# Annual Report 2014

## 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**

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**Japan**

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# Greeting from the President

## The National Cancer Center's Activities for Further Development

Along with a revision of the Act on the General Rules for Incorporated Administrative Agencies, the National Cancer Center (NCC) was reorganized in April 2015 as a national research and development corporation "aiming to maximize the outcomes of research and development by addressing challenges that are difficult for universities and private companies." Since its foundation in 1962, the NCC as a national institution for oncology research and services has been engaged in activities to elucidate the pathology of cancer and promote equal accessibility to advanced research outcomes and medical services for the development of treatment methods based on findings from them. It is expected to contribute to the overcoming of cancer by further improving its research and development abilities and obtaining outcomes. In FY 2015, the National Cancer Center Hospital and Hospital East have been approved as clinical research centers to play a central role mainly in international-level clinical research projects, as defined by the Medical Service Law. Two among the four hospitals approved this fiscal year belong to the NCC, which is a historical event for us. At the same time, it indicates the necessity of appropriately recognizing our important roles and responsibilities. FY 2014 was a year during which all our executives cooperated to perform their activities toward a new stage based on new visions as a national center specializing in oncology.

In the research field, collaboration among the NCC Research Institute and its hospitals has facilitated the promotion of translational research. For example, preclinical studies to examine nucleic acid-based drugs selectively suppressing miR-133a and investigator-initiated clinical trials on those suppressing ribophorin II (RPN2) gene expression for the treatment of breast cancer have been established. In addition, multicenter screening for FGFR2 fusion genes, involved in biliary tract cancer and newly identified by the Research Institute, and investigator-initiated clinical trials on treatment targeting RET fusion genes, similarly identified by it, have started. The number of new joint basic and clinical research projects has been the highest ever, at 90. Furthermore, a nationwide cancer genome screening based on industry-academia liaison and multiplex diagnostic panels with next-generation sequencing, entitled: The SCRUM-Japan, is attracting marked attention as a basis for the provision of individualized medical services. The project will develop next-generation oncological diagnosis systems that will enable diagnosticians to identify 13 types of cancer only by a single blood sampling using microRNA as an index. In 2014, the Center for Research Administration and Support was also organized to unitarily manage and support all basic and clinical research projects implemented by each division of the NCC, which has improved the effectiveness and efficiency of our research support activities.

In the aspect of medical treatment, we have provided advanced and pioneering medical services by performing approximately 2,000 endoscopic (EMR, ESD) and 4,500 interventional radiology (IVR) procedures for esophageal, gastric, and colorectal cancers. These numbers are among the highest in the world. We have also been engaged in the development of new radiotherapy techniques, such as using the CyberKnife and combining proton therapy and chemotherapy. We actively offer advanced medical services, and the numbers of our service provisions corresponding to categories Medical Services A and B with the approval of the Ministry of Health, Labour, and Welfare have been 2 and 10, respectively. The daily mean number of outpatient chemotherapy sessions is 240, approximately 10% of which are provided as part of clinical trials. The establishment of the Rare Cancer Center has been regarded as a useful approach to highlight domains in which it is difficult to promote the provision of specialized medical services and development of treatment methods on a nationwide basis. Regarding team medicine, the Supportive Care Center and nutritional support team have provided active approaches while home palliative care conferences have been regularly held through cooperation with related medical institutions.

Concerning policies, the NCC has contributed to the development of indices for the interim evaluation of the Basic Plan to Promote Cancer Control Programs Phase II, based on the results of studies, such as a major survey on patients' experiences. It has organized a preparatory office to develop systems for a national cancer registry scheduled from January 2016. Furthermore, it has played a central role in preparing expert panel reports to develop the 10-year Strategies to Promote Oncology Research as a base for the Japan Cancer Research Project to be promoted under the direction of the Japan Agency for Medical Research and Development (AMED) which was established in April 2015.

While offering advanced and pioneering oncology services, the NCC is socially expected to play a key role in approaches to maintain/improve patients' and their families' long-term care-related quality of life and develop social systems that enable people to live with a sense of security even in the presence of cancer by collaborating with cancer centers throughout Japan, promoting clinical research networks, providing palliative care, and establishing models for the provision of consultation, support, and information. For its further development, all employees implement their professional duties based on their specialties and extensively utilize the outcomes of such activities within and outside Japan.

This annual report is a record clarifying the NCC's achievements in FY 2014 and future challenges. We would be grateful if we could hear your frank opinions and advice on our activities.

Your continued guidance and support would be very much appreciated.

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

## Organization of National Cancer Center

President:
Tomomitsu Hotta

- Board of Directors
- Auditors
- Executive Advisers to President
  - Bruce A Chabner
  - Chikara Tsukamoto
- Strategic Planning Bureau
  - Director-General: Yasuhiro Fujiwara
- Center for Research Administration and Support
  - Director: Teruhiko Yoshida
- Center for Education and Professional Career Development
  - Director: Yuichiro Ohe
- Office for Advanced Medical Care Evaluation
  - Chief: Yasuhiro Fujiwara
- Directors' Meeting
  - Hospital
    - Director: Yasuaki Arai
  - Hospital East
    - Director: Toshirou Nishida
  - Research Center for Innovative Oncology
    - Director: Atsushi Ohtsu
  - Research Institute
    - Director: Hitoshi Nakagama
  - Exploratory Oncology Research & Clinical Trial Center
    - Director: Atsushi Ohtsu
  - Research Center for Cancer Prevention and Screening
    - Director: Shoichiro Tsugane
  - Center for Cancer Control and Information Services
    - Director: Fumihiko Wakao
  - Administrative Departments
    - Director: Yukio Kosuda

# Sections Directed by President

# Office of Policy, Strategic Planning Bureau

**Yasuhiro Fujiwara, Chikara Tsukamoto, Teruhiko Yoshida, Toshikazu Ushijima, Tatsuhiro Shibata, Takashi Kohno, Kenkichi Masutomi, Hisao Asamura, Minoru Esaki, Akira Kawai, Hidehito Horinouchi, Kenji Tamura, Miyuki Sone, Ken Ohashi, Ken Shimizu, Ayako Mori, Yoshinori Makino, Atsushi Ohtsu, Toshihiko Doi, Tetsuo Akimoto, Takayuki Yoshino, Akimasa Ito, Atsushi Ochiai, Takeharu Yamanaka, Katsuya Tsuchihara, Miho Kurihara, Yasuhiko Ichida, Fumihiko Wakao, Takahiro Higashi, Taro Shibata, Toshio Miyata, Nobuko Ushirozawa, Shigeto Toya, Kota Tagawa, Shoko Koike, Hiroshi Nokihara, Miyako Horikoshi, Chie Shirai, Yuki Hatada, Seiichiro Yamamoto, Sakiko Suzuki, Maria Imada, Mitsuko Ohtani**

The Strategic Planning Bureau was founded as a think tank for the chairman of the board of directors. The Bureau cooperates with both the Center for Cancer Control and Information Services of the Division of Health Services Research and the Center for Cancer Prevention and Screening Research of the Division of Health Policy Research. This cooperative organizes issues related to cancer management in all of Japan, not just limited in those issues within the National Cancer Research Center, and handles strategic and policy planning for data and policy proposals made for industry, government, and academia.

In 2014, we (1) took on secretarial duties for "Research on reporting and evaluating the third comprehensive anti-cancer strategy" from the Scientific Research Grant Group of the Ministry of Health, Labour and Welfare (MHLW); summarized self-inspection reports from researchers who received grants as part of the third strategy for cancer control, in preparation for an evaluation conducted by the Council for Science, Technology and Innovation in the Cabinet Office of the Government of Japan; and implemented an external committee's evaluations; and (2) reviewed and developed submission documents regarding the role of the National Center in innovative medical treatments and technologies for the Health and Medical Treatment Strategies Council Meeting.

1) Evaluation of the third anti-cancer comprehensive strategy

President Hotta was the research representative from January to March 2014. In April 2014, Strategic Planning Director Fujiwara became the new research representative. As part of the third 10-year anti-cancer comprehensive strategy from 2004 to 2013, we summarized and reported the analysis of the third anti-cancer comprehensive research project. At the same time, we evaluated the third anti-cancer comprehensive research grants supported by scientific research grants from the MHLW (hereinafter, the "third anti-cancer"), based on the aforementioned report and follow-up research data.

First Evaluation Committee
May 25, 2014 (Sunday) 10:30–13:30
Second Evaluation Committee
September 21, 2014 (Sunday) 10:30–14:00

In future, the evaluation report of the third anti-cancer comprehensive strategy and research projects summarized by the said committee will be used to evaluate the general direction of research development in Japan. The evaluation will be conducted by the MHLW, which advanced the 10-year comprehensive strategy, as well as the Council for Science, Technology and Innovation.

2) Review of submissions for the Health and Medical Treatment Strategies Council Meeting

The Health and Medical Treatment Strategies Council Meeting investigates important matters related to policies for research development in the field of medicine, as well as growth strategies for health and medical therapy.

Reviews and draft articles regarding proposals for future policies were produced with participation of President Horita. They can be found at:
http://www.kantei.go.jp/jp/singi/kenkouiryou/sanyokaigou/kaisai.html.

# Office of Public Relations, Strategic Planning Bureau

**Hiroshi Nokihara, Kiyotaka Watanabe, Miyako Horikoshi, Chie Shirai, Yuki Hatano, Hironobu Ohmatsu, Shinichiro Takahashi, Rika Kojima, Kajitsu Ogawa**

## Introduction

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

## Activities

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

- Homepage renewal: NCC top page, site of Hospital and Hospital East, site of Rear Cancer Center etc.
- Public information magazine "The National Cancer Center News": for external hospitals, academia, research institutions, administrative agencies
- Public information magazine "hibiho": for patients in center Hospital and east Hospital
- Intramural information brochure "challenge": for staff members and their family in NCC Hospitals
- Support of the event, seminar and public information
  (idea exhibition for daily life 2014, Black-Jack seminar 2014, the eighth east hospital campus day, etc.)
- Media support at press conference, press release and media coverage

We held nine cases of press conference (new establishment of Rear Cancer Center, industry-academia-government cooperation project of developing novel next-generation system for cancer diagnosis, projected cancer incidence and deaths in 2014, etc.) and published 32 cases of press releases.

## The future direction

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

# Office of International Affairs, Strategic Planning Bureau

**Seiichiro Yamamoto, Sakiko Suzuki, Mitsuko Otani**

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

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

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

Focusing on the number 1 above, we have proudly signed the Memorandum of Understanding with 3 institutions; US National Cancer Institute (NCI), Massachusetts General Hospital, and French National Cancer Institute (Originally, Institut National Du Cancer, abbreviated as INCa), which the Office worked on since the year before. The MoU with NCI was brought up as a topic during the talk between Prime Minister of Japan and President of United States in April when the President visited Japan in April.

To the NCI, one Medical oncologist was dispatched since last March, as a part of personnel exchanges. Currently the Office is preparing for other personnel exchanges of a nurse and a pathologist for the next year.

In August, the NCC invited the INCa President to Japan and exchanged ideas on situations in Japan and France. We had a mutual understanding that INCa and the NCC will work closely together.

Collaborative studies

The NCC has many collaborative works that have completed or are currently on-going and some of them have achieved major accomplishments. See the details in the reported activities of each department.

Visiting fellowship (mainly observership)

One of the NCC's longstanding medical contributions is to accommodate medical professionals around the globe as visiting fellows. The NCC began this fellowship as far back as almost the NCC's establishment. In the year 2014, the NCC has had 138 visiting fellows (at both campuses of Tsukiji and Kashiwa). This is about 1.5 times more than last year's. As for the few-day visitors, the NCC had 146 visitors. (See the table below for details.) Including a few hour visitors, the NCC has had nearly 400 visitors in total last year. Visitors are mainly come from Asian countries, but there also are visitors from institutions that are renowned world widely. The Office continues to support former fellows through the alumni organization of fellows which the Office started last year.

As an another important topic, the NCC works closely with the Japanese government such as the Ministry of Health, Labour, and Welfare, the Ministry of Economy, Trade and Industry, the Ministry of Internal Affairs and Communications, and Medical Excellence JAPAN, a company aiming to expand Japanese medicine globally. As experts, the NCC gives advises to those ministries and support their projects.

## Table 1. January - December, 2014 Visiting fellowship (with and without fee) - Hospital

| Visitors by region | Country of home organization | Hospital | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Head & Neck Surg. | Plastic & Reconstructive Surg. | Breast Surg. | Esophageal Surg. | Gastric Surg. | Colorectal Surg. | Gastrointestinal Endoscopy | Raspiratory Endoscopy | Urology | HPB Surg. | Gynecology | Diagnostic Radiology | Pathology | Gastrointestinal Medical Oncology | HPB Oncology | Musculokeletal Oncology & Rehabilitation | Thoracic Surg. | Breast & Medical Oncology | Total # by division* | Total (Actual #) |
| | India | | | | | | | 2 | 2 | | | | | | | | | | | 4 | 4 |
| | Singapore | | | | | 1 | | | 1 | | | | | | | | | | | 2 | 2 |
| | Sri Lanka | | | | | | | | | | 1 | | | | | | | | | 1 | 1 |
| Asia | Thailand | | | | 1 | 3 | 1 | 8 | 1 | | 1 | 4 | | 1 | | | | | | 20 | 16 |
| | China | | | 1 | | 4 | | 9 | 1 | | 1 | | | 1 | 1 | 1 | 1 | | | 20 | 16 |
| | Taiwan | | | 1 | | | | 12 | 2 | 1 | | | 6 | | | | | | | 22 | 21 |
| | Hong Kong | | | | | | | | 1 | | | | | | | | | | | 1 | 1 |
| | Philippines | 1 | 1 | | 1 | 1 | 1 | | 3 | | 1 | | 1 | 1 | | | | 1 | | 12 | 7 |
| 70 | Viet Nam | | | | | | | 1 | | | | | | | | | | | 1 | 2 | 2 |
| Oceania | Australia | | | | | 1 | | 1 | | | | | | 1 | | | | | | 3 | 3 |
| 3 | | | | | | | | | | | | | | | | | | | | | |
| North America | USA | | | | | | | 3 | | | | | | | | | | | | 3 | 3 |
| 3 | | | | | | | | | | | | | | | | | | | | | |
| Latin America | Chile | | | | | | | 1 | | | | | | | | | | | | 1 | 1 |
| | Honduras | | | | | | | | | | | | | 1 | | | | | | 1 | 1 |
| 3 | Mexico | | | | | 1 | | 1 | | | | | | | | | | | | 2 | 1 |
| Middle East | Turkey | | | | 1 | | | | | | | | | | | | | | | 1 | 1 |
| 2 | Egypt | | | | | | 1 | | | 1 | | | | | | | | | | 2 | 1 |
| Europe | Italy | | | | | | | 3 | | | | | | | | | | | | 3 | 3 |
| | UK | | | | 3 | 2 | | 9 | | | | | 1 | | | | | | | 15 | 12 |
| | The Netherlands | | | 1 | | | | | | | | | | | | | | | | 1 | 1 |
| | Kazakhstan | | | 1** | | | | | | | | | | | | | | | | 0 | 1 |
| | Spain | | | 1 | 2 | 3 | | 5 | | | | | | | | | | | | 11 | 9 |
| | Germany | | | | | | | | | | | | 1 | | | | | | | 1 | 1 |
| | Poland | | | | | 1 | | | | | | | | | | | | | | 1 | 1 |
| | France | | | | | | | 1 | | | | | | 1 | 1 | | | | | 3 | 2 |
| 35 | Russia | | | | | | | 4 | | | | | | 1 | | | | | | 5 | 5 |
| | Total | 1 | 1 | 4 | 8 | 17 | 3 | 60 | 11 | 2 | 4 | 4 | 9 | 7 | 2 | 1 | 1 | 1 | 1 | 137 | 116 |

* Total number by division (Some visitors rotate multiple divisions)

** Currently enrolled in a graduate school in Japan, but count as Kazakhstan because the one is going back to its home country Kazakhstan soon.

| Total # by facility/# of visitors | | Hospital | Hospital East | Research Institute | Cntr. for Cancer control and Info. Services | Research Cntr. for Prevention & Screening | EPOC *** | Cntr. for Research Administration & Support | # of visitors |
|---|---|---|---|---|---|---|---|---|---|
| | Visiting fellowship (with and without fee) | 116 | 21 | 4 | 0 | 0 | 0 | 0 | 138* |
| | Short term Visit (within 3 days) | 141 | 11 | 4 | 4 | 0 | 3 | 1 | 155** |

* 3 visitors had fellowship both hospoitals in Tokyo and Chiba

** Some visitors visited divisions beyond

*** Exploratory Oncology Research & Clinical Trial Center

## Table 2. January - December, 2014 Visiting fellowship (with and without fee) - All centers except Hospital

| Visitors by region | Country of home organization | Hospital East | | | | | | | | | | Research Institute | | | | | Cntr. for Cancer Control & Info. Services | Research Cntr. for Cancer Prevention & Screening | Exploratory Oncology Research & Clinical Trial Cntr. | Cntr. for Research Administration & Support |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Plastic & Reconstructive Surg.* | Gastric Surg. | Gastrointestinal Endoscopy | Pathology | Colorectal Surg. | Head & Neck Surg. | Palliative Medicine | Nursing | Total # by division* | Total # of visitors | Virology | Molecular & Cellular medicine | Metastasis & Invasion Signaling | Total # by division* | Total # of visitors | Total | Total | Total | Total |
| | Sri Lanka | | | | | | 1 | | | 1 | 1 | | | | | | | | | |
| Asia | China | | 2 | 3 | 1 | 1 | | 1 | 1 | 9 | 8 | | | | | | | | | |
| | Taiwan | | | | | | | | 10 | 10 | 10 | | | | | | | | | |
| | Philippines | 1 | | | | | | | | 1 | 1 | | | | | | | | | |
| 21 | Malaysia | | | | | | | | | | | 1 | | | 1 | 1 | | | | |
| North America | USA | | | | | | | | | | | | | 1 | 1 | 1 | | | | |
| 1 | | | | | | | | | | | | | | | | | | | | |
| Europe | Spain | | | 1 | | | | | | 1 | 1 | | 1 | | 1 | 1 | | | | |
| Other** | Japan | | | | | | | | | | | | 1 | | 1 | 1 | | | | |
| 1 | | | | | | | | | | | | | | | | | | | | |
| | Total | 1 | 2 | 4 | 1 | 1 | 1 | 1 | 11 | 22 | 21 | 1 | 2 | 1 | 4 | 4 | 0 | 0 | 0 | 0 |

* Total number by division (Some visitors rotate multiple divisions)

