the ubiquitin-proteasome pathway. A diagnostic test for predicting the prognosis of missense *MEN1* mutant gene carriers has been developed by exploiting this reduced stability. This method was evaluated for its clinical usefulness in collaboration with many hospitals in Japan. A previously unreported single nucleotide alteration in the *MEN1* gene, initially thought to be a missense variant, was shown to be a splicing mutation (1). Another missense menin variant identified in a patient suspected of harboring the MEN1 syndrome was determined as a causative mutation based on the reduction of mutant menin stability. This finding encouraged us to conduct the presymptomatic genetic test for this mutation among the patient's family members, which led to the identification of asymptomatic mutation carriers. Thus, the menin stability test was proven useful for genetic diagnosis and counseling of MEN1 patients (2).

Drug resistance of prolactinoma

Dopamine (DA) agonists are used in the first-line treatment of prolactinoma, and normalize prolactin levels and reduce tumor size in most of the cases. However, some prolactinomas are resistant to DA agonists from the beginning of the treatment and need to be treated surgically. A few prolactinomas initially respond to DA agonists but become resistant after prolonged treatment with DA. Although the reduction of the dopamine D2 receptor (DRD2) expression in tumor cells may explain the resistance, the exact mechanism is not fully understood. 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 mRNA levels were lower in the resistant tumors than in sensitive tumors. The DNA methylation patterns in the *DRD2* gene promoter region were not different between sensitive and resistant tumors. Thus, resistance of prolactinoma to dopamine agonists is correlated with a reduction in D2L expression levels. Silencing of the *DRD2* gene by methylation in the promoter region is unlikely to play a role in dopamine agonist resistance in prolactinoma (3).

Effects of rikkunshito on endocrine cells

Rikkunshito is widely used to treat appetite loss associated with various disorders, and may be a useful regimen for cancer cachexia. In order to examine possible effects of rikkunshito on hormone production in endocrine cells, we measured intracellular cAMP, which is a major regulator of biosynthesis and release of several hormones. Growth hormone-producing pituitary cell GH3, ACTH-producing pituitary cell AtT-20 and catecholamine-producing adrenal chromaffin cell PC12 were treated with rikkunshito with or without forskolin, a direct adenylate cyclase activator. Intracellular cAMP levels increased in all these cell

lines following the treatment with rikkunshito and/or forskolin in a dose-dependent manner. The amounts of catecholamines released from PC12 cells increased after treatment with rikkunshito. The mRNA of tyrosine hydroxylase, the rate-limiting enzyme of catecholamine biosynthesis, also increased. These findings suggest that rikkunshito acts directly on endocrine cells and enhances the biosynthesis and secretion of several hormones.

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### Journal


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# Division of Multistep Carcinogenesis

**Jun Yokota, Naoto Tsuchiya, Reika Iwakawa-Kawabata, Hiroko Ogata-Kawata, Mariko Sasaki, Yuko Fujiwara, Masataka Takenaka, Daisuke Kurioka, Yusuke Kimura, Momoyo Nishida, Tomoyo Kobayashi, Yoshiaki Onozato**

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. For this reason, molecular genetic studies on lung cancer have been performed over the long term in the Division of Multistep Carcinogenesis. In 2012, the following results were obtained.

Activation of the EGFR, KRAS, and ALK oncogenes is known to define 3 different pathways of molecular pathogenesis in lung adenocarcinoma (LADC). However, many tumors lack activation of any pathway (triple-negative LDACs) thereby posing a challenge for prognosis and treatment. We reported on an extensive genome-wide expression profiling of 226 primary human stage I–II LADCs which elucidated the molecular characteristics of tumors that harbor ALK mutations or that lack EGFR, KRAS, and ALK mutations, that is, triple-negative LADCs. One hundred and seventy-four genes were selected as being upregulated specifically in 79 LADCs without EGFR and KRAS mutations. Unsupervised clustering using a 174-gene signature, including ALK itself, classified these 2 groups of tumors into ALK-positive cases and 2 distinct groups of triple-negative cases (groups A and B). Notably, group A triple-negative cases had a worse prognosis for relapse and death, compared with cases with EGFR, KRAS, or ALK mutations or group B triple-negative cases. In ALK-positive tumors, 30 genes, including ALK and GRIN2A, were commonly overexpressed, whereas in group A triple-negative cases, 9 genes were commonly overexpressed, including a candidate diagnostic/therapeutic target DEPDC1, that were determined to be critical for predicting a worse prognosis. Our findings are important because they provide a molecular basis of ALK-positive LADCs and triple-negative LADCs and further stratify more or less aggressive subgroups of triple-negative LADCs, possibly helping identify patients who may gain the most benefit from adjuvant chemotherapy after surgical resection.

Homozygous germline mutations of the PARK2 gene are responsible for the development of early-onset Parkinson's disease (PD). Homozygous PARK2 mutations have been also detected in LADCs. However, since heterozygous PARK2 germline mutations are present in a subset of non-PD individuals, the timing for the occurrence of two-hit PARK2 mutations in LADC progression is unclear. Therefore, we comprehensively analyzed mutations, expression and copy number variations of the PARK2 gene in 267 primary LADCs together with the corresponding noncancerous lung cells and 39 LADC cell lines. Heterozygous germline exonic deletions were detected in five patients with LADC, and loss of heterozygosity including the PARK2 locus was detected in 31/267 (11.6%) LADCs. However, homozygous PARK2 inactivation was not detected in any of them, including the five patients with germline mutations. Homozygous PARK2 inactivation was detected in 6/39 (15%) cell lines, two exonic deletions, one exonic duplication, and three point mutations, while heterozygous PARK2 inactivation was detected in two cell lines (both by exonic deletions). These results strongly indicate that somatic PARK2 mutations occur rarely (or do not occur) in LADC development and that germline PARK2 mutations could contribute to LADC progression but not to LADC development.

In collaboration with a research group in the Miyazaki University, the following results were also obtained. The development of oral squamous cell carcinoma (OSCC) is a multistep process that requires the accumulation of genetic alterations. To identify the genes responsible for OSCC development, we performed high-density single nucleotide polymorphism array analysis and genome-wide gene expression profiling on OSCC tumors. These analyses indicated that the absent in melanoma 2 (AIM2) gene and the interferon-inducible gene 16 (IFI16) mapped to the amplified region of chromosome 1q23 are overexpressed in OSCC. Both AIM2 and IFI16 are cytoplasmic double-stranded DNA sensors for innate immunity and act as tumor suppressors in several human cancers. Knockdown of AIM2 or IFI16 in OSCC cells resulted in the suppression of cell growth and apoptosis, accompanied by the downregulation of the nuclear factor kappa-light-chain-enhancer of activated B cells activity. Because all OSCC cell lines have reduced p53 activity, wild-type p53 was introduced in p53-deficient OSCC cells. The expression of wild-type p53 suppressed cell growth and induced apoptosis via suppression of the nuclear factor kappa-light-chain-enhancer of

activated B cells activity. Finally, the co-expression of AIM2 and IFI16 significantly enhanced cell growth in p53-deficient cells; in contrast, the expression of AIM2 and/or IFI16 in cells bearing wild-type p53 suppressed cell growth. Moreover, AIM2 and IFI16 synergistically enhanced nuclear factor kappa-light-chain-enhancer of activated B cells signaling in p53-deficient cells. Thus, expression of AIM2 and IFI16 may have oncogenic activities in the OSCC cells that have inactivated the p53 system.

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# Division of Virology

**Tohru Kiyono, Takashi Yugawa, Nagayasu Egawa, Tomomi Nakahara, Kenji Yamada, Satomi Kikawa, Shinichi Ohno, Takako Ishiyama, Katsuyuki Tanaka**

## Introduction

Approximately 15% of human cancers have a viral etiology, and seven viruses have been elucidated as being associated with human cancers. Among these recognized viruses, research in the Division of 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). The E6 and E7 proteins of HR-HPVs are known to inactivate the major tumour suppressors, p53 and retinoblastoma protein (pRB), respectively. By using an *in vitro* multistep carcinogenesis model for cervical cancer, we are elucidating the roles of E6, E7 and cellular oncogenes in multistep carcinogenesis (Figure 1).

## A critical role of MYC in cervical carcinogenesis

Recently, we have demonstrated that transduction of oncogenic HRAS, $HRAS^{G12V}$, and MYC together with HPV16 E6E7 was sufficient for tumorigenic transformation of normal human cervical keratinocytes (HCKs) (Narisawa-Saito et al., Cancer Research, 2008). Then we showed that transduction of $HRAS^{G12V}$ against the background of E6E7 expression caused accumulation of MYC protein and tumorigenic transformation of not only normal HCKs but also other normal primary human cells, including tongue keratinocytes and bronchial epithelial cells as well as hTERT-immortalized foreskin fibroblasts (1). Subcutaneous transplantation of as few as 200 HCKs expressing E6E7 and $HRAS^{G12V}$ resulted in tumor formation within 2 months. Dissecting RAS signaling pathways, constitutively active forms of AKT1 or MEK1 did not result in tumor formation with E6E7, but tumorigenic transformation was induced with the addition of MYC. Increased MYC expression endowed resistance to calcium- and serum-induced terminal differentiation and activated the mammalian target of rapamycin (mTOR) pathway. An mTOR inhibitor, Rapamycin, and MYC inhibition at a level not affecting proliferation in culture both markedly suppressed tumor formation by HCKs expressing E6E7 and $HRAS^{G12V}$. These results suggested that a single mutation of HRAS could be oncogenic in the background of the deregulated expression of E6E7, and MYC plays a critical role in cooperation with the RAS signaling pathways in tumorigenesis. Thus inhibition of MYC and/or the downstream mTOR pathway could be a therapeutic strategy not only for the MYC-altered but also RAS-activated cancers.

## HPV16 maintenance replication without E1 helicase

Papillomavirus genomes are thought to be amplified to about 100 copies per cell soon after infection, maintained constant at this level in basal cells, and amplified for viral production upon keratinocyte differentiation. Viral helicase E1 has been thought to be essential for the viral replication. By using human cervical keratinocytes harboring wild-type and an E1-deficient HPV16 genome, we demonstrate that the E1 protein is dispensable for maintenance replication but not for initial and productive replication of HPV16. Deregulated expression of E6 and E7 genes of "high risk" human papillomaviruses (HPVs) in the basal cells of stratified epithelia is a key step for malignancy, and is often caused by accidental integration of the viral genome. The E1 helicase is the only enzyme encoded by HPV and thought to be a good molecular target of anti-HPV drugs. However, our results imply that the rationale for development of E1 inhibitors as anti-HPV drugs may be more restricted than formerly envisaged (2). In collaboration with dermatologists, a novel type of HPV, HPV126, was isolated from skin warts (3).

## Immortalization of normal and precancerous human cells

We have immortalized various types of normal and precancerous human cells. Among them, ovarian endometrioma cells were immortalized to analyze carcinogenesis of endometrial carcinoma (4). Immortalized skin fibroblasts from Cornelia de Lange syndrome patients were used for analyzing the abnormal cohesion acetylation cycle by HDAC8

mutations (5). From normal human tissues, corneal endothelial cells and nonluteinized granulosa cells have been newly immortalized (6, 7). Several immortalized human epithelial cells were also used for analyzing novel functions of trichoplein and CHK1 (8, 9).

### A role of actin -related protein 4 in the BRG1 chromatin remodeling complex.

We found that ARP4 can form a heterocomplex with β-actin. Some mutant ARP4 which showed reduced binding to β-actin also showed reduced incorporation into BRG1 complexes. They also showed impaired interaction with Myc-associated complexes as well as TIP60 HAT complexes. Based on these findings, we proposed that β-actin-ARP4 complex formation might be a crucial feature in some chromatin-modifying enzyme complexes, such as the BRG1 complex (10).

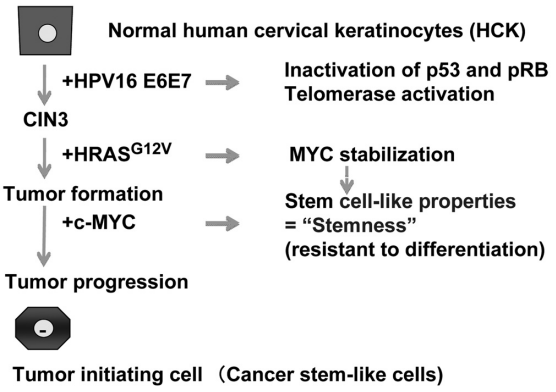


**Figure 1. An *in vitro* multistep carcinogenesis model for cervical cancer**

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# Division of Cancer Development System

**Koji Okamoto, Yoshitaka Hippou, Yukari Totsuka, Daisuke Shiokawa, Masako Ochiai, Hirokazu Ohata, Tatsuya Ishiguro, Kousuke Ishino, Masanori Gotoh, Yuki Aihara, Akihiro Sekine, Aya Sakaizawa, Aya Ohno, Emi Fukai, Waka Kato, Sachiko Dobashi, Ai Sato, Hiroaki Sakai, Emiko Yamamoto, Mayumi Mizuta, Yumi Miyamoto, Hisako Okuda**

## Introduction

Recent research in many laboratories has revealed the importance of cancer stem cells during the development of refractory cancer with a highly metastatic potential. In our Division, we focus on studying the dynamic regulation of stem cell-related characteristics during cancer development. The main goals of our research center around elucidation of the biological properties of cancer stem cells, and understanding the mechanisms as to how such cells develop from normal tissues. We take several experimental approaches to address these issues.

## Routine activities

A weekly conference is held with members of the Division of Cancer Development System.

## Research activities

*In vitro* cultivation and characterization of cancer stem cells from human colon and ovarian cancer

Accumulating reports indicate that "cancer stem cells" exist in various types of cancer, and that 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. We found that inhibition of Rho kinase 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 expressed various levels of CD44, and that $CD44^{high}$ cells exhibited characteristics associated with cancer stem 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 we hypothesize a model in which the transition from the $CD44^{-/low}$ to $CD44^{high}$ state enhances tumorigenicity by maintaining a $CD44^{high}$ fraction in colon cancer.

We also found that inhibition of Rho kinase also promoted the establishment of spheroids from primary ovarian cancer. Biochemical and biological evaluation of the established spheroid cells is in progress.

Functional identification and characterization of regulatory factors of cancer metastasis

We developed an experimental model in which liver metastasis of colon cancer was generated with high efficiency in highly immunocompromised NOG mice. This metastasis model was used to functionally isolate regulatory factors involved in the metastasis to the liver of colon cancer cells. First we looked for miRNAs that could inhibit liver metastasis of colon cancer cells by applying a systematic screening approach (dropout screening). Through the dropout screening of a miRNA library after the introduction of HCT116 colon cancer cells, miR-493 was isolated that reproducibly inhibited metastasis of colon cancer cells to the liver. Subsequently 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, our data indicated that, in a subset of colon cancer, up-regulation of miR-493 during carcinogenesis may prevent liver metastasis via the induction of cell death of the metastasized cells.

We also 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 for miRNA. Screening of the shRNA library identified several candidate genes, and individual evaluation of these genes is in progress.

Establishment of *in vitro* model of the early steps of colon carcinogenesis

We established an *in vitro* model of colon epithelium based on a recent report (Sato et al,

Nature 2009). These experiments resulted in the formation of a caricature of the colon / intestine epithelium or "organoid" *in vitro* in the presence of defined growth factors. Such organoids will develop from normal epithelium as well as from mouse colon cancerous tissue, and could be used to examine the dynamic alteration of the colon epithelium during early colon carcinogenesis. In addition, we showed that xenograft tumors could be generated from the organoids after lentivirus-mediated knockdown of APC and p53 in the presence of oncogenic K-ras, potentially establishing a novel model for CRC *in vitro*. Similar approaches will be taken to study human colon carcinogenesis using surgery specimens.

Identification of Novel Mutagens/Carcinogens

Nanomaterials are useful for their characteristic properties, and are commonly used in various fields. The assessment of the genotoxicity and safety of nanomaterials is therefore of serious concern. So far, we have examined the genotoxic effects of multi-walled carbon nanotubes (MWCNTs) using *in vitro* micronuclei, sister chromatid exchange, *in vivo* DNA damage and mutation assays. Overall, MWCNTs were shown to be genotoxic both in *in vitro* and *in vivo*; the mechanisms probably involve oxidative stress and inflammatory responses. Reports related to other environmental mutagens/carcinogens can be found in the attached list of references.

## List of papers published in 2012
### Journal


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# Division of Hematological Malignancy

**Kitabayashi, Kazutsune Yamagata, Takuo Katsumoto, Yutaka Shima, Yoko Ogawara, Emi Takamatsu, Yukiko Aikawa, Mika Shino, Akiko Kittaka, Ryusuke Yamauchi, Miu Adachi, Mariko Saito**

## Introduction

AML is the most common leukemia in Japan and the U.S. With current standard chemotherapy, approximately 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. However, many of the AML patients relapse and only 25-30% of young adults and fewer than 10% of older patients survive longer than 5 years, suggesting the presence of chemotherapy-resistant AML stem cells. Thus, AML stem cell eradication is thought to be crucial to offer a complete cure for AML. Chromosome abnormalities, which result in the generation of specific fusion genes, are observed in ~50% of AML patients. Cases with AML who are associated with fusion genes involving *MLL, MOZ, CALM* or *NUP98* have an extremely poor outcome. Normal cytogenetics portend average-risk AML. Recent genome analysis has revealed that mutations in NPM, IDH1/IDH2/TET2, DNMT3a and FLT3 genes are often simultaneously observed in patients with normal cytogenetics. The purpose of our research was to establish new therapeutic methods by identifying the molecular targets that are essential for the maintenance of AML cells, especially AML stem cells.

## Research activities

To investigate the molecular mechanism of AML, we established mice models. AML models with fusion genes, MOZ-TIF2, MLL-AF10, NUP98-HOXA9 or CALM-AF10, were generated by introducing the respective genes to bone marrow cells. We have found that the expression of M-CSFR was specifically high in stem cells of mice AML models and human AML patients. Using transgenic mice expressing a drug-inducible suicide gene controlled by the M-CSFR promoter, we demonstrated that AML was cured by eradication of M-CSFR-high cells. Administration of an mM-CSFR-specific ADCC-antibody reduced the numbers of leukemia cells and slowed the progression of AML in the mouse model. To develop antibody medicine, we obtained hM-CSFR-specific antibodies in collaboration with the RIKEN institute (adopted by the Program for Dug Discovery and Medical Technology Platforms).

We found that the expression of M-CSFR, HOXA9 and c-KIT was high in AML stem cells, and that MOZ- and MLL-fusions induced the expression of m-csfr, c-kit and hoxa9 by interacting with PU.1, c-MYB and BRPF1, respectively. Analysis using mice deficient for these factors demonstrated that PU.1, c-MYB, BRPF1 and M-CSFR were essential for MOZ-TIF2 to induce and maintain AML. These results indicated that the PU.1/M-CSFR, c-MYB/cKIT and BRPF1/HOX pathways were critical for maintenance of AML stem cells. A dual kinase inhibitor for M-CSFR and cKIT (PLX3397) slowed the progression of AML in mice.

While AML1/RUNX1 is a frequent target of chromosome translocations and mutations in myeloid and B-cell leukemias, upregulation of AML1 is observed in some cases of T-cell leukemias and lymphomas. We showed that the incidence of thymic lymphoma in p53-null mice is less frequent in an *Aml1*$^{+/-}$ than in an *Aml1*$^{+/+}$ background. AML1 is upregulated in p53-null mouse bone marrow cells and embryonic fibroblasts. p53 binds to and inhibits the distal *AML1* promoter in the steady state. When the cells are exposed to stressors, *AML1* is induced. Overexpression of AML1 stimulates T-lymphocyte proliferation. These results suggest that the upregulation of AML1 induced by the loss of p53 promotes lymphoid cell proliferation, thereby inducing lymphoma development.

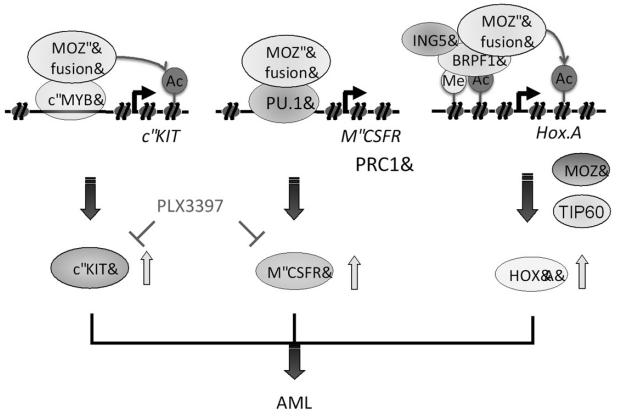


**Figure 1**

# Division of Metastasis and Invasion Signaling

**Ryuichi Sakai, Hideki Yamaguchi, Hitoyasu Futami, Takamasa Uekita, Takuya Shirakihara**

## Introduction

The malignant characteristics of cancers causing the invasion into surrounding tissue and metastasis to distant organs are serious threats to the clinical treatment of cancer. Interaction of cancer cells with neighboring cells such as cancer associated fibroblasts (CAFs) has recently been shown to have critical roles in this procedure. It is also 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 signaling molecules during cancer metastasis and invasion. One of the goals of our research is to establish models of the novel therapy of progressed cancer by regulating phosphotyrosine-dependent signals in cancer cells and their microenvironments.

## Models of cancer invasion and metastasis

Scirrhous gastric carcinoma (SGC) has the worst prognosis among the various types of gastric cancer, owing to its rapid expansion through progressive invasion, peritoneal dissemination and frequent metastasis to lymph nodes. Because massive proliferation of stromal fibroblasts occurs within SGC lesions, CAFs have been proposed to support the progression of SGC. However, the biological and molecular basis of the interaction between SGC cells and CAFs remains largely unknown. We investigated the role of CAFs in invasion and extracellular matrix (ECM) remodeling by SGC cells. When SGC cells were cocultured with CAFs on three-dimensional (3D) Matrigel, they were attracted together to form large cellular aggregates that invaded the Matrigel. Time-lapse imaging of SGC and CAFs along with fluorescent microspheres embedded in the Matrigel revealed that this process was associated with extensive contraction and remodeling of the ECM. Phosphorylation of the myosin light chain significantly increased in CAFs when they were cocultured with SGC cells and blebbistatin, a myosin II inhibitor, blocked the 3D invasion and ECM remodeling by SGC cells and CAFs. These results indicated that SGC cells promote the actomyosin-mediated contractility of CAFs to remodel ECM during invasion.