** An American citizen, enrolled in a university in Japan

## Table 3. January - December, 2014 Short term (within 3 days) Visit - Hospital

| | | | Hospital | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visitors by region | Country of home organization | Gastrointestinal Endoscopy | "Hematopoietic Stem Cell Transplantation" | Diagnostic Radiology | Radiation Oncology | Dermatologic Oncology | Ophthalmic Oncology | Pathology | Colorectal Surg. | Appearance Support Cntr. | Office for Advanced Medical Care Evaluation | Crinical Trial Support Office | Pharmacay | Patient relations | Total # of visitors |
| | South Korea | | 1 | 2 | | | | | | 4 | 3 | | | | 10 |
| | India | | | | 1 | | | | | | | | | | 1 |
| | Indonesia | 2 | | | | | | | | | | | | | 2 |
| Asia | Thailand | 1 | | 2 | | | | 4 | | | | | | | 7 |
| | China | 12 | | | | | | | | | | | | | 12 |
| | Taiwan | | | 2 | | | | | | | | | | 9 | 11 |
| | Philippines | 2 | | | | | | | | | | | | | 2 |
| 46 | Malaysia | 1 | | | | | | | | | | | | | 1 |
| Oceania | Australia | | 1 | 2 | | | | | | | | | | | 3 |
| 3 | | | | | | | | | | | | | | | |
| North America | USA | 1 | | 2 | | | | | | | | | | | 3 |
| 3 | | | | | | | | | | | | | | | |
| South America | Argentina | 1 | | | | | | | | | | | | | 1 |
| 2 | Chile | 1 | | | | | | | | | | | | | 1 |
| | UK | | | | | | 1 | | | | | | | | 1 |
| | Italy | | | 1 | | | | | | | | | | | 1 |
| Europe | Austria | | | 20 | 40 | | | | | | | | | | 60 |
| | Hungary | 1 | | | | | | | | | | | | | 1 |
| | Belgie | | | | | | | | 1 | | | | | | 1 |
| | France | | | | | 1 | | | | | | | | | 1 |
| Mid. East | UAE | 1 | | | | | | | | | | | | | 1 |
| 1 | | | | | | | | | | | | | | | |
| Unknown* | Unknown | 19 | | | | | | | 1 | | | 1 | 1 | | 21 |
| 21 | | | | | | | | | | | | | | | |
| | Total | 42 | 2 | 31 | 41 | 1 | 1 | 4 | 2 | 4 | 3 | 1 | 1 | 9 | 141 |

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

## Table 4. January - December, 2014 Visiting fellowship (with and without fee) - All centers except Hospital

| | | Hospital East | | | | | Research Institute | | Cntr. for Cancer Control & Info. Services | | Research Cntr. for Cancer Prevention & Screening | Exploratory Oncology Research & Clinical Trial Cntr. | | | Cntr. for Research Administration & Support | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visitors by region | Country of home organization | Gastrointestinal Endoscopy | Radiation Oncology | Diagnostic Radiology | HPB Oncology | Total | Cancer Genomics | Total | Cancer Survivorship Research | Total | Total | Experimental Therapeutics | Immunotherapy | Total | Research Promotion Division / JCOG Operations Office | Total |
| | China | | 1 | 1 | | 2 | | | | | | | | | | |
| | Thailand | | | | | | 4* | 4 | | | | | | | | |
| Asia | India | | 1 | | | 1 | | | | | | | | | | |
| | Viet Nam | | | | 2 | 2 | | | | | | | | | | |
| | Taiwan | | | | | | | | | | | | 1 | 1 | | |
| 5 | South Korea | | | | | | | | 4** | 4 | | | | | | |
| Oceania | New Zealand | 2 | | | | 2 | | | | | | | | | | |
| 2 | | | | | | | | | | | | | | | | |
| Europe | UK | | | 3 | | 3 | | | | | | | | | | |
| | Russia | | | | | 0 | | | | | | | | | | |
| | Belgie | | | | | | | | | | | | | | 1*** | 1 |
| 3 | Germany | | | | | | | | | | | 1 | | 1 | | |
| Unknown**** | Unknown | | | | | | | | | | | | 1 | 1 | | |
| | Total | 2 | 2 | 4 | 2 | 10 | 0 | 4 | 4 | 4 | 0 | 1 | 2 | 3 | 0 | 1 |

* Same visitor as the visitor at Pathology division of Hospital
** Same visitor as the visitor at Appearance Support Center of Hospital
*** Same visitor as the visitor at Colorectal Surgery of Hospital
**** Because application for short term visit does not require a country of home organization of applicant, it is unknown otherwise declared by applicant

# Center for Research Administration and Support

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

## Introduction

The Center for Research Administration and Support (CRAS) was established in July 16, 2014 by approximately 160 staffs. The CRAS comprises diverse functions and specialties, ranging from research fund administrations, alliance with private sectors, intellectual properties, Clinical Research Coordinators (CRC) and Data Managers (DM), monitoring and audit, biostatistics support, offices for research ethics (IRB) and COI committees. Dr. Hotta, President of NCC, explained the reason and the purpose of the CRAS creation in the NCC News 2014 Vol.5/No.3 (in Japanese). National Cancer Center (NCC) was founded in 1962, and since then, it has added several new segments and organizations to evolve as a comprehensive cancer center. Because each segment needed its own research infrastructures, support activities in NCC have become fragmented and scattered with possible gaps and redundancies. Meanwhile, Dr. Hotta assembled the "NCC New Vision" in 2014, in which he proposed integration and communications of various research support functions in NCC.

(Future Prospects)

The mission of CRAS is to enhance research support and administration capabilities of NCC based on the "NCC New Vision." Although the integration and communications are primary agenda of CRAS, it is also crucial to make the most of the existing, well-functioning subsystems. The CRAS will evolve through some further trials and errors to find the best-fit system, but NCC has placed an important step forward to the Challenge and Change.

## Activities and Future Prospects of each Division/Section

1. Research Administration Division

1.1 Research Administration Section

The Research Administration Section has been a central office in charge of various administrative works related to research funding including application and reporting. The major external funding sources are competitive grants from the government, such as the MHLW, MEXT and METI, and from government-supported agencies, such as the JST, NiBio and NEDO. The Section also serves as an administrative office for the National Cancer Center Research and Development Fund, which is provided directly from the government to NCC for fulfillment of its mission as the national core institute of the cancer control. The Section organized seminars regarding research funding and its rules to prevent financial misconducts.

(Future Prospects)

The Guidelines for Managing and Auditing Public Research Funds at Research Institutes has been updated by the MEXT in February 2014 and adopted by the MHLW in March 2014. In 2015, the Section will lead NCC to establish a new system for research fund administration, which is fully compatible with the new Guidelines.

1.2 Research Administrator

Research administrators (RA) functioned as a secretariat of study group “Enforcement and Assessment of Research and Development Management concerning Practical Research for Innovative Cancer Control (representative: Tomomitsu Hotta)” to monitor the 165 awarded grants of a research program “Practical Research for Innovative Cancer Control” granted by the Ministry of Health, Labour and Welfare in Japan.

RA has also supported the promotion of the commercial viability of research outcomes based

upon 3 main pillars: comprehensive alliance with the companies, academic drug discovery research with Drug Discovery Support Network, and supporting NCC-launched venture companies. A development candidate compound is provided by the cooperation with the business enterprise, and 4 themes are in progress as a Drug Discovery Support Network, and 1 venture company is established.

(Future Prospects)

RA collect information and make cross-sectorial coordination among researchers to obtain large-scale research funds and promote the commercial viability of research outcomes based upon three main pillars.

1.3 Research Auditor

For clinical studies led by NCC's investigator, 6 audits were conducted on GCP trials, and 3 on B type advanced medical service trials. Also 14 internal audits were conducted on departments in NCC conducting clinical research, as part of self-inspection required in the ethics guideline. Other activities included GCP-related training and consultation as well as support of regulatory inspection management.

(Future Prospects)

Audit and its related activity will be continued to boost quality of NCC's clinical research. In addition, as clinical studies with invasion and intervention will come into audit targets from October 2015 along with the implementation of "Ethics Guideline Regarding Medical Research on Human", preparation of process and technique will be critical for the new type of audit.

1.4. Research Alliance Section and 1.5. Intellectual Property Section

The Research Alliance Section promotes collaborative research arrangements with private sectors in order for NCC's research outcomes to bring into useful products available to cancer patients. As of December 31, 2014, No. of collaboration is 181, the research fees from private sectors amount to ca. 260 million yen (Fig. 1). Both figures would exceed by the end of the fiscal year on a year-to-year comparison. NCC has been formed comprehensive collaboration research system with a partner company or academic institution (Fig. 3). The Section supported a nationwide genomic screening project with the participation of over 10 pharmaceutical companies and institutions across Japan (SCRUM-Japan "Cancer Genome Screening Project for Individualized Medicine in Japan"), that is about to launch soon. The Section has also assisted collaboration with medium-sized medical device companies in regions.

The Intellectual Property (IP) Section constantly reviews IPs and abandons ones that has not received business inquiry for a certain period (Fig. 2). Then limited budget should be focused on IP which is commercially viable.

As a part of contributions in education, staff members actively participate in seminars with regard to the IP laws and regulations to update their knowledge and elevate their skills to promote academic-industrial alliance. Their competency in problem solution gained through OJT and effective consultation with experts will enable them to new challenge to innovative affairs.

(Future Prospects)

In a trend of openness on innovation, the Sections support creation of systemic and effective collaborative research framework. It also foresees the possibility of new laboratory setup where research is being performed by researchers from both industry and NCC, and lead to more functional collaboration.

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

2. Research Coordination Division

The Research Coordination Division has a role of clinical study management and coordination. This Division consists of the Research Management Section and Clinical Research Coordinator Section.

The Research Management Section supports planning and management through protocol development, essential document management, project management, and source document verification. The Clinical Research Coordinator Section support facilitates and coordinates the daily clinical trial activities and plays a critical role in the conduct of the study.

(Future Prospects)

Add the stuff to deal with increasing study number and promote rationalization and efficiency in routine practice. Promote education about Good Clinical Practice to all concerned in clinical trials.

3. Research Promotion Division

The Research Promotion Division is responsible for data management and study monitoring in the investigator-initiated clinical trials for cancer therapeutic development. The Division consists of Data Management Section in each campus, Tsukiji and Kashiwa, for data management and central monitoring, and the Multicenter Clinical Trial Section for coordinating multi-institutional clinical trials. In 2014, the Data Management Sections worked on data management and monitoring for JCOG trials, EPOC trials and in-house clinical trials, and made effort to develop electric data capturing (EDC) system. The Multicenter Clinical Trial Section organized the Japanese Cancer Trial Network (JCTN), which is a voluntary consortium consisting of 6 major cancer cooperative groups in Japan (JALSG, JCOG, J-CRSU, JGOG, JPLSG, and WJOG) and issued 3 common guidelines: (i) central monitoring, (ii) site visit audit and (iii) adverse events reporting.

(Future Prospects)

In 2015, the Division emphasizes the translocation of JCOG Biobank into BioBank Japan and conducting related translational researches, facilitates clinical trials with off-label drug use under the Advanced Medical Care B system, and explores the online report and review system for adverse events.

4. Biostatistics Division

The Biostatistics Division has a role of responsibility in study design, analysis, interpretation and statistical aspect of publications, especially in JCOG and EPOC clinical trials. We are also providing introductory Biostatistics lecture series to investigators in NCC as basic training in quantitative research methods. A cumulative total of more than 950 investigators participated in the 9 lectures provided in 2014. Furthermore, we are providing biostatistical consultation and expertise, which supports NCC investigators working on basic, translational, clinical and epidemiological researches. We offered advice to about 80 problems for which biostatistical consultation was requested in 2014.

(Future Prospects)

The NCC has a critical role for providing clinical service, education, conducting researches and making policy recommendation/proposal, which are all required to make a decision on the basis of solid and scientific evidence from reliable data and information. The mission of the Biostatistics Division is to contribute to the providing best evidence and the improvement of clinical practice and public health through the development and application of quantitative methods. The Biostatistics Division is expanding on its independent and collaborative research with a range of areas including observational and interventional researches for prevention and policy recommendation/proposal, as well as clinical trials. We are also opening up a new methodological research area in which mathematical approach will serve as a solid basis.

5. Regulatory Science Section

Achievements in clinical trials and clinical researches include 2 important aspects: the academic accomplishments and the providing solutions based on the scientific evidence to clinical practice. With the object of the latter, clinical trials and clinical researches for development of new drugs and medical devices are conducted complying and/or conforming to the regulations and rules under the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act,

formerly known as the Pharmaceutical Affaires Law. All the current members of the Regulatory Science Section have experience in working at the PMDA. Our division provided a support to develop study strategies in conducting investigator initiated clinical trials and to formulate road map for marketing approval/reimbursement under the National Health Insurance.

(Future Prospects)

The Regulatory Science Section is considering the new framework and concrete shape of our activities including consultation and supporting system.

6. Human Research Protection Section

The major role of the Human Research Protection Section has been its function as a secretariat for review board committees in NCC for human subject research. In 2014, the Section was involved in the establishment of the Special Certified Committee for Regenerative Medicine. The current challenge for the Section is the waiting list of the review. It is partly due to the increased demand both in the quality and quantity of the ethical and COI reviews following several widely publicized misconducts in clinical research and by the coming enforcement of the new Ethical Guidelines for Medical and Health Research Involving Human Subjects in April 2015. However, the more fundamental problem is the paucity of the human resource in the field of the research ethics review. The major reason for the resignation is the high level of knowledge and understanding required for the job and the often stressful dialogue with the researchers during the review process. On the other hand, a significant progress in 2014 was that the long-awaited web review system was launched, which is expected to be a powerful tool to cope with the increasing number of the protocols submitted to the committee.

(Future Prospects)

The Section should seek further understanding and cooperation from the researchers for the effective and sustainable review process. By the April 2015, when the Ethical Guidelines for Medical and Health Research Involving Human Subjects will come into effect, the Section will extensively review and revise the NCC rules and procedure manuals. In a more mid to longer term perspective, demand for the ethics review seems to be proliferating and spreading to the realm of the clinical practice, such as the reviews for the regenerative medicine, patient request medical treatment and Japanese version of the compassionate use of the investigational drugs. NCC may need to start discussing the scope and positioning of the Human Research Protection Section within the NCC organization.

For clinical studies led by NCC's investigator, 6 audits were conducted on GCP trials, and 3 on B type advanced medical service trials. Also 14 internal audits were conducted on departments in NCC conducting clinical research, as part of self-inspection required in the ethics guideline. Other activities included GCP-related training and consultation as well as support of regulatory inspection management.