CDCP1 (CUB-domain-containing protein 1) is a transmembrane protein that regulates anchorage-independent growth and cancer cell migration and invasion. Expression of CDCP1 is detected in a number of cancer cell lines and tissues and is closely correlated with a poor prognosis. Invadopodia are actin-based protrusions on the surface of invasive cancer cells that promote the degradation of the extracellular matrix (ECM) via localized proteolysis, which is mainly mediated by membrane-type 1 matrix metalloproteinase (MT1-MMP). MT1-MMP accumulates in the invadopodia through targeted delivery via membrane trafficking. We have revealed that CDCP1 is required for ECM degradation by invadopodia in human breast cancer and melanoma cells. CDCP1 localized to caveolin-1-containing vesicular structures and lipid rafts and was detected in close proximity to invadopodia. Further biochemical analysis revealed that CDCP1 was an essential regulator of the trafficking and function of MT1-MMP- and invadopodia-mediated invasion of cancer cells.

We demonstrated that CDCP1 was required for the functional link between Ras and Src 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 activation of the Ras pathway. Inhibition of CDCP1 expression using small interfering RNAs (siRNAs) induced cell death of suspended cancer cells without generating cleaved caspase-3, a marker of apoptosis, and the cell death was not inhibited by a general caspase inhibitor, suggesting that the loss of CDCP1 could induce caspase-independent cell death. Instead, the loss of CDCP1 induced LC3-II protein and the formation of autophagosomes. Moreover, the cell death of suspended lung cancer cells induced by the CDCP1 siRNA was reduced by an autophagy inhibitor, 3-Methyladenine. These results indicated that CDCP1 signaling plays a critical role in inhibition of autophagy which contributes to the anoikis resistance of lung cancer cells.

## Oncogenic signals in neuroblastomas

Recently, activation of anaplastic lymphoma kinase (ALK), either by mutation or overexpression, has been indicated as a significant oncogenic factor in neuroblastoma formation. To investigate the role of ALK receptor tyrosine kinase in neuroblastoma oncogenesis, we investigated phosphotyrosine-containing proteins associated with ALK in neuroblastomas using mass-spectrometry analysis. Various types of phosphoproteins were identified as binding partner of ALK in neuroblastoma tumors. Flotillin-1 (FLOT1), a plasma membrane protein known to be involved in endocytosis, was found among those binding partners of ALK. It was suggested that FLOT1 controls the amount of ALK protein at the cell surface through the regulation of receptor endocytosis. Decreased binding affinity of oncogenic ALK mutants to FLOT1 may cause the activation of ALK signaling which leads to the poor prognosis of neuroblastoma cases harboring these mutations. Further studies on the tumor suppressive function of FLOT1 in neuroblastomas are currently in progress.

On the other hand, it was observed that expression of Ret, a receptor tyrosine kinase 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 the activation of Ret kinase by its ligands such as GDNF was shown to contribute anchorage independent growth of neuroblastoma cells, the 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 is being analyzed for evaluation of its clinical significance.

# Division of Molecular and Cellular Medicine

**Takahiro Ochiya, Fumitaka Takeshita, Masaki Kawamata, Nobuyoshi Kosaka, Ryou-U Takahashi, Ayako Inoue, Wakako Kobayashi, Maki Abe, Makiko Ono, Yu Fujita, Takeshi Katsuda, Luc Gailhouste, Muriel Thirion, Satoshi Seino, Hiroaki Miyazaki, Yusuke Yoshioka, Keitaro Hagiwara, Naoomi Tominaga, Keita Uchino, Shingo Ikeda**

## 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 2012 were as follows: 1) Studies on microRNA regulation in cancer cells and development of RNAi-based therapeutics; 2) An exosome-carrying microRNAs as a novel diagnosis and therapeutic tool against cancer; 3) Generation of genetically modified rats from embryonic stem cells for development of novel animal models for cancer research; and 4) Hepatic differentiation of mesenchymal stem cells and its therapeutic application.

### 1) Studies on microRNA Regulation in Cancer Cells and Development of RNAi-based Therapeutics

Since small interfering RNA (siRNA) and microRNA (miRNA) are silencing small RNAs that can modulate tumor-related genes and pathways, siRNA and miRNA are expected to be an attractive new class of anticancer drugs (1, 19). The novel RNAi agents have been developed that are single stranded RNAs with high stability (2).

We previously identified Ribophorin-2 (RPN2) as a novel regulator for drug resistance and maintenance of cancer stem cells (CSCs) in breast cancer. For the clinical application of siRNA targeting RPN2, pre-clinical trials with naturally-occurring breast cancer in dogs have been performed (20). For analysis of CSCs in colon cancer, stable cell lines having CSC properties from colon cancer patients were established (3). In these cell lines, irinotecan could induce the transition from LGR5(+) to LGR5(-) drug-resistant state. These results provide new biological insights into drug resistance of CSCs.

The alteration of methylation in promoter regions coding miRNA is linked to transcriptional change in cancers. The analyses of methylations and expression of miRNAs in the drug resistant cell lines derived from human breast cancer revealed the epigenetic similarities and differences between miRNA and protein-coding genes (4).

We also have focused on the elucidation of regulation for iron homeostasis in cancer. The miR-210 suppresses two molecules for iron homeostasis, transferrin receptor 1 (TfR) and ISCU (5). Our study reveals that miR-210 works as an iron sensor and is involved in the maintenance of iron homeostasis by sustaining the TfR expression to affect the cell proliferation and survival in the hypoxic region within tumors.

The safe dietary intake of natural products could reduce the risk of a wide range of human cancers. We reported that resveratrol promotes the expression and activity of Ago2, thereby inhibiting breast cancer stem-like cell characteristics by increasing the expression of tumour-suppressive miRNAs, including miR-16, -141, -143, and -200c (6). Our study suggested that the dietary intake of natural products contributed to the prevention and treatment of cancer by regulating the RNAi pathway.

### 2) An exosome-carrying microRNAs as a Novel Diagnosis and Therapeutic Tool against Cancer

Circulating miRNAs could be found in variety of body fluids including serum, plasma, urine, saliva and breast milk (7). The existence of circulating miRNAs in the blood of cancer patients has raised the possibility that miRNAs may serve as a novel diagnostic marker (8). For this reason, a new method for the highly sensitive detection of circulating miRNAs has been developed (9). The circulating miRNAs are secreted from variety types of cell via the extracellular vesicles called exosomes. We provided a method to directly detect and quantify exosomes in human serum from prostate cancer patients using anti-CD63 and anti-CD9 antibodies. These results suggested that the ExoScreen system enabled us to detect circulating exosomes, and thus provided a novel biomarker. Normal epithelial cells regulate the secretion of humoral factors that prevent aberrant growth of neighboring cells. In this homeostatic regulation, exosomal tumor-suppressive miRNAs secreted by normal cells acted as anti-proliferative signal entities (10, 11). In addition, the application of exosomal tumor-suppressive miRNAs has been proposed as a novel nucleic acid therapy against cancer development.

3) Generation of Genetically Modified Rats from Embryonic Stem Cells for Development of Novel Animal Models for Cancer Research

For cancer studies, development of suitable animal models for human cancer is essential (12). Rats have important advantages as an experimental system for pharmacological investigations. We have established rat embryonic stem cells (ESCs) and generated Oct4-Venus transgenic rats. Using this transgenic ESC line, we have succeeded in generating p53 knockout rats. Homozygous KO males developed normally, whereas females rarely survived due to neural tube defects. The homozygous male died within 4 months due to tumor development. In contrast to this phenotype, knockout chimeras generated via blastocyst injection with p53-null ESCs exhibited high rates of embryonic lethality in both sexes. These results demonstrate that p53 functions as a guardian of embryogenesis as well as a tumor suppressor in rats (13).

4) Hepatic Differentiation of Mesenchymal Stem Cells and Its Therapeutic Application

Adipose-derived mesenchymal stem cells (ADSCs) are attractive in the context of future clinical applications (14). It was found that ADSCs and induced pluripotent stem cells could differentiate into hepatocytes and demonstrate the functional properties of primary human hepatocytes (15-18).

## List of papers published in 2012
### Journal


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# Division of Cancer Biology

**Hirofumi Arakawa, Yasuyuki Nakamura, Hiroki Kamino, Masaki Yoshida, Ryuya Murai, Yuri Saito, Hitoya Sano, Izumi Hyo**

## Introduction

The scope of the research at the Division of Cancer Biology is broad, covering numerous areas including the cloning of genes involved in carcinogenesis, biological and structural analyses of proteins, analyses of animal models, and the development of new strategies for cancer therapy. In particular, the 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 preventive, diagnostic, and therapeutic strategies could be developed.

## Research activities

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. Thus far, a number of p53-target genes including *DFNA5*, *SEMA3F*, *BLNK*, *UNC5A*, *NEEP21*, and *TMPS* have been identified and characterized at the Division. Along the way, a new p53-target gene was identified, and designated *Mieap* for mitochondria-eating protein, reflecting the unusual function of the protein. Surprisingly, the function of Mieap is involved in mitochondrial quality control (MQC).

Mieap-induced accumulation of lysosome-like organella within mitochondria

Mieap controls mitochondrial quality via two distinct novel mechanisms. One of the mechanisms has been designated MALM for Mieap-induced accumulation of lysosome-like organelles within mitochondria (PLoS ONE 6: e16054, 2011). In this mechanism, Mieap induces the accumulation of intramitochondrial lysosomal proteins in order to eliminate oxidized mitochondrial proteins in response to mitochondrial damage. This leads to a decrease in reactive oxygen species generation and an increase in mitochondrial ATP synthesis activity, implying that MALM plays a role in repairing unhealthy mitochondria.

BNIP3 and NIX, mitochondrial outer membrane proteins, were identified as Mieap-interacting proteins (1), and were shown to mediate the translocation of lysosomal proteins from the cytosol into mitochondria during MALM by forming an unknown pore in the mitochondrial double membrane (1). 14-3-3$\gamma$ was also identified as a Mieap-interacting protein to mediate the degradation of oxidized mitochondrial proteins within mitochondria during MALM (2).

Mieap-inudced vacuole

Alternatively, the other mechanism has been designated MIV for Mieap-induced vacuole (PLoS ONE 6: e16060, 2011). When MALM is inhibited, Mieap induces a vacuole-like structure, MIV. The MIV engulfs the damaged mitochondria and accumulates lysosomes, leading to the degradation of unhealthy mitochondria. MIV likely represents a novel mechanism for mitochondrial autophagy, also called "mitophagy". Therefore, Mieap controls mitochondrial quality by repairing or eliminating unhealthy mitochondria via MALM or MIV generation, respectively (Figure 1).

Mitochondrial quality control and cancer

The accumulation of unhealthy mitochondria results in mitochondrial dysfunction, which has been implicated in aging, degenerative diseases and cancer. In cancer cell lines, we found that the Mieap-regulated MQC is frequently inactivated by p53 mutations or Mieap-methylation or BNIP3 methylation. In order to evaluate the clinical significance of the Mieap-regulated MQC, the status of p53 (gene mutation), Mieap (methylation), and BNIP3/NIX (methylation) are being examined in primary cancer tissues of colorectal and pancreatic cancer patients.

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 the accumulation of unhealthy mitochondria

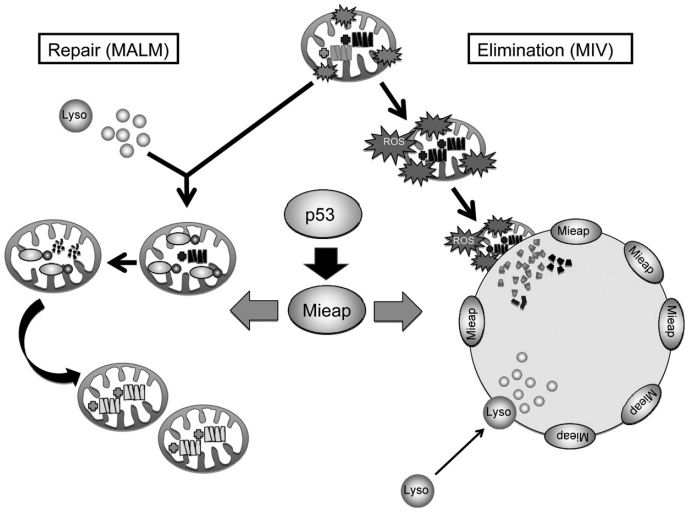


**Figure 1.**

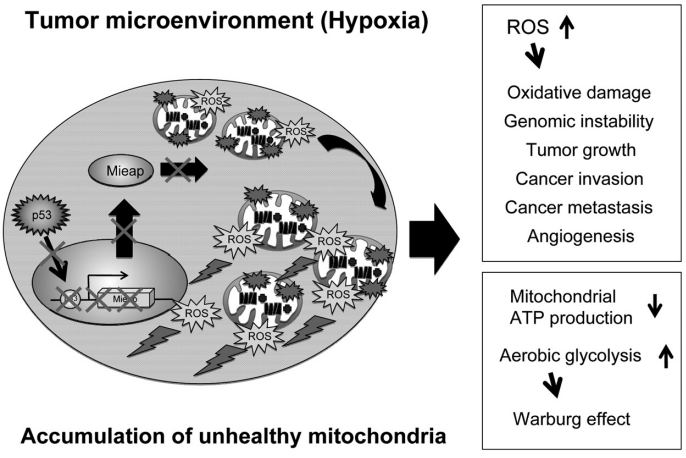


**Figure 2.**

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 in this Division.

New therapeutic strategies for cancer therapy

Adenovirus-mediated gene transfer of *Mieap* has been found to strongly suppress 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 in this Division.

## List of papers published in 2012

### Journal

1. Nakamura Y, Kitamura N, Shinogi D, Yoshida M, Goda O, Murai R, Kamino H, Arakawa H. BNIP3 and NIX mediate Mieap-induced accumulation of lysosomal proteins within mitochondria. PLoS One, 7:e30767, 2012

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# Division of Epigenomics

**Toshikazu Ushijima, Eriko Okochi-Takada, Satoshi Yamashita, Kiyoshi Asada, Tohru Niwa, Hideyuki Takeshima, Naoko Hattori, Yasuyuki Shigematsu, Takamasa Takahashi, Yukie Yoda, Jeong Goo Kim, Emil Rehnberg, Mika Wakabayashi, Akiko Mori, Kana Kimura, Yuko Miyaji, Naoko Kobayashi, Aya Nakajima, Satoshi Yoshida, Liang Zong**

This Division has been focusing on the epigenetic mechanisms of carcinogenesis, mainly DNA methylation, and has identified many aberrantly methylated CpG islands (CGIs) in various cancers, i.e. gastric cancers, breast cancers, pancreatic cancers, lung cancers, ovarian cancers, neuroblastomas, and melanomas. This has led to identification of a novel tumor-suppressor gene (TSG) in gastric cancers, development of a powerful prognostic marker in neuroblastomas, and establishment of the concept 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

Identification of TSGs silenced by aberrant methylation is important, but has been hampered by a large number of genes methylated as passengers of carcinogenesis. To overcome this issue, this Division took advantage of the fact that the majority of genes methylated in cancers lack, in normal cells, RNA polymerase II (Pol II) and have trimethylation of histone H3 lysine 27 (H3K27me3) in their promoter CGIs. It was shown that some TSGs had Pol II and lacked H3K27me3 in normal cells, being outliers to the general rule, and that novel TSGs could be identified by searching for such outliers (1).

Aberrant hypermethylation is known to be present in predisposed epithelial cells. In a study conducted this year, hypomethylation of repetitive elements was shown to be present in the background mucosae of esophageal squamous cell carcinoma (2). 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 induced by *Helicobacter pylori* infection was deeply involved in predisposition to gastric cancers (epigenetic field for cancerization). Based on the fact, accumulation levels of aberrant methylation are expected to become a useful gastric cancer risk marker. This year, novel risk markers, highly informative among individuals with past *H. pylori* infection, were developed (Figure 1) (3). A prospective clinical study is being conducted to bring these risk markers into practical application.

Detection of lymph node metastasis is critically important for determination of the treatment strategy for gastric cancers, and this Division identified CGIs whose methylation levels were associated with the presence of lymph node metastasis in gastric cancers (4). In neuroblastomas, the clinical usefulness of the prognostic marker mentioned above is being analyzed using materials prospectively collected.

## Development of epigenetic therapy

Epigenetic therapy is expected to be a next-generation strategy in cancer chemotherapy. Since many genes are known to be silenced in a single cancer, simultaneous reversal of silencing of multiple genes is expected to be an effective treatment. This Division is working on this strategy as a novel therapeutic concept using neuroblastomas as a model. At the same time, a screening system for novel epigenetic drugs is also being developed.

## Induction mechanisms of epigenetic alterations

Clarification of the 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 (5). Regarding components of inflammation, it

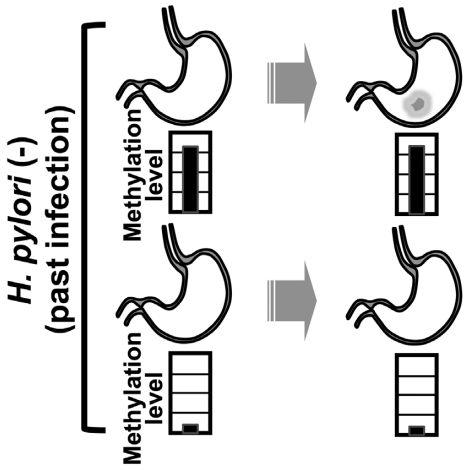


**Figure 1. Novel gastric cancer risk marker, informative among individuals with past *H. pylori* infection**

was shown that functional T and B cells are non-essential for the epigenetic field for cancerization by analysis of aberrant methylation in severe combined immunodeficiency mice in a mouse colitis model (6).

Although aberrant DNA methylation is involved in the field for cancerization, it had been unclear for H3K27me3. This Division demonstrated that aberrant H3K27me3 could be induced by exposure to a specific environment, such as colitis, and suggested that aberrant histone modification, in addition to aberrant DNA methylation, was involved in the formation of a field for cancerization (7).

## Other activities

This Division assisted in the epigenetic analysis of *miR-7-1* in gastric cancers (8), that of *Mat1A* and *Mat2A* in liver cancers (9), and research on gastric cancer risk (10). This Division also contributed to communicating recent findings in inflammation-associated cancer development and epigenetic changes (11).

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## Journal


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11. Chiba T, Marusawa H, Ushijima T. Inflammation-associated cancer development in digestive organs: mechanisms and roles for genetic and epigenetic modulation. Gastroenterology, 143:550-563, 2012

# Division of Pharmacoproteomics

**Tadashi Kondo, Daisuke Kubota, Hiroshi Ichikawa, Noriyuki Hosoya, Takashi Tajima, Kenta Mukaihara, Kazutaka Kikuta, Yoko Takai, Ruriko Sakamoto, Kazuya Arai, Mayo Kikuchi, Yukiko Nakamura, Fusako Kito, Marimu Sakumoto, Yutaka Sugihara, Hirotaka Yonemori, Ayako Haga, Ryosuke Yamaka**

## Introduction

The aim of this Division is to create clinically useful tools through cancer research and to contribute to the better clinical outcome of cancer patients (Figure 1). For this aim, we challenge biomarker research to optimize therapeutic strategies, and also attempt to elucidate drug targets. The Division is characterized by the applications based on an original proteomics approach, and the use of clinical materials/ clinical-pathological information on the basis of collaborations with clinicians and pathologists in the National Cancer Center Hospital and domestic/ overseas hospitals (Table 1). Development of novel proteomics modalities is one of the major themes of this Division, and interdisciplinary collaborations have been established with universities and companies. Among many malignancies investigated in the Division, sarcomas are presently the most focused on, based on the long time collaboration with orthopedicians.

## Research activities

1. Biomarker research for personalized medicine

Biomarkers to optimize the therapeutic strategy were challenged using the proteomics modality. Proteomic biomarker research for sarcomas generated many promising biomarkers, and external validation and *in vitro* functional studies were undertaken (1-3).

In gastrointestinal stromal tumors (GISTs), DDX-39 was identified as a biomarker to predict metastasis after surgery, and its clinically significant characteristics were immunohistochemically validated (4). The immunohistochemical validation of a novel prognostic biomarker, pfetin, which was previously discovered as a prognostic biomarker for GISTs in this Division, was conducted in combination with DDX-39 (5). The immunohistochemical validation study on the prognostic values of pfetin was performed in approximately 500 GIST cases from six domestic hospitals.

In hepatocellular carcinomas (HCCs), the decreased expression of selenium-binding protein 1 (SBP-1) promoted tumor invasiveness by increasing the activity of glutathione peroxidase 1 and diminishing HIF-1$\alpha$ (6). Immunohistochemistry revealed that SBP-1 was a novel prognostic biomarker for HCCs. A novel serum biomarker for microvascular invasion was discovered with mass spectrometry, and its clinical utilities were confirmed with an ELISA. APC-binding protein EB1 (EB1), which was previously discovered as a prognostic biomarker for HCC in this Division, was identified as a potential prognostic biomarker in colorectal cancer (7). A proteomic study was performed on cholangiocarcinomas, using tumor tissues, a xenograft model, and primary culture cells from the patients with different response to gemcitabine treatments, and macrophage-capping protein (CapG) was identified as a novel predictive biomarker. The prognostic values of CapG were immunohistochemically confirmed (8).

Other biomarkers were also discovered by comprehensive profiling of proteins and microRNA in osteosarcoma, gastric cancer, and renal cell carcinoma. An external immunohistochemical validation study and functional assessment of the identified biomarkers were undertaken, and promising candidates were discovered. The clinical applications of the identified proteins will be our next big challenge.

2. Discovery of therapeutic targets

Identification of targets was performed with the focused proteomics approach for druggable proteins. The comprehensive expression profiling of tyrosine kinases identified many promising drug candidates in sarcomas. Unique enzymes in the protein complex of biomarker candidates were identified by the interactome approach using gel electrophoresis and mass spectrometry. *In vitro* inhibition assays were performed to evaluate the possibility for further investigation.

3. Development of proteomics modalities and their application in cancer research

Proteomics modalities to investigate the heterogenous tumor tissues were developed and used to identify the proteins associated with malignant cancer features. Using laser microdissection and a large format two-dimensional difference gel electrophoresis (2D-DIGE) technology, we identified cathepsin D as a unique protein to lung adenocarcinoma (10), and validated its clinical utilities with a tissue microarray. A novel application of the technology associated with Laser-assisted in Situ Keratomileusis (LASIK) was developed for proteomic studies, and applied to invadopodia of breast cancer cells, resulting in the identification of novel metastasis-associated proteins. *In vitro* functional validation confirmed the biological significances (11).

The combination of gel electrophoresis and mass spectrometry was employed to perform a comprehensive expression study on intact proteins to enable further understanding of the molecular backgrounds behind the clinical utility of biomarker proteins such as nucleophosmin (NPM), which was identified as a prognostic biomarker for Ewing sarcoma in this Division. The clinically significant characteristics of NPM-binding proteins were confirmed with a meta-analysis of mRNA data. An automatic protein sample processor is under development for comprehensive and quantitative protein expression study in collaboration with commercial manufacturer.

The application of antibody libraries is one of the challenging approaches for cancer research. Using monoclonal antibodies for approximately 600 nuclear factors, the proteins for early recurrence were identified in HCC. The *in vitro* and *in vivo* functional assessments and immunohistochemical validation using the tissue microarray technique were performed to assess the clinical usefulness of the identified nuclear factors. Posttranslational modifications of the proteins from chromosome 21 were examined using antibodies from the Human Protein Atlas and a unique Western blotting method (12). Detailed and comprehensive studies on posttranslational modifications of proteins will be challenged using antibodies.

4. Contribution to research community

The Division contributed to the guidelines in the worldwide public antibody databases such as the Human Proteome Project (Human Proteome Organization) and the Antibodypedia (Nature Publishing Group). The division also contributed to the Chromosome-centric Human Proteome Project (Human Proteome Organization)(12).

**Table 1. Cases examined for biomarker research and target discovery in 2012**

| | Malignancies | Research theme | No. of cases examined* |
|---|---|---|---|
| 1 | Osteosarcoma | Biomarker to predict response to pre-operative chemotherapy | 37 |
| 2 | Rhabdomyosarcoma | Biomarker for differential diagnosis | 23 |
| 3 | Myxoid liposarcoma | Biomarker to predict prognosis after surgery | 29 |
| 4 | Mixofibrosarcoma | Biomarker for differential diagnosis | 27 |
| 5 | Alveolar soft part sarcoma | Discovery of drug target | 13 |
| 6 | Epithelioid sarcoma | Discovery of drug target | 12 |
| 7 | Gastrointestinal stromal tumor | Biomarker to predict metastasis after surgery | 371 |
| 8 | Lung cancer | Discovery of drug target | 40 |
| 9 | Gastric cancer | Biomarker to predict lymph node metastasis before surgery | 217 |
| 10 | Colorectal cancer | Biomarker to predict prognosis after surgery | 200 |
| 11 | Hepatocellular carcinoma | Serum biomarker for microvascular invasion | 727 |
| 12 | Renal cell carcinoma | Biomarker to predict prognosis after surgery | 89 |
| 13 | Metastatic bone tumor | Discovery of drug target | 11 |
| Total | | | 1796 |

*Cases include those from the National Cancer Center Hospital and the other domestic and overseas hospitals

## List of papers published in 2012
## Journal

1. Kondo T, Kubota D, Kawai A. Application of proteomics to soft tissue sarcomas. Int J Proteomics, 2012:876401, 2012
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12. Uhlén M, Oksvold P, Älgenäs C, Hamsten C, Fagerberg L, Klevebring D, Lundberg E, Odeberg J, Pontén F, Kondo T, Sivertsson Å. Antibody-based protein profiling of the human chromosome 21. Mol Cell Proteomics, 11:M111.013458, 2012
13. Mimae T, Tsuta K, Kondo T, Nitta H, Grogan TM, Okada M, Asamura H, Tsuda H. Protein expression and gene copy number changes of receptor tyrosine kinase in thymomas and thymic carcinomas. Ann Oncol, 23:3129-3137, 2012
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# Division of Genome Biology

**Takashi Kohno, Hideaki Ogiwara, Kouya Shiraishi, Yoko Shimada, Tatsuji Mizukami, Teruhide Ishigama, Takashi Mitachi, Norihide Yoshikawa, Olivia Schreiber, Hideyuki Hayashi**

## Introduction

Somatic mutations in the cancer genome and inter-individual variations in the human genome are critical keys to improving the efficacy of treatment in cancer clinics. The aim of our division is to find "seeds" that improve the treatment and prevention of cancer by identifying and elucidating the biological significance of somatic mutations in cancer genomes and genetic polymorphisms of cancer patients (Figure 1). 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 activities

1. Genes for personalized therapy

Novel genes rearranged in lung cancer were searched for by conducting whole RNA sequencing of lung adenocarcinoma tissues supplied from the National Cancer Center Biobank using high-speed DNA sequencers. We identified in-frame fusion transcripts of KIF5B (the kinesin family 5B gene) and the RET oncogene, which are present in 1–2% of lung adenocarcinomas (LADCs) from patients in Japan and the United States (1). The KIF5B-RET fusion leads to aberrant activation of RET kinase and is considered to be a new driver mutation of LADC because it segregates from mutations or fusions in EGFR, KRAS, HER2 and ALK, and a RET tyrosine kinase inhibitor, vandetanib, suppresses the fusion-induced anchorage-independent growth activity of NIH3T3 cells. Kinase inhibitors are now standard treatment for patients with lung cancer whose tumors harbor specific mutant kinases, and the RET fusion protein was considered potentially to be responsive to existing targeted therapies using RET kinase inhibitors. The development of assays to assess RET fusions and other driver mutations in each patient will offer the potential to routinely parse lung cancer into multiple different clinically relevant molecular disease types in the near future. A project focusing on this issue has started in collaboration with NCC staff from hospitals. An investigator-initiated clinical trial to address the therapeutic efficacy of vandetanib will start in 2013.

Whole gene expression profiling data of human primary lung epithelial cells stimulated with epidermal growth factor (EGF) in the presence or absence of a clinically used EGF receptor tyrosine kinase (RTK)-specific inhibitor, gefitinib, were subjected to a mathematical simulation using the State Space Model. A risk scoring model was constructed to classify high- or low-risk patients based on the expression signatures of 139 gefitinib-sensitive genes in surgical specimens of lung adenocarcinomas (2). This system will be useful to identify early stage lung adenocarcinoma patients with a poor prognosis who will benefit from adjuvant therapy after a surgical operation.

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) and homologous recombination (HR) are major repair pathways for DNA double strand breaks (DSBs) generated by ionizing radiation and anti-cancer drugs. We revealed that CBP/p300 histone acetyltransferases (HATs) promote DSB repair by facilitating NHEJ and HR (3), and are therefore possible target for sensitization of tumors to radio- and chemotherapies. In fact, garcinol, a natural compound with an inhibitory activity against CBP/p300 HATs, was identified as a promising radiosensitizer (4).

2. Genes for personalized prevention

Genetic factors underlying the specific risk of lung adenocarcinoma in Asians are being searched for to comprehensively understand the molecular mechanism of lung carcinogenesis (5-6). A genome-wide association study comprising a total of 6,029 individuals with lung adenocarcinoma (cases) and 13,535 controls confirmed two previously reported risk loci, 5p15.33 (rs2853677, $P = 2.8 \times 10^{-40}$, odds ratio (OR) = 1.41) and 3q28 (rs10937405, $P = 6.9 \times 10^{-17}$, OR = 1.25), and identified two new susceptibility loci, 17q24.3 (rs7216064, $P = 7.4 \times 10^{-11}$, OR = 1.20) and 6p21.3 (rs3817963, $P = 2.7 \times 10^{-10}$, OR = 1.18) (7). Another genome-wide association study of 5,510 never-smoking female lung cancer cases and 4,544 controls, which were drawn from 14 studies from mainland China, South Korea, Japan, Singapore, Taiwan and

Hong Kong, identified three new susceptibility loci at 10q25.2 (rs7086803, $P = 3.54 \times 10^{-18}$), 6q22.2 (rs9387478, $P = 4.14 \times 10^{-10}$) and 6p21.32 (rs2395185, $P = 9.51 \times 10^{-9}$) (8). These data provide evidence supporting a role for genetic susceptibility in the development of lung adenocarcinoma in Asians. These results represent basic information to improve the prevention of lung adenocarcinoma through identification of high-risk individuals for development.

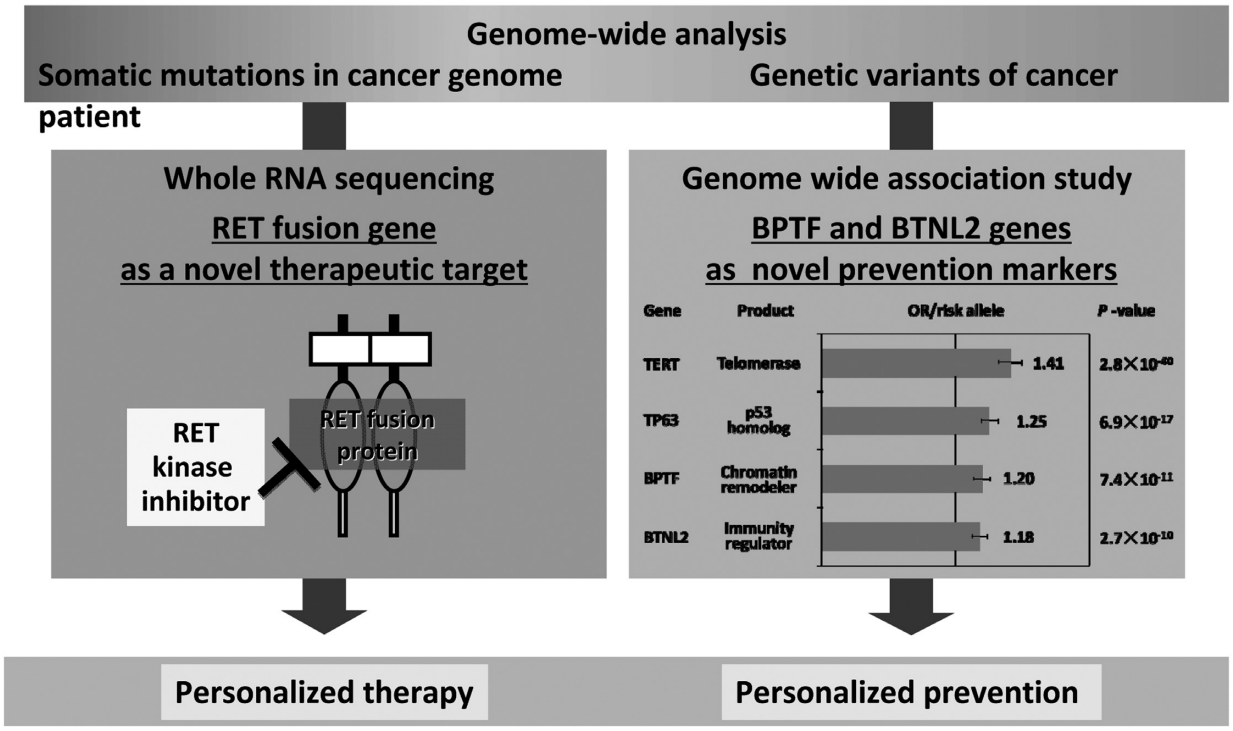


Figure 1

## List of papers published in 2012
## Journal


1. Kohno T, Ichikawa H, Totoki Y, Yasuda K, Hiramoto M, Nammo T, Sakamoto H, Tsuta K, Furuta K, Shimada Y, Iwakawa R, Ogiwara H, Oike T, Enari M, Schetter AJ, Okayama H, Haugen A, Skaug V, Chiku S, Yamanaka I, Arai Y, Watanabe S, Sekine I, Ogawa S, Harris CC, Tsuda H, Yoshida T, Yokota J, Shibata T. KIF5B-RET fusions in lung adenocarcinoma. Nat Med, 18:375-377, 2012

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# Division of Cancer Genomics

**Tatsuhiro Shibata, Fumie Hosoda, Yasushi Totoki, Mamoru Kato, Yasuhito Arai, Hiromi Nakamura, Natsuko Hama, Wataru Munakata, Tomoki Shirota, Naoko Okada, Tomoko Urushidate, Hiroko Shimizu, Shoko Ohashi, Wakako Mukai, Isao Kurosaka**

## Introduction

The Division of Cancer Genomics focuses on comprehensive characterization of the cancer genome on the basis of tumor pathology and aims to make a "breakthrough" by identifying novel cancer-related genes, including potential therapeutic targets and biomarkers, and to understand the cancer genome as 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.

## Research activities

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 worldwide. 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.

Whole genome sequencing of 27 hepatocellular carcinoma (HCC) cases including 14 hepatitis B and 11 C virus-associated HCCs 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 (1, 2).

Whole genome sequencing and genetic analysis of sarcomas

Chondrosarcoma accounts for more than 20% of primary bone sarcomas, with an overall incidence estimated at approximately one in 200,000. However, the etiological background of chondrosarcomagenesis remains largely unknown, along with detailed information on molecular alterations, including potential therapeutic targets. We performed massive parallel sequencing of 10 chondrosarcoma genomes along with the matched normal genomes to identify somatic mutations, structural alterations including fusion genes, and mutation signatures that may help to comprehensively characterize the molecular features of this tumor. Frequent co-amplification and co-expression of CDK4 and MDM2 genes was elucidated in high-grade osteosarcoma specimens (3).

Whole exome sequencing analysis of breast cancer

Metastasis is the main cause of therapeutic failure and death in cancer patients. To understand the genetic basis underlying metastatic progression of breast cancer, a whole exome sequencing (WES) analysis of 16 trios of primary breast cancer, lymph node metastatic tumor and their matched noncancerous tissue has been done. A preliminary result of the WES analysis identified some nonsynonymous mutations which were commonly observed in primary and metastatic tumors and a large number of mutations specific to primary or metastatic tumors, respectively. The result suggests that heterogeneous genetic alterations occur during the tumor progression and the metastatic process in individual breast cancers. Pathological analysis of chemosensitivity in triple-negative breast cancers was performed (4).

Genome-wide genetic analyses of childhood cancer and other tumors

Comprehensive analysis of the five key genes, *WT1, CTNNB1, WTX, IGF2* and *RASSF1*, from Japanese Wilms tumor patients revealed that methylation of the RASSF1 promoter was a prognostic biomarker (5), and that loss of IGF2 imprinting was specifically low in the Japanese cohort (6). In germ cell tumors, meiosis error and subsequent genetic and epigenetic alterations may have caused malignant transformation (7). Frequent deletion of the TNFAIP3/A20 gene was identified in classical Hodgkin lymphoma (8).

Oncogenic fusion genes in lung cancer

To explore the molecular genetics of, and identify new molecular targets in lung cancer, whole transcriptome analysis was performed in non-small cell lung cancer (NSCLC) tissues. We identified novel in-frame fusion kinase genes, EZR-ROS1 and others,

and showed their transforming activities in colony formation were suppressed by the corresponding kinase inhibitors. Established transgenic mouse lines specifically expressing EZR-ROS1 in lung alveolar epithelial cells developed multiple adenocarcinoma nodules in both lungs at an early age.

Transcriptome sequencing analysis of gastric cancer

To understand the genetic basis underlying the development of gastric cancer and to identify new drug targets in the diffused type of gastric cancer, a transcriptome sequencing approach has been undertaken. RNA sequence analysis predicted 43 fusion gene candidates in 27 out of 37 tumors examined. Twenty-four in-frame gene fusions have been identified among the candidates with the RT-PCR method. Those fusion genes including two oncogenic protein kinase-fusions could be good candidates for therapeutic targets.

Metabolome analysis of the NRF2 oncogene

NRF2, a key regulator for the maintenance of redox homeostasis, has been shown to contribute to malignant phenotypes of cancers including aggressive proliferation. However, the mechanisms with which NRF2 accelerates proliferation are not fully understood. We showed that NRF2 redirects glucose and glutamine into anabolic pathways, especially under the sustained activation of PI3K-Akt signaling (9).

Bioinformatics platform and support for clinical sequencing and other cancer research

As a part of a Phase I Center, we developed a computer system for clinical sequencing which utilizes the latest DNA sequencing technology to identify DNA aberrations in clinical samples to achieve personalized medicine. We also supported a bioinformatics analysis to classify DNA adducts in mass-spec data, to identify micro-RNAs related to carcinogens, and to characterize genes related to cancer stem cells. In addition, we collaborated with research groups outside NCC on identification of a new gene in neuroblastoma and analysis of small RNA (10).



## List of papers published in 2012

### Journal


1. Fujimoto A, Totoki Y, Abe T, Boroevich KA, Hosoda F, Nguyen HH, Aoki M, Hosono N, Kubo M, Miya F, Arai Y, Takahashi H, Shirakihara T, Nagasaki M, Shibuya T, Nakano K, Watanabe-Makino K, Tanaka H, Nakamura H, Kusuda J, Ojima H, Shimada K, Okusaka T, Ueno M, Shigekawa Y, Kawakami Y, Arihiro K, Ohdan H, Gotoh K, Ishikawa O, Ariizumi S, Yamamoto M, Yamada T, Chayama K, Kosuge T, Yamaue H, Kamatani N, Miyano S, Nakagama H, Nakamura Y, Tsunoda T, Shibata T, Nakagawa H. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. Nat Genet, 44:760-764, 2012
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9. Ohnishi Y, Totoki Y, Toyoda A, Watanabe T, Yamamoto Y, Tokunaga K, Sakaki Y, Sasaki H, Hohjoh H. Active role of small non-coding RNAs derived from *SINE/B1* retrotransposon during early mouse development. Mol Biol Rep, 39:903-909, 2012
10. Munakata W, Nomoto J, Takahashi N, Taniguchi H, Maeshima AM, Asamura H, Tanosaki R, Heike Y, Fukuda T, Tobinai K, Kobayashi Y. Carcinoma of donor origin after allogeneic peripheral blood stem cell transplantation. Am J Surg Pathol, 36:1376-1384, 2012

# Division of Chemotherapy and Clinical Research

**Tesshi Yamada, Masaya Ono, Kazufumi Honda, Mari Masuda, Nami Miura, Ayako Mimata, Masahiro Kamita, Tomoko Umaki, Naoko Yasuno, Yuko Miyamoto, Hiroko Ito, Haruyo Tozaki, Akihiko Miyanaga, Takafumi Watanabe, Yukio Watabe**

## Introduction

Even for cancers having the same origin and histology, their clinical courses may vary among individuals. Accurate prediction of disease progression and therapeutic efficacy is therefore essential for optimization of therapy in individual patients. The so-called "-omics" technologies have made rapid advances in recent years. It is anticipated that application of these technologies will greatly facilitate the discovery of molecules reflecting the diverse clinical behaviors of cancers. As cancer development occurs in parallel with protein dysfunction, comprehensive analyses of cancer proteomes would seem to be a more practical approach for the development of diagnostics and therapeutics.

## Novel post-translational regulation of the PML tumor suppressor function

Using a comprehensive shotgun mass spectrometry approach, we had previously identified PML as one of 70 proteins commonly co-immunoprecipitated with the anti-T-cell factor-4 (TCF4) antibody from two colorectal cancer cell lines. PML is a tumor suppressor involved in the pathogenesis of acute promyelocytic leukemia (APL). Loss of PML-NBs has been reported in many different human neoplasms, including colorectal carcinoma, but the mechanisms involved have not been fully elucidated. We show for the first time that β-catenin interacts with PML isoform IV and disrupts PML-IV function and PML-NB formation by inhibiting RanBP2-mediated SUMOylation of PML-IV.

## Plasma and serum biomarker discovery using 2DICAL

2DICAL (2-dimensional image converted analysis of liquid chromatography and mass spectrometry) is a proteomics analysis system originally developed at the NCCRI and applied for medical and biological proteomics. With regard to the medical application of 2DICAL, biomarkers have been discovered for two urological cancers. Carbonic anhydrase I (CAI) was detected by 2DICAL as a novel plasma biomarker of prostate cancer. The 2DICAL result was validated with an enzyme-linked immunosorbent assay (ELISA) of 185 plasma samples, and this confirmed that the plasma CAI concentration significantly increased in prostate cancer patients. Especially in the PSA "gray zone" of 4 -10 ng/ml, determination of the plasma CAI concentration increased the prostate cancer discrimination rate when combined with the PSA test. In clear cell renal cell carcinoma, 2DICAL identified fibronectin 1 as a novel plasma biomarker. Using Amplified Luminescent Proximity Homogeneous Assay technology (AlphaLISA), the identified biomarker candidate was validated in a cohort of 77 patients with clear cell renal cell carcinoma and 130 healthy controls.

Reviewing the 2DICAL approach for biomarker discovery, we have adopted a pathway of sample recruitment, sample preparation, biomarker discovery, and validation. 2DICAL has played an important part in the discovery of new biomarkers. Using this approach, we have succeeded in finding plasma or serum biomarkers for pancreatic cancer and colorectal cancer, and have become better able to predict both the adverse effects of chemotherapy for pancreatic cancer and the survival of patients.

## Proteomics approach for biological experiments

The interactome is a comprehensive proteomics approach for discovery of proteins that bind specifically to others. 2DICAL interactome analysis (IP-2DICAL) has identified NPM1 (nucleophosmin), which binds to DDX31 (DEAD box polypeptide 31) shown to be upregulated exclusively in clear cell renal cell carcinoma with a genome-wide gene expression profiling analysis. The interaction between DDX31 and NPM1 plays a critical role in carcinogenesis through interruption of the p53–HDM2 pathway of apoptosis by blocking the interaction between HDM2 and NPM1 in the nucleoplasm or cytoplasm.

Mieap is an important P53-related protein that controls the quality of mitochondria. 2DICAL

has identified 14-3-3γ as a novel Mieap-interacting protein. Biological investigations have revealed a critical role of 14-3-3γ in eliminating oxidized mitochondrial proteins during the MALM (Mieap-induced accumulation of lysosome-like organelles within mitochondria) process by interacting with Mieap within mitochondria. Thus, interactome analysis is a very useful tool for revealing novel interactions of molecules that are of specific interest to researchers.