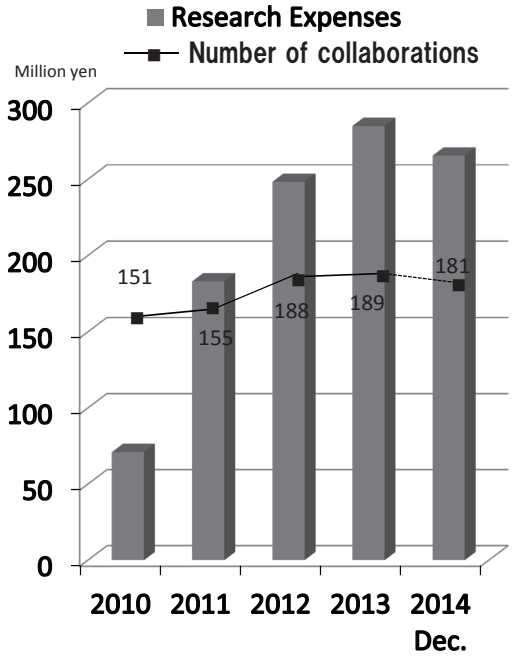



Figure 1. Collaborative Research with Industry

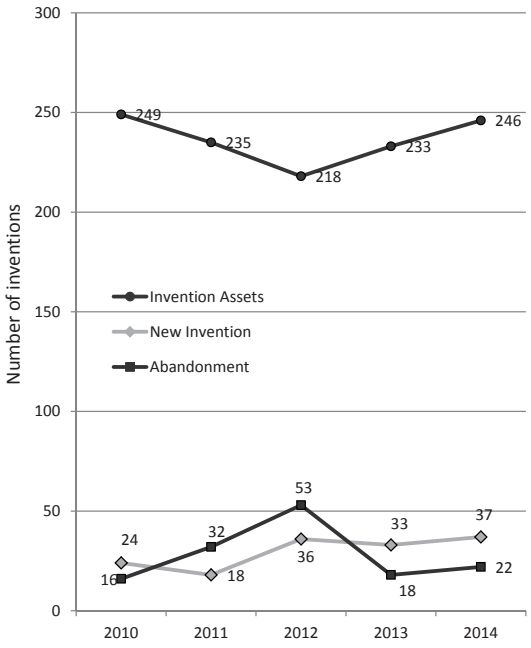



Figure 2. Invention Management

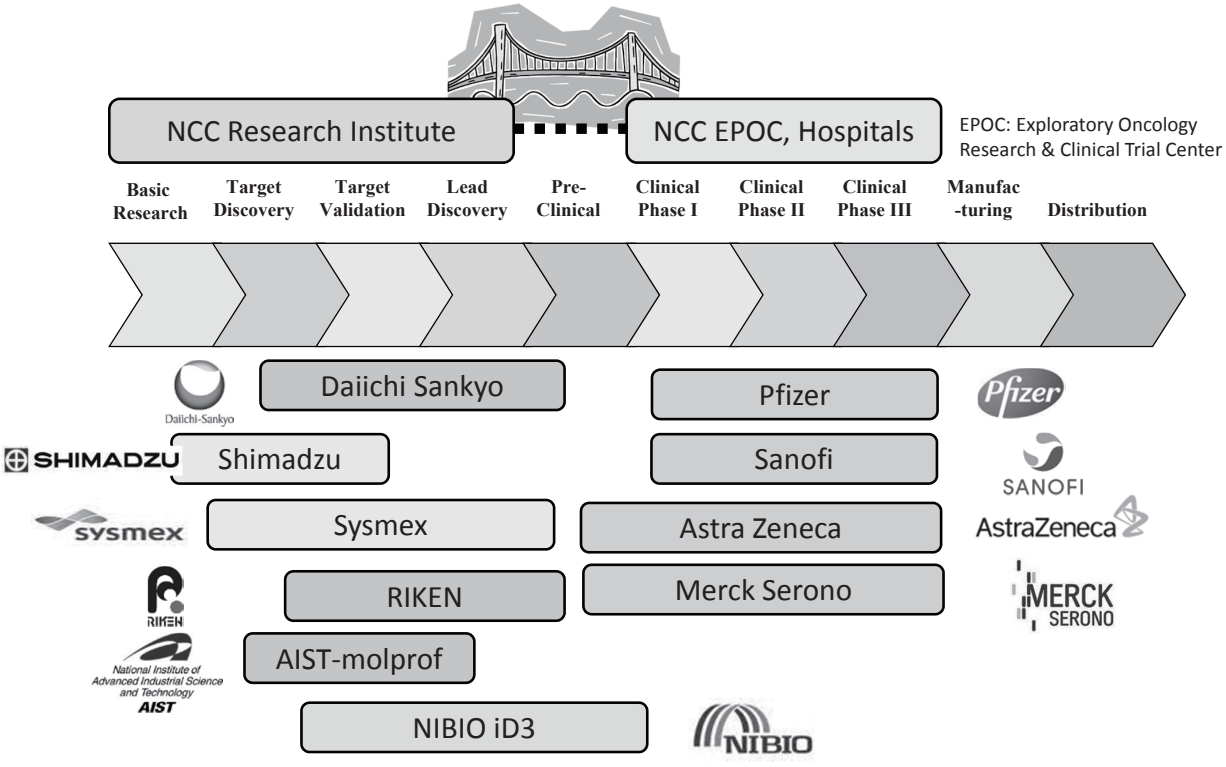
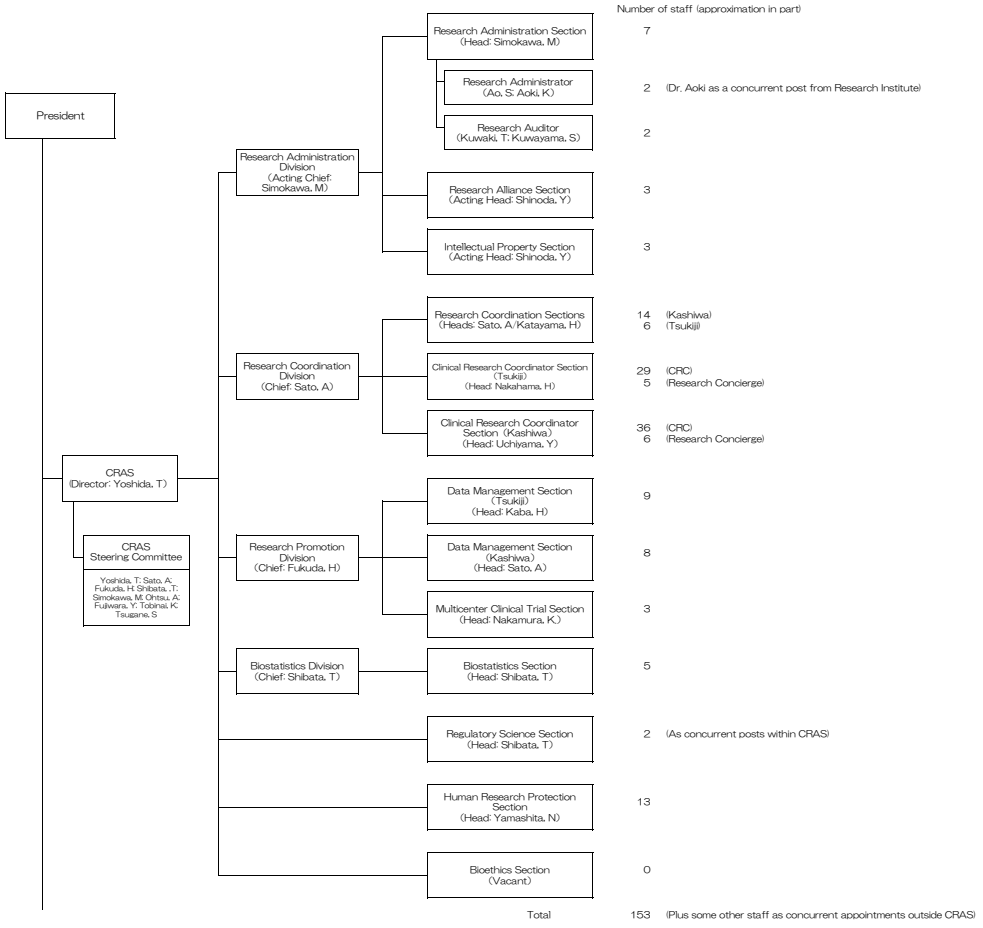



Figure 3. Strategic Alliance with industry

Organization of Center for Research Administration and Support (CRAS) (as of November 1, 2014)




## List of papers published in 2014

## Journal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# Center for Education and Professional Career Development

**Yuichiro Ohe, Hidehito Horinouchi, Tomonori Yano, Masaru Furuichi, Mika Asari, Yukiyo Fujita, Tosikazu Usijima, Shuichi Shimma, Gen Fujii, Takahiro Ochiya, Akihiro Sato, Noriko Yamashita, Hatoe Sakamoto, Kayoko Miyata, Ayako Mori, Mayumi Tsukagoshi, Naoko Nishikimi, Yoshinori Makino, Tomohiko Aso, Yoshihisa Abe, Satoshi Nakajima, Mayumi Miyauchi, Noriko Kobayashi, Miki Ito, Miho Kurihara, Kazue Hayasaka, Yasuhiko Ichida, Yoshihisa Muramatsu, Mitsuhiro Yoshida, Eichi Yoshikawa, Yumi Ochiai, Miki Fukutani, Kazuyuki Fukuda, Satoshi Koda, Hiroji Yamakabe, Hideyuki Yoshizumi, Shinichi Kouno**

## Introduction

The Center for Education and Professional Career Development has been established on July, 2014. The purposes are upbringing and securing of able human resource, clarification of the career path in each type of job, improvement of systematic educational program. Under the director of center and two vice-directors, the Office for Career Management, the Office for Graduate Medical Education, and the Office for Professional Education Management are placed.

## Routine activities

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

In 2014, hearings were carried out in each section to clarify what kind of personnel training, education was carried out in each section and what kind of career path was built. The systematic personnel training, education was carried out in medical doctors, nurses and pharmacists section which relatively had a lot of staff but enforcement of the systematic personnel training, education was difficult in the small sections. Moreover the career path was not clear in small sections. Because it was a facility specialized in cancer, an opinion that it was difficult to perform the education and training for the benign disorder enough was sent from plural sections, and it was thought that an opportunity of the training in other facilities was necessary.

A resident educational program of the National Cancer Center (NCC) has the history for nearly 50 years, but it started the re-examination of the resident educational program to produce more able cancer specialists effectively. We carry out a discussion in the working group, the hearing from chief doctor of each department, the questionnaire to persons who completed resident and senior resident educational program to build a new resident educational program that can cope with change of a new board certification system which will start in 2017, the medical and social situation and the request from the young doctors.

## Education

The cooperative post-graduate school program with Keio University and Juntendo University were started in 2012. As of in 2014, 14 and 44 post-graduate students, 58 in total were registered at the cooperative post-graduate school program with Keio University and Juntendo University, respectively. 4 post-graduate students of them received a Ph.D. degree.

## Future prospects

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

# Office for Advanced Medical Care Evaluation

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

## Introduction

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

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

## Routine activities

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

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

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

# Hospital

# Preface

The National Cancer Center Hospital (NCCH) provides the highest level of standard care with its missions to research and develop the whole area of cancer from novel diagnosis and treatment, palliative care, to patient support.

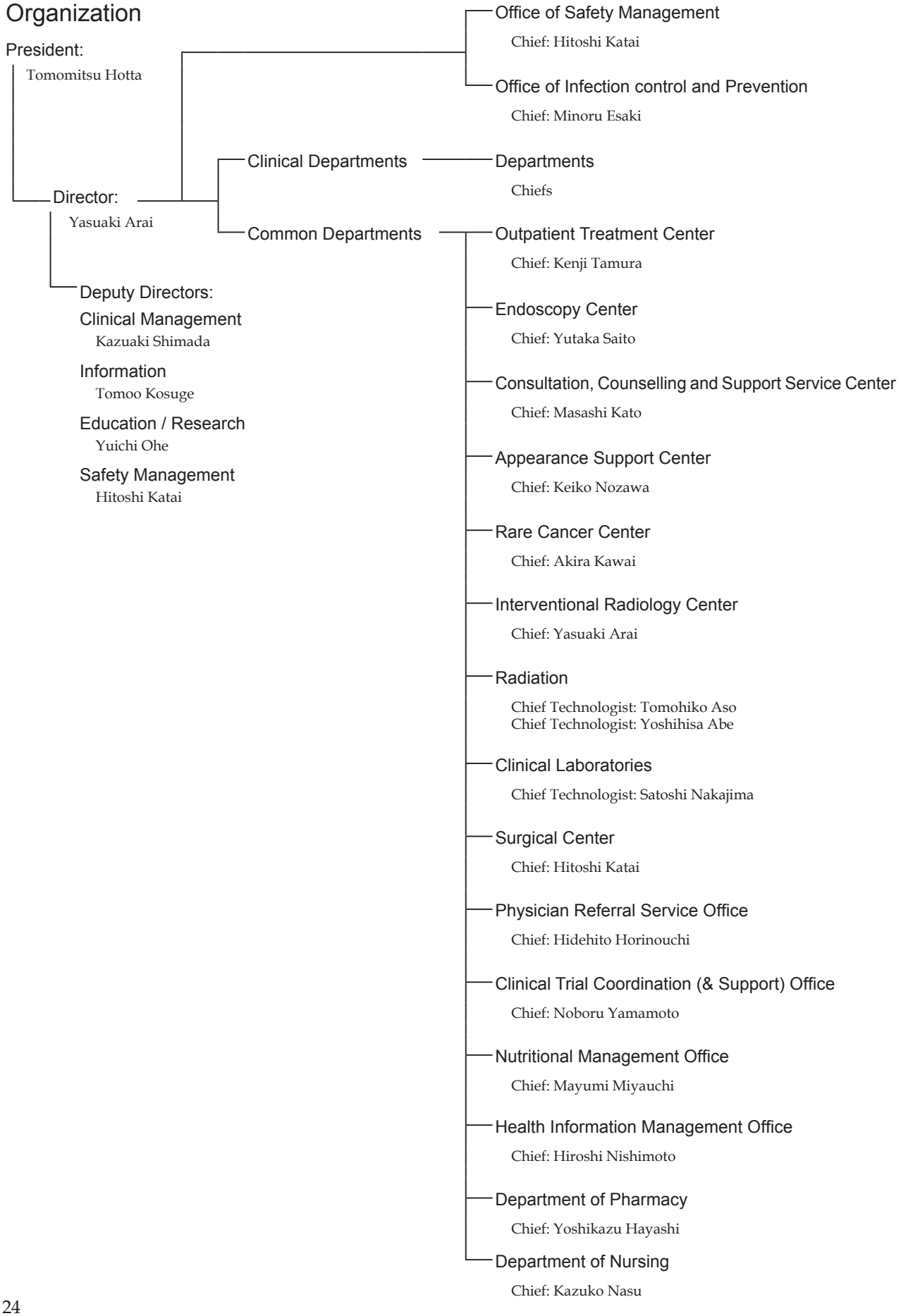
Following to the major reorganization to 14 common departments and 30 clinical departments in 2013, we newly set up two departments: the Interventional Radiology (IR ) Center with a hotline which accepts patients requiring for difficult IR treatments; and the Second Outpatient Treatment Center with 62 beds where facilities area available for conducting pharmacokinetic analysis and coping with emergent issues in clinical trials. The Outpatient Treatment Center aims to provide better outpatient treatment and extend outpatient clinics for clinical studies at an early phase. Moreover, we reorganized research facilities to improve the effectiveness of system for translational research with the NCC Research Institute and the Exploratory Oncology Research & Clinical Trial Center (EPOC).

To strengthen the system to care patients with complications, the NCCH concluded a comprehensive cooperation agreement with the Jikei University School of Medicine and prepared for concluding a clinical cooperation agreement with Saiseikai Central Hospital. In addition, we established the medical care ethics committee in collaboration with the NCCH East, and two innovative treatments were started at patients' own expense after their deliberation. For a better supportive care, the Patient Support Center (tentative) is planned to be open. We continue to work for a better hospital management through enhancing staff members' awareness of management improvement.

In this year, we have completed in improving clinical and research as well as management systems and promoting collaboration with other institutes for expansion of clinical practices.

Yasuaki Arai, MD
Director of the Hospital
National Cancer Center

# Organization



## Clinical Departments

Director:
Yasuaki Arai

Deputy Directors:

Clinical Management
Kazuaki Shimada

Information
Tomoo Kosuge

Education/Research
Yuichiro Ohe

Safety Management
Hitoshi Katai

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

# Activities of the Departments

# Department of Neurosurgery and Neuro-Oncology

**Yoshitaka Narita, Yasuji Miyakita, Makoto Ohno, Masamichi Takahashi, Hideyuki Arita, Takahiro Ogawa, Motoki Yonezawa, Sakura Kuzuoka**

## Introduction

Patients with primary and metastatic brain tumors are treated by 4 neurosurgeons and 1 senior resident in the Department of Neurosurgery and Neuro-Oncology. 317 patients were admitted and 96 craniotomies for tumor removal were carried out in 2014 including 34 gliomas, 42 brain metastases, 5 primary CNS lymphomas, and 7 meningiomas (Table 1). The site of the craniotomy and the extent of tumor removal were visualized on the intraoperative MRI in real time, contributing to safer and more precise surgery. Intraoperative monitoring with motor- and sensory evoked potential (MEP and SEP) recording as well as preoperative functional MRI and MR tractography were also used to preserve patient neurological function. 12 awake surgeries were also performed, particularly for removal of gliomas near the speech center. Patients with malignant brain tumors were treated with postoperative radiotherapy and chemotherapy. In order to design a more effective chemotherapy regimen, molecular biological studies for drug resistance, growth factors, cell kinetic studies on individual tumors and several clinical trials are ongoing.

## Routine activities

A weekly conference of treatment of patients with brain tumors is held with doctors of the Department of Radiation Oncology on diagnosis and the Division of Brain Tumor Translational Research. Usually 20 patients are hospitalized and 2 or 3 of them undergo surgical treatment every week. The patients with malignant brain tumors receive postoperative radiotherapy and chemotherapy. Statistical analysis revealed that surgical removal of as much of the tumor as possible yielded better survival rates even for the most malignant glioblastomas, which usually recur soon after 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 (BTRJ). High dose methotrexate is administered to the patients with primary CNS lymphoma before radiotherapy.

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

## Research activities

Patients with brain tumors have been registered in the BTRJ since 1969. More than 100,000 patients have been registered and followed up. The Department of Neurosurgery and Neuro-Oncology, the National Cancer Center Hospital, contributes as a managing office of the BTRJ and established on-line registration using the University Hospital Medical Information Network (UMIN) system in 2009. Clinical data during 2001 and 2004 were collected and the report will be published in 2014 as a supplement of the official journal of the Japan Neurosurgical Society.

An analysis of gene expression profiles in malignant gliomas is being carried out in order to determine specific genes that have an influence on the effects of chemotherapy and radiation therapy in cooperation with the Division of Brain Tumor Translational Research, the National Cancer Center Research Institute. The determination of the methylation status of O6-methylguanine-DNA methyltransferase (MGMT) and the mutation of IDH1/2 and TERT are also carried out to predict the prognosis of the patients with malignant gliomas.

## Clinical trials

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

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

## Education

Our Department plays roles as an office of general secretary of JCOG-Brain tumor study group and brain tumor registry of Japan, we conducted many clinical trials and brain tumor registry. We educate many neurosurgeons and oncologist about surgical techniques of awake craniotomy and intraoperative MRI and the effective usage and adverse effects of many chemotherapeutic agents about malignant brain tumors.

## Future Prospects

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

**Table 1. Number of patients**

| | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| Surgeries | 145 | 123 | 132 | 140 | 128 |
| Craniotomy | 115 | 92 | 98 | 106 | 96 |
| Glioma | 51 | 35 | 47 | 39 | 34 |
| Brain metastases | 42 | 39 | 33 | 40 | 42 |
| Meningioma | 9 | 5 | 7 | 12 | 7 |
| Lymphoma | 4 | 6 | 4 | 7 | 5 |
| Spinal tumors | | | 2 | 4 | 1 |
| Others | 4 | 7 | 5 | 8 | 7 |
| Neuroendoscope, shunt | 30 | 31 | 34 | 34 | 32 |

## List of papers published in 2014

## Journal


1. Narita Y, Tsukagoshi S, Suzuki M, Miyakita Y, Ohno M, Arita H, Saito Y, Kokojima Y, Watanabe N, Moriyama N, Shibui S. Usefulness of a glass-free medical threedimensional autostereoscopic display in neurosurgery. Int J Comput Assist Radiol Surg, 9:905-911, 2014
2. Committee of Brain Tumor Registry of Japan. REPORT OF BRAIN TUMOR REGISTRY OF JAPAN (2001-2004) 13th Edition. Neurol Med Chir (Tokyo), 54:1-102, 2014
3. Arita H, Narita Y, Miyakita Y, Ohno M, Sumi M, Shibui S. Risk factors for early death after surgery in patients with brain metastases: reevaluation of the indications for and role of surgery. J Neurooncol, 116:145-152, 2014
4. Fukushima S, Yoshida A, Honda K, Maeshima AM, Narita Y, Yamada T, Shibui S, Tsuda H. Immunohistochemical actinin-4 expression in infiltrating gliomas: association with WHO grade and differentiation. Brain Tumor Pathol, 31:11-16, 2014
5. Fukushima S, Otsuka A, Suzuki T, Yanagisawa T, Mishima K, Mukasa A, Saito N, Kumabe T, Kanamori M, Tominaga T, Narita Y, Shibui S, Kato M, Shibata T, Matsutani M, Nishikawa R, Ichimura K. Mutually exclusive mutations of KIT and RAS are associated with KIT mRNA expression and chromosomal instability in primary intracranial pure germinomas. Acta Neuropathol, 127:911-925, 2014
6. Fukushima S, Narita Y, Yonezawa M, Ohno M, Arita H, Miyakita Y, Ichimura K, Yoshida A, Shibui S. Short communication: sclerosing meningioma in the deep sylvian fissure. Brain Tumor Pathol, 31:289-292, 2014
7. Saito K, Mukasa A, Narita Y, Tabei Y, Shinoura N, Shibui S, Saito N. Toxicity and outcome of radiotherapy with concomitant and adjuvant temozolomide in elderly patients with glioblastoma: a retrospective study. Neurol Med Chir (Tokyo), 54:272-279, 2014
8. Sato A, Okada M, Shibuya K, Watanabe E, Seino S, Narita Y, Shibui S, Kayama T, Kitanaka C. Pivotal role for ROS activation of p38 MAPK in the control of differentiation and tumor-initiating capacity of glioma-initiating cells. Stem Cell Res, 12:119-131, 2014
9. Okada M, Sato A, Shibuya K, Watanabe E, Seino S, Suzuki S, Seino M, Narita Y, Shibui S, Kayama T, Kitanaka C. JNK contributes to temozolomide resistance of stem-like glioblastoma cells via regulation of MGMT expression. Int J Oncol, 44:591-599, 2014
10. Kinoshita M, Sasayama T, Narita Y, Yamashita F, Kawaguchi A, Chiba Y, Kagawa N, Tanaka K, Kohmura E, Arita H, Okita Y, Ohno M, Miyakita Y, Shibui S, Hashimoto N, Yoshimine T. Different spatial distribution between germinal center B and non-germinal center B primary central nervous system lymphoma revealed by magnetic resonance group analysis. Neuro Oncol, 16:728-734, 2014
11. Aihara K, Mukasa A, Gotoh K, Saito K, Nagae G, Tsuji S, Tatsuno K, Yamamoto S, Takayanagi S, Narita Y, Shibui S, Aburatani H, Saito N. H3F3A K27M mutations in thalamic gliomas from young adult patients. Neuro Oncol, 16:140-146, 2014
12. Yoshida A, Tsuta K, Ohno M, Yoshida M, Narita Y, Kawai A, Asamura H, Kushima R. STAT6 immunohistochemistry is helpful in the diagnosis of solitary fibrous tumors. Am J Surg Pathol, 38:552-559, 2014

# Department of Ophthalmic Oncology

**Shigenobu Suzuki, Yukiko Aihara, Shuichi Sano**

## Introduction

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

## Routine activities

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

1) Retinoblastoma

Unless the patient's family has anxiety about preserving the affected eye, if the eye has already suffered from complication such as 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) Choroidal melanoma

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

3) Orbital tumors

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

4) Eyelid tumors

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

5) Conjunctival tumors

Conjunctival malignant tumors are treated by excisional resection with a safety margin combined with cryotherapy at the resection margin. Diffuse conjunctival tumors or tumors with orbital invasion are 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 developed in our hospital from 1987, and has been modified and performed after 2009 in more than 20 countries. We are planning the clinical trial on selective ophthalmic artery injection therapy for initial treatment methods.