### Multi-institutional validation study

Among patients with the more common human malignancies, those with invasive ductal carcinoma of the pancreas have the worst prognosis. The poor outcome seems to be at least partly attributable to difficulty in early detection. In fact, over 95% of patients with pancreatic cancer are not diagnosed until the disease has progressed to stage III or IV. We have performed a comprehensive comparative plasma proteomic analysis of pancreatic cancer patients and healthy controls using a newly developed quantitative mass spectrometry system. We reported that two modified forms of plasma/serum apolipoproteins were reduced in patients with pancreatic diseases. Although their reduction is not specific to pancreatic cancer, it has considerable potential for early detection of the disease. The significance of this discovery was further validated using a total of 1099 plasma/serum samples, consisting of 3 cohorts collected from 8 medical institutions in two countries.

### List of papers published in 2012
### Journal


1. Fukawa T, Ono M, Matsuo T, Uehara H, Miki T, Nakamura Y, Kanayama H, Katagiri T. DDX31 regulates the p53-HDM2 pathway and rRNA gene transcription through its interaction with NPM1 in renal cell carcinomas. Cancer Res, 72:5867-5877, 2012
2. Honda K, Okusaka T, Felix K, Nakamori S, Sata N, Nagai H, Ioka T, Tsuchida A, Shimahara T, Shimahara M, Yasunami Y, Kuwabara H, Sakuma T, Otsuka Y, Ota N, Shitashige M, Kosuge T, Buchler MW, Yamada T. Altered plasma apolipoprotein modifications in patients with pancreatic cancer: protein characterization and multi-institutional validation. PLoS One, 7:e46908, 2012
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# Division of Cancer Pathophysiology

**Yasuhito Uezono, Seiji Shiraishi, Masami Suzuki, Kanako Miyano, Yuka Sudo, Yumi Sawada, Junko Ezuka, Yukiko Araki, Kiyoshi Terawaki, Katsuya Morita, Katsuya Ohbuchi, Junichi Ogata, Koichiro Minami, Shun Muramatsu, Naoyo Motoyama, Tohru Yokoyama, Maho Ashikawa, Miki Inoue, Naofumi Oyanagi, Yohei Kashiwase, Yoshihiko Tasaki, Atsumi Nagasawa, Akinobu Yokoyama**

## 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 also clinical to basic translational collaborative research with the divisions of Palliative Care and Psychooncology 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, the opioids currently available can prove ineffective in not a few patients. For such patients, development of clinically available novel opioid analgesics is indispensable and attractive. We are studying distinct pharmacological properties among each of the opioid analgesics to finally develop and then introduce novel opioids in the clinical field; such a trial is one of our main research themes. In addition, several adjuvant analgesics such as anti-convulsants, anti-depressants, anesthetics, anti-arrhythmias and the $GABA_B$ receptor against baclofen are used for pain control; they are chosen based mainly on the history of their 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, 5, 6). 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 (1, 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 signals such as pain. We are trying to investigate the mechanisms of the TRP family functions (2).

## 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* and other compounds improved cancer anorexia-cachexia symptoms in cancer cachexia (7, 8). The roles of neuropeptides and/or neurotransmitters in the central nervous system on the cause and emergence of cancer cachexia are also investigated in our Division (9, 10). Additional interests in our Division are the roles of neurotransmitters/neuropeptides in the brain in other pathophysiological states (10, 11).

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## Journal


1. Horishita T, Ueno S, Yanagihara N, Sudo Y, Uezono Y, Okura D, Sata T. Inhibition by pregnenolone sulphate, a metabolite of the neurosteroid pregnenolone, of voltage-gated sodium channels expressed in *Xenopus* oocytes. J Pharmacol Sci, 120:54-58, 2012
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9. Suzuki M, Narita M, Ashikawa M, Furuta S, Matoba M, Sasaki H, Yanagihara K, Terawaki K, Suzuki T, Uezono Y. Changes in the melanocortin receptors in the hypothalamus of a rat model of cancer cachexia. Synapse, 66:747-751, 2012
10. Hashimoto H, Uezono Y, Ueta Y. Pathophysiological function of oxytocin secreted by neuropeptides - A mini review. Pathophysiology, 19:283-298, 2012
11. Yamamoto M, Takeya M, Ikeshima-Kataoka H, Yasui M, Kawasaki Y, Shiraishi M, Majima E, Shiraishi S, Uezono Y, Sasaki M, Eto K. Increased expression of aquaporin-4 with methylmercury exposure in the brain of the common marmoset. J Toxicol Sci, 37:749-763, 2012
12. Suzuki M, El-Hage N, Zou S, Hahn YK, Sorrell ME, Sturgill JL, Conrad DH, Knapp PE, Hauser KF. Fractalkine/$CX_3CL1$ protects striatal neurons from synergistic morphine and HIV-1 Tat-induced dendritic losses and death. Mol Neurodegener, 6:78, 2011

# Division of Cancer Stem Cell

**Kenkichi Masutomi, Satoko Yamaguchi, Mami Yasukawa, Keita Kinoshita, 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

It is widely known that the 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 analyzed in detail the mechanisms of telomere elongation at single seeded telomeres in human cells, and we reported that telomere elongation was strictly regulated both temporally and spatially in the S phase of the cell cycle (1). We also found that in addition to *hTERC*, hTERT binds a second non-coding RNA, *RMRP*, the RNA component of RNase MRP, and TERT and *RMRP* act as 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 (Figure 1). Moreover, we confirmed that the phenotypes of *RMRP* null mice are embryonicaly lethal. From these observations, we considered the possibilities that the hTERT-*RMRP* complex might be essential for ontogeny and biological functions.

## Telomerase and cancer stem cells

Previous studies indicated 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 contributes to tumor susceptibility and alters stem cell cycling *in vivo* even when telomere lengths are not limited. 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 through telomere-independent mechanisms (Figure 2). We also confirmed that the cells that constitutively express NS/GNL3L exhibited increased beta-catenin signaling and elevated MYC, OCT3/4, KLF4 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. Because 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 a high NS proportion, TWIST intensity, and an advanced pathological N (lymph nodes) stage significantly correlated with poor relapse-free survival (2). Moreover, we confirmed that a high NS proportion, strong TWIST intensity, and an advanced pathological N stage 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 (2). 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 (2). These observations implicated NS and TWIST as the predictive markers for postoperative recurrence, and suggest that the expression level of NS was correlated with the clinical prognosis in esophageal cancer patients. Moreover, these represented the first practical attempt to examine the clinical impact of the cancer stem cell factor(s) of NS in esophageal cancer.

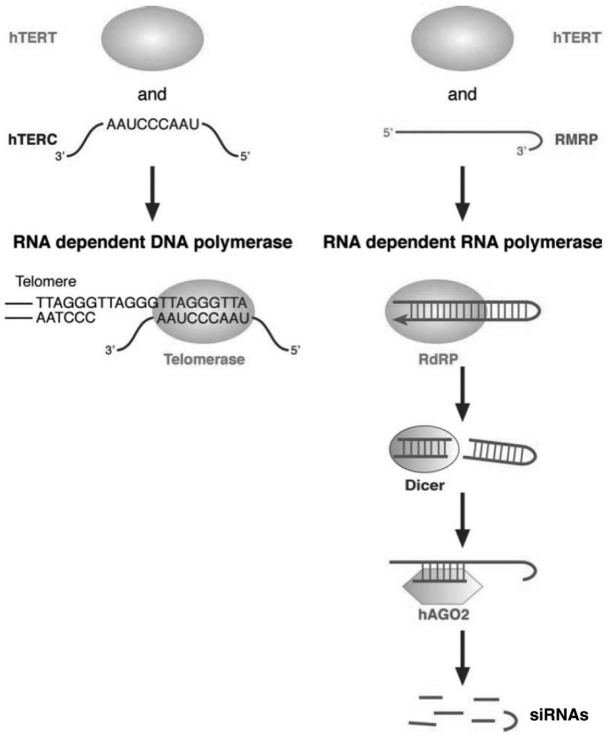


Figure 1

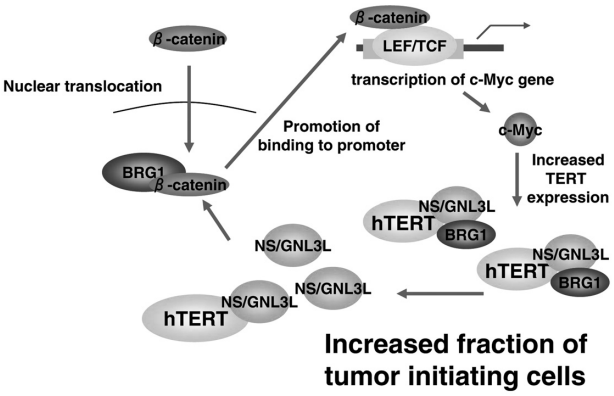


Figure 2

## Telomerase and epigenetics

Previously reports have shown that functional non-coding RNA is widely involved in the physiology of organisms through its epigenetic regulation. We therefore focused 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. It is thus important to understand the detailed mechanisms of epigenetics regulation. Since previous studies have shown that hTERT expression reduces the frequency of dicentric chromosomes and suppresses aneuploidy, we speculated that hTERT would monitor 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 (Figure 1). These observations indicated 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.

## List of papers published in 2012

1. Hirai Y, Masutomi K, Ishikawa F. Kinetics of DNA replication and telomerase reaction at a single-seeded telomere in human cells. Genes Cells, 17:186-204, 2012

2. Nakajima TE, Yoshida H, Okamoto N, Nagashima K, Taniguchi H, Yamada Y, Shimoda T, Masutomi K. Nucleostemin and TWIST as predictive markers for recurrence after neoadjuvant chemotherapy for esophageal carcinoma. Cancer Sci, 103:233-238, 2012

# Division of Gene and Immune Medicine

**Kazunori Aoki, Kenta Narumi, Naoko Goto, Yoko Kobayashi, Kouichirou Aida, Takeshi Udagawa, Koji Suzuki, Reina Miyakawa, Yuki Yamamoto, Naoto Shimokawatoko, Kazuki Miura, Keito Taniwaka**

## 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 by the library approach. The specific activities in 2012 were as follows: 1) Preclinical study of intratumoral injection of IFN-β plasmid/liposome complex for sarcomas; 2) Mechanism of antitumor immunity induced by the combination of hematopoietic stem cell transplantation and immune gene therapy; 3) Development of a peritoneal dissemination-targeting adenovirus vector.

## Research activities

Type I IFN gene therapy against sarcomas

Sarcomas at advanced stages remain a clinically challenging disease. Interferons (IFN) can target cancer cells by multiple antitumor activities including the induction of cancer cell death and enhancement of the innate and adaptive immune response. The Division examined whether a type I IFN gene transfer could induce an effective antitumor effect against sarcomas. First, the Division found that a type I IFN gene transfer significantly suppressed the cell growth of various sarcoma cell lines. Then, to examine the antitumor effect *in vivo*, the legs of BALB/c nude mice were inoculated with 143B human osteosarcoma or SK-UT-1B leiomyosarcoma cells, and an IFN-β-liposome complex was then injected directly into the tumors 3 or 6 times. The IFN-β gene transfer showed a significant suppressive effect against the 143B tumors in a dose-dependent manner, while a three-time injection of IFN-β plasmid-liposome was sufficient to eradicate the SK-UT-1B tumors. No adverse effect was recognized in the treated mice. The results showed that an intratumoral IFN gene transfer could be a promising therapeutic strategy for sarcomas. To translate the basic research to a clinical setting, the Division is collaborating with the Central Hospital, and is planning a Phase I clinical trial on intratumoral injection of an IFN-β plasmid/liposome complex in patients with sarcomas at advanced stages. At present, the protocol is under review in the Gene Therapy Ethics Committee of the National Cancer Center.

Combination of hematopoietic stem cell transplantation and immune gene therapy against solid cancers

T cells recognize tumor-associated antigens under the condition of lymphopenia-induced homeostatic proliferation (HP), however, HP-driven antitumor responses gradually decay in association with tumor growth. The Division examined whether a tumor-specific immune response induced by IFN could enhance and sustain HP-induced antitumor immunity in CT26 murine colon cancer models. An intratumoral IFN gene transfer resulted in marked tumor suppression when administered in the early period of syngeneic hematopoietic stem cell transplantation, and was evident even in distant tumors that were not transduced with the IFN vector (1). IFN gene transfer was then combined with syngeneic HSCT in murine osteosarcoma models. Intratumoral IFN gene transfer markedly suppressed the growth of vector-injected tumors and inhibited formation of spontaneous lung and liver metastases in syngeneic HSCT mice, and an infiltration of many immune cells was recognized in metastatic tumors of the treated mice (2). The treated mice showed no significant adverse events. To clarify the mechanism of antitumor immunity induced by the combination therapy, $CD11c^+$ cells were isolated from the regional lymph nodes of treated tumors. Flow-cytometry showed that an intratumoral delivery of the IFN gene promoted the maturation of $CD11c^+$ cells in the tumors and effectively augmented the antigen-presentation capacity of the cells. An analysis of the cytokine profile showed that the $CD11c^+$ cells in the treated tumors secreted a large amount of immune-stimulatory cytokines including IL-6. The $CD11c^+$ cells rescued effector T-cell proliferation from regulatory T cell-mediated suppression, and IL-6 played a dominant role in this phenomenon (1)(Fig. 1). The intratumoral IFN gene transfer created an environment strongly supporting the enhancement of antitumor immunity in reconstituted lymphopenic recipients through the induction of tumor-specific immunity and suppression of immunotolerance.

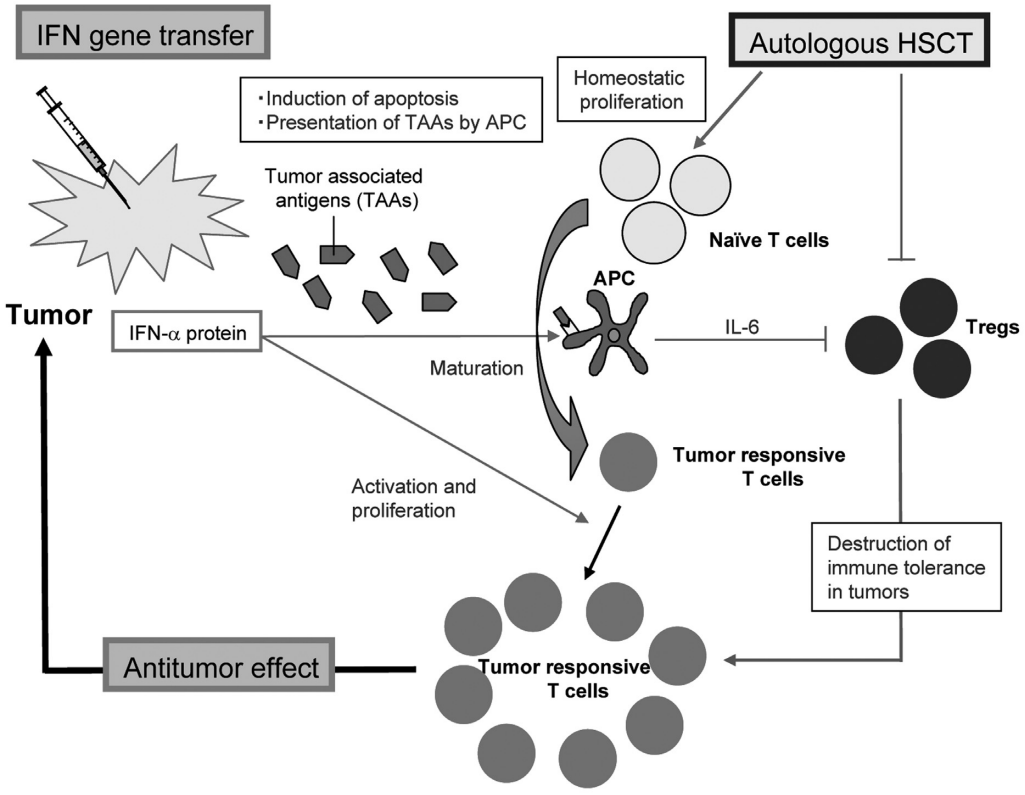


**Figure 1**

Development of cancer-targeting vectors using the peptide-display adenovirus library

The targeting of gene transfer at the cell-entry level is one of the most attractive challenges in vector development. To develop cancer-targeting adenovirus vectors, the Division has constructed a random peptide library displayed on the adenoviral fiber knob, and has successfully selected targeted vectors by screening the library on cancer cell lines *in vitro*. The infection of targeted vectors was considered to be mediated by specific receptors on target cells. However, the expression levels and kinds of cell surface receptors may be substantially different between an *in vitro* culture and *in vivo* tumor tissue. Therefore, the Division screened the peptide display-adenovirus library in the peritoneal dissemination model of AsPC-1 pancreatic cancer cells. The vector displaying a selected peptide (PFWSGAV) showed higher infectivity in the AsPC-1 peritoneal tumors but not in organs and other peritoneal tumors as compared with a non-targeted vector (3). Furthermore, the infectivity of the PFWSGAV-displaying vector for AsPC-1 peritoneal tumors was significantly higher than that of a vector displaying a peptide selected by *in vitro* screening, indicating the usefulness of *in vivo* screening in exploring the targeting vectors.

## List of papers published in 2012
### Journal


1. Narumi K, Udagawa T, Kondoh A, Kobayashi A, Hara H, Ikarashi Y, Ohnami S, Takeshita F, Ochiya T, Okada T, Yamagishi M, Yoshida T, Aoki K. *In vivo* delivery of *interferon-α* gene enhances tumor immunity and suppresses immunotolerance in reconstituted lymphopenic hosts. Gene Ther, 19:34-48, 2012
2. Udagawa T, Narumi K, Goto N, Aida K, Suzuki K, Ochiya T, Makimoto A, Yoshida T, Chikaraishi T, Aoki K. Syngeneic hematopoietic stem cell transplantation enhances the antitumor immunity of intratumoral type I interferon gene transfer for sarcoma. Hum Gene Ther, 23:173-186, 2012
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# Division of Genome Stability Research

**Mitsuko Masutani, Ken-ichi Yoshioka, Hiroaki Fujimori-Sakuma, Kengo Inoue, Takahisa Hirai, Anna-Margareta Rydén, Yasuhisa Okajima, Hiromi Harada, Junhui Wang, Soichiro Saito, Yuko Atsumi, Yuko Kudo, Tomoyuki Osawa, Hiroaki Mukai, Shuhei Yoshida, Tasuku Itoh, Miyuki Hozumi, Masako Yamazaki, Tsubasa Sekiguchi**

## Introduction

This Division pursues mechanisms underlying the genomic stability against diverse direct and indirect DNA damage caused by radiation, chemotherapeutic agents and various forms of cellular stress. In parallel with these studies, research projects into the development of novel strategies for chemotherapy and radiation therapy have been conducted in collaboration with institutions and clinical researchers inside and outside of the NCC. The 31st meeting of Molecular Pathology was organized in Ena by this Division.

## Research activities

Radiation damage response and radiosensitization

For the studies on radiosensitization, evaluated irradiation systems delivering a variety of radiation types are necessary. An X-ray irradiation system in the Research Institute has been set up and physical and biological evaluation were carried out in collaboration with the Departments of Radiation Oncology of the NCC. A model for metastasized tumors in the mouse brain and a treatment model with local X-ray irradiation were optimized.

Radiosensitization by a PARP inhibitor for low and high LET (linear energy transfer) radiation was observed and the involvement of a possible increase of DSB (double strand break)-like lethal DNA lesions (Figure 1) has been investigated (2). Using an shRNA library, target genes for radiosensitization were widely screened and more than 100 candidate genes of various categories, including cell cytoskeleton, DNA damage response, and transcription, were picked up and are being validated using siRNA.

Basic research on BNCT

Boron neutron capture therapy (BNCT) is a unique cancer cell-targeted therapeutic strategy, for which clinical trials are now ongoing. To understand the mechanism of tumor cell death induced by BNCT and to optimize BNCT condition, we used rat tumor graft models with boronophenylalanine and histological and biochemical analyses was carried out focusing on DNA damage response in collaboration with other institutions. The persistent staining of γH2AX and poly(ADP-ribose) (PAR) suggested accumulated double-strand breaks after BNCT. The γH2AX and PAR were found to be the markers for monitoring DNA damage induced by BNCT. Collaboration studies for the biomarkers of BNCT have also been started with Kyoto University Research Reactor Institute and several other institutions.

Epigenetic dysregulation caused by PARP inhibitor

Clinical trials have demonstrated the significance of PARP inhibitors in the treatment of tumors showing *BRCA* dysfunction. Utilizing mouse embryonic stem cells (ESCs) as a model, the effect on epigenetic regulation was investigated. Dysregulation of DNA methyltransferases and DNA hypomethylation were induced in ESCs by a PARP inhibitor, which accompanied up-regulation of particular genes and a differentiation disorder. This study suggested that a PARP inhibitor might cause epigenetic dysregulation possibly affecting therapeutic efficacy and may also cause potential side-effects to normal cells, especially to stem cells (4, 5).

Functional studies of PARG and development of PARG inhibitors for cancer therapy

PARG is involved in DNA repair and its inhibition has been shown to cause accumulation of PAR synthesis. PAR accumulation also triggers cell death. PARG siRNA knockdown suggests that PARG dysfunction enhances the cell death caused by γ- and carbon-ion irradiation as well as alkylating agents. PARG inhibitors may enhance the effect of radiation therapy and chemotherapeutic agents. Specific and potent PARG inhibitors are not known. Screening of PARG inhibitors from chemical libraries and an optimization study have been conducted as a collaborative study with other institutions. Several PARG inhibitors have been developed and structural optimization is being investigated.

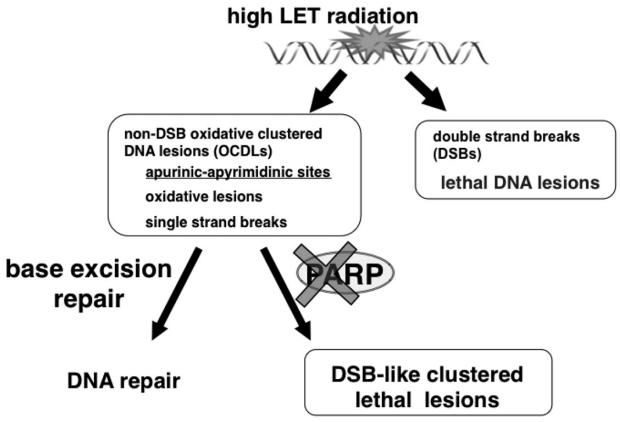


**Figure 1. A model for increase of DSB-like clustered lethal DNA lesions by PARP inhibitor after exposure to high LET radiation**

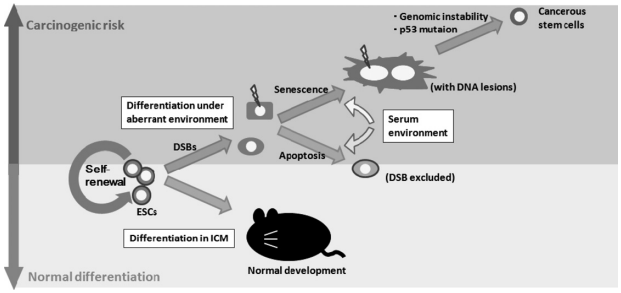


**Figure 2. Transformation of ESCs under aberrant niche or environment**

Induction of genomic instability in stem cells

Although stem-cell maintenance depends on their microenvironment, it remains to be elucidated whether an environmental aberrancy can act as a carcinogenic stressor for cellular transformation of differentiating stem cells into cancer stem cells. Utilizing mouse ESCs as a model, environmental aberrancy during differentiation was demonstrated to lead to the emergence of pluripotent cells showing cancerous characteristics (Figure 2). This suggests that stem cells differentiating in an aberrant environment are at a risk of cellular transformation into malignant counterparts (1).

Arf/p53-dependent downregulation of H2AX and sensitivity to anti-cancer drugs

Cancer cells are generally more sensitive to anticancer drugs than normal somatic cells. However, the factors that determine this differential sensitivity are poorly understood. It was observed that Arf/p53-dependent downregulation of H2AX induced the selective survival of normal cells, resulting in the preferential targeting of cancer cells (3). Treatment with camptothecin, a topoisomerase I inhibitor, caused normal cells to downregulate H2AX while inducing a quiescent cellular state, a process which required both Arf and p53. In contrast, transformed cells are generally mutated in either Arf or p53, thereby not down-regulating H2AX and sensitively responding to the drug, unless they have developed drug resistance. This effect of discrimination between normal and cancer cells is much larger than that of p53-mediated apoptosis induction. Therefore both the H2AX expression level and γH2AX level are critical factors that determine drug sensitivity, which should be considered when administering chemotherapeutic agents.



## List of papers published in 2012

### Journal


1. Fujimori H, Shikanai M, Teraoka H, Masutani M, Yoshioka K. Induction of cancerous stem cells during embryonic stem cell differentiation. J Biol Chem, 287:36777-36791, 2012
2. Hirai T, Shirai H, Fujimori H, Okayasu R, Sasai K, Masutani M. Radiosensitization effect of poly(ADP-ribose) polymerase inhibition in cells exposed to low and high linear energy transfer radiation. Cancer Sci, 103:1045-1050, 2012
3. Yoshioka KI, Atsumi Y, Fukuda H, Masutani M, Teraoka H. The Quiescent Cellular State is Arf/p53-Dependent and Associated with H2AX Downregulation and Genome Stability. Int J Mol Sci, 13:6492-6506, 2012
4. Masutani M. The pioneering spirit of Takashi Sugimura: his studies of the biochemistry of poly(ADP-ribosylation) and of cancer. J Biochem, 151:221-228, 2012


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5. Osada T, Masutani, M. Chapter 14, PolyADP-ribosylation in postfertilization and genome reprogramming: implications for carcinogenesis. In: Gomes AS (ed), Polymerization / Book 1, Rijeka, Croatia, In Tech, pp321-330, 2012

# Division of Integrative Omics and Bioinformatics

**Hitoshi Nakagama, Tsutomu Ohta, Akinobu Hamada, Masaru Katoh, Mamiko Miyamoto, Yuuki Yamamoto, Teruaki Tsuji, Shuichi Shimma, Yuki Takashima**

## Introduction

This Division, consisting of Ohta's Unit, Hamada's Unit and Katoh's Unit, is focused on development of innovative cancer diagnosis and treatment as well as analyses of pharmaco-dynamics based on an integrative omics approach.

## Ohta's unit

Oxidative and electrophilic stresses are sensed by Keap1, which activates transcription factor Nrf2 to achieve cytoprotection by regulating the expression of drug-metabolizing and anti-oxidative stress enzymes/proteins. Constitutive activation of Nrf2 leads to resistance against anti-cancer drugs and growth stimulation in lung cancer. This suggests that inhibition of *NRF2* may provide a new direction for therapeutic approaches in lung cancers with activation of Nrf2. The inhibitors for NRF2 have been searched for using *in vitro* and *in vivo* analyses.

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 functions of SYT-SSX. The SYT-SSX fusion protein produces a dominant-negative function for the SYT, which is a transcriptional co-activator. The SYT-SSX fusion protein complex is purified from cells and the association proteins are analyzed using mass spectrometry.

## Hamada's unit

Research in clinical pharmacology and pharmaco-imaging is focused on the PK/PD analysis of anticancer agents in clinical trial and the development of an integrated pharmacokinetics system. This novel system provides drug exposure levels in the blood and tissue using a high-sensitivity triple-quadrupole mass spectrometer and non-label pharmaco-imagining (*i.e.*, imaging mass spectrometry in a mass microscope). Our aim and research goal are to provide a revolutionary new analyzing system for clinical pharmacology and drug development for use in clinical trials.

Imaging mass spectrometry (IMS) is now widely used in several research fields for pharmacology in particular, IMS can provide novel visualization information that differs from conventional pharmaco-imaging technologies such as autoradiography and positron emission tomography, due to its non-labeled feature. The parent drug and its metabolites can be individually visualized using IMS. The basic of IMS is tissue surface analysis using mass spectrometry. The workflow of IMS is shown in Fig.1. Tissue sections are prepared in a cryo-microtome, after which a thin matrix layer is formed on the tissue surface to absorb UV laser for ionization using a spray or chemical vapor deposition. In IMS, matrix-assisted laser desorption/ionization (MALDI) is used as an ionization method. During IMS measurement, all mass spectra obtained directly from the tissue surface are stored with ionization position information. A peak intensity map of interested *m/z* is reconstructed using the spectra. Here, *m/z* means the mass-to-charge ratio which depends on molecular weight. Therefore, if we can confirm *m/z* peaks correspond to the target drug compounds, tissue distribution is available without labeling.

## Katoh's unit

Atypical Cadherin Fat, involved in tumor suppression and planar cell polarity (PCP), is a *Drosophila* homolog of human FAT1, FAT2, FAT3 and FAT4. FAT1 and FAT4 undergo the first proteolytic cleavage by Furin and are predicted to undergo the second cleavage by γ-secretase to be released into the intracellular domain. Ena/VAPS-binding to FAT1 induces actin polymerization at lamellipodia and filopodia to promote cell migration, while Scribble-binding to FAT1 induces phosphorylation and functional inhibition of YAP1 to suppress cell growth. *FAT1* is preferentially downregulated in invasive breast cancer and is repressed in oral cancer due to homozygous deletion or epigenetic silencing. On the other hand, *FAT1* is upregulated in leukemia. Prognosis of preB-acute lymphocytic leukemia (ALL) patients with *FAT1* upregulation is poor. FAT4 directly interacts with MPDZ/MUPP1

to recruit membrane-associated guanylate kinase MPP5/PALS1. FAT4 is involved in the maintenance of PCP and inhibition of cell proliferation. *FAT4* mRNA is repressed in breast cancer and lung cancer due to promoter hypermethylation. The *FAT4* gene is recurrently mutated in several types of human cancers, such as melanomas, pancreatic cancer, gastric cancer and hepatocellular carcinomas. FAT1 and FAT4 suppress tumor growth via activation of Hippo signaling, whereas FAT1 promotes tumor migration via induction of actin polymerization. FAT1 is tumor suppressive or oncogenic in a context-dependent manner, whereas FAT4 is tumor suppressive. The copy number aberration, translocation and point mutation of the *FAT1*, *FAT2*, *FAT3*, *FAT4*, *FRMD1*, *FRMD6*, *NF2*, *WWC1*, *WWC2*, *SAV1*, *STK3*, *STK4*, *MOB1A*, *MOB1B*, *LATS1*, *LATS2*, *YAP1* and *WWTR1*/*TAZ* genes should be comprehensively investigated in various types of human cancers to elucidate the mutation landscape of the FAT Hippo signaling cascades. Because YAP1 and WWTR1 are located at the crossroads of adhesion, the G-protein-coupled receptor (GPCR), receptor-type tyrosine kinase (RTK) and the stem cell signaling network, cancer genomics of the FAT signaling cascades could be applied for diagnostics, prognostics and therapeutics in the era of personalized medicine.

Katoh contributes to the global science community based on manuscript publication, reviewer activity and editor activity. Katoh carried out peer reviews of grant proposals or journal manuscripts written in English 70 times in 2012. Katoh is an editorial board member of several scientific journals, such as *PLoS ONE*, the *Asia-Pacific Journal of Clinical Oncology*, and t*he International Journal of Oncology*. Katoh made editorial decisions regarding 135 manuscripts submitted to *PLoS ONE* in 2012.

The manuscript citation count in the Web of Science Database (Thomson Reuters) is a surrogate marker of contribution to the global science community. Katoh's manuscripts were cited 530 times by others in 2012.

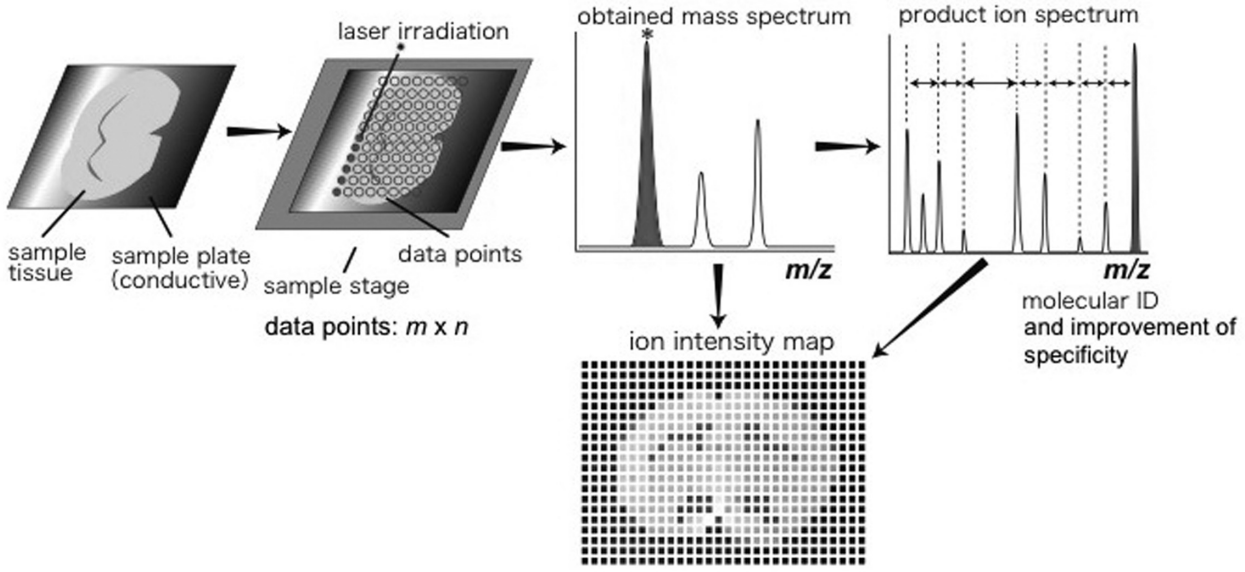


**Figure 1. Workflow of imaging mass spectrometry**

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### Journal


1. Tsubata Y, Hamada A, Sutani A, Isobe T. Erlotinib-induced acute interstitial lung disease associated with extreme elevation of the plasma concentration in an elderly non-small-cell lung cancer patient. J Cancer Res Ther, 8:154-156, 2012
2. Hamada A, Sasaki J, Saeki S, Iwamoto N, Inaba M, Ushijima S, Urata M, Kishi H, Fujii S, Semba H, Kashiwabara K, Tsubata Y, Kai Y, Isobe T, Kohrogi H, Saito H. Association of ABCB1 polymorphisms with erlotinib pharmacokinetics and toxicity in Japanese patients with non-small-cell lung cancer. Pharmacogenomics, 13:615-624, 2012
3. Kato T, Hamada A, Mori S, Saito H. Genetic polymorphisms in metabolic and cellular transport pathway of methotrexate impact clinical outcome of methotrexate monotherapy in Japanese patients with rheumatoid arthritis. Drug Metab Pharmacokinet, 27:192-199, 2012
4. Iwata K, Aizawa K, Kamitsu S, Jingami S, Fukunaga E, Yoshida M, Yoshimura M, Hamada A, Saito H. Effects of genetic variants in SLC22A2 organic cation transporter 2 and SLC47A1 multidrug and toxin extrusion 1 transporter on cisplatin-induced adverse events. Clin Exp Nephrol, 16:843-851, 2012
5. Satoh T, Kubo A, Shimma S, Toyoda M. Mass Spectrometry imaging and structural analysis of lipids directly on tissue specimens by using a spiral orbit type tandem time-of-flight mass spectrometer, SpiralTOF-TOF. Mass Spectrometry, 1: A0013, 2012
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7. Katoh M. Function and cancer genomics of *FAT* family genes. Int J Oncol, 41:1913-1918, 2012


### Book


8. Katoh M. FGF (Fibroblast growth factor). In: Choi S (ed), Encyclopedia of signaling molecules. USA, Springer, pp 603-608, 2012
9. Katoh M. FZD (Frizzled). In: Choi S (ed), Encyclopedia of signaling molecules. USA, Springer, pp 681-687, 2012

# Division of Refractory Cancer Research

**Hitoshi Nakagama, Masato Enari, Shinichi Yachida, Rieko Ohki, Yuko Hibiya, Yukie Aita, Ryo Otomo, Makoto Miyazaki, Yoshinori Asano, Issei Ezawa, Kozue Saito, Shoko Ohde, Miku Shimizu, Shiori Suzuki, Chen Yu, Yuhei Takano**

## Introduction

The Division's 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. The specific activities in 2012 were as follows: 1) p53 inactivation by anaplastic lymphoma kinase through the direct tyrosine phosphorylation of p53; 2) PH domain-only protein PHLDA3, a p53-regurated repressor of Akt and a novel suppressor of endocrine tumors; 3) clinicopathologic and genetic analysis of pancreatic cancers.

## p53 inactivation by anaplastic lymphoma kinase through the direct tyrosine phosphorylation of p53

The tumour suppressor protein p53 is a transcription factor that activates various genes which are responsible for cell growth arrest and apoptosis in response to cellular stress. The inactivation of the p53 pathway is crucial for tumour formation. We have previously found that the nuclear clathrin heavy chain (CLTC) protein, which has been identified as a cytosolic protein functioning that functions in endocytosis and protein sorting, binds to p53 and is required for p53-mediated transcription (Genes Dev. 20,1087-1099, 2006; Oncogene 27, 2215-2227, 2008; J. Mol. Biol. 394, 460-471, 2009). To investigate the role of CLTC in tumours, we first examined the instances of CLTC in various tumors which had fused to anaplastic lymphoma kinase (CLTC-ALK) generated by chromosomal translocation, and investigated the function of the CLTC-ALK fusion on p53-mediated pathways. Unexpectedly, we found that CLTC-ALK inhibited the p53 pathway through ALK-mediated tyrosine kinase activity. Other ALK-fusion proteins including NPM-ALK and EML4-ALK also inhibited the p53 pathway, suggesting that tyrosine phosphorylation was required for the inhibition of the p53 pathway. We performed an immunoprecipitation assay to explore the ALK-phosphorylated proteins that interact with p53 and strikingly found that p53 is directly phosphorylated by ALK-fusion proteins. Mutational analyses revealed that three tyrosine residues in the DNA-binding and C-terminal domains of p53 were phosphorylated to inhibit the p53 pathway. These phosphorylation events enhance Mdm2 binding, leading to decreased p53 stability and the retention of p53 in the cytoplasm. The relationship between ALK and p53 has so far been unclear and we proposed that oncogenic ALK-fusion proteins inhibit p53 function through the direct tyrosine phosphorylation of p53.

## PH domain-only protein PHLDA3; a p53-regulated repressor of Akt and a novel tumor suppressor of endocrine tumors

p53 and Akt are critical players regulating tumorigenesis with opposite effects: while p53 transactivates target genes to exert its function as a tumor suppressor, Akt phosphorylates its substrates and transduces downstream oncogenic signals. In addition, p53 and Akt negatively regulate each other to balance oncogenic and tumor-suppressive signals within a cell. We have identified PHLDA3 as a p53 target gene, which encodes a PH domain-only protein. We found that PHLDA3 competes with the PH domain of Akt for binding of membrane lipids, thereby inhibiting Akt translocation to the cellular membrane and activation (Cell 136, 535-550, 2009). We demonstrated the suppression of anchorage-independent cell growth by PHLDA3, and furthermore, frequent loss of the PHLDA3 genomic locus in primary endocrine tumors. In addition, we demonstrated hyperactivation of Akt and hyperplasia in endocrine tissues in PHLDA3 deficient mice. These results collectively indicate that PHLDA3 is a novel tumor suppressor of endocrine tumors. Our results reveal a new mode of coordination between the p53 and Akt pathways, and show that PHLDA3 is an important downstream mediator of p53 to regulate Akt activity.

## Clinicopathologic and genetic analysis of pancreatic cancers

Pancreatic ductal adenocarcinoma is an aggressive malignancy, usually with widespread metastatic disease. Genetic alterations of *KRAS*, *CDKN2A*, *TP53*, and *SMAD4* are the most frequent events in pancreatic ductal adenocarcinoma. We determined the extent to which these 4 alterations were coexistent in the same carcinoma, and their impact on patient outcome. Pancreatic cancer patients who underwent an autopsy were studied (n = 79). The number of genetically altered driver genes in the adenocarcinoma tissues was variable, with identification of an alteration in all 4 genes being seen in only 29 patients (37%). The number of altered driver genes was significantly correlated with disease free survival, overall survival and metastatic burden at autopsy. On multivariate analysis, the number of driver gene alterations in pancreatic ductal adenocarcinoma remained independently associated with overall survival. Carcinomas with only 1 to 2 driver alterations were enriched for those patients with the longest survival (median 23 months, range 1 to 53). Determinations of the status of the 4 major driver genes in pancreatic cancer, and specifically the extent to which they are coexistent in an individual patient's cancer, provides distinct information regarding disease progression and survival that is independent of the clinical stage and treatment status. We also confirmed the clinical significance of the number of driver gene alterations as a predictive marker of postoperative survival outcome in a population of Japanese patients (Ann Surg 2013, *in press*).

Pancreatic neuroendocrine neoplasms are the second most common tumor among pancreatic tumors. They include well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Furthermore, NECs are divided into large cell NEC and small cell NEC. We reported that small cell NECs are genetically similar to large cell NECs, and these genetic changes are distinct from those reported in NETs.

## List of papers published in 2012
## Journal


1. Yachida S, White CM, Naito Y, Zhong Y, Brosnan JA, Macgregor-Das AM, Morgan RA, Saunders T, Laheru DA, Herman JM, Hruban RH, Klein AP, Jones S, Velculescu V, Wolfgang CL, Iacobuzio-Donahue CA. Clinical significance of the genetic landscape of pancreatic cancer and implications for identification of potential long-term survivors. Clin Cancer Res, 18:6339-6347, 2012
2. Yachida S, Vakiani E, White CM, Zhong Y, Saunders T, Morgan R, de Wilde RF, Maitra A, Hicks J, Demarzo AM, Shi C, Sharma R, Laheru D, Edil BH, Wolfgang CL, Schulick RD, Hruban RH, Tang LH, Klimstra DS, Iacobuzio-Donahue CA. Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. Am J Surg Pathol, 36:173-184, 2012
3. Yachida S. Novel therapeutic approaches in pancreatic cancer based on genomic alterations. Curr Pharm Des, 18:2452-2463, 2012
4. Inoue T, Yachida S, Usuki H, Kimura T, Hagiike M, Okano K, Suzuki Y. Pilot feasibility study of neoadjuvant chemoradiotherapy with S-1 in patients with locally advanced gastric cancer featuring adjacent tissue invasion or JGCA bulky N2 lymph node metastases. Ann Surg Oncol, 19:2937-2945, 2012
5. Fu B, Yachida S, Morgan R, Zhong Y, Montgomery EA, Iacobuzio-Donahue CA. Clinicopathologic and genetic characterization of traditional serrated adenomas of the colon. Am J Clin Pathol, 138:356-366, 2012

# Division of Cancer Prevention Research

**Hitoshi Nakagama, Michihiro Mutoh, Gen Fujii, Rikako Ishigamori, Masami Komiya, Ruri Nakanishi**

## Introduction

Obesity and abnormal lipid metabolism are associated with the development of many cancers, including colon and pancreas cancer. Dyslipidemia, alterations of adipocytokine balance and pro-inflammatory status have been suggested to be involved in the development of colon and pancreatic cancer (1). In animal studies, improvement of dyslipidemia and an abnormal adipocytokine balance suppressed both colon and pancreas carcinogenesis (2, 3). However, the 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.

## Research activities

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. Last year we clearly showed that obese 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 triglyceride, Pai-1, leptin and IL-6 levels and low adiponectin levels. Thus, we examined the effects of pioglitazone on AOM-induced colorectal ACF development in KK-$A^y$ mice. Pioglitazone is a peroxisome proliferator-activated receptorγ (PPARγ) agonist, which used as an anti-diabetic drug with the potential to improve dyslipidemia. Administration of pioglitazone reduced the number of KK-$A^y$ colon ACF / mouse with significant reduction of serum triglyceride and insulin levels (4). Moreover, mRNA levels of Pai-1 and leptin in the visceral fat also decreased. Along the lines of developing novel cancer chemopreventive agents, we demonstrated that a novel chemically synthesized compound SK-1009 suppressed IL-6 mRNA levels in human colon cancer cells through blocking NF-kappaB pathways. As IL-6 is an important biological mediator playing an important role in inflammation and cancer, but few inhibitors and suppressors are known, it is possible that our data may provide important information to enable further development of chemopreventive agents (5). Moreover, one of the promising colorectal cancer chemopreventive agents, indomethacin, also suppresses lung carcinogenesis in urethane treated male A/J mice. This examination also indicated that respiration-gated X-ray micro-computed tomography (micro-CT) was a useful non-invasive imaging approach for evaluating the characteristics and suppression of lung tumors in mice treated with cancer chemopreventive agents (6). In addition, it has been shown that *in vivo* SPECT imaging with $^{111}$In-DOTA-c(RGDfK) was a useful method to detect early pancreatic cancer in a hamster pancreatic carcinogenesis model (7).