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

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 checking overlapping. This registry covers almost all patients in Japan now, and providing epidemiological data.

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

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

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

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

## Future Prospects

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

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

| | |
|---|---|
| Retinoblastoma | 53 |
| Choroidal melanoma | 15 |
| Other intraocular tumors | 25 |
| Eyelid tumor | 18 |
| Conjunctival tumor | 10 |
| Orbital tumor | 21 |
| Ocular adnexal lymphoma | 11 |
| Other | 23 |
| Total | 176 |

**Table 2. Type of procedure**

| | |
|---|---|
| Retinoblastoma | |
| Selective ophthalmic arterial injection | 117 |
| Laser and/or vitreous injection | 131 |
| Ruthenium brachytherapy | 7 |
| Enucleation | 19 |
| Examination under general anesthesia | 5 |
| Choroidal melanoma | |
| Ruthenium brachytherapy | 8 |
| Enucleation | 3 |
| Resection of ciliary body tumor | 2 |
| Resection of eyelid tumor | 6 |
| Resection of conjunctival tumor | 8 |
| Resection of orbital tumor | 16 |
| Total | 322 |

## List of papers published in 2014

### Journal

1. Harada K, Murakami N, Kitaguchi M, Sekii, S, Takahashi K, Yoshio K, Inaba K, Morota, M, Ito Y, Sumi M, Suzuki S, Tobinai K, Uno, T, Itami J. Localized ocular adnexal mucosaassociated lymphoid tissue lymphoma treated with radiation therapy: a long-term outcome in 86 patients with 104 treated eyes. Int J Radiat Oncol Biol Phys, 88:650-654, 2014

# Department of Head and Neck Oncology

**Seiichi Yoshimoto, Fumihiko Matsumoto, Kenya Kobayashi, Daisuke Maki, Sadahiro Kishishita**

## Introduction

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

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

## Routine activities

The Department of Head and Neck Oncology at NCCH consists of 5 head and neck surgeons. Many operations are performed under general and local anesthesia with or without microsurgical reconstructive surgery. In addition to radiotherapy, concurrent chemo-radiotherapy is performed with the Department of Radiation Oncology.

In 2014, 345 patients with head and neck tumor underwent surgery under local or general anesthesia; 91 and 254, respectively, including 57 patients with major ablation and reconstructive surgery. Table 1 shows the number of surgical cases with each primary site. Table 2 shows the number of each surgical procedure.

## Research activities

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

## Education

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

## Future Prospects

We recently have started trans-oral resection for superficial laryngo-pharyngeal cancer. Trans-oral resection will be indicated for more patients. Cetuximab is used for many patients with recurrent or metastatic tumor. We will be able to get useful information about the response rate of Cetuximab for Japanese patients.

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

| | |
|---|---|
| Tongue | 38 |
| Oral Cavity ( without tongue) | 56 |
| Nasal and paranasal cavity | 16 |
| Nasopharynx | 6 |
| Oropharynx | 35 |
| Hypopharynx | 53 |
| Cervical esophagus | 9 |
| Larynx | 29 |
| Salivary Gland | 20 |
| Thyroid | 34 |
| Parathyroid | 0 |
| Neck | 43 |
| Others | 6 |
| Total | 345 |

**Table 2. Type of procedure**

| | |
|---|---|
| Skull base (+reconstruction) | 4(3) |
| Maxillectomy (+reconstruction) | 11(3) |
| Glossectomy (+reconstruction) | 35(7) |
| Resection of Oral Cavity (+reconstruction) | 46(11) |
| Nasopharyngectomy | 5(2) |
| Oropharyngectomy (+reconstruction) | 27(7) |
| Endoscopic resection of hypopharynx | 24 |
| Trans-oral resection of hypopharynx | 4 |
| Partial pharyngectomy (+reconstruction) | 5(5) |
| Total laryngopharyngectomy (+recon.) | 15(14) |
| Trans-oral resection of larynx | 5 |
| Partial laryngectomy | 4 |
| Total laryngectomy (+reconstruction) | 6 |
| Thyroidecotmy | 26(1) |
| Parotidectomy | 10 |
| Neck dissection (+reconstruction) | 28(1) |
| Resection of parapharyngeal tumor | 3 |
| Voice prosthesis | 9 |
| Lymphadenectomy | 48 |
| Others (+reconstruction) | 30(3) |
| Total | 345(57) |

## List of papers published in 2014

## Journal


1. Yoshimoto S, Nakashima T, Fujii T, Matsuura K, Otsuki N, Asakage T, Fujimoto Y, Hanai N, Homma A, Monden N, Okami K, Sugasawa M, Hasegawa Y, Nibu K, Kamata S, Kishimoto S, Kohno N, Fukuda S, Hisa Y. Japanese Board Certification System for head and neck surgeons. Auris Nasus Larynx, 41:327-330, 2014
2. Fukunaga Y, Sakuraba M, Miyamoto S, Kayano S, Kurosawa K, Fujiki M, Sakisaka M, Yoshimoto S. One-stage reconstruction of a tracheal defect with a free radial forearm flap and free costal cartilage grafts. J Plast Reconstr Aesthet Surg, 67:857-859, 2014
3. Watabe Y, Mori T, Yoshimoto S, Nomura T, Shibahara T, Yamada T, Honda K. Copy number increase of ACTN4 is a prognostic indicator in salivary gland carcinoma. Cancer Med, 3:613-622, 2014
4. Murakami N, Mori T, Yoshimoto S, Ito Y, Kobayashi K, Ken H, Kitaguchi M, Sekii S, Takahashi K, Yoshio K, Inaba K, Morota M, Sumi M, Itami J. Expression of EpCAM and prognosis in early-stage glottic cancer treated by radiotherapy. Laryngoscope, 124:E431-436, 2014

# Department of Plastic and Reconstructive Surgery

**Shimpei Miyamoto, Masahide Fujiki, Masaki Arikawa**

## Introduction

Department of Plastic and Reconstructive Surgery has mainly focused on surgical reconstruction after cancer ablation. In our institution, reconstructive procedures using free flap transfer with microvascular anastomosis are the most important operations. In addition, several methods such as tissue transfer with pedicled 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 ablative surgery. The quality of life (QOL) of the patient can be improved by the functional and morphological reconstruction.

## Routine activities

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

## Research activities

Multi-institutional analysis of postoperative function after microvascular tongue reconstruction is now going on. Also, laboratory research of flow-through flap using a rat model is now going on.

**Table 1. Reconstructive procedures**

| | |
|---|---|
| Free flap | 131 |
| DIEP | 34 |
| ALT | 35 |
| Jejunum | 26 |
| LD (or TAP) | 17 |
| RAMC | 10 |
| Fibula | 3 |
| Scapula | 5 |
| Dorsalis Pedis | 1 |
| Other microsurgical procedures | 15 |
| Supercharge | 3 |
| Extremity revascularization | 3 |
| Hepatic artery | 3 |
| Others | 6 |
| Total (Microsurgery) | 146 |
| Pedicled flap | 39 |
| LD (or TAP) | 12 |
| Pectoralis Major | 7 |
| ALT | 6 |
| RAMC | 4 |
| Others | 10 |

**Table 2. Breast reconstruction**

| | |
|---|---|
| Tissue expander | 56 |
| Silicone implant | 29 |
| DIEP | 30 |
| LD | 5 |

## List of papers published in 2014

### Journal


1. Miyamoto S, Fukunaga Y, Shinozaki T, Yasunaga Y, Hayashi R, Sakuraba M. T-shaped Pectoralis Major Musculocutaneous Flap for Reconstruction of an Extensive Circumferential Pharyngeal Defect. Plast Reconstr Surg Glob Open, 2:e129, 2014
2. Miyamoto S, Kayano S, Fujiki M, Chuman H, Kawai A, Sakuraba M. Early Mobilization after Free-flap Transfer to the Lower Extremities: Preferential Use of Flow-through Anastomosis. Plast Reconstr Surg Glob Open, 2:e127, 2014
3. Miyamoto S, Kayano S, Fujiki M, Sakuraba M. Combined use of the cephalic vein and pectoralis major muscle flap for secondary esophageal reconstruction. Microsurgery, 34:319-323, 2014
4. Miyamoto S, Kayano S, Kamizono K, Fukunaga Y, Nakao J, Nakatani F, Kobayashi E, Sakuraba M. Pedicled superficial femoral artery perforator flaps for reconstruction of large groin defects. Microsurgery, 34:470-474, 2014
5. Miyamoto S, Kayano S, Umezawa H, Fujiki M, Nakao J, Sakuraba M. Efficient design of a latissimus dorsi musculocutaneous flap to repair large skin defects of the upper back. Microsurgery, 34:20-22, 2014

# Department of Breast Surgery

**Takayuki Kinoshita, Takashi Hojo, Sota Asaga, Kenjiro Jimbo, Eriko Iwamoto, Kanae Taruno, Takuya Ogura**

## Introduction

The Department of Breast Surgery deals with treatment of breast cancer thorough surgeries, as well as diagnosis of breast diseases and assessment of lymph nodes in the axillary and clavicular regions which are suspected harboring metastases. The trend of surgical procedure has been changing year by year. Although breast-conserving therapy (BCT) has accounted for 43% of the total surgeries in our Department in 2014, BCT are on the decline in recent years. One of the reasons is increasing needs of immediate reconstruction surgeries. In 2010, immediate breast reconstruction became one of the choices for these patients in whom breast preservation was impossible, and a total of 75 immediate breast reconstructions were performed in 2014, comprising more than 14% of all the cases. The number of cases of immediate breast reconstruction has gradually increased year by year to match the increase needs of patients. Sentinel lymph node (SLN) biopsies (SLNB) were performed in 67% of the cases. Following SLNB, the axillary lymph node dissection (ALND) could be avoided when the SLNB was negative. One-step nucleic acid amplification (OSNA) assay, that quantitatively measures CK19 mRNA detects sentinel lymph node metastases even in molecular levels, in conjunction with this assay and conventional microscopic method, we began to be able to evaluate the SLN more precisely. Further, by comparing the OSNA results with that of conventional histological diagnosis, we try to search the possibility of omitting axillary lymph node dissection by using two methods. Thus, to meet the diverse needs of breast cancer patients, we are striving continuously.

## Routine activities

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

Surgery

We perform surgeries from Monday to Friday, regularly 10 to 12 cases of breast cancer in a week.

Table 1 showed a total number of patients with primary breast cancer (including breast primary sarcoma) and other breast disease. The types and number of operative procedures are shown in Table 2. The rate of mastectomy was 51% (262/514), including 75 cases of immediate reconstruction. SLNB was performed in 331 patients, and 251 patients were spared from ALND.

## Research activities and Clinical trials

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

Trial of image-guided radiofrequency ablation (non-surgical therapy) has accomplished for early-stage breast carcinomas of less than 1.0

cm in diameter (Phase I/II study; Kinoshita et al.). 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. Our secondary goals are to determine the size, configuration and pathological features of acute RFA treatment of breast cancers, and have been conducted clinical study to evaluate the oncologic safety of RFA in terms of local recurrence.

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

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

4) Scalp-cooling device during chemotherapy

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

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

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

6) Registration Data-base System of the breast cancer patient who carried out the lymph node metastasis diagnosis by the OSNA® method (LynoLog Data-base)

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

7) Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer (OlympiA)

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

**Table 1. Number of patients**

| | | 2012 | 2013 | 2014 |
|---|---|---|---|---|
| Primary breast cancer (or sarcoma) | | 494 | 555 | 514 |
| cStage | 0 | 76 | 99 | 106 |
| | II | 199 | 215 | 184 |
| | II | 194 | 203 | 189 |
| | III | 17 | 33 | 27 |
| | IV | 8 | 5 | 3 |
| unknown | | 2 | 0 | 6 |

16 and 11 case were bilateral breast cancer in 2013 and 2014.

**Table 2. Type of procedure**

| | 2011 | | 2012 | | 2013 | | 2014 | |
|---|---|---|---|---|---|---|---|---|
| Total number of operations | 576 | | 581 | | 613 | | 566 | |
| Total number of Primary breast cancer | 525 | | 494 | | 555 | | 514 | |
| Mastectomy (%) | 250 | (48) | 234 | (45) | 263 | (47) | 262 | (51) |
| Breast-conserving surgery (%) | 269 | (51) | 275 | (53) | 283 | (51) | 222 | (43) |
| Radiofrequency ablation (%) | 6 | (1) | 6 | (1) | 9 | (2) | 30 | (6) |
| Axillary lymph node dissection (ALND) (%) | 205 | (42) | 188 | (38) | 93 | (18) | 83 | (17) |
| Sentinel lymph node biopsy (SLNB) (%) | 402 | (81) | 409 | (83) | 347 | (66) | 331 | (67) |
| ALND after SLNB (%) | 113 | (23) | 103 | (21) | 83 | (16) | 80 | (16) |
| Immediate breast reconstruction (%) | 74 | (14) | 62 | (13) | 65 | (12) | 75 | (14) |
| Neoadjuvant therapy | 57 | (11) | 45 | (8) | 38 | (7) | 36 | (7) |

**Table 3. Survival (2006.1-2007.12)**

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

## List of papers published in 2014

## Journal


1. Shien T, Iwata H, Fukutomi T, Inoue K, Aogi K, Kinoshita T, Ando J, Takashima S, Nakamura K, Shibata T, Fukuda H. Tamoxifen plus tegafur-uracil (TUFT) versus tamoxifen plus Adriamycin (doxorubicin) and cyclophosphamide (ACT) as adjuvant therapy to treat node-positive premenopausal breast cancer (PreMBC): results of Japan Clinical Oncology Group Study 9404. Cancer Chemother Pharmacol, 74:603-609, 2014
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# Department of Breast and Medical Oncology

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

## Introduction

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

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

## Clinical activities

1. Setup

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

2. Performance

There were a total of 898 first visits of new patients in 2014 (Table 1). Approximately two-thirds of the new patients were referred from other departments of the National Cancer Center Hospital (NCCH). About a half of new patients are breast cancer patients, but it is noteworthy that there was approximately 50% increase in patients with adult sarcoma this year as a result of our devotion to the Rare Cancer Center. The number of outpatient chemotherapy delivered by our Division were 9,662, which accounts for 37% of the total number and rank first of the number of treatments delivered at of the Outpatient Treatment Center.

We have approximately 27 (range 22-33) inpatients daily. Terminally-ill patients are transferred to palliative care units or in-home care clinics outside the NCCH, whereas 24 patients of our Division passed away in the NCCH in 2014. Autopsy was undertaken in five patients.

3. Conference

The one-hour briefing medical conference is held every morning to discuss the evidenced-based care for individual patients. Basic and translational research conference is held on Tuesday, a journal club on Wednesday, a clinical trial conference on Thursday, and a weekend and outpatient follow-up conference on Friday. A Multidisciplinary Case Conferences with diagnostic radiologists, surgeons, and pathologists is held with members of Department of Breast Surgery, Gynecology, Musculoskeletal Oncology and Rehabilitation, Radiation Oncology and Pathology, once or twice (Breast) per week, respectively. We also participate in Exploratory Oncology Research and Clinical Trial Center Conference (Phase 1 team) twice per week as its active members.

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

4. Coordination of care

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

## Research activities

Our research interest extends across xtends across a wide range of topics related to treatment and clinical program development. Many of our researches are secured by public and consignment research grants. In 2014, we conducted ten research programs as primary investigator and also participated in additional nine programs as co-investigator in research programs secured by competitive research funds.

In 2014, we actively enrolled patients in phase I studies (including first in human or global) as well as national and international phase II and III studies (Table 2). Of note, we launched pharmacokinetic and dose-finding study of eribulin/olaparib, and phase II study of eribulin in neoadjuvant setting in triple negative breast cancer as our fourth and fifth investigator-initiated clinical trial (IIT* in Table 2). New molecular imaging studies are launched in cooperation with the Research Institutes. We also conducted many type of prospective cohort translational studies to find novel biomarker.

We value cancer survivorship as a research theme in order to develop a patient-centered comprehensive care program. In 2014, we published a guideline on fertility and fertility preservation for young breast cancer patients in cooperation with gynecologist and reproductive specialists. Also, we took the lead of a multidisciplinary collaborative study group on End-of-life decision support for patients with advanced cancer.