## List of papers published in 2012
## Journal

1. Nakano K, Yamamoto M, TakahashiM, Fujii G, Hifumi Y, Shimura M, Nakanishi R, Komiya M, Yanaka A, Mutoh M. Effects of triglyceride on colon epithelial cells during colon carcinogenesis. Ulcer Res, 39:196-200, 2012
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3. Takasu S, Mutoh M, Takahashi M, Nakagama H. Lipoprotein lipase as a candidate target for cancer prevention/therapy. Biochem Res Int, 2012:398697, 2012
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7. Yoshimoto M, Hayakawa T, Mutoh M, Imai T, Tsuda K, Kimura S, Umeda IO, Fujii H, Wakabayashi K. In vivo SPECT imaging with $^{111}$In-DOTA-c(RGDfK) to detect early pancreatic cancer in a hamster pancreatic carcinogenesis model. J Nucl Med, 53:765-771, 2012

# Division of Brain Tumor Translational Research

**Koichi Ichimura, Shintaro Fukushima, Kensuke Tateishi, Ayaka Otsuka, Emiko Yamomoto, Hideyuki Arita, Yuko Matsushita**

## Introduction

Our laboratory focuses on translational research on brain tumors. The prognosis of malignant brain tumors, which make up approximately one third of all primary brain tumors, is dismal. In adults, the great majority of primary malignant brain tumors are gliomas. Glioblastomas (WHO grade IV) are the most malignant and fatal brain tumor, the patients' median survival being only about 14 months after surgical removal. Glioblastomas with MGMT methylation respond to temozolomide better than those without, especially among elderly patients. The presence of IDH1/2 mutations is associated with longer survival and defines a biologically distinct subtype among adult gliomas. Thus, accurately assessing those molecular markers in gliomas is critical in interpreting the outcome of clinical trials in these tumors, as well as in routine clinics. The on-going genome-wide studies using high throughput sequencing technologies will undoubtedly identify novel molecular markers and possibly a therapeutic target. However, to fully evaluate the significance of newly identified glioma-associated genes, an extensive validation using a large cohort of tumors as well as functional analysis are necessary using a suitable model system such as cultured cells.

In contrast to adults, brain tumors are very common among children, being the most frequent solid malignancy in pediatric patients. The spectrum of brain tumors in children differs from that of adults. Recent extensive genetic studies in medulloblastomas, pilocytic astrocytomas, pediatric glioblastomas and ependymomas have identified a number of novel molecular features in these tumors. Based on those findings, medulloblastomas are now subdivided into four groups that have distinctly different molecular profiles and clinical courses. The results are now being translated into molecular classifications and may possibly lead to the development of individualized treatment. Intracranial germ cell tumors (iGCTs) are one of the few pediatric brain tumors that are yet to be explored. They are the second most common brain tumor in children under the age of 14 in Japan. iGCTs are histopathologically divided into 5 subtypes, *i.e.*, germinomas, teratomas, embryonal carcinomas, choriocarcinomas and yolk sac tumors. Mature teratomas may be surgically removed, and germinomas generally respond to combined radio-chemotherapeutic regimens. However a subset of germinomas and other iGCTs may be resistant to therapy and the patients' prognosis may be poor. Their molecular pathogenesis is largely unknown. These tumors require more attention and full molecular investigations.

## Study of MGMT methylation and clinical trials

As outlined above, MGMT methylation is one of the most important molecular markers in glioblastomas as well as other brain tumors such as anaplastic astrocytomas and primary central nervous system lymphomas (PCNSL). Methylation testing of MGMT is employed in most major clinical trials involving gliomas using various methods such as methylation-specific PCR. However an optimal method is yet to be agreed upon. The quantitative MSP-based method used in the Phase III trials in Europe and USA is not available in Japan. We have developed a robust pyrosequencing-based MGMT methylation assay. To validate the efficacy of the assay for predicting the prognosis of the patients, the assay is being compared with the outcome of approximately 140 primary glioblastomas which were treated with radiation and temozolomide. Brain tumor specimens from all clinical trials that take place in Japan will then be collected and analyzed in our laboratory. The optimized assay will also be made available for routine neurosurgical clinics through a diagnostic company with whom we have formed a collaborative partnership.

## Molecular profiling of gliomas and PCNSL

To validate the significance of novel candidate oncogenes/tumor suppressor genes (TSG) for brain tumors, we are currently setting up a large series of tumor samples for gliomas and PCNSL. So far, through a collaborative effort, over 200 tumor samples have been collected from the Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, as well as other neurosurgical centers. Genetic profiling of known genes, such as

IDH1, as well as chromosomal abnormalities (e.g., total 1p/19q loss) has been performed to stratify the sample cohort. Target genes will be selected based on the results of the on-going genome analysis of gliomas and PCNSL. We are also generating a cellular model of gliomas through serial introduction of genetic alterations into human neural stem cells. A neuronal stem cell line has been established in the lab and the recombinant adeno-associated vectors have been provided from Horizon Discovery.

### Genome analysis of intracranial germ cell tumors

To comprehensively study the biology of iGCTs, we have organized and established the Intracranial Germ Cell Tumors Genome Analysis Consortium of Japan, a nation-wide collaborative initiative to centrally collect patients' materials and clinical information. Over 40 centers in Japan and 3 in Korea have joined the Consortium, through which nearly a hundred iGCT cases of various histological subtypes have been obtained so far. DNA and RNA have been extracted from all tumors. A set of genes involved in the MAPK pathway, including c-kit and RAS, have been examined for the presence of mutations. mRNA /protein expression of c-kit and copy number abnormalities have also been studied. The results showed that mutations of c-kit are very common and associated with its elevated expression in germinomas but not in other types of iGCTs. A whole exome sequencing for 40 iGCTs is being carried out. The results will be validated in an independent cohort of tumors of up to 100.

### List of papers published in 2012
### Journal


1. Mulholland S, Pearson DM, Hamoudi RA, Malley DS, Smith CM, Weaver JMJ, Jones DTW, Kocialkowski S, Backlund LM, Collins VP, Ichimura K. MGMT CpG island is invariably methylated in adult astrocytic and oligodendroglial tumors with IDH1 or IDH2 mutations. Int J Cancer, 131:1104-1113, 2012
2. Ichimura K, Nishikawa R, Matsutani M. Molecular markers in pediatric neuro-oncology. Neuro Oncol, 14 Suppl 4:iv90-99, 2012
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# Central Animal / Radioisotope Divisions

**Toshio Imai, Mami Takahashi, Tetsuya Ishikawa, Yoshinori Ikarashi, Kotomi Otsubo, Naoaki Uchiya, Momoko Kobayashi, Natsumi Suda, Teruo Komatsu, Masashi Yasuda, Manabu Tsuchida, Masahiro Nakashima, Ayami Kawashima, Daiju Mutoh, Satoshi Ikeda, Kouki Tamasaka, Junichi Zukeyama, Takuya Matsuyama, Shumpei Ohnami**

## Introduction

The Central Animal Division belongs to the Core Facilities for Research and Innovative Medicine, and a pivotal role of this division is supportive actions for basic/clinical/public health researchers on the basis of biological resources in the National Cancer Center.

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.

## Routine activities

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, histopathological techniques for animal tissues and establishment of expandable cells from clinical cancer tissues.

## Research activities

Research activities of the Central Animal Division 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. Research activities of the Central Radioisotope Division have been performed in collaboration with the Division of Genetics and the Division of Gene and Immune Medicine.

1) Fatty infiltration in the pancreas in association with invasive ductal carcinogenesis in hamsters and man

The influence of obesity and pancreatic fatty infiltration (FI) in pancreatic carcinogenesis is being investigated in human and animal models. Syrian golden hamsters, which are susceptible to chemical carcinogenesis in the pancreatic ducts, are in a hyperlipidemic state and suffer severe FI of the pancreas. The association between the degree of pancreatic FI and pancreatic cancer was investigated in a case-control study in humans. The degree of FI in non-cancerous parts of pancreatic sections was significantly higher in pancreatic cancer patient cases than in the controls, and was positively associated with pancreatic cancer development. In addition, there was a case in which severe fatty pancreas had been observed on CT-scan imaging 5 years before detection of pancreatic adenocarcinoma. These data suggest that severe pancreatic FI could be a risk factor for pancreatic cancer.

2) Pancreatic ductal carcinogenesis and epithelial mesenchymal transition 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 Slug accumulation, which was associated with cytoplasmic/nuclear localization of a membrane-bound mucin MUC1, in invasive areas of carcinoma but not in early stage lesions and glandular areas of carcinoma. The results might suggest that the activation of MUC1 plays a role in EMT via Slug accumulation in pancreatic carcinoma cells.

3) Mechanisms of promotion/progression of mammary carcinogenesis associated with a high-fat diet

The effects of a high-fat diet (HFD) during prepubertal and pubertal stages were investigated

in 7, 12-dimethyl -benz(a)anthracene-induced mammary carcinogenesis in female F344 rats. The results obtained indicated that HFD promoted carcinogenesis, and, in addition, affected aggressive phenotypes of the induced carcinomas. Molecular mechanisms of the promotion/progression as assessed with DNA microarray analysis for the carcinoma tissues were speculated to be associated with increased expression of a couple of cell cycle-related genes, which were reported to be up-regulated in human breast carcinoma cell lines.

4) *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) and donor cell engraftment. The *in vivo* fluorescence imaging technique can visualize GFP donor cells and is a very useful tool for exploring immunomodulatory reagents for GVHD and understanding the action and mechanism of the reagents.

5) Human induced malignant stem cells and human induced hepatic stem cells for compound and/or target screening in anti-cancer drug discovery

Gene transfer of OCT3/4, SOX2, KLF4, and (c-Myc) was able to establish human induced malignant stem (iMS) cells and human hepatic stem (iHS) cells from normal or cancer tissues. The expandable iMS cells and iHS cells are similar to human embryonic stem (ES) cells and induced pluripotent stem (iPS) cells in morphology. Human iHS cells markedly expressed hepatocyte-specific genes and human iMS cells have aberrations such as mutations in endogenous tumor suppressor genes and/or endogenous cancer-related genes. In addition, these cells express ES/iPS cell-specific genes at an equivalent level. Such iMS cells and iHS cells would be useful for compound and/or target screening in anti-cancer drug discovery.

6) Functional analysis of genetic polymorphisms associated with folate metabolism

Epidemiological and clinical studies have suggested an inverse association between folate intake and risk for cancer, in particular pancreatic, colon and esophagus cancer, whereas folate deficiency is associated with DNA strand breaks, impaired DNA repair, increased mutations and aberrant DNA methylation. Some genetic polymorphisms involved in folate metabolism such as methylenetetrahydrofolate reductase (*MTHFR C677T* and *A1298C*) and methionine synthase reductase (*MTRR G66A* and *C1862T*), may modulate the effect of dietary folate on DNA methylation and cancer susceptibility.

To elucidate the functional significance of the *MTHFR* or *MTRR* variants, we transfected the plasmid vector expressing the *MTHFR* or *MTRR* cDNA to human embryonic kidney 293 cells, which express an undetectable level of endogenous MTHFR or MTRR protein. We found that the exogenous MTHFR protein was produced at lower levels in the *MTHFR* transfectants harboring the *MTHFR 677TT* or *1298CC* cDNA, as compared with the *677CC* or *1298AA* transfectants harboring the wild-type. On the other hand, the exogenous MTRR protein showed no obvious differences between the *MTRR 66AA* or *1862TT* variants and wild-type. All *MTHFR* transfectants showed dramatically decreased homocysteine levels in culture mediums and a lower level of the total methyl-CpG content than those of Lac-Z control transfectants, but not in *MTRR* transfectants.

These preliminary results may facilitate our understanding of the functional genetic polymorphisms associated with folate metabolism that affect susceptibility to cancer through individual variation.

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### Journal


1. Cho YM, Imai T, Takami S, Ogawa K, Nishikawa A. Female heterozygous (+/*fa*) Zucker rats as a novel leptin-related mammary carcinogenesis model. J Toxicol Sci, 37:1025-1034, 2012
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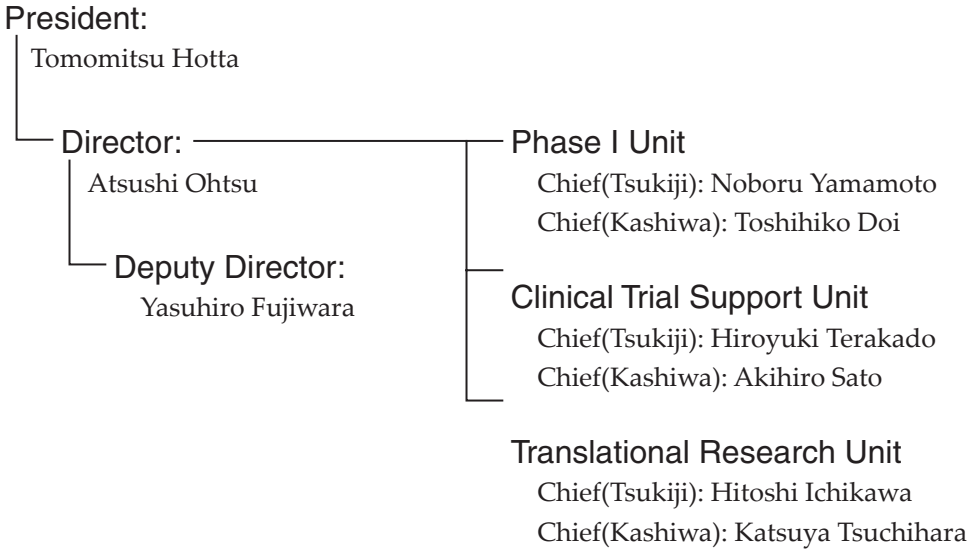
# Exploratory Oncology Research & Clinical Trial Center

# Preface

In 2011, our National Cancer Center was selected as one of the five designated centers for early/exploratory clinical trial. With a budget support from the Japanese Ministry of Health, Labour and Welfare ( MHLW), we organized "the Exploratory Oncology Research and Clinical Trial Center" (NCC-EPOC) through the Kashiwa and Tsukiji campuses consisting of a phase I unit in each campus, central/data center functions for clinical trials, and a translational research (TR) unit. There are three missions of the NCC-EPOC: to conduct first-in-human (FIH) trials, investigator-initiated trials (IIT) with unapproved agents, and TRs during early clinical studies. To date, 10 sponsor-initiated FIH trials have already been conducted in total at both campuses. We have initiated one IIT with an unapproved agent, TAS-102, which was originally developed in Japan and has already completed its accrual in collaboration with 6 major cancer centers. Additional 8 IITs are being planned of which 5-6 studies will start in early 2013 including new agent/vaccines originally developed in the Research Center for Innovative Oncology. We have started a nation-wide screening program for the RET fusion gene, which was newly discovered in the Research Institute of our center, in patients with non-small cell lung cancer (NSCLC), for accrual to a phase II IIT with a RET inhibitor. This study is the first trial for RET positive NSCLC with a large screening program in the world. There are several new seeds from academia in Japan currently being planned for FIH or IIT under discussion with the regulatory authorities and two international studies. TR projects with whole exon sequencing in some cancers are underway to establish molecular epidemiologic data in Japanese patients and a cancer encyclopedia. A genome-guided individualized therapy system in collaboration with Hospital East named the ABC study has also been started, which will be followed by other collaborating institutions. These efforts will contribute to the activation of early clinical trials on new agents and to the organization of an active academic research organization (ARO). The goal of NCC-EPOC is to establish a top innovative ARO in the world based on close alliances between academia-industry-government.

Atsushi Ohtsu, M.D., Ph.D.
Director, Exploratory Oncology Research & Clinical Trial Center

## Organization

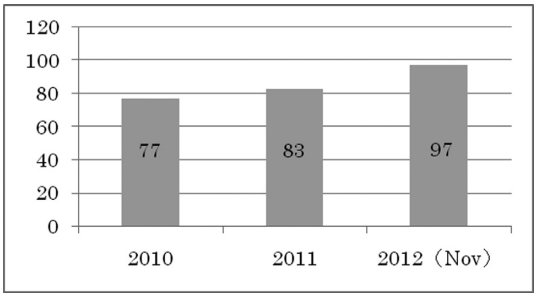


# Activities of the Divisions

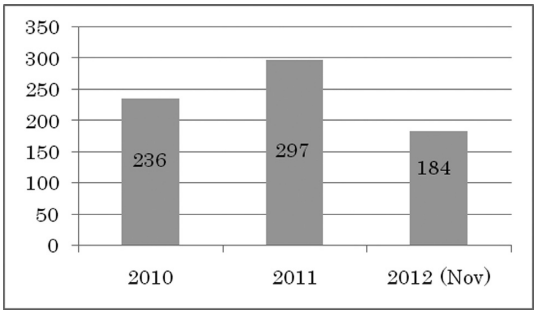
# Phase I Unit

## Overview of the NCC-EPOC Phase I Unit

The NCC-EPOC Phase I Unit was established in 2012. The NCC-EPOC Phase I Unit consists of two sub-units (NCC & NCCE) which are organized by each Hospital. The goal of both NCC-EPOC Phase I Units is to perform initial clinical evaluation of promising new anti-cancer compounds emerging from the laboratory. We conducted over 100 Phase 1 trials (including FIH trials) and enrolled over 200 patients. Our Phase I Unit is the largest program in Japan, indeed in Asia, and we contribute to the development of new cancer drugs through early phase trials.




**Number of contracted phase I trial**




**Number of accrual pts in Phase I trial**

## Phase I Unit

The Phase I Unit, with its firm cooperation with all the divisions, serves as the core of the NCC-EPOC clinical development. The cross-divisional phase I team in each hospital consists mainly of investigators from the NCC/NCCE hospitals. The members are as follows:

In addition to the members as above, many young investigators including staff doctors, residents, senior residents, many paramedical staff as well as researchers join the Phase I Unit. Furthermore, the Clinical Trial Coordinating Office and supporting unit of NCC-EPOC in each hospital back us up to jointly implement registration trials and investigator initiated clinical trials.

On a weekly basis, we share information on the progress of the sponsor-initiated clinical trial and the investigator-initiated clinical trial with those core members.

## Facilities

At each hospital, based on many years of achievement, advanced equipment as well as abundant specimens and skillful experts are openly available as follows:

- Clinical Trial Wards
- Outpatient Treatment Center
- Clinical Trial Coordinating Office
- Clinical Laboratory Division
- Pharmacy Division
- Diagnostic Radiology Division
- The Research Institute

| | NCCHE | NCCH |
|---|---|---|
| Director of Phase I Unit | Toshihiko Doi | Noboru Yamamoto |
| core member | Takayuki Yoshino | Yasuhide Yamada |
| | Takashi Kojima | Kenji Tamura |
| | Kouhei Shitara | Yoshitaka Narita |
| | Nozomu Fuse | Hideki Ueno |
| | Kiyotaka Yoshino | Yukio Kobayashi |
| | Yoichi Naito | Atsushi Makimoto |
| | Nobuaki Matsubara | Motokiyo Komiyama |
| | Izumi Ohno | Fumihiko Nakatani |
| | Shigeki Uemura | Naoya Yamazaki |
| | | Ken Ohashi |

# Clinical Trial Support Unit

**Akihiro Sato, Miki Fukutani, Hiromi Hasegawa, Shogo Nomura, Yasuko Nishikubo, Akiko Nakayama, Yasutaka Watanabe, Yukie Kimura, Hiroyuki Terakado, Tamie Sukigara, Nobuko Ushirozawa, Yushi Nagai, Hiroko Nakahama, Noriko Kobayashi, Miki Ito, Shuuzi Misawa, Harue Ui**

## Introduction

The support unit of EPOC supports seamlessly from the standpoints of planning, protocol development, project management, data management, monitoring, statistical analysis and CRC support across the entire early clinical trial program. This unit is a multidisciplinary team which consists of a clinical research coordinator (CRC), Data manager, Clinical research associate, Medical writer, biostatistician, and various other specialists.

## Routine activities

CTM group
- Project management
- Study management
- Site visit monitoring
- Medical writing

DM group
- Data base and CRF form design
- Data management
- Central monitoring
- System administration

Statistical group
- Study design
- Statistical analysis
- Consultation

CRC group
- Support clinical trials that are conducted in the National Cancer Center

IRB office
- Oversees all IRB activities

## Research activities and clinical trials

We supported 5 investigator-initiated IND trials using unapproved anti-cancer drugs and 8 non-IND trials using unapproved drugs and medical devices in 2012. Through these studies an electronic data capturing (EDC) system, clinical data management system, and various standard operating procedures were implemented. The CRC group supported over 100 early clinical trials initiated either by industry or investigators in the National Cancer Center in 2012.

Our research activities are mainly focused on clinical trial methodology, organizing infrastructure, and managing early/exploratory clinical trials. For these purposes, we are developing new EDC system, sampling the source document verification (SDV) method and comprehensive information sharing for safety in these trials.

# Translational Research Unit

**Katsuya Tsuchihara, Yasuhiro Matsumura, Shingo Matsumoto, Hideki Makinoshima, Sachiyo Mimaki, Atsushi Ochiai, Takeshi Kuwata, Akiko Nagatsuma, Yuka Nakamura, Hitoshi Ichikawa, Tatsuhiro Shibata, Natsuko Hama, Takashi Kohno, Akinobu Hamada, Shuichi Shimma, Fumiaki Koizumi, Yasuo Kodera**

## Introduction

Basic and translational researchers at the Research Center for Innovative Oncology (Kashiwa Campus) and the Research Institute (Tsukiji Campus) are involved in this Unit, the aim of which is to develop novel anti-cancer therapeutics as well as to prove their concepts. The unit also closely collaborates with intramural and extramural clinical research teams to develop companion diagnostic systems and identify biomarkers contributing to individualized cancer therapy.

## Routine activities

Translational Research Conferences have been regularly held in both campuses to discuss the strategic approaches to develop novel clinical trials.