## Education

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

## Future prospects

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

**Table 1. Demographics of Patients at their 1st Visit to the Clinic of the Breast and Medical Oncology Division (Jan - Dec, 2014)**

| Number of new patients | n | % |
|---|---|---|
| Total | 898 | |
| Breast | 410 | 45.6 |
| GYN | 160 | 17.8 |
| Sarcoma | 121 | 13.4 |
| Cancer of primary unknown | 110 | 12.2 |
| Others | 97 | 10.8 |
| | | |
| Reason for visits of new patients | | |
| 2nd opinion | 58 | 6.4 |
| Treatment at NCCH | 300 | 33.4 |
| Referrals from other hospitals | 55 | 6.1 |
| Referrals from other divisions in NCCH | 481 | 53.5 (100) |
| Breast surgery | 310 | (64.4) |
| GYN | 68 | (14.1) |
| Urology | 26 | (5.4) |
| Orthopedics | 20 | (4.1) |
| Others | 57 | (11.8) |
| Others | 4 | 0.4 |

**Table 2. Active Clinical Trials (Jan. 2014-Dec. 2014)**

| Disease | Clinical setting | Phase | Protocol | Regimen | Status |
|---|---|---|---|---|---|
| Breast | Neo-adjuvant | II (IIT*) | Neo-Eribulin (TNBC) | Eribulin followed by FEC | Active |
| | Follow up | III | JCOG1204 | Intensive follow up vs standard follow up | Active |
| | Adjuvant | III | BEATRICE (TNBC) | CTx vs CTx + Bevacizumab | Active, not recruiting |
| | | III | ALTTO (HER2) | Lapatinib vs HCN vs Lapa/HCN | Active, not recruiting |
| | | III | CREATE-X (JBCRG04) | Capecitabine vs none post-NAC | Active, not recruiting |
| | | III | D-CARE | Denosumab vs placebo | Active, not recruiting |
| | | III | APHINITY (HER2) | CTx+HCN/placebo vs CTx/HCN/Pertuzumab | Active |
| | | III | POTENT | HTx+S1 vs HTx alone | Active |
| | | III | KAITLIN (HER2) | Taxane/Trastuzumab/Pertuzumab vs. T-DM1/Pertuzumab | Active |
| | Metastatic | III | JCOG1017 | Surgery vs no surgery for primary Stage IV BC | Active |
| | | III | MARIANNE (HER2) | RO5304020+/- RO4368451 vs HCN/PTX | Active |
| | | III | NK105 | NK105 vs Paclitaxel | Active, not recruiting |
| | | III | PALOMA-2 (HR+) | Letrozole +/- PD0332991 | Active |
| | | III | ELTOP (WJOG) | Lapa/Capecitabine vs HCN/Capecitabine | Active |
| | | III | OlympAD (BRCA+) | Olaparib vs TPC | Active |
| | | II | CAPTURE (HR+) | Paclitaxel/Bevacizumab vs maintenance endocrine therapy | Active |
| | | II | BEECH | AZD5363+PTX | Active |
| | | II | TARGET (HR+) | Tamoxifen vs high-dose Tamoxifen /CIP2D6 | Active |
| | | II | lapaHER (HER2) | Lapatinib/HCN | Active |
| | | II | CBDCA/S1 (TNBC) | CBDCA/S1 | Active |
| | | I/II | CAPIRI | Capecitabine/CPT-11 | Active |
| | | I/II | S1/docetaxel | S1/docetaxel | Active |
| | | I/II | Lapa/eriburin (HER2) | Lapatinib/eriburin | Active |
| | | I/II (*IIT) | EO (TNBC) | Eribulin/AZD2281 | Active |
| | | I/II | PD0332991 | Letrozole +PD0332991 | Active |
| | | I (exp) | AZD5363 (AKT+ or PIK3CA+) | AZD5363 | Active |
| | | PK/PD/PGx | Eriburin PK | Eriburin | Active |
| Ovary | Adjuvant | III | AZD2281 | Chemotherapy+/-Olaparib | Active, not recruiting |
| | Advanced | III | JCOG0602 | Primary surgery vs NAC | Active |
| | | III | JGOG3017 | TC vs. CDDP/CPT-11 | Active |
| | | III | GOG213 | TC +/- bevacizumab | Active |
| | | III | GOG218 | TC +/- bevacizumab | Active, not recruiting |
| | | III | AMG386 | PTX+/-AMG386 | Active, not recruiting |
| | | III | GW786034 | Pazopanib | Active, not recruiting |
| | | II | GOG268 | TC+Temsirolimus | Active |
| Cervical cancer | Advanced | I | S1/CDDP | S1/CDDP chemoradiation | Active |
| Ovary/Endometrial/Cervical | | II | Perifosine (PIK3CA+) | Perifosine | 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 | AZD2281 | Olaparib | Active |
| | | I | AZD1208 (global FIH)) | AZD1208 | Active |
| | | I | AZD5363 | AZD5363 | Active, not recruiting |
| | | I | PD0332991 | PD0332991 | Active |
| | | I | Veriparib (BRCA+) | Veriparib | Active |
| | | I | BAY1179470 (FGFR+) | BAY1179470 | Active |
| | | I | MK3475 (PDL1+) | MK3475 | Active |
| | | I | GDC0032 | GDC0032 | Active |
| | | I | Ds5573a (FIH) | Ds5573a | Active |
| Soft tissue sarcoma | | II | ET-743 | ET-743 | Active |
| CIPN SNPs | | TR | Paclitaxel induced peripheral neuropathy | Paclitaxel | Active |
| Molecular Imaging | | TR | Cu64-trastuzumab/PET | Nano-dose, radio-labeled trastuzumab as PET probe | Active |
| | | TR | Cu64- cetuximab/PET | Nano-dose, radio-labeled trastuzumab as PET probe | Active |
| | | TR | MAS- imaging | MAS-imaging for solid tumor | Active |
| Liquid Biopsy | | TR | CTC | CTC/breast, gynecologic (blood) | Active |
| | | TR | ADCC | Quantitative ADCC (blood) | Active |
| | | TR | miRNA in exosome | miRNA in exosome (blood) | Active |
| Genomic test | | TR | TOP-GEAR (NGS) | Genome screening for phase I | Active |
| (NGS, Sequencing at hot spots, Whole Exon Sequence) | | TR | HER-Antibody induced heart failure | HER-Antibody | Active |
| | | TR | Sequencing | Methylation of promoter BRCA | Active, not recruiting |
| | | TR | Sequencing | Methylation of promoter TERT | Active |
| | | TR | Sequencing | AKT1P, PIK3CA | Active |

*IIT; investigator-initiated clinical trial, TNBC; triple negative breast cancer, CTx; chemotherapy, HTx; hormonal therapy, HR; hormone receptor, TPC; therapy of physician's choice, TR; translational, NGS; next generation sequence

## List of papers published in 2014

## Journal


1. Ando M, Yamauchi H, Aogi K, Shimizu S, Iwata H, Masuda N, Yamamoto N, Inoue K, Ohono S, Kuroi K, Hamano T, Sukigara T, Fujiwara Y. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. Breast Cancer Res Treat, 145:401-409, 2014
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5. Takiguchi Y, Sekine I, Iwasawa S, Kurimoto R, Sakaida E, Tamura K. Current status of medical oncology in Japan--reality gleaned from a questionnaire sent to designated cancer care hospitals. Jpn J Clin Oncol, 44:632-640, 2014
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# Department of Thoracic Surgery

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

## Introduction

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

## Routine activities

The Department has 4 attending surgeons. Attending surgeons and residents perform all of the inpatient care, operations, examinations, and outpatient care. In 2014, we performed a total of 667 operations; for lung cancer in 485 patients, metastatic tumor in 80, mediastinal tumor in 18, and others in 84.

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

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

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

As for meetings, there are 2 department meetings. One is for the preoperative evaluation and postoperative inpatient review on Friday and the other is for the journal club on Tuesday. In addition, the chest group has a plenary meeting to share basic information about the current issues for diagnosis and treatment of patients with lung malignancy on Thursday

## 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 have conducted a clinical trial to evaluate the feasibility of RFA for poor-risk patients with malignant tumors of the lung. The accrual for the RFA trial has been closed in 2013. The results will be announced in a little while.

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

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

## Clinical trials

Due to the advent of new technologies in CT scanning, small-sized lung cancers are being found in a screening setting and also by chance. They usually present as "ground-glass opacity (GGO)" on CT, and pathologically they are considered early adenocarcinoma. The surgical management of such GGO-type lung cancer remains undetermined in terms of the extent of pulmonary parenchymal resection and lymph node dissection. Some cases might be followed up with careful monitoring by CT, since indolent tumors are known to exist. We are seeking the appropriate way to manage these patients. A clinical trial to determine the appropriateness of limited resection for early adenocarcinoma had been planned in the Japan Clinical Oncology Group (JCOG)- Lung Cancer Study Group, and 2 clinical trials (a phase III trial, JCOG 0802; a phase II trial, JCOG 0804) have been conducted since the end of 2009. In addition, another phase II trial (JCOG1211), a confirmatory trial of segmentectomy for clinical T1N0 lung cancer dominant with GGO, was started in 2013. The accrual for JCOG 0804 trial has been already closed. The accrual for JCOG0802 has been closed in 2014. 37 cases have been registered for JCOG 1211 from our Department.

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. This trial completed the full accrual of 960 patients in 2013. A phase III clinical trial (JCOG 1205) to compare Irinotecan/Cisplatin with Etoposide/Cisplatin for adjuvant chemotherapy of resected pulmonary high-grade neuroendocrine carcinoma has been started in 2013.

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

| | |
|---|---|
| Primary lung cancer | 485 |
| Metastatic lung tumor | 80 |
| Mediastinal tumor | 18 |
| Pleural disease | 19 |
| Chest wall tumor | 13 |
| Benign lung nodule | 37 |
| Others | 15 |
| Total | 667 |

**Table 2. Type of procedure in 2014**

| | |
|---|---|
| Lung resection | 588 |
| Lobectomy | 363 |
| Pneumonectomy | 16 |
| Segmentectomy | 74 |
| Wedge resection | 135 |
| Tracheal resection | 0 |
| Surgery for mediastinal tumors | 19 |
| Surgery for pleural tumors | 24 |
| Surgery for chest wall tumors | 13 |
| Others | 23 |
| Total | 667 |

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

| Pathological stage (TNM-7) | No. of pts | 5-yr survival (%) |
|---|---|---|
| IA | 1,902 | 94.2 |
| IB | 556 | 83.5 |
| IIA | 320 | 71.7 |
| IIB | 208 | 64.4 |
| IIIA | 453 | 48.3 |
| IIIB | 82 | 34.9 |
| IV | 30 | 26.8 |
| Operation period: 2003.1-2011.12 | Total 3,551 | |



## List of papers published in 2014

### Journal


1. Watanabe S. Lymph node dissection for lung cancer: past, present, and future. Gen Thorac Cardiovasc Surg, 62:407-414, 2014
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# Department of Thoracic Oncology

**Yuichiro Ohe, Noboru Yamamoto, Hiroshi Nokihara, Yutaka Fujiwara, Hidehito Horinouchi, Shintaro Kanda, Yasushi Goto, Kuniko Sunami, Tetsuhiko Asao, Shinsuke Kitahara**

## Introduction

Lung cancer is the leading cause of cancer death in Japan and worldwide. The incidence of lung cancer in Japan is still increasing, especially in elderly populations. The Department of Thoracic Oncology provides care for patients with primary lung cancer, mediastinal tumors, and pleural tumors. The goals of the Department are to provide the highest quality treatment and establish new effective treatments against lung cancer and other thoracic malignancies through innovative clinical and translational research. To provide assistance to our patients through multidisciplinary care, the staff members of the department work closely with thoracic surgeons, radiation oncologists, pharmacists, clinical research coordinators, and psychiatrists who have expertise in these areas. The Department includes 7 staff physicians. Moreover, residents and trainees from other institutions have joined the Thoracic Oncology Program.

## Routine activities

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

A total of 332 new patients were admitted in 2014, and the backgrounds and initial treatments of these patients are shown in Table 1 and 2. The initial treatments were chemotherapy in 169, adjuvant chemotherapy after surgery in 53, chemoradiotherapy in 52, curative radiotherapy in 5, and supportive care including palliative radiotherapy in 31. Survival of lung cancer patients treated in 2005-2009 is shown in Table 3.

## Research activities

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

## Clinical trials

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

## Education

In 2014, three chief residents, 19 residents and one research resident are joined the Department. Monthly research conference is held to discuss about clinical and translational research conducted by young doctors.

## Future Prospects

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

**Table 1. Number of new inpatients in 2014**

| | |
|---|---|
| Thoracic malignancies total | 328 |
| NSCLC | 274 |
| Adenocarcinoma | 192 |
| Squamous cell carcinoma | 52 |
| Others | 30 |
| SCLC | 38 |
| Mesothelioma | 5 |
| Thymic cancer | 8 |
| Thymoma | 3 |

**Table 2. Initial treatments for new inpatients with lung cancer in 2014**

| | |
|---|---|
| Chemotherapy | 169 |
| Chemoradiotherapy | 52 |
| Adjuvant chemotherapy after surgery | 53 |
| Chemoradiotherapy followed by surgery | 2 |
| Curative radiotherapy | 5 |
| Supportive care including palliative radiotherapy | 31 |

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

| Disease | Stage | Treatment | N | Survival rate (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 1y | 2y | 3y | 4y | 5y |
| NSCLC | 52 | chemotherapy | 654 | 63 | 38 | 21 | 12 | 8 |
| NSCLC | 53 | chemoradiotherapy | 178 | 80 | 55 | 38 | 29 | 26 |
| SCLC | 2 | chemotherapy | 128 | 55 | 17 | 5 | 5 | 4 |
| SCLC | 5 | chemoradiotherapy | 68 | 91 | 69 | 45 | 35 | 29 |

## List of papers published in 2014

## Journal


1. Saito M, Shiraishi K, Matsumoto K, Schetter AJ, Ogata-Kawata H, Tsuchiya N, Kunitoh H, Nokihara H, Watanabe S, Tsuta K, Kumamoto K, Takenoshita S, Yokota J, Harris CC, Kohno T. A three-microRNA signature predicts responses to platinum-based doublet chemotherapy in patients with lung adenocarcinoma. Clin Cancer Res, 20:4784-4793, 2014

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9. Mizugaki H, Fujiwara Y, Yamamoto N, Yagishita S, Kitazono S, Tanaka A, Horinouchi H, Kanda S, Nokihara H, Tsuta K, Asamura H, Tamura T. Adjuvant chemotherapy in patients with completely resected small cell lung cancer: a retrospective analysis of 26 consecutive cases. Jpn J Clin Oncol, 44:835-840, 2014

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# Department of Esophageal Surgery

**Yuji Tachimori, Hiroyasu Igaki, Kazuo Koyanagi, Hidetsugu Nakazato, Jun Iwabu**

## Introduction

More than 300 new patients with esophageal tumors are admitted to the National Cancer Center Hospital (NCCH) every year. The multidisciplinary treatment plans are determined by the stage of the tumor in close cooperation with other teams. The Department of Esophageal Surgery particularly cooperates with the Department of Gastrointestinal Medical Oncology and the Department of Radiation Oncology for preoperative chemotherapy and chemoradiotherapy and salvage surgery after definitive chemoradiotherapy, and the Department of Endoscopy for diagnosis and endoscopic resection. We also maintain close cooperation with the Department of Head and Neck Surgery for cervical esophageal carcinomas and with the Department of Gastric Surgery for adenocarcinomas in the esophagogastric junction. Patients who required laryngectomy for resection of cervical esophageal cancer were operated in the Department of Head and Neck Surgery. In our department, squamous cell carcinomas still constitute the largest proportion of esophageal tumors, and only three patients with adenocarcinomas of esophagogastric junction underwent esophagectomy in 2014. Most patients with Siewert Type II and III adenocarcinoma were operated in the Department of Gastric Surgery.

## Routine activities

The Department of Esophageal Surgery consists of three staff surgeons, one chief resident and 1-2 rotating senior residents. A multidisciplinary conference (Esophageal Tumor Board) is held weekly in which surgeons, medical oncologists, radiation oncologists, endoscopists, radiologists, and pathologists who are involved in the treatment of esophageal diseases meet and discuss the diagnosis, staging, and treatment plans for patients with esophageal tumors. Every week, 2-3 patients with esophageal cancer undergo surgery. One hundred and five patients underwent esophagectomy including 4 patients with cervical esophageal cancer, three with carcinosarcoma, two with malignant melanoma, and one with neuroendocrine tumor. Four patients with gastric cancer after esophagectomy, a patient with cervical squamous cell carcinoma after esophagectomy, and a patient with cervical adenocarcinoma after esophagectomy underwent surgery. Preoperative chemotherapy was recommended for 52 patients and preoperative chemoradiotherapy was recommended for 8 patients with resectable Stage II-IV esophageal squamous cell cancer. A three-field dissection, including the whole upper mediastinum and supraclavicular area in addition to the lower mediastinum and abdomen, was performed in 74 patients as our standard procedure. Video-assisted thoracic surgery was introduced for esophagectomy as minimally invasive surgery in 42 patients. Two hospital deaths occurred due to postoperative complication including pneumonia after salvage esophagectomy and bronchial necrosis after salvage esophagectomy.

In a paradigm shift toward organ-sparing therapy, the number of patients who receive definitive chemoradiotherapy as their primary treatment for resectable tumor, especially Stage I squamous cell carcinoma, is increasing. However, the number of patients who accept minimally invasive esophagectomy also increased. Persistent or recurrent loco-regional disease is not infrequent after chemoradiotherapy. Eleven patients underwent salvage esophagectomy after the failure of definitive chemoradiotherapy in 2014. A three-field dissection is avoided for salvage esophagectomy.

## Research activities

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

## Clinical trials

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

## Education

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

**Table 1. Number of patients**

| | |
|---|---|
| Thoracic esophageal squamous cell carcinoma | 94 |
| Adenocarcinoma of esophagogastric junction | 3 |
| Cervical esophageal squamous cell carcinoma | 3 |
| Cervical Barrett adenocarcinoma after esophagectomy | 1 |
| Carcinosarcoma | 3 |
| Malignant melanoma | 2 |
| Neuroendocrine tumor | 1 |
| Large leiomyoma | 1 |
| Gastric cancer after esophagectomy | 4 |
| Esophago-pulmonary fistula | 1 |

**Table 2. Type of surgical procedure**

| | |
|---|---|
| Open thoracic esophagectomy | 57 |
| Video-assisted esophagectomy | 42 |
| Transhiatal esophagectomy | 2 |
| Cervical esophagectomy | 4 |
| Gastrectomy for esophagogastric junction cancer | 3 |
| Gastrectomy for gastric cancer after esophagectomy | 4 |
| Esophageal bypass | 1 |
| Esophageal reconstruction after conduit necrosis | 1 |
| Esophageal reconstruction for anastomotic stenosis | 1 |
| Salvage lymph node dissection after definitive chemoradiotherapy | 8 |
| Cervical esophagostomy | 1 |

## List of papers published in 2014

### Journal


1. Hiramatsu T, Sugiyama M, Kuwabara S, Tachimori Y, Nishioka M. Effectiveness of an outpatient preoperative care bundle in preventing postoperative pneumonia among esophageal cancer patients. Am J Infect Control, 42:385-388, 2014
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3. Wang S, Tachimori Y, Hokamura N, Igaki H, Nakazato H, Kishino T. Prognostic analysis of salvage esophagectomy after definitive chemoradiotherapy for esophageal squamous cell carcinoma: the importance of lymphadenectomy. J Thorac Cardiovasc Surg, 147:1805-1811, 2014
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# Department of Gastric Surgery

**Hitoshi Katai, Takeo Fukagawa, Shinji Morita, Hisataka Fujiwara, Takeyuki Wada**

## Introduction

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

## Routine activities

The Department includes 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 Department shares a ward with the Department of Gastrointestinal Medical Oncology, so that specialists from both departments 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 tumor.

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 2014, more than 20 surgeons from various countries visited this department for 1 week to 3 months to learn about the management of gastric cancer patients, especially surgical techniques for lymph node dissection and postoperative care. All staff surgeons have sufficient experience in teaching in English.

## Research activities

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

## Clinical trials

Our Department has been playing a central role in conducting multi-institutional clinical trials. H. Katai is a representative of the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG). Patients with gastric cancer are, when eligible, invited to participate in one of the ongoing clinical trials mentioned below. 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 completed for accrual. 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 to prove the non-inferiority of laparoscopic gastrectomy over its open counterpart for patients with clinical stage IA and IB gastric cancer has also been completed for accrual. The JCOG1002, phase II study of systemic chemotherapy with Docetaxel, CDDP, and S-1 followed by surgery in advanced cancer with extensive lymph node metastasis has been completed for accrual. JCOG1302-A is a study to evaluate accuracy of pre-operative staging for advanced tumor. Phase II study to check feasibility of Oxaliplatin, and S-1 neoadjuvant chemotherapy for Stage III disease was carried out. Now, we designed a new phase II trial to prove feasibility of laparoscopic total and proximal gastrectomy for Stage IA and IB gastric cancer (JCOG1401).

## Education

The education of surgical operation has been introduced for chief and rotating residents throughout perioperative management of more than 400 gastric cancer patients.

## Future prospects

D2 gastrectomy is considered the standard surgical treatment for advanced gastric cancer but multi-modality treatments combined with surgery will further improve survival. However, the results of this gastrectomy are not sufficient stage III disease. We plan new clinical trial to evaluate D2 gastrectomy plus duplet chemotherapy including neoadjuvant chemotherapy. There are several surgical options for early gastric cancer depending on the risk of nodal metastasis. The efficacy of laparoscopic surgery for early gastric cancer has to be being assessed.

**Table 1. Number of Patients**

| | |
|---|---|
| Adenocarcinoma | 400 |
| GIST | 10 |
| Others | 27 |
| Total | 437 |

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

| | Number of patients | % |
|---|---|---|
| Major complications | 31 | 9.9 |
| Minor complications | 47 | 15.1 |
| Postoperative hospital deaths | 0 | 0 |
| Total | 312 | |

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 | 111 |
| Total gastrectomy | 85 |
| Completion gastrectomy | 8 |
| Pylorus-preserving gastrectomy | 32 |
| Proximal gastrectomy | 24 |
| Wedge resection | 10 |
| Laparoscopic total gastrectomy | 1 |
| Laparoscopic distal gastrectomy | 25 |
| Laparoscopic pylorus preserving gastrectomy | 26 |
| Other (bypass, exploration, etc.) | 115 |
| Total | 437 |

**Table 4. Survival Rates**

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

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

## List of papers published in 2014

## Journal


1. Maruyama K, Katai H. Surgical treatment of gastric cancer in Japan, trend from standardization to individualization. Chirurgia (Bucur), 109:722-730, 2014
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# Department of Colorectal Surgery

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## Introduction

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

## Routine activities

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

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 setting. Although preoperative radiotherapy is not performed routinely for advanced rectal cancer, patients with T4b rectal cancers or rectal cancers with multiple lymph node metastases are treated with preoperative chemoradiotherapy and surgery. Patients with symptoms caused by unresectable tumors are treated with palliative surgery including palliative resection, bypass, and stoma before chemotherapy. To evaluate the survival benefit and safety of primary resection plus chemotherapy compared to chemotherapy alone in asymptomatic Stage IV colorectal cancer with synchronous unresectable metastatic disease, a randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer is ongoing (JCOG1007, iPACS). Another randomized controlled trial is ongoing to evaluate the non-inferiority of overall survival of laparoscopic surgery to open surgery for palliative resection of primary tumor in incurable Stage IV colorectal cancer (JCOG1107, ENCORE). Symptomatic, Stage IV colorectal cancer patients with non-curable metastasis are pre-operatively randomized to either open or laparoscopic colorectal resection. Patients with resectable liver metastasis are treated in cooperation with the Department of Hepatobiliary and Pancreatic Surgery and adjuvant chemotherapy

regimens are being evaluated in a clinical trial (JCOG0603 study).

## Research activities

As described in "Routine Activities", clinical trials are integrated into our routine work. Many clinical trials are underway, and the details are described in "Clinical Trials". Long-term clinical outcomes from a randomized controlled trial to evaluate laparoscopic versus open complete mesocolic excision (CME) for Stage II, III colorectal cancer: Japan Clinical Oncology Group Study JCOG0404 (NCT00147134) was out. A total of 1,057 patients were randomized (OP: 528, LAP: 529) between October 2004 and March 2009. 5-years' OS is 90.4% (87.5-92.6%) in OP, and 91.8% (89.1-93.8%) in LAP. 5-years' RFS is 79.7% (76.0-82.9%) in OP, and 79.3% (75.6-82.6%) in LAP. The non-inferiority of laparoscopic CME in OS was not demonstrated (1.056; 0.790-1.413, p=0.0732).

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.

## Clinical trials

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

1. JCOG0212: A randomized study that compares mesorectal excision (ME) to ME with pelvic lateral lymph node dissection for clinical stage II or stage III lower rectal cancer patients. Seven hundred and one eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
2. JCOG0603: A randomized study that compares adjuvant modified FOLFOX (5-FU + l-LV +Oxaliplatin) to surgery alone after hepatic resection for liver metastasis from colorectal cancer. One hundred and seventy patients have been enrolled and recruitment continues.
3. JCOG1006: A randomized study that compares conventional techniques to the no-touch isolation technique for clinical T3 or T4 colon cancer. Five hundred and seventy patients have been enrolled and recruitment continues.
4. JCOG1007: A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer is ongoing.
5. JCOG1018: A randomized phase III study of mFOLFOX7 or CAPOX plus bevacizumab versus 5-Fluorouracil/leucovorin or capecitabine plus bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer is ongoing.
6. JCOG1107: A randomized controlled trial comparing laparoscopic surgery with open surgery in palliative resection of primary tumor in incurable Stage IV colorectal cancer is ongoing.

**Table 1. Operative Procedures**

| | Number of patients | |
|---|---|---|
| | Open | Laparoscopic |
| Colectomy | 94 | 107 |
| High anterior resection | 9 | 15 |
| Low anterior resection | 51 | 21 |
| Abdomino-perineal resection | 11 | 3 |
| Hartmann's operation | 3 | |
| Intersphincteric resection | 10 | 7 |
| Robot-assisted suregery | | 18 |
| Total extirpation of large intestine | 0 | 0 |
| Total pelvic exenteration | 2 | |
| Total pelvic exenteration with sacrectomy | 1 | |
| Bypass | 4 | |
| Colostomy or ileostomy | 48 | |
| Local excision | 1 | |
| Other | 35 | |

## List of papers published in 2014

## Journal


1. Shimada Y, Hamaguchi T, Mizusawa J, Saito N, Kanemitsu Y, Takiguchi N, Ohue M, Kato T, Takii Y, Sato T, Tomita N, Yamaguchi S, Akaike M, Mishima H, Kubo Y, Nakamura K, Fukuda H, Moriya Y. Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. Eur J Cancer, 50:2231-2240, 2014
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# Department of Gastrointestinal Medical Oncology

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## Introduction

The Department of Gastrointestinal Medical Oncology focuses on the development of new drugs and standard chemotherapy combined with or without surgery and radiation therapy for advanced colorectal, gastric and esophageal cancer, gastrointestinal stromal tumor and other gastrointestinal (GI) malignancies.

Over recent years, new therapeutic agents have been developed. The highlights include the development of a molecular-targeted antibody, bevacizumab (BV), directed against vascular endothelial growth factor (VEGF) and the finding that it causes changes in the microenvironment of the tumor by inhibiting angiogenesis. Other two molecular target drugs are the anti-epidermal growth factor receptor (EGFR) antibodies, cetuximab and panitumumab, which were approved in 2008 and 2010 for metastatic colorectal cancer. For gastric cancer, an anti-HER2 monoclonal antibody, trastuzumab, was also approved in 2011. Moreover, for colorectal cancer, multi-kinase inhibitor regorafenib was approved in 2013, and a new cytotoxic agent, TPI/FTD (TAS-102) was also approved in March 2014. In near future, new anti-VEGF agent, ramucirumab will be also approved for gastric cancer and colorectal cancer based on the results of randomized controlled trials. On the other hand, in recent years, the efficacy of the immune-checkpoint inhibitor is also being evaluated for GI malignancies.

We expect to identify other novel agents for the treatment of metastatic GI cancers that inhibit intracellular signal transduction and cellular interactions. However, many unique adverse effects and a marked increase in medical cost have led to extensive discussion on more optimal targeting of the population using biomarkers. Although the response rates of these molecular-targeted drugs up to now have not been high (about 5% to 20%) when used broadly to 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, RAS mutation in tumor tissue is one of negative predictive factors for lack in the efficacy of cetuximab/panitumumab. Accordingly, the identification of molecular markers that can be used to predict tumor shrinkage and prognosis will be critical for the identification of possible new targets and for tailored treatments based on tumor genotype or marker expression.

## Routine activities

The staff of the Department consists of 8 medical oncologists, 3 senior residents, and 3 or 4 residents. We hold a daily case conference together at 8 am before the morning rounds. Intergroup meetings with surgical departments (Colorectal, Gastric, and Esophageal Surgery departments) and the Department of Radiation Oncology are held weekly to decide treatment strategies for each individual case or to discuss future treatment strategies for the disease. Palliative care considering the physical and psychological aspects of each case is another important issue to be discussed with co-medical staff. The palliative care team and psycho-oncologists advise us on how to minimize patient discomfort and anxiety throughout end-of-life care. In 2014, we treated 1,869 hospitalized patients (576 of whom were newly diagnosed). Of these patients, 154 were entered in protocol studies.

## Research activities

An endoscopic biopsy and blood sampling before and after chemotherapy provide an excellent opportunity to study biomarkers related to the efficacy of each treatment. We are collecting these fresh samples from patients with gastric cancer to evaluate the correlations between gene expression profiles and patients' outcome by using genome sequencing, microarray or real time (RT) -PCR techniques.

We also have measured the gene expressions of possible predictive biomarkers by using paraffin-

embedded GI cancer specimens obtained from surgical resection or endoscopic biopsy, and investigated the correlation between enzymes related to anti-cancer drug metabolism and clinical outcomes. Some of these results on the correlation between gene mutation profile and cancer outcomes led to propose novel molecular targeted drugs, for example an anti-FGF (fibroblast growth factor) antibody or FGF kinase inhibitor for gastric cancer.

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

## Clinical trials

We carried out several clinical trials in collaboration with the surgery and radiation oncology departments in our hospital and other institutes. Details of clinical trials are summarized in the Table. Some trials are conducted in collaboration with JCOG (Japan Clinical Oncology Group).

1. Colorectal and Anal Canal Cancer

In first-line treatment, we established the combination chemotherapy regimens based on the oral fluoropyrimidine, S-1 (S-1/oxaliplatin/BV [SOXB], S-1/irinotecan/BV [SIRB]). A combination treatment with oral fluoropyrimidines is an important treatment option to improve patient QOL, medical cost and medical staff burden. From the result of SOFT trial, non-inferiority of SOXB to FOLFOX(5-FU/l-LV/oxaliplatin) plus BV has been demonstrated (Yamada Y et al. Lancet Oncol. 2014). We also investigated whether SIRB regimen is non-inferior to XELOX (capecitabine/oxaliplatin) plus BV in a multicenter phase III trial (TRICOLORE), and finished patient accrual on schedule. A randomized trial to investigate the superiority of fluoropyrimidine/oxaliplatin/BV to fluoropyrimidine/BV targeted at frail or elderly patients (JCOG1018) is also ongoing.

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

In salvage-line treatment, TAS-102 (Lonsurf®) was approved in Japan on March 2014 for patients' who failed to respond to standard treatment based on the results of a randomized phase II trial in Japan (J003-10040030) and global phase III trial (RECOURSE). TAS-102 is an oral combination drug of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD is an antineoplastic nucleoside analog, which is incorporated directly into DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase. Moreover, a randomized trial to investigate the efficacy of the peptide therapeutic vaccine (OCV-C02) compared with best supportive care (BSC) was also carried out.

As an adjuvant treatment, JCOG0910, comparing S-1 with capecitabine, finished patients recruitment in 2013 on schedule, and the result was shown in ASCO 2015. A randomized trial comparing adjuvant mFOLFOX6 with observation after complete resection of liver metastasis from colorectal cancer, JCOG0603 is going.

The phase II part of JCOG0903, a phase I/II trial of definitive chemoradiotherapy with S-1/MMC for locally advanced anal canal squamous cell carcinoma, will complete recruitment soon.

2. Gastric cancer

In a first-line treatment, a new pivotal phase III trial comparing S-1/CDDP (CS) to S-1/CDDP/Docetaxel (DCS) has been started from April, 2012, and progressing as expected. A phase II/III study, comparing FLTAX with 5FU alone for patients who are unfit for CDDP usage due to severe peritoneal dissemination is also ongoing. From the result of G-SOX trial comparing SOX with CS at first-line, non-inferiority of SOX to CS has been demonstrated. Therefore, in 2014, oxaliplatin was approved for unresectable or metastatic gastric cancer in Japan.

In second-line treatment, molecular-targeted drugs for advanced gastric cancer as well as colorectal cancer have been investigated. For HER2 negative gastric cancer, a phase III trial which evaluate the additional effect of nimotuzumab, anti-EGFR antibodies, combined with irinotecan in a second-line chemotherapy (ENRICH) started as targeted on patients with high expression of EGFR. Two phase III trials which evaluate the additional effect of (i) olaparib (PARP inhibitor), (ii) BBI608 (an inhibitor targeted at cancer stem cell), combined with paclitaxel

in a second-line treatment are also ongoing. For HER2 positive gastric cancer, we finished a phase III trial which evaluate the additional effect of pertuzumab with capecitabine and cisplatin plus trastuzumab in a first-line treatment (JACOB), and a phase II/III trial comparing TDM-1, ado-trastuzumab emtansine, with paclitaxel in second-line treatment (GATSBY).

In salvage-line treatment, a randomized trial to investigate the efficacy of ONO-4538, anti-programed cell death 1 (PD-1) immune-checkpoint inhibitor antibody, compared with best supportive care (BSC) is ongoing.

3. Esophageal Cancer

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

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

In salvage-line treatment, two phase II studies (i) ONO-4538, PD-1 immune-checkpoint inhibitor, (ii) Sym004, a mixture of two synergistic full-length anti-EGFR antibodies, which bind to two separate non-overlapping epitopes on EGFR, were conducted to investigate the efficacy and safety.

4. Other

For metastatic neuroendocrine carcinoma (NEC) in GI-tract or hepato-billiary-Pancreatic field, a phase III trial comparing irinotecan plus CDDP with etoposide plus CDDP at first-line treatment started in JCOG from August 2014. Several phase I studies have also been conducted as shown in Table.

**Table 1. Number of Patients Treated**

| Number of Patients Treated | Total no. of hospitalized pts | No. of newly diagnosed pts | No. of pts. enrolled protocol |
|---|---|---|---|
| 1) Esophageal cancer | 646 | 189 | |
| CF-RT±salvage surgery JCOG0909 (phase II) | | | 3 |
| neoCF vs neoDCF vs neo CF-RT NExT study JCOG1109 (phase III) | | | 10 |
| CF vs biweekly-DCF MIRACLE study JCOG1314 (phase III) | | | 2 |
| Induction-DCF + conversion surgery or CF-RT COSMOS (phase II) | | | 3 |
| Sym004 (phase II) | | | 7 |
| ONO4538 (phase II) | | | 16 |
| IMRT for Ce-esophageal cancer (phase II) | | | 2 |
| 2) Gastric cancer | 628 | 121 | |
| CS vs DCS JCOG1013 (phase III) | | | 25 |
| XP+Tmab±Pertuzumab for HER2+ pts JACOB (phase III) | | | 1 |
| CPT-11±Nimotuzmab for EGFR++ pts ENRICH (phase III) | | | 12 |
| FL vs FLTAX for ascites++ pts JCOG1108 (phase II/III) | | | 2 |
| weely-nabPTX vs triweekly-nabPTX vs wPTX (phase III) | | | 15 |
| TDM-1 vs wPTX for HER2+ pts GATSBY (phase II) | | | 2 |
| wPTX±Olaparib (phase III) | | | 3 |
| wPTX±BBI068 (phase III) | | | 3 |
| ONO4538 vs BSC (phase III) | | | 6 |
| CS for elderly patients (phase II) | | | 18 |
| 3) Colorectal cancer | 472 | 225 | |
| FOLFOX/CAPOX+BV vs S-1+CPT-11+BV TRICOLORE (phase III) | | | 10 |
| mFOLFOX7/CAPOX+BV vs FL/Cape＋BV for eldery pts JCOG1018 (phase III) | | | 9 |
| XELIRI±BV vs FOLFIRI±BV AXEPT (phaseIII) | | | 12 |
| Anal canal cancer S-1/MMC-RT JCOG0903 (phase I/II) | | | 3 |
| Cetuximab+LGX818±BYL719 for BRAF-MT (phase II) | | | 6 |
| OCV-C02 vs BSC (phase III) | | | 3 |
| CPT-11 + Cmab + Bmab (phase I) | | | 4 |
| Regorafenib (Observational study) | | | 8 |
| 4) Others | 123 | 41 | |
| EP vs IP for GI & HBP-NEC TOPIC-NEC JCOG1213 (phase III) | | | 1 |
| BYL719 (phase I) | | | 0 |
| Neo-adjuvant imatinib for GIST (phase II) | | | 1 |
| High risk GIST (Observational study) | | | 2 |
| Oranzapin (phase II) | | | 37 |
| 5) Translational research | | | |
| Biomarker for Gastric Cancer | | | 22 |
| CTC | | | 22 |
| Immune monitoring | | | 42 |
| Fibrin degradation product | | | 40 |
| GI-SCREEN | | | 35 |
| Total | 1,869 | 576 | 387 |

## List of papers published in 2014

## Journal


1. Koyama N, Saito K, Nishioka Y, Yusa W, Yamamoto N, Yamada Y, Nokihara H, Koizumi F, Nishio K, Tamura T. Pharmacodynamic change in plasma angiogenic proteins: a doseescalation phase 1 study of the multi-kinase inhibitor lenvatinib. BMC Cancer, 14:530-537, 2014
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4. Takahari D, Hamaguchi T, Yoshimura K, Katai H, Ito S, Fuse N, Konishi M, Yasui H, Terashima M, Goto M, Tanigawa N, Shirao K, Sano T, Sasako M. Survival analysis of adjuvant chemotherapy with S-1 plus cisplatin for stage III gastric cancer. Gastric Cancer, 17:383-386, 2014
5. Shimada Y, Hamaguchi T, Mizusawa J, Saito N, Kanemitsu Y, Takiguchi N, Ohue M, Kato T, Takii Y, Sato T, Tomita N, Yamaguchi S, Akaike M, Mishima H, Kubo Y, Nakamura K, Fukuda H, Moriya Y. Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. Eur J Cancer, 50:2231-2240, 2014
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10. Takahashi N, Yamada Y, Taniguchi H, Fukahori M, Sasaki Y, Shoji H, Honma Y, Iwasa S, Takashima A, Kato K, Hamaguchi T, Shimada Y. Clinicopathological features and prognostic roles of KRAS, BRAF, PIK3CA and NRAS mutations in advanced gastric cancer. BMC Res Notes, 7:271, 2014
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# Department of Endoscopy, Gastrointestinal Endoscopy Division

**Yutaka Saito, Takahisa Matsuda, Ichiro Oda, Yasuo Kakugawa, Takeshi Nakajima, Shigetaka Yoshinaga, Haruhisa Suzuki, Satoru Nonaka, Taku Sakamoto, Seichiro Abe and Minori Matsumoto (Gastrointestinal Endoscopy, National Cancer Center Hospital)**
**Yuji Matsumoto, Shinji Sasada, Takaaki Tsuchida and Takehiro Izumo (Bronchoscopy)**

## Introduction

Our Department of Endoscopy have moved to the New Endoscopy Center from 20th Jan. 2014 and we believe this is the biggest Endoscopy Center in Japan at this moment (15 Endoscopy Rooms (251.112 $m^2$) and 136.788 $m^2$ Recovery Rooms in two floors of 1949.554 $m^2$).