## Research activities

Individual cancers harbor a set of genetic aberrations such as mutations and gene fusions, and some of them are expected to become informative biomarkers to predict therapeutic response and minimize adverse drug reaction in molecular targeted therapies. In the Tsukiji campus, as a collaborative work with the Center Hospital and Research Institute, systematic genetic testing using hiagh-throughput sequencer (clinical sequencing) is planned to start in 2013, to identify mutations and fusions of potentially targetable genes. This year, sequencing platform comparison and construction of computational analysis pipelines for rapid detection of genetic aberrations were performed. In the Kashiwa campus, the "Analyses of Biopsy Samples for Cancer Genomics study (ABC study)" was planned and carried out in collaboration with the TR unit and all the oncology departments of the Hospital East. The study verified the feasibility of the clinical sequencing. Biopsy samples from the patients, in whom drug therapies were planned, were collected and genomic DNA samples were analyzed with commercially available amplicon sequencing panels containing known hot-spots of cancer-related genes at the validated clinical testing laboratory. In the first 7 months, more than 100 cases have been enrolled and amplicon sequence starting with 10 ng of genomic DNA was successfully performed. The study will be expanded to verify the utility of being able to direct clinical applications in the near future.

# 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

President:
Tomomitsu Hotta

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 ,Takehiro Izumo, Gen Iinuma* Yosuke Otake*, Takahiro Kasamatsu*, Tomoyasu Kato*, Mitsuya Ishikawa*, Syunichi Ikeda*, Satoshi Okada*, Shiho Gomi*, Masahiro Suzuki*, Takeshi Murano*, Naoki Shimada*, Akiko Nagoshi*, Junko Sonehara*, Shigeyuki Hasuo*, Motoi Miyakoshi*, Midori Hashimoto*, Akiko Sakurai*, Emi Masuda*, Daisuke Kano, Yoshie Nagumo*, Yoshi Kosai, Miyuki Mandai, Akiko Kutsuzawa, Michiko Hirota , Mari Kanega, Mizuho Nomoto, Miho Ishikawa, Teiko Oki, Yoshie Iga (*NCCH)**

## Introduction

In April 2008, a change in the Research Center for Cancer Prevention and Screening (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 National Cancer Center Hospital (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 (1.5 T and 3.0 T), 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 has been prepared for lung and female genital cancers, including cancer of the uterus and ovary, breast cancer and gastrointestinal cancer. Blood samples are also obtained for biochemistry and tumor markers such as CA19-9, CEA, CA125, PSA, and genetic analysis.

2. Eligibility criteria for participants

The cancer screening program at the Research Center for Cancer Prevention and Screening has been planned for applicants 40 years or older who give written informed consent for the screening, including blood samples for genetic analysis, and who take the questionnaire survey concerning lifestyles. These study protocols have been approved by The Institutional Review Board (IRB). Applicants who have been diagnosed as having cancer, and/or have a history of cancer treatment, such as surgery or endoscopic mucosal resection or chemotherapy within the previous one year, are excluded.

3. Cancer screening methods

In the multiphasic cancer screening programs, CT for lung cancer, abdominal US for cancer of the liver, gall bladder, pancreas, and kidney, MRI for cancer of the uterus and ovary, gynecological examinations with Pap-smear, and MMG and US for breast cancer are performed on the first day. On the following day, gastroscopy for cancer of the esophagus and stomach, and total colonoscopy for cancer of the colon and rectum are conducted. If a barium enema is chosen, the examination is carried out on the third day. Moreover, from the beginning of December 2010, CT-colonography (CTC) has been provided as an optional method for cancer screening. FDG-PET is offered on the first day as an option, if the participants wish to undergo the examination.

4. Results of cancer screening

Recent accurate data on cancers have not been obtained due to lack of adequately long follow-up data from our 2012 patients. We have therefore presented confirmed data from the previous year. Two thousand seven hundred and sixty four participants underwent multi-phasic programs (new, 1210; repeater, 1554). Malignant tumors were

detected in 43 out of 1210 new participants and in 32 out of 1554 repeaters who underwent multi-phasic clinical programs in 2011 (Tables 1 and 2). Detection rates were 3.55% and 2.06%, respectively.

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 with 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 are in the process of evaluation. The usefulness of the adjunction of digital breast tomosynthesis to full-field digital mammography in evaluation of the pathological response after neoadjuvant chemotherapy for breast cancer detected at the NCCH has been assessed.

(2) The clinical usefulness of CT-colonography has been assessed.

(3) In order to establish guidelines for the management of pulmonary nodules detected with low-dose chest CT screening, patients with pulmonary nodules between 5 mm and 10 mm in size are being examined in the follow-up clinic.

(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 (3.0 T) in the cancer screening of the uterus and /or ovaries 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 the follow-up data has been started.

**Table 1. Cancerous detection rate in new participants (2011)**

| | No. of cancerous cases | No. of new participants | Detection rate (%) |
|---|---|---|---|
| colo-rectum | 14 | 1210 | 1.16 |
| stomach | 10 | 1210 | 0.83 |
| breast | 3 | 420 | 0.71 |
| prostate | 4 | 790 | 0.51 |
| lung | 4 | 1210 | 0.33 |
| uterus | 1 | 420 | 0.24 |
| thyroid | 2 | 1210 | 0.17 |
| esophagus | 1 | 1210 | 0.08 |
| pancreas | 1 | 1210 | 0.08 |
| kidney | 1 | 1210 | 0.08 |
| others | 2 | 1210 | 0.17 |
| total | 43 | 1210 | 3.55 |

**Table 2. Cancerous detection rate in repeat participants (2011)**

| | No. of cancerous cases | No. of repeat participants | Detection rate(%) |
|---|---|---|---|
| colo-rectum | 7 | 1526 | 0.46 |
| stomach | 8 | 1526 | 0.52 |
| breast | 4 | 524 | 0.76 |
| prostate | 5 | 1030 | 0.49 |
| lung | 1 | 1554 | 0.06 |
| uterus | 1 | 524 | 0.19 |
| thyroid | 1 | 1554 | 0.06 |
| esophagus | 2 | 1526 | 0.13 |
| pancreas | 3 | 1554 | 0.19 |
| total | 32 | 1554 | 2.06 |

## List of papers published in 2012

### Journal

1. Goshima S, Kanematsu M, Kobayashi T, Furukawa T, Zhang X, Fujita H, Watanabe H, Kondo H, Moriyama N, Bae KT. Staging hepatic fibrosis: computer-aided analysis of hepatic contours on gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid-enhanced hepatocyte-phase magnetic resonance imaging. Hepatology, 55:328-329, 2012
2. Watanabe H, Kanematsu M, Goshima S, Kondo H, Kajita K, Kawada H, Noda Y, Moriyama N. Detection of focal hepatic lesions with 3-T MRI: comparison of two-dimensional and three-dimensional T2-weighted sequences. Jpn J Radiol, 30:721-728, 2012
3. Watanabe H, Kanematsu M, Kato H, Kojima T, Miyoshi T, Goshima S, Kondo H, Kawada H, Noda Y, Moriyama N. Enhancement of anatomical structures and detection of metastatic cervical lymph nodes: comparison of two different contrast material doses. Jpn J Radiol, 30:846-851, 2012
4. Kanematsu M, Goshima S, Watanabe H, Kondo H, Kawada H, Noda Y, Moriyama N. Diffusion/perfusion MR imaging of the liver: practice, challenges, and future. Magn Reson Med Sci, 11:151-161, 2012
5. Inoue K, Kurosawa H, Tanaka T, Fukushi M, Moriyama N, Fujii H. Optimization of injection dose based on noise-equivalent count rate with use of an anthropomorphic pelvis phantom in three-dimensional 18F-FDG PET/CT. Radiol Phys Technol, 5:115-122, 2012
6. Kakinuma R, Ashizawa K, Kobayashi T, Fukushima A, Hayashi H, Kondo T, Machida M, Matsusako M, Minami K, Oikado K, Okuda M, Takamatsu S, Sugawara M, Gomi S, Muramatsu Y, Hanai K, Kaneko M, Tsuchiya R, Moriyama N. Comparison of sensitivity of lung nodule detection between radiologists and technologists on low-dose CT lung cancer screening images. Br J Radiol, 85:e603-608, 2012
7. Umeda I, Tani K, Tsuda K, Kobayashi M, Ogata M, Kimura S, Yoshimoto M, Kojima S, Moribe K, Yamamoto K, Moriyama N, Fujii H. High resolution SPECT imaging for visualization of intratumoral heterogeneity using a SPECT/CT scanner dedicated for small animal imaging. Ann Nucl Med, 26:67-76, 2012
8. Kanematsu M, Kondo H, Goshima S, Tsuge Y, Watanabe H, Moriyama N. Giant high-flow type pulmonary arteriovenous malformation: coil embolization with flow control by balloon occlusion and an anchored detachable coil. Korean J Radiol, 13:111-114, 2012
9. Watanabe H, Kanematsu M, Goshima S, Yoshida M, Kawada H, Kondo H, Moriyama N. Is gadoxetate disodium-enhanced MRI useful for detecting local recurrence of hepatocellular carcinoma after radiofrequency ablation therapy? AJR Am J Roentgenol, 198:589-595, 2012
10. Kakinuma R, Ashizawa K, Kuriyama K, Fukushima A, Ishikawa H, Kamiya H, Koizumi N, Maruyama Y, Minami K, Nitta N, Oda S, Oshiro Y, Kusumoto M, Murayama S, Murata K, Muramatsu Y, Moriyama N. Measurement of focal ground-glass opacity diameters on CT images: interobserver agreement in regard to identifying increases in the size of ground-glass opacities. Acad Radiol, 19:389-394, 2012
11. Tateishi U, Terauchi T, Akashi-Tanaka S, Kinoshita T, Kano D, Daisaki H, Murano T, Tsuda H, Macapinlac HA. Comparative study of the value of dual tracer PET/CT in evaluating breast cancer. Cancer Sci, 103:1701-1707, 2012

### Book

12. Uchiyama N, Kinoshita T, Hojo T, Asawa S, Suzuki J, Kawawa Y, Otsuka K. Optimization of digital breast tomosynthesis (DBT) for breast cancer diagnosis. Mammography recent advances INTECH, Croatia, pp 355-370, 2012
13. Uchiyama N. Breast CAD (computer aided detection) in FFDM (full field digital mammography). Mammography recent advances INTECH, Croatia, pp 281-292, 2012
14. Uchiyama N, Kinoshita T, Hojo T, Asawa S, Suzuki J, Kawawa Y, Otsuka K. Usefulness of adjunction of digital breast tomosynthesis (DBT) to full-field digital mammography (FFDM) in evaluation of pathological response after neoadjuvant chemotherapy (NAC) for breast cancer. Breast imaging, 11th international workshop, IWDM 2012, Philadelphia, proceedings, Springer-Berlin Heidelberg, pp 354-361, 2012
15. Uchiyama N, Kinoshita T, Hojo T, Asawa S, Suzuki J, Kawawa Y, Otsuka K. Diagnosis impact of adjunction of digital breast tomosynthesis (DBT) to full-field digital mammography (FFDM) and in comparison with full field digital mammography (FFDM). Breast cancer. Breast imaging, 11th international workshop, IWDM 2012, Philadelphia, proceedings, Springer-Berlin Heidelberg, pp 354-361, 2012

# Screening Assessment and Management Division

**Hiroshi Saito, Chisato Hamashima, Kumiko Saika, Yuri Mizota, Chikako Yamaki, Ryoko Machii, Koichi Nagata, Ayako Aoki, Yoshiki Ishikawa, Sayuri Amanuma, Junko Asai, Kanoko Matsushima, Kazuko Matsuda, Noriaki Takahashi, Hiromi Sugiyama, Keiko Kawarabata, Akiko Totake**

## Introduction

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 2007and revised in 2012. Thus, our Division has developed and updated screening guidelines (Cancer Screening Assessment) and constructed quality assurance systems for the screening programs (Cancer Screening Management).

## Routine activities

- Development of Cancer screening guidelines

Guidelines on screening for breast cancer have been developed and will be published in 2013.

- Quality Assurance (QA) in cancer screening at municipalities

The Division collected the information related to implementation of cancer screening and the situation regarding its management using Checklists (CLs) as a structure indicator in quality assurance at municipalities. The division also evaluated process indicators such as rate of work-up, and ranked those indicators in all cities by prefecture in order of grade so that each city compares its indicator with those of other cities.

- Calculation of standardized screening rate

The reported screening rate from the Ministry of Health, Labour and Welfare has not been standardized, because the method used to estimate the target population differs by municipality. The Division calculated the standardized screening rate using the same method. This activity was performed in part as a project of the Center for Cancer Control and Information Services and will be continued on an annual basis. The calculated data were released on the website of the Center for Cancer Control and Information Services.

- Workshop on cancer screening management

The Division held several educational workshops for the members of prefectural committees of cancer screening management, aiming at activating quality assurance activities in each of 47 prefectures. The themes this year were the stomach and colorectum. The main contents of the workshops were the methods of quality assurance of the screening programs within each prefectures. The committees were encouraged to release the evaluation results of the screening management status of each municipality in the prefectures. Other basic issues necessary for conducting organized cancer screening programs, such as issues concerning screening assessment, were also included in the workshop programs.

There were 69 participants in the workshops from 43 prefectures, who consisted of administrative officers (one-third) and chairmen of each committee (two-thirds). This activity was performed as the project of the Center for Cancer Control and Information Services and will be continued on an annual basis.

In the previous year, the Division held a workshop on lung cancer. According to the survey, 32 prefectures held meetings to discuss cancer screening management and 8 prefectures released the evaluation results. To evaluate the effect of the workshop on the activity of the prefectural committees, the Division will scrutinize the performance of each committee through surveillance in the municipalities.

## Research activities

- A randomized controlled trial of colonoscopic screening

A randomized controlled trial evaluating one-time colonoscopic screening (CS) for colorectal cancer was started in 2009. The Division has been responsible for designing and managing the study as the head office of the study. The study fields were extended throughout the neighboring Daisen city which has a population of 43,000 as of this year. However, participation rate in the study was unexpectedly as low as one-third in the new field as compared to the previously-involved fields. Finally, the cumulative number of subjects who gave informed consent, and who were thus enrolled in the study, was 5001 during the 41 months after starting recruitment, corresponding to half of the planned number. Low participation in the new field was mainly due to the inadequate recruiting activity infrastructure, , which is different from that in the previously involved fields and is now being redesigned to allow effective recruitment. In addition, low awareness of colon cancer and colonoscopy, such as fear of colonoscopy-related pain was confirmed as a major barrier. A campaign aimed at promoting knowledge of colorectal cancer screening, which was effective in the initially involved fields, was also put in place.

- Evaluation and accuracy studies on gastric cancer screening

A comparative study without randomization evaluating endoscopic screening for gastric cancer was started in Niigata City in 2011. The sensitivities of endoscopic and radiographic screening for gastric cancer were calculated by the detection method and the incidence method based on the results of community-based screening in Japan. Endoscopic screening for gastric cancer had a higher sensitivity than radiographic screening by the incidence method in the prevalence and incidence screening rounds.

- Studies on Raising Participation Rates in Screening Programs

Several randomized controlled studies to evaluate the call-recall system and various invitation tools for screening participation, which were developed by a health-communication technique, were conducted for colorectal cancer screening as well as breast cancer screening, It was demonstrated that messages to individual subjects, tailored according to the characteristics of those persons, could raise screening uptake more efficiently than the usual invitation letter.

## List of papers published in 2012
## Journal


1. Lambert R, Saito H, Lucas E, Sankaranarayanan R. Survival from digestive cancer in emerging countries in Asia and Africa. Eur J Gastroenterol Hepatol, 24:605-612, 2012
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# Epidemiology and Prevention Division

**Shoichiro Tsugane, Shizuka Sasazuki, Motoki Iwasaki, Norie Sawada, Taichi Shimazu, Taiki Yamaji, Ai Noda, Izumi Suenaga, Hadrien Charvat, Azusa Hara, Yoshitaka Tsubono, Masayuki Tatemichi, Tsutomu Miura, Minatsu Kobayashi, Yuko Yamano, Junko Ishihara, Sana Yokoi, Ribeka Takachi, Takehiro Michikawa, Manami Inoue, Keiko Mori, Thomas Svensson, Kayo Ohashi, Yuri Ishii, Yingyan Gong, Jun Umesawa, Tomomi Mukai, Koichi Kawamura, Michiko Okajima, Ayako Toyama, Hideyo Ochi, Yurie Shinozawa, Izumi Matsumoto, Yasuko Iba**

## Introduction

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.

## Research activities

Population-based prospective study (the JPHC study and the JPHC-NEXT 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 22,911 deaths, 18,376 cases of cancers, 6,105 cases of strokes and 1,189 cases of myocardial infarctions, had been documented as of September, 2012.

In the cohort, lifestyle factors that were assessed in the baseline and/or 5 and/or 10 year follow up questionnaire, examination data from health checkups or stored blood samples were investigated in relation to the subsequent risk of total death, total or specific cancer and other lifestyle-related diseases.

Total Cancer: The association between five combined healthy lifestyle factors (not smoking, moderate drinking, eating minimum salt-preserved foods, being physically active, and having an appropriate body mass index) and cancer incidence was evaluated and the risk was reduced 14% and 9% by each one healthy lifestyle for men and women, respectively, suggesting that the combined lifestyle factors have a considerable impact on preventing cancer (1). The association between cadmium exposure and incidence of cancer was examined but no association was observed (2). Stomach Cancer: The association between isoflavone intake and stomach cancer incidence was investigated but no association was seen. Colorectal Cancer: The association between zinc and heme iron intakes and colorectal cancer incidence was investigated but no association was observed (4). Liver Cancer: The association between fish and n-3 polyunsaturated fatty acids (PUFA) consumption and hepatocellular carcinoma (HCC) incidence was investigated and consumption of n-3 PUFA-rich fish and individual n-3 PUFAs was inversely associated with HCC irrespective of hepatitis B virus (HBV) or hepatitis C virus (HCV) status (5). A risk estimation model for the 10-year risk of hepatocellular carcinoma (HCC) was developed (6). Ovarian Cancer: The risk factors for invasive primary epithelial ovarian cancer were evaluated among the female subjects and inverse associations were seen for giving birth more than once and a usual sleep duration of more than 7 hours per day (7). Thyroid Cancer: The association between consumption of seaweed that is rich in iodine and the thyroid cancer incidence among the female subjects in which most of the cases were papillary carcinoma and an increased risk of papillary carcinoma was observed in postmenopausal women but not in premenopausal women (8). The others: Not only cancer but also other non-communicable diseases (NCDs) are designed to be endpoints of the cohort study. Associations between lifestyle factors and stroke (9, 10), coronary heart disease (11), cardiovascular disease (CVD) (12, 13), dentition status (14) and diabetes (15) were investigated. The reproducibility and validity of dietary patterns assessed with a food frequency questionnaire (FFQ) used in the 5-year follow-up survey were examined (16).

Recruitment for the JPHC-NEXT study and the collaborative studies set for 100,000 participants started in 2011 and is in progress in several areas in order to update evidence with the current generation. Men and women of 40-74 years old of age at the baseline survey are to be followed up for

20 years. Overall survival and NCDs such as cancer, CVD, diabetes and mental illness are listed as the main endpoints. The collected data and samples are to be analyzed with up-to-date technology including genomics. A standard protocol for a molecular epidemiology cohort study in Japan is projected to be developed based on the JPHC-NEXT protocol. To conduct verification of the feasibility and validation study to consolidate data together with the other cohort study and its original protocol, a new cohort study by Strategic Funds for the Promotion of Science and Technology was launched and about 1800 men and women were recruited in 2 areas in 2012. The eventual goal of the project is to promote the Japanese Consortium for Cohort Studies of Molecule and Lifestyle presenting a vision of all molecular epidemiology cohort studies united nationwide.

Epidemiological study of Japanese Brazilians (Sao 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 case-control study was conducted with subjects in Nagano, Japan, and São Paulo, Brazil to clarify the association between particular genetic markers of immunoglobulin G (IgG) and susceptibility to breast cancer. The GM 3 allele was significantly associated with susceptibility to breast cancer in white subjects from Brazil (17). A colorectal adenoma case-control study in Japanese Brazilians in São Paulo is in progress. The validity of the FFQ used in the study was examined.

Studies in Nagano and Hiraka and other intramural projects

Based on a cross-sectional study of women in Nagano, a higher folate intake was significantly associated with a lower level of global methylation of leukocyte DNA (18), whereas postmenopausal endogenous sex hormones were not (19). Vitamin C supplementation in relation to inflammation in individuals with atrophic gastritis was assessed in a randomised controlled trial at Hiraka, in Akita Prefecture, an area of high stomach cancer incidence, suggesting that vitamin C supplementation may not have a strong effect on reducing infections in individuals with atrophic gastritis. 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). The association between plasma 25-hydroxyvitamin D and colorectal adenoma according to dietary calcium intake and vitamin D receptor polymorphism was investigated. The results suggested that Vitamin D might protect against colorectal neoplasia, mainly through mechanisms other than the indirect mechanism via calcium metabolism (20). The association of biomarkers for insulin and the insulin-like growth factor (IGF) axis with colorectal adenoma was investigated and a significant gender difference was observed in the results (21). A comprehensive analysis using data from the Lung Cancer Database Project was conducted to search for clinical biopsychosocial risk factors for depression in lung cancer patients, suggesting that depression was most strongly linked with personality traits and coping style (22). The design of a Japanese multicenter prospective cohort study on endoscopic resection for early gastric cancer using a Web registry (J-WEB/EGC) was introduced to the public (23).

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 (24-28) and some pooled analyses (29-31) were conducted. 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/) and distribution of booklets. Based on the judgments, current evidence-based cancer prevention recommendations for Japanese provided by the study group were also updated. The evidence-based materials to develop the recommendations were handed in to develop measures and policies in national health promotions. A systematic assessment was performed to estimate the current burden of cancer attributable to known preventable risk factors in Japan (32). Prediction model applications that calculate changes in risk through lifestyle modification were put on the internet based on results from the JPHC study. Data on the probability of 10-year survival free from cancer and cardiovascular incidence, and, for men, of the 10-year risk of colorectal cancer development are now available (http://epi.ncc.go.jp/riskcheck/).

International collaborative projects

International collaborative projects to contribute on to the global scale with a focus on Asian cancer prevention strategies (Japan-China cooperative research work, Asia Cohort Consortium (ACC) (33), Asia Breast Cancer Consortium (34, 35), Pooling project of Prospective Studies of Diet and Cancer (36), Collaborative Group on Hormonal

Factors in Breast Cancer (37), etc.) are in progress.