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

The Gastrointestinal Endoscopy Division has 11 staff physicians in the National Cancer Center Hospital and in the Screening Technology and Development Division, four chief residents, 7 residents, two trainees and several rotating residents.

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

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

## Routine Activities in GI Endoscopy

Various diagnostic techniques including chromoendoscopy, magnifying endoscopy and endoscopic ultrasonography (EUS) are used to detect and evaluate early malignant lesions. Capsule endoscopy also has been accepted as being far less invasive. In our facility, small intestine capsule endoscopy has been performed since 2005. In order to obtain more accurate endoscopic diagnosis of gastrointestinal disease, we routinely use the recently developed narrow-band imaging (NBI) system. A total of 11,481, 3,881, 496, 82, 175, 79 and 105 screening and/or diagnostic procedures by gastroscopy, colonoscopy, EUS, EUS-fine needle aspiration (EUS-FNA), endoscopic retrograde cholangiopancreatography (ERCP), capsule endoscopy and double balloon endoscopies, respectively, were performed in 2014 (Table 1).

Due to the increasing number of patients with superficial gastrointestinal neoplasms, the number of therapeutic endoscopy procedures is also increasing in this field. In 2014, 2,187 endoscopic resections were carried out (pharynx 23, esophagus 165, stomach 340 and colon 1,659). Among these, ESD, which was developed for large en-bloc resections with a low-risk of local recurrence, was performed for 100 superficial esophageal cancers, 340 early gastric cancers and 194 superficial colorectal neoplasms. For colorectal ESDs and some esophageal ESDs, the newly developed ball-tip bipolar needle knife (B-knife) and IT-knife nano were used together with $CO_2$ insufflation. Our colleagues originally developed these procedures and devices.

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,

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

| Year | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|---|
| Upper GI Endoscopy | 10,910 | 10,909 | 10,174 | 10,644 | 10,810 | 11,193 | 11,314 | 11,481 |
| Colonoscopy | 3,569 | 3,161 | 2,670 | 2,756 | 2,924 | 3,232 | 3,367 | 3,881 |
| EUS | 373 | 375 | 402 | 395 | 372 | 393 | 477 | 496 |
| EUS-FNA | - | - | - | 48 | 59 | 69 | 85 | 82 |
| Total number of Therapeutic Procedures | 1,854 | 1,848 | 1,849 | 1,756 | 1,984 | 2,077 | 2,146 | 2,164 |
| Gastric EMR/ESD | 24/410 | 19/397 | 36/375 | 23/334 | 23/343 | 361 | 375 | 340 |
| Esophageal EMR/ESD | 89/25 | 94/25 | 95/43 | 102/45 | 132/61 | 115/66 | 97/92 | 65/100 |
| Colorectal EMR/ESD | 1,212/97 | 1,216/97 | 1,177/123 | 1,132/120 | 1,210/125 | 1,402/133 | 1,398/184 | 1,465/194 |
| Duodenal EMR | 7 | 7 | 9 | 11 | 8 | 23 | 38 | 32 |
| Pharyngeal EMR/ESD | 18 | 7 | 8 | 9 | 20 | 24 | 34 | 23 |
| DBE, Stent, etc. | | | | | | 29 | 91 | 105 |
| ERCP, etc. | | | | | 49 | 104 | 140 | 175 |
| Capsule Endoscopy (Small bowel/colon) | 25 | 30 | 25 | 22/- | 37/44 | 43/21 | 45/0 | 60/19 |

lymph-node swelling, submucosal tumors of the GI tract, etc.

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

## 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 reported this paper at a Plenary Session of the American Society for Gastrointestinal Endoscopy (ASGE) in 2011 and this study has been 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 multi-center 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.

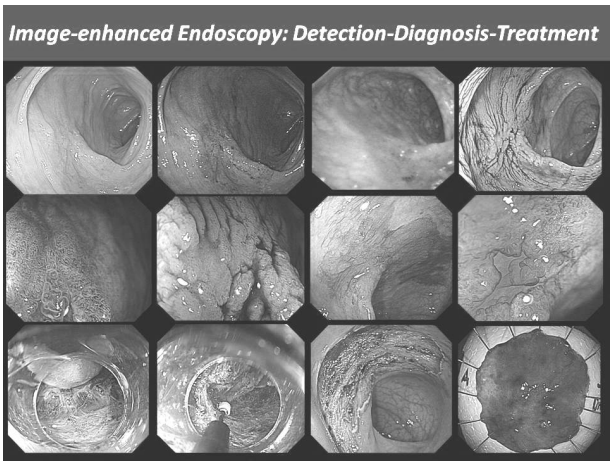


**Figure 1. Endoscopic diagnosis using image-enhanced endoscopy (high-resolution endoscopy, narrow-band imaging and autofluorescence imaging) and endoscopic submucosal dissection (ESD) procedure for treating early colon cancer**

## Clinical Trials in GI Endoscopy

A multicenter clinical trial has been underway to identify the proper surveillance after EMR for superficial esophageal squamous cell carcinoma. Our division has cooperated as a participating institution in a Phase II study on the efficacy of EMR combined with chemo-radiotherapy for clinical stage I esophageal carcinoma (JCOG 0508).

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

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

Little is known about the long-term outcomes of patients with submucosal invasive colorectal cancer who undergo endoscopic or surgical resection. We performed a retrospective analysis of long-term outcomes of patients treated for submucosal colon and rectal cancer. We collected data from 549 patients with submucosal colon cancer and 209 with submucosal rectal cancer who underwent endoscopic or surgical resection at 6 institutions, over a median follow-up period of 60.5 months. We assessed recurrence rates, 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). Considering this study result, we are now planning a prospective cohort study for the possibility of chemo-radiotherapy for high-risk rectal submucosal cancer after endoscopic resections.

A nationwide cancer registry system has been also developed for early colorectal cancer treated with ESD. A five-year multicenter prospective cohort study has been ongoing using this cancer registry system since 2013. A total of 2066 patients were enrolled to this multicenter cohort study and this should be the largest cohort study in colorectal ESD in the world.

Molecular imaging endoscopy is one of new era for very early cancer diagnosis and detection of metastasis. We have just started a collaborative

study between Endoscopy Division, Colorectal and Gastric Surgery Division, Pathology Division, Research Institute, Tokyo University and Jikei University.

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

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



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# Department of Endoscopy, Respiratory Endoscopy Division

**Takehiro Izumo, Yuji Matsumoto, Takaaki Tsuchida**

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

Endobronchial stenosis patients were treated with airway stent placement, photodynamic therapy and endobronchial electrocautery ablation. Medical thoracoscopy under local anesthesia in the operation suite was performed in 17 cases with unknown pleural effusion or a pleural tumor. Some of these cases underwent an electrocautery (IT knife) pleural biopsy because of pleural thickening.

## Research activities

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

Endobronchial ultrasound elastography is a new technique for describing the stiffness of tissue during endobronchial ultrasound-guided transbronchial needle aspiration. In classifying Type 1 as ‘benign’ and Type 3 as ‘malignant,’ the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy rates were 100, 92.3, 94.6, 100 and 96.7%, respectively.

A new middle-range diameter bronchoscope with large channel combined with endobronchial ultrasound with a guide sheath can enhance the efficacy of transbronchial sampling to its maximal

potential to diagnose peripheral pulmonary lesions safely and accurately, particularly for patients who have tumors away from the visceral pleura.

## Clinical trials

We conducted a multi-center prospective study for evaluation of photodynamic therapy for peripheral lung cancer.

## Education

Flexible bronchoscope has a history that has been developed in this hospital for the first time in the world and a large number of residents and overseas doctors wish to be trained at our hospital. I was given the opportunity of writing papers and making conference presentations to many residents. Overseas training doctors included three from Philippines, one from Singapore, one from China, and three from India.

## Future prospects

A multicenter trial of photodynamic therapy for peripheral lung cancer is expected to be carried out.

**Table 1. Number of Patients Treated**

| | |
|---|---|
| Diagnostic bronchoscopy without X-ray | 155 |
| Diagnostic bronchoscopy under X-ray fluoroscopy | 565 |
| Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) | 176 |
| Medical thoracoscopy | 17 |
| Tharapeutic bronchoscopy | 4 |
| Total | 917 |

## List of papers published in 2014

### Journal


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# Department of Hepatobiliary and Pancreatic Surgery

**Kazuaki Shimada, Tomoo Kosuge, Minoru Esaki, Satoshi Nara, Yoji Kishi, Yasuhito Iwao, Hironobu Suto**

## Introduction

The Department of Hepatobiliary and Pancreatic (HBP) Surgery 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 Departments of Diagnostic Radiology, HBP Oncology, and Pathology and Clinical Laboratories.

## Routine activities

The Department of HBP Surgery consists of 5 staff surgeons and we perform around 300 surgeries each year, along with 1 chief resident and 3 or 4 residents. Occasionally, trainees from both Japan and overseas join our group.

*Operation and perioperative care*

Usually 5 to 7 major operations for hepatobiliary and pancreatic malignancies are performed every week. 1 staff surgeon and 1 resident are in charge of each patient, and conduct the operation and provide postoperative care. The chief resident attends all the operations, supervises the residents and manages the care of all inpatients.

*Conferences*

We have several clinical or educational conferences on the treatment of HBP malignancies. At the "Ward Conference", the clinical conditions of the perioperative patients and surgical strategies for preoperative cases are discussed. At "Cherry Conference," surgeons and radiologists discuss imaging studies of mainly the patients scheduled for surgery. An "HBP Case Conference" is held by surgeons and medical oncologists to discuss the clinical course of both surgical and medical patients as well as common issues among HBP malignancies. The "Micro Conference" is a pathological conference on postoperative cases, where surgeons, radiologists, and pathologists participate in the discussion. In the "Research conference", which is held every 3 months, progress situation of academic studies including clinical research and paper writing are evaluated.

*Surgical strategies for HBP malignancies*

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

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

Biliary cancer – cholangiocarcinoma & 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 caudate lobe and extrahepatic bile duct resection is considered as the first-line procedure for perihilar cholangiocarcinoma. When necessary, portal vein and/or hepatic artery resection and reconstruction is performed to achieve curative resection.

## Research activities

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. conducted 3 prospective randomized trials to evaluate the efficacy of surgical devises 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 devise 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)". In all these studies, patients' recruit and registration have finished and the results of each study are being prepared for publication. Dr. Nara et al. has finished a study to evaluate the feasibility of laparoscopic hepatectomy in this hospital. Now Dr. Shimada and the colleagues plan to launch other new 3 randomized controlled trials.

All the studies above are supported by Grants-in-Aid for scientific research from the Ministry of Health, Labour and Welfare of Japan.

**Table 1. Number of patients**

| Type of disease | n |
|---|---|
| Invasive pancreatic cancer | 82 |
| Other pancreatic neoplasms | 46 |
| Hepatocellular carcinoma | 43 |
| Hepatic metastases | 61 |
| Intrahepatic cholangiocarcinoma | 2 |
| Bile duct cancer | 32 |
| Gallbladder cancer | 12 |
| Ampullary cancer | 5 |
| Duodenal cancer | 4 |
| Others | 34 |
| Total | 321 |

## Education

During 3 to 6 months of trainee period, each resident attend 1 to 2 major HBP surgeries mainly as a first assistant every week. They also have chance to be an operator depending on their skill. For each case, they learn how to decide the indication and type of procedure. In the operation room, the residents learn not only each step of HBP surgery, but also the tips how to help safely proceed the surgery. Chief resident trains in two-year-program. In the first year, they devote to the management of all inpatients and attend basically every surgery. Depending on development of the skill, they have opportunity to be an operating surgeon for major HBP surgery. In the second year, chief resident works on research studies and publish several English papers.

Visitors both from domestic and foreign institutions are anytime welcome.

## Future prospects

HBP malignancy often requires technically demanding surgical procedures, whereas the long-term prognosis so far is not satisfactory. Our most important mission is to establish safer and more feasible surgical techniques including perioperative patients' management, and to promote the survival outcomes by multidisciplinary approaches. For these objectives, we continue making efforts to create new skills and treatment strategies.

**Table 2. Type of procedures**

| Procedure | n |
|---|---|
| Hepatectomy without biliary resection | 106 |
| Hepatectomy with biliary resection | 17 |
| Hemihepatectomy and pancreaticoduodenectomy (HPD) | 2 |
| Substomach preserving pancreaticoduodenectomy (SSPPD) or Classical Whipple (PD) | 17 |
| Pylorus-preserving pancreaticoduodenectomy (PPPD) | 55 |
| Distal pancreatectomy | 38 |
| Appleby operation | 3 |
| Medial pancreatectomy | 4 |
| Total pancreatectomy* | 10 |
| Extended cholecystectomy | 16 |
| Other resections | 21 |
| No resection | 32 |
| Total | 321 |

*includes total resection of remnant pancreas

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

a) IDC (2002-2011)

| Stages | n | 3-year survival rate (%) | 5-year survival rate (%) |
|---|---|---|---|
| I | 12 | 57 | 57 |
| II | 7 | 83 | 63 |
| III | 106 | 61 | 47 |
| IVa | 269 | 41 | 26 |
| IVb | 122 | 27 | 14 |
| Total | 516 | 43 | 29 |

b) HCCJ (2002-2011)

| Stages | n | 3-year survival rate (%) | 5-year survival rate (%) |
|---|---|---|---|
| I | 35 | 88 | 74 |
| II | 139 | 88 | 82 |
| III | 196 | 72 | 58 |
| IV | 67 | 61 | 47 |
| Total | 437 | 77 | 66 |

## List of papers published in 2014

## Journal


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# Department of Hepatobiliary and Pancreatic Oncology

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

## Introduction

The Department of Hepatobiliary and Pancreatic Oncology treats tumors originating from the liver, biliary system or pancreas, which include hepatocellular carcinoma (HCC), biliary tract cancer and pancreatic cancer. As part of the multi-disciplinary care given at the National Cancer Center Hospital (NCCH), we work closely with surgeons and radiologists who have 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 Department consists of 5 staff oncologists and 3 to 4 residents. In 1990, the Department 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. Systemic or intra-arterial chemotherapeutic regimens are indicated in advanced HCC patients for whom locoregional intervention and surgery are unsuitable or had been unsuccessful. In patients with unresectable pancreatic cancer or biliary tract cancer, chemotherapy is performed in clinical practice or as a clinical trial to develop active treatment. Patients with locally advanced pancreatic cancer may receive chemoradiotherapy, which has shown some clinical benefits for symptom control and survival.

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

## Research activities

We carried out a phase II study to examine the efficacy and safety of FOLFIRINOX in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer (Okusaka T, et al. Cancer Sci. 2014). The response rate was 38.9%; median overall survival, 10.7 months; and median progression-free survival, 5.6 months. There were no treatment-related deaths. FOLFIRINOX can be a standard regimen showing favorable efficacy and acceptable toxicity profile.

We analyzed the outcomes of systemic chemotherapy for advanced neuroendocrine carcinoma (NEC) of the digestive system (Yamaguchi T, et al. Cancer Sci. 2014). Clinical data from 258 patients with unresectable or recurrent NEC of the gastrointestinal tract (GI) or hepato-biliary-pancreatic system (HBP), who received chemotherapy, were collected from 23 Japanese institutions and analyzed retrospectively. HBP primary sites and elevated lactate dehydrogenase levels are unfavorable prognostic factors for survival.

We analyzed how specific end-of-life (EOL) care, especially anticancer therapies, selected by patients with pancreatic carcinoma affected their place of death (POD) in Japan (Kondo S, et al. BMJ Open. 2014). Certain factors such as gender, medical environment and EOL care selection might influence the POD. Patients who pursue aggressive anticancer therapies, such as CAM use, were possibly deprived of a chance of early reference to

a primary care unit (PCU).

We conducted a nationwide survey to examine the situation of patients with HCC treated with sorafenib who obtained a complete response (CR) (Shiba S, Hepatol Res. 2014). Significant factors in the CR group were a female sex, a low bodyweight (<59 kg), an early clinical stage and a small initial dose of sorafenib ($P < 0.05$). Specific adverse events (palmar-plantar erythrodysesthesia syndrome, hypertension, diarrhea, alopecia, fatigue, nausea and anorexia) were frequently observed in the CR group ($P < 0.05$).

## Clinical trials

18 clinical trials are ongoing and 6 are in planning, including 12 phase I or I/II trials, 3 phase II or II/III trials, and 9 phase III trials such as adjuvant chemotherapy after resection versus resection alone for patients with resectable tumor, and chemotherapy with a new regimen versus standard therapy for patients with advanced tumor. Our studies are supported by the National Cancer Center Research and Development Fund (Grant No. 26-A-4), Health and Labour Sciences Research Grants (Grant No. H25-kakushintekiganippan-076, 081, 142) from the Ministry of Health, Labour, and Welfare of Japan.

## Education

Our staff members are working with residents and chief residents closely to support their skill development and knowledge expansion in both clinical and research fields. We are conducting conferences dairy for clinical practice and weekly for research development. The residents in our department have published 5 papers as a first author in peer-reviewed journals in 2014, and are performing 8 ongoing studies as a leading researcher, with assistance from staff members.