Reviews and others

The effects of 16 risk factors on cause-specific deaths and life expectancy in Japan were estimated from data from the National Health and Nutrition Survey, epidemiological studies and statistics (38). Two reviews on alcohol, smoking, and obesity epidemiology in Japan (39) and epidemiological evidence for insulin resistance and cancer (40) and a commentary on translational research for preventive medicine (41) were published.

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# Center for Cancer Control and Information Services

## Preface

The Center for Cancer Control and Information Services (CIS) is a nationally funded program established in 2006, as an essential part of NCC's extramural activities.

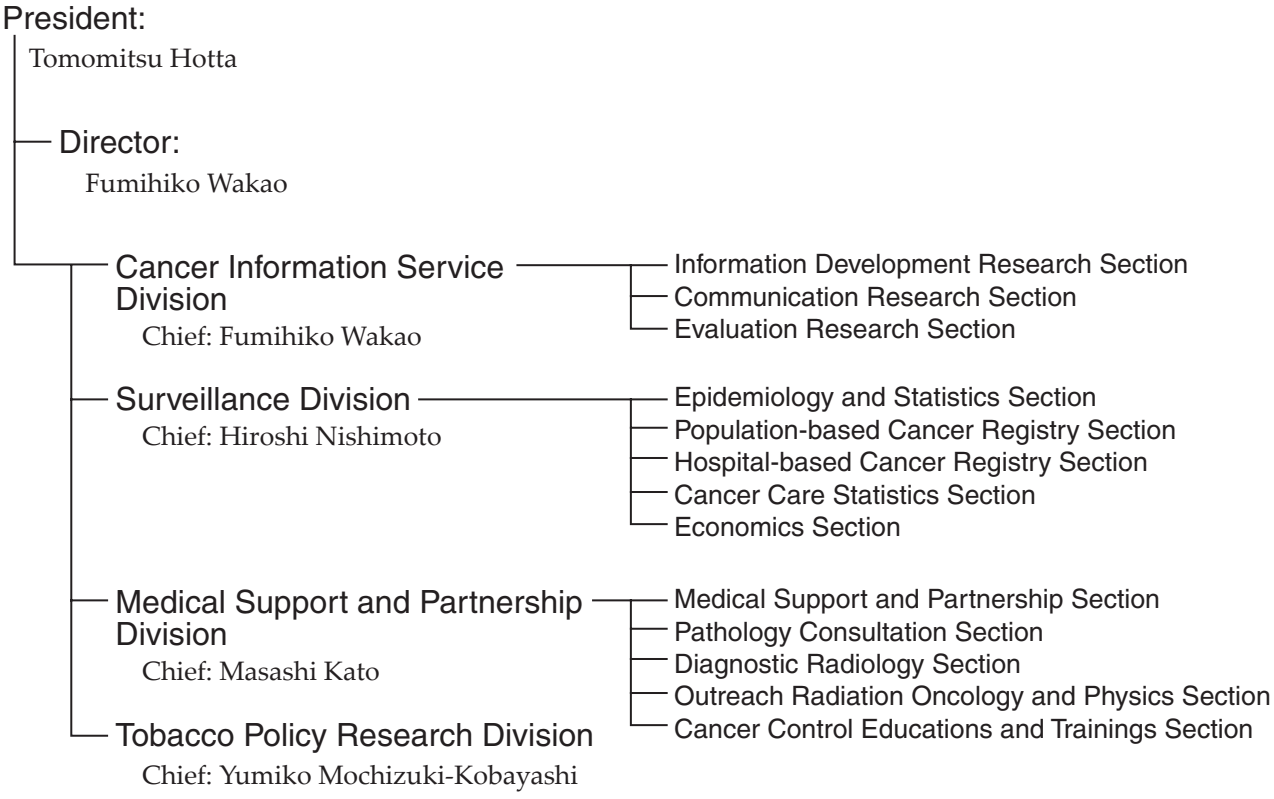
The mission statement of the CIS is as follows: "The Center for Cancer Control and Information Services provides information needed to promote comprehensive and systematic cancer control program in Japan." In collaboration with designated cancer care hospitals, the Ministry of Health Labour and Welfare and other relevant Ministries, the Center plays a central role in the planning, management and evaluation of 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 the CIS website (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 we truly appreciate your continued support.

Fumihiko Wakao, M.D.
Director, Center for Cancer Control and Information Services

## Organization



# Activities of the Divisions

# Cancer Information Service Division

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## Introduction

The mission of the Cancer Information Services is to provide credible information about cancer. In the National Cancer Information Network, the Cancer Information Services 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 397 designated cancer care hospitals and their respective cancer information and 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 including websites such as "ganjoho.jp-www.ganjoho.jp". Followed by publications for patients with an initial cancer diagnosis, the spring 2012 launch of a cancer information handbook for patients with recurrent cancer, the "When cancer returns: Information for patients and families", represented an important step in this direction. Over 80,000 copies have been disseminated among healthcare professionals, with a view to making the language of this handbook the *lingua franca* between cancer patients, their physicians and other healthcare professionals. In order to disseminate information effectively to citizens, we concluded agreements for the spread of information with health insurance companies and pharmaceutical companies.

## Line of service

Cancer Information Development 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 patient education brochures and more recently, a 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 an extensive library of articles on 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 the collaboration among relevant stakeholders, such as the cancer information & counseling centers in designated cancer hospitals (397 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 handles large volumes of inquiries to cancer information services and to call centers, prepares and manages the collaborative work with the "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 are accumulated as evidence repositories. This Section plays a role as the editorial office of the Cancer Information Service.

## 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 a timely impact, and which stakeholders in the community needs to be part of the delivery/ dissemination network. Increasingly, we are also involving regional community stakeholders, patients and care providers, to help compile more a regionally pertinent set 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 social marketing methods 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.

## List of papers published in 2012

### Journal


1. Mizota Y, Yamamoto S. Prevalence of Breast Cancer Risk Factors in Japan. Jpn J Clin Oncol, 42:1008-1012, 2012

2. Okayama H, Takashi T, Ishii Y, Shimada Y, Shiraishi K, Iwakawa R, Furuta K, Tsuta K, Shibata T, Yamamoto S, Watanabe S, Sakamoto S, Kumamoto K, Takenoshita S, Gotoh N, Mizuno H, Sarai A, Kawano S, Yamaguchi R, Miyano S, Yokota J. Identification of Genes Up-regulated in ALK-positive and EGFR/KRAS/ALK-negative Lung Adenocarcinomas. Cancer Res, 72:100-111, 2012

# Surveillance Division

**Hiroshi Nishimoto, Kota Katanoda, Tomohiro Matsuda, Akiko Shibata, Koichi B. Ishikawa, Ayako Matsuda, Kumiko Saika (joint), Takahiro Higashi, 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, the general 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. In the year 2012, the entire Japanese population was covered by population-based prefectural cancer registries. The Division supports all 47 of these registries, 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 in charge of cancer control who were new to their post, a total of 38 participants; and organizing 2-day educational workshops for cancer registrars and administrative officers, a total of 211 participants, in December. The Division also provided site visiting as part of training for the Standard Database System (SDS), to promote the protection of personal information, and for cancer registry start-up preparation. This activity supported a total of 19 prefectures this year. Standardization of the population-based cancer registry has steadily advanced: 43 registries out of 47 use the standard registry items. Thirty-seven registries had introduced the SDS as of December 2012. Introduction is in progress in one registry and 4 are planning to introduce it in 2013. The self-check software on security control in cancer registration, and security educational materials for new workers was updated and provided by the division.

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 397 designated cancer care hospitals (DCCHs) and over 300 other hospitals in 2012. In collaboration with other relevant parties, the division develops data standards for all HCRs, modifies datasets, and distributes the standardized software "Hos-CanR PLUS", which is used in about 400 hospitals. In 2012, individual records for 484,771 cancer cases diagnosed in 2010 were collected from 387 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 32 DCCHs in 2012.

Cancer Statistics

The Division is in charge of providing information on cancer statistics. The updated data on cancer mortality, incidence, survival, and prevalence, the secular trends of cancer mortality and incidence, and the framework of cancer control in Japan have been published both on the website and in a book titled "Cancer Statistics in Japan".

## Research activities

Population-based Cancer Registries

The national cancer incidences in 2007 were estimated based on the data from 33 cancer registries. The estimation for the incidences in 2008 is ongoing. The prefectures that have met the data quality standards have increased since last year.

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 have been presented at conferences both in Japan and abroad.

Quality Indicators

Ensuring the 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 are now 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 cancer burden attributable to tobacco were conducted based on the WHO mortality database and Global Report. The population attributable fraction of mortality was estimated for various risk factors among the Japanese population. A trend analysis of cancer incidence in Japan was conducted using selected population-based cancer registries. A trend analysis was also conducted for chronic myelogenous leukemia and adult T-cell leukemia/lymphoma. The effect of tobacco control policies on the smoking prevalence was estimated for the Japanese population. A systematic review was conducted regarding the association between adiponectin and smoking status.

Economic studies on cancer care

The development and analysis of large-scale health care datasets is crucial in understanding current status and future projections related to cancer care. Using a historical dataset at the National Cancer Center Hospital, the course of care for chemotherapy patients is analyzed to clarify changes in chemotherapeutic regimens. The GIS database of cancer care facilities, their practice volumes and future population projections has been formulated to assess regional accessibility to care and changes in the coming years.

**Table 1. Population-based Cancer Registries from Prefectural Registries**

| Year of Diagnosis | Prefectures | Number of New Cancer Cases |
|---|---|---|
| 2007 | 33 (21 for estimation) | 704,090 |
| 2008 | 34 (25 for estimation) | Work in progress |

**Table 2. Data on Cancer Patients from Hospital-based Cancer Registries at Designated Cancer Care Hospitals**

| Year of Diagnosis | Applied Hospitals | Number of New Cancer Cases |
|---|---|---|
| 2009 | 370 | 484,771 |
| 2010 | 387 | 548,979 |

## List of papers published in 2012
## Journal

1. Saika K, Matsuda T. Time trends in liver cancer mortality (1980-2008) in Japan, the USA and Europe. Jpn J Clin Oncol, 42:84, 2012
2. Saika K, Machii R. Cancer mortality attributable to tobacco in Asia based on the WHO Global Report. Jpn J Clin Oncol, 42:985, 2012
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11. Katanoda K, Yako-Suketomo H. Mortality attributable to tobacco by selected countries based on the WHO Global Report. Jpn J Clin Oncol, 42:561-562, 2012
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15. Ikeda N, Inoue M, Iso H, Ikeda S, Satoh T, Noda M, Mizoue T, Imano H, Saito E, Katanoda K, Sobue T, Tsugane S, Naghavi M, Ezzati M, Shibuya K. Adult mortality attributable to preventable risk factors for non-communicable diseases and injuries in Japan: a comparative risk assessment. PLoS Med, 9:e1001160, 2012
16. Chihara D, Ito H, Matsuda T, Katanoda K, Shibata A, Saika K, Sobue T, Matsuo K. Decreasing trend in mortality of chronic myelogenous leukemia patients after introduction of imatinib in Japan and the U.S. Oncologist, 17:1547-1550, 2012
17. Chihara D, Ito H, Katanoda K, Shibata A, Matsuda T, Tajima K, Sobue T, Matsuo K. Increase in incidence of adult T-cell leukemia/lymphoma in non-endemic areas of Japan and the United States. Cancer Sci, 103:1857-1860, 2012

# Medical Support and Partnership Division

**Masashi Kato, Hitoshi Tsuda, Hiroaki Onaya, Jun Itami, Yoshinori Makino, Miki Hosoya, Hiroko Yako-Suketomo, Toshiyuki Minemura, Yuko Ogo, Saran Yoshida, Yoko Nakazawa, Kyohei Fukata, Takashi Hanada, Tadakazu Shimoda, Yoshihiro Matsuno, Satoshi Ishikura, Megumi Fukuda, Ritsuko Chinda, Hiroyo Ohchi, Chisako Ito, Yoshiko Suzuki**

## Introduction

The Division builds partnerships with Designated Cancer Hospitals to support all health allied professionals concerned with cancer control in Japan. The Medical Support and Partnership Section (MSPS) plays a unique role in suggesting the cancer control policy in Japan. The Pathology Consultation Section makes effort 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 the following support programs for designated regional cancer centers and institutions participating in clinical trials. The Cancer Control Educations and Trainings Section (CCET), Medical Support and Partnership Division and the Center for Cancer Control and Information Services, produce, or plan and operate several training programs in the clinical and cancer registry disciplines to provide a 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 Hospitals in all parts of the country.

## Routine activities

A. Networking among Designated Cancer Hospitals

The MSPS formed a network among the designated cancer hospitals to build partnership for cancer control in Japan. The designated cancer hospitals are important partners with the NCC to promote comprehensive cancer control in Japan. The MSPS hold conferences in which the prefectural designated cancer hospitals participate. Currently, mailing lists prepared with the permission of participants have been in use for sharing some information among the participating hospitals.

B. Pathology consultation service

The pathology slides of lesions arising in various organs were submitted from clients. Eighty-four consultant pathologists who are specialists in various fields are registered, and one pathologist who was assigned as a consultant examined the slides and rapidly sent back the report of their opinion to each client. Most of the clients expressed satisfaction with the contents of the report and this consultation system. The activity of the Section was presented in the annual meeting of the Japanese Society of Pathology. We started the selection of typical and educational consultation cases from accumulated archival slides and the construction of a referential data base.

C. Radiology consultation service

Eighty-one consultation reports have been put together for requests mainly from the Kanto and Kyushu regions. Hepato-biliary-pancreatic, musculoskeletal, and lung lesions were the common subjects. Consultation with a specialist was the most frequent reason comprising 39.1% for consultation. The client radiologists have evaluated 213 (91.8%) of the 232 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 2011, about 100000 per month. Cases with lung cancers (n=14), hypopharyngeal cancers (n=4), glioblastoma (n=6), cases with cancers who underwent interventional radiology (n=5) and other cancers have been published, resulting in the total provision of 245 cases.

E. Radiotherapy case service

Mailed dosimetry and on-site dosimetry were performed in 36 institutions and 9 institutions, respectively. All data of the institutions were within the permissible limit. In clinical trials, radiotherapy case reviews were performed in 100 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. (Table 1) The training programs are intended for Health Allied Professionals (palliative care physicians, psycho-oncologists, pharmacists, nurses and technologists, CI specialists), for Palliative Care consultation and Chemotherapy teams, and members of In-hospital cancer registries. In the pharmacists education section, we have operated two new programs under the following titles; "Seminar for pharmacists on dispensing neoplastic agents to be trainers" and "On the job training for pharmacists dispensing neoplastic agents to be trainers"

## Research activities

Suggestion for Cancer Control Policy

To suggest a policy for cancer control and the guidelines for establishing designated cancer hospitals, the fact-finding survey of cancer medical care in Japan was conducted.

Build Family Support System

To suggest comprehensive psycho-social support for cancer patients and their families, a database was established on the family support system.

Diffuse Cancer Education for School Children

To suggest a policy on cancer education for school children, an interview survey was conducted on cancer education for teachers.

Trend of pathology consultation services

In 2012, the Pathology Consultation Section received histopathology slides of 364 cases for a specialist's second opinion regarding the histopathological diagnosis. The number of consultation cases represented a 24% increase in comparison with the number in 2011.

Develop and use of a teleradiology system

The section 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.

Develop the RTPS quality control support program

The Outreach Radiation Oncology and Physics Section have been developing enforcement of "the Radiation Treatment Planning System (RTPS) quality control support program" to confirm the beam modeling data of the RTPS in 9 institutions. We examined enforcement of the on-site dosimetry regarding the output dose of Intensity Modulated Radiotherapy (IMRT) for designated regional cancer centers.

## Clinical trials

In the Japan Clinical Oncology Group 1015 (JCOG1015), we performed on-site dosimetry regarding the output dose of IMRT in 4 institutions.

**Table 1. Training programs conducted during April 2011 - March 2012**

| Subjects and programs | Education and Training program title | No. of participants |
|---|---|---|
| Oncology nurses education | Continuing education and development of oncology nursing Workshop for trainers | 55 |
| | Oncology nursing seminar for trainers | 194 |
| | Oncology nursing on the job training for trainers | 4 |
| | Oncology nursing on the job training for trainers-Follow up course | 17 |
| CI specialists education | CI Specialist Education Program -Basic course 1 | 674 |
| | CI Specialist Education Program -Basic course 2 | 610 |
| | CI Specialist Education Program -Basic course 3 | 281 |
| | CI Specialist Education Program for trainers | 57 |
| Hospital-based cancer registrars training | Training program for instructors of hospital-based cancer registrars | 20 |
| | Supplementary training program for instructors of hospital-based cancer registrars | 57 |
| | Continuous training program for instructors of hospital-based cancer registrars | 2 |
| | Basic training program for hospital-based cancer registrars | 1335 |
| | Supplementary training program for hospital-based cancer registrars of basic course completion | 637 |
| | Advanced training program for hospital-based cancer registrars | 106 |
| | Supplementary training program for hospital-based cancer registrars of advanced course completion (UICC TNM-7) | 301 |
| | Site visiting program on hospital-based cancer registries in national cancer center hospital | 97 |
| Population-based cancer registrars and administrative officers in charge of cancer control training | Basic training programs on a population-based cancer registry for cancer registrars and administrative officers | 174 |
| Technologists education | Trainer training for oncologic radiology technologists | 22 |
| | Trainer training for oncologic laboratory medical technologists | 2 |
| Pharmacists education | Seminar for pharmacists of dispensing neoplastic agents to be trainers | 56 |
| | On the job training for pharmacists of dispensing neoplastic agents to be trainers | 5 |
| Palliative care physicians education | Palliative care education meeting for trainers | 64 |
| Psycho-oncologists education | Psycho-oncology education meeting for trainers | 35 |
| Palliative care team education | Palliative care team workshops for consultation-Basic course | 106 |
| Chemotherapy Team education | Chemotherapy Team workshops to introduce a new drug safety | 64 |

## List of papers published in 2012
## Journal


1. Yoshida S, Shiozaki M, Sanjo M, Morita T, Hirai K, Tsuneto S, Shima Y. Pros and cons of prognostic disclosure to Japanese cancer patients and their families from the family's point of view. J Palliat Med, 15:1342-1349, 2012
2. Yoshida S, Shiozaki M, Sanjo M, Morita T, Hirai K, Tsuneto S, Shima Y. Practices and evaluations of prognostic disclosure for Japanese cancer patients and their families from the family's point of view. Palliat Support Care, 1-6, 2012
3. Yamagishi A, Morita T, Miyashita M, Yoshida S, Akizuki N, Shirahige Y, Akiyama M, Eguchi K. Preferred place of care and place of death of the general public and cancer patients in Japan. Support Care Cancer, 20:2575-2582, 2012
4. Yako-Suketomo H, Katanoda K. Burden of cancer incidence in Asia extrapolated from the cancer incidence in five continents Vol. IX. Jpn J Clin Oncol, 42:1233, 2012
5. Kishi Y, Kato M, Okuyama T, Thurber S. Treatment of delirium with risperidone in cancer patients. Psychiatry Clin Neurosci, 66:411-417, 2012

# Tobacco Policy Research Division

**Yumiko Mochizuki, Seiko Ishiuchi, Jun'ichi Adachi, Saori Ikuyo, Yuri Kuronuma, Sayuri Takise**

## Introduction

Every year, tobacco kills more than six million people in the world and 130-200 thousands 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 also be prevented by human efforts, it can be referred to as a "man-made disaster". To help counteract this trend, 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 this tobacco epidemic in our lifetime. The WHO 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 its international responsibilities as well as its domestic requirements. Based on the Health Promotion Act and Cancer Control Act, the government recently released its future vision on tobacco with reduction of adult smoking prevalence by 40% within 10 years. 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.

## Routine activities

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 to protect the public from exposure to tobacco smoke, were the first to be implemented rigorously. As the Division is being involved in policy development processes at national and local level, accurate and convincing scientific evidence to mobilize political will and obtain public supports is essential to dispel emotional and doubtful messages among stakeholders. We have been developing a relational database on tobacco-related literature from Ministry of Health, Labour and Welfare grant studies since 1997 to compile the data from their output and to follow up the outcomes of these data as scientific papers. This enables both researchers and policy makers to know how the governmental funded research could contribute to the tobacco control research and to allow them to perform research mapping. 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 would be able to disregard, 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 on tobacco control, the roles of health professionals are essential but their potential remains unfulfilled. We developed a smoking cessation guide for pharmacists to respond to their need for capacity building. In order to build an interactive platform of information sharing, we jointly work with the Japan National Committee for UICC (Union for International Cancer Control) to launch the Tobacco Free Women TV (http://www.ustream.tv/channel/tobaccofreewomentv) project, developed as the world's first-ever streamed channel specifically for tobacco control. This project has developed more than 70 live and recorded programs on its website and obtained nearly 10,000 total views of our program reaching more than 3,000 individual viewers. This is an innovative way of information infrastructure at a lower cost and at a maximum impact and flexibility, and has increased the communication capacity of local NGOs and academic communities.

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 an annual series of tobacco control meetings, such as the "World No Tobacco Day (WNTD) Symposium", with the Ministry of Health, Labour and Welfare, and has translated WHO related materials such as guidelines of the WHO Framework Convention on Tobacco Control and other technical reports.

# Tobacco Free Women TV

www.ustream.tv/channel/tobaccofreewomentv

- Various contents
  - Epidemiology, youth, women, politics, beauty, dental medicine, industry tactics, movie reviews, civil movements, academic activities, prevention, cessation, smokefree policy, empowerment, advocacy, global trends, etc.
- Various guests
  - Doctors, dentists, nurses, public health nurses, pharmacists, business men/women, teachers, school nurses, administrators, politicians, high school students, college students, university students, NGOs, activists, journalists, singers, etc.
- Various areas and communities
  - Akita, Yamagata, Miyagi, Ibaragi, Yamanashi, Tokyo, Aichi, Gifu, Kyoto, Shiga, Osaka, Hyogo, Kagawa, Kumamoto, Fukuoka, Okinawa, cancer, cardiovascular, universities, etc.

**Figure 1.**

Tobacco Free Women TV: samples of streaming live show


Since March 2012
Total view over 10,000
Live program 70
CM 20, action reports 5

**Figure 2.**

# Annual Report 2012

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