## Future prospects

Our Department strives to maintain provision of the best and latest diagnosis, treatment and supportive care, and to develop more effective methods and techniques for all patients with hepatobiliary and pancreatic cancer, not only in this country but also worldwide. Among these approaches, conducting clinical trials with novel promising agents for this disease is considered one of the most important tasks, and establishment of cutting-edge medical treatments in this field is the most significant mission for us. To achieve our aim, we are initiating screening for biliary cancer patients with gene-mutations in the Kanto area as a first step, and are going to expand it to a nation-wide program for accrual to clinical trials for new molecular targeted agents.

**Table 1. Primary tumor**

| | No. of pts |
|---|---|
| Pancreatic cancer | |
| Invasive ductal | 185 |
| Neuroendocrine | 20 |
| Others | 31 |
| Biliary tract cancer | |
| Extrahepatic bile duct | 22 |
| Gallbladder | 25 |
| Papilla of Vater | 4 |
| Liver cancer | |
| Hepatocellular | 187 |
| Intrahepatic cholangio | 23 |

**Table 2. Treatment**

| | No. of pts |
|---|---|
| Pancreatic cancer | |
| Systemic chemotherapy | 202 |
| Chemoradiotherapy | 2 |
| Adjuvant | 31 |
| Biliary tract cancer and Intrahepatic cholangio carcinoma | |
| Systemic chemotherapy | 71 |
| Adjuvant | 3 |
| Hepatocellular carcinoma | |
| Ethanol injection | 5 |
| Radiofrequency ablation | 48 |
| Transcatheter arterial (chemo)embolization | 97 |
| Intra-arterial chemotherapy | 19 |
| Systemic chemotherapy | 24 |
| Radiotherapy | 8 |

## List of papers published in 2014

## Journal


1. Totoki Y, Tatsuno K, Covington KR, Ueda H, Creighton CJ, Kato M, Tsuji S, Donehower LA, Slagle BL, Nakamura H, Yamamoto S, Shinbrot E, Hama N, Lehmkuhl M, Hosoda F, Arai Y, Walker K, Dahdouli M, Gotoh K, Nagae G, Gingras M-C, Muzny DM, Ojima H, Shimada K, Midorikawa Y, Goss JA, Cotton R, Hayashi A, Shibahara J, Ishikawa S, Guiteau J, Tanaka M, Urushidate T, Ohashi S, Okada N, Doddapaneni H, Wang M, Zhu Y, Dinh H, Okusaka T, Kokudo N, Kosuge T, Takayama T, Fukayama M, Gibbs RA, Wheeler DA, Aburatani H, Shibata T. Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. Nat Genet, 46:1267-1273, 2014
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# Department of Urology

**Hiroyuki Fujimoto, Motokiyo Komiyama, Takashi Kawahara, Tomohiko Hara, Yasuo Shinoda, Tsukasa Narukawa**

## Introduction

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

## Routine activities

The urology team consists of 5staff physicians and 1 resident. In addition, with the participation of a radiation oncologist, multi-disciplinary treatments for advanced disease including renal cancer, urothelial cancer, hormone-refractory prostate cancer and metastatic germ cell tumors, are performed. Every morning clinical rounds are started at 7:30 a.m., and a weekly conference to discuss inpatient management is held on Monday evenings.

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

(1) Renal cell carcinoma: M0, partial or radical nephrectomy; M1: chemotherapy with target drugs with TKI or mTOR with or without palliative nephrectomy.

(2) Bladder cancer. Carcinoma in situ: BCG instillation therapy. Ta, T1, transurethral resection of bladder cancer (TURBT), often combined with preoperative or postoperative BCG instillation. T2-T4, radical cystectomy with or without neoadjuvant chemotherapy with M-VAC/GC regimen. N+, systemic chemotherapy, radiation; sometimes urinary diversion alone. M+, chemotherapy with M-VAC or GC regimen.

(3) Prostate cancer. Organ-confined disease, active surveillance, robotic-assisted or open radical prostatectomy, irradiation, or endocrine therapy. Specimen-confined disease, extended radical prostatectomy without neoadjuvant endocrine therapy, radiation therapy with endocrine therapy, or endocrine therapy alone. M1 disease, endocrine therapy and palliative radiation if necessary. For castration refractory disease, DTX chemotherapy is indicated.

(4) Testicular germ cell tumor (GCT): Stage I, careful observation regardless of a pathological element. Stage II or higher, EP (etoposide + CDDP) or BEP (BLM + etoposide + CDDP) chemotherapy as the first line. In nonseminomatous cases, a salvage operation is performed after induction chemotherapy. In seminoma cases, careful observation rather than surgery is selected.

## Research activities

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

1. Urothelial cancer: The effectiveness of a phase III study to confirm the efficacy of BCG instillation for high grade T1 bladder cancer (JCOG1019) is ongoing. For metastatic disease, a weekly CBDCA + PTX regimen has been indicated.
2. Prostate cancer: A phase II study to evaluate the efficacy of robotic assisted laparoscopic radical prostatectomy for 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. For DTX refractory prostate cancer, a study on a vaccine regime with IKT1 is ongoing.

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

## Clinical trials

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

1. A phase III study: BCG instillation for high grade T1 bladder cancer (JCOG1019)
2. A phase II study: Robotic assisted laparoscopic prostatectomy for low and intermediate risk prostate cancer
3. A phase III study: Salvage radiation vs hormone ablation for postoperative PSA failure in T1c-T2 prostate cancer (JCOG0401)
4. A phase II study: IKT1 for chemo-refractory prostate cancer

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

| | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| Radical/partial nephrectomy | 35 | 30 | 46 | 39 | 33 |
| Nephroureterectomy | 15 | 12 | 17 | 8 | 10 |
| Total cystectomy | 31 | 24 | 25 | 24 | 17 |
| TURBT | 130 | 140 | 130 | 117 | 142 |
| M-VAC | 62 | 50 | 62 | 45 | 46 |
| GC | 71 | 84 | 83 | 70 | 83 |
| Radical prostatectomy | 98 | 111 | 87(RALP 2) | 84(RALP32) | 56(RALP 42) |
| Prostatic biopsy | 168 | 175 | 151 | 128 | 144 |
| High orchyectomy | 12 | 8 | 6 | 6 | 5 |
| Retroperitoneal lymphadenectomy | 8 | 13 | 6 | 5 | 7 |
| Chemotherapy for testicular cancer | 14 | 30 | 35 | 7 | 3 |
| Retroperitoneal tumor resection | 15 | 10 | 18 | 13 | 32 |

## List of papers published in 2014

## Journal


1. Fujimoto H, Nakanishi H, Miki T, Kanayama HO, Ohyama C, Suzuki K, Nishiyama H, Eto M, Naito S, Fukumori T, Kubota Y, Takahashi S, Homma Y, Kamoi K. Oncological outcomes of renal pelvic and ureteral cancer patients registered in 2005: the first large population report from the Cancer Registration Committee of the Japanese Urological Association. Int J Urol, 21:527-534, 2014
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# Department of Gynecology

**Tomoyasu Kato, Mitsuya Ishikawa, Shunichi Ikeda**

## Introduction

The Gynecologic Oncology Department 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 3 common gynecologic cancers, i.e., cervical, endometrial and ovarian cancer, are now on the rise in Japan.

## Routine activities

1. The staff members of the Department of Gynecology comprise 3 gynecologic oncologists. In addition, our Division includes 3 residents in training. Current topics in the diagnosis and treatment of gynecologic malignancies are periodically discussed after the Monday general meeting. All patients under treatment are the subjects of presentation and discussion at the weekly joint conference on Wednesdays. A joint clinic pathological conference is held on the second Tuesday of each month.

2. Treatment strategy for uterine cervical cancer: Either conization or simple total hysterectomy is the treatment of choice for persistent CIN III, carcinoma in situ, or cervical cancer Stage Ia1. Patients with Stages Ia2 to IIb usually undergo radical hysterectomy and pelvic lymphadenectomy. Postoperative whole pelvic irradiation following radical hysterectomy is only considered for patients with metastasis to the pelvic nodes or parametrial tissue as confirmed by pathological examination. Furthermore, in 2012, intensity-modulated radiation therapy (IMRT) started to be employed for postoperative adjuvant radiotherapy. Thereafter none had radiation enterocolitis. Radiotherapy alone or concurrent chemo-radiotherapy is given to patients at any Stage. Chemotherapy is occasionally used for the treatment of distant metastasis.

3. Treatment strategy for endometrial cancer: The primary treatment choice is hysterectomy with bilateral salpingo-oophorectomy. Pelvic lymph node dissection is also performed for patients with a high risk of metastasis. Para-aortic node dissection is limited to those with biopsy proven nodal metastasis. Postoperative adjuvant chemotherapy is performed for patients with extra-uterine disease.

4. Treatment strategy for ovarian cancer: A simple total hysterectomy, bilateral salpingo-oophorectomy and omentectomy with or without combined resection of the involved intestine are the standard procedures for the treatment of ovarian cancer. When an intraperitoneal tumor can be optimally debulked and node metastasis is confirmed by pathologic sampling during the operation, combined pelvic and para-aortic lymph node dissection is indicated. For patients with advanced-stage cancer, surgery is followed by combination chemotherapy containing Carboplatin and Paclitaxel (TC or dose dense TC). Patients with more advanced Stage III and IV disease, who are unlikely to be optimally debulked, are treated with primary chemotherapy (NAC). After 3 of 4 courses of chemotherapy, an interval debulking surgery (IDS) is usually performed for 3 patients. Surgery alone can offer the chance of cure for patients with recurrence, but only when the disease is completely resectable. The type of patient number and surgical procedure are shown in Tables 1 and 2, respectively.

## Research activities

A phase III study of dose dense TC chemotherapy (JCOG 1311) for patients with advanced or recurrent cervical cancer has approved. In addition, a nonrandomized confirmatory trial of post-operative irradiation using Intensity modulated radiotherapy (IMRT) for patients with cervical cancer who have undergone a radical hysterectomy (JCOG PC1402) and a randomized phase III study to verify treatment significance of para-aortic lymph node dissection for endometrial carcinoma with risk of lymph node metastasis (JCOG PC1412) are now being projected. Either project is expected to provide a higher evidence level of treatment modality.

We have been doing the translational research with research institute of NCC. We investigate the chemoresistance of ovarian clear cell adenocarcinoma of the ovary. Cancer stem cells (CSCs) are thought to be one of the causes of chemoresistance, Recently, human telomerase reverse transcriptase (hTERT) has been reported to promote CSC-like traits. We found that a mitotic inhibitor, eribulin mesylate (eribulin), effectively inhibited growth of platinum-resistant ovarian cancer cell lines. Eribulin-sensitive cells showed a higher efficiency for sphere formation, suggesting that these cells possess an enhanced CSC-like phenotype. Moreover, these cells expressed a higher level of hTERT, and suppression of hTERT expression by siRNA resulted in decreased sensitivity to eribulin, suggesting that hTERT may be a target for eribulin. Our article has published in Plos One.

## Clinical trials

1. A phase III study to compare treatment starting with neoadjuvant chemotherapy and primary cytoreductive surgery followed by postsurgical chemotherapy for advanced ovarian cancer (JCOG 0602) had closed for enrollment.
2. A nonrandomized confirmatory trial of modified radical hysterectomy for patients with FIGO Stage Ib1 (< 2 cm) uterine cervical cancer (JCOG1101) is ongoing as planned.
3. A non-randomized verification study regarding selection of fertility-sparing surgery for patients with epithelial ovarian cancer (JCOG1203) has started.

**Table 1. Number of patients**

| Primary site | number of patients |
|---|---|
| Cervix | 39 |
| Endometrium | 69 |
| Endomerium+Ovary | 1 |
| Ovary/tube/peritoneum | 76 |
| Vagina | 1 |
| Vulva | 5 |
| Benign or Others | 38 |

**Table 2. Type of procedure**

| | |
|---|---|
| Radical hysterectomy | 24 |
| Modified radical hysterectomy | 4 |
| TAH+/-BSO+/-omentectomy+Paraaortic lymphadenectomy | 18 |
| TAH+/-BSO+/-omentectomy+pelvic lymphadectomy | 12 |
| TAH+/-BSO+/-omentectomy+/-LAR | 3 |
| TAH+/-BSO+/- omentectomy+/-retroperitoneal lymphnode biopsy | 121 |
| Radical vulvectomy | 1 |
| Simple vulvectomy | 3 |
| Conization | 9 |
| Others | 34 |

## List of papers published in 2014

## Journal




1. Yamaguchi S, Maida Y, Yasukawa M, Kato T, Yoshida M, Masutomi K. Eribulin mesylate targets human telomerase reverse transcriptase in ovarian cancer cells. PLoS One, 9:e112438, 2014
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3. 3. Murakami N, Kasamatsu T, Wakita A, Nakamura S, Okamoto H, Inaba K, Morota M, Ito Y, Sumi M, Itami J. CT based three dimensional dose-volume evaluations for highdose rate intracavitary brachytherapy for cervical cancer. BMC Cancer, 14:447, 2014
4. Nishio S, Ushijima K, Yamaguchi T, Sasajima Y, Tsuda H, Kasamatsu T, Kage M, Ono M, Kuwano M, Kamura T. Nuclear Y-box-binding protein-1 is a poor prognostic marker and related to epidermal growth factor receptor in uterine cervical cancer. Gynecol Oncol, 132:703-708, 2014
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6. Matsubara A, Sekine S, Ogawa R, Yoshida M, Kasamatsu T, Tsuda H, Kanai Y. Lobular endocervical glandular hyperplasia is a neoplastic entity with frequent activating GNAS mutations. Am J Surg Pathol, 38:370-376, 2014

# Department of Musculoskeletal Oncology and Rehabilitation

**Hirokazu Chuuman, Akira Kawai, Fumihiko Nakatani, Yoshikazu Tanzawa, Eisuke Kobayashi, Daisuke Kubota, Nokitaka Setsu, Kouki Shimizu, Yusuke Minami, KensakuYamaga**

## 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.

## Routine activities

The musculoskeletal oncology division of the NCCH consists of 5 staff doctors (Drs. Hirokazu Chuuman, 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 consultations are held every weekday. A constant number of about 28 patients are hospitalized for operation, chemotherapy or radiation therapy. Five or six major operations are routinely performed every week. In 2014, 320 operations were performed, including palliative operations for pathological fractures or spinal cord compression from metastatic bone and soft tissue tumors. Sarcomas in the trunk, including the 4 thoracic wall, 19 retroperitoneal space and 2 head and neck lesions were excised in cooperation with thoracic, general, urological or head-neck surgeons, respectively. A total of 58 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, where necessary in collaboration with medical oncologists. We have been collaborating with pediatric oncologists for chemotherapeutic treatment of children and adolescents with sarcomas.

## Research activities

Since 2004, we have been collaborating with the NCC Research Institute to develop novel molecular target therapies or tailor-made treatments for sarcoma patients. With a genome-wide microarray system or a protein-wide two dimensional fluorescence difference gel electrophoresis (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 with the aim of developing novel molecular targeted therapies or biomarkers.

## Clinical trials

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

1. A multi-institutional phase III clinical trial of multidrugs adjuvant chemotherapy for osteosarcomas (JCOG 0905) since 2010.
2. A multi-institutional phase 3 study of trabectedin for advanced soft tissue sarcoma since 2012.
3. A multi-institutional phase II study of Eribulin (an inhibitor of microtubule dynamics) for advanced soft tissue sarcoma since 2011.
4. A multi-institutional phase III clinical trial of multidrugs adjuvant chemotherapy for highgrade soft tissue sarcomas (JCOG 1306) since 2014.

## Education

Each resident performed 60-70 operations supervised by staff members one year, joined many domestic and international conferences and published several medical articles or reports during training courses. All staff member teach all clinical procedure or knowledge about oncological skills for bone and soft part sarcomas.

## Future prospects

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

**Table 1. New patients (2013)**

| | | |
|---|---|---|
| 1 | Soft tissue sarcomas | 201 |
| 2 | Bone sarcomas | 25 |
| 3 | Benign bone and soft tissue tumors | 106 |
| 4 | Spine or bone metastasis | 26 |
| Total | | 332 |

**Table 2. Type of procedure**

| | | |
|---|---|---|
| 1 | Soft tissue sarcomas | 107 |
| 2 | Bone sarcomas | 34 |
| 3 | Benign bone and soft tissue tumors | 85 |
| 4 | Spine or bone metastasis | 14 |
| 5 | biopsy | 31 |
| 6 | amputation | 9 |
| 7 | others | 32 |
| | Plastic surgery combined | 58 |
| | Reconstruction with prosthesis | 18 |
| | Spine surgery | 6 |
| Total | | 320 |

## List of papers published in 2014

## Journal


1. Trautmann M, Sievers E, Aretz S, Kindler D, Michels S, Friedrichs N, Renner M, Kirfel J, Steiner S, Huss S, Koch A, Penzel R, Larsson O, Kawai A, Tanaka S, Sonobe H, Waha A, Schirmacher P, Mechtersheimer G, Wardelmann E, Buttner R, Hartmann W. SS18-SSX fusion protein-induced Wnt/ β -catenin signaling is a therapeutic target in synovial sarcoma. Oncogene, 33:5006-5016, 2014
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12. Kataoka K, Tanaka K, Mizusawa J, Kimura A, Hiraga H, Kawai A, Matsunobu T, Matsumine A, Araki N, Oda Y, Fukuda H, Iwamoto Y. A randomized phase II/III trial of perioperative chemotherapy with adriamycin plus ifosfamide versus gemcitabine plus docetaxel for highgrade soft tissue sarcoma: Japan Clinical Oncology Group Study JCOG1306. Jpn J Clin Oncol, 44:765-769, 2014
13. Kobayashi E, Koyama T, Kobayashi K, Setsu N, Kawashima M, Kawai A. Reversible hair depigmentation in a Japanese female treated with pazopanib. J Dermatol, 41:1021-1022, 2014
14. Kobayashi E, Satow R, Ono M, Masuda M, Honda K, Sakuma T, Kawai A, Morioka H, Toyama Y, Yamada T. MicroRNA expression and functional profiles of osteosarcoma. Oncology, 86:94-103, 2014

# Department of Dermatologic Oncology

**Naoya Yamazaki, Arata Tsutsumida, Akira Takahashi, Kenjiro Namikawa, Wataru Omata, Kohei Oashi, Kohei Nojima, Takehiro Onuma, Yoshio Nakamura, Saori Kan, Miki Sugiyama, Mika Hashimoto**

## 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 2,000 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. Of particular note, the number of patients with malignant melanoma was 206, which was approximately twice - the number 4 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 4 staff dermatologic oncologists, 1 chief resident and 4 residents. We are also engaged in routine outpatient activities on Wednesdays and Thursdays in the National Cancer Center East.

Our Department is a high-volume center, where we have seen an average of more than 200 patients with malignant melanoma annually in the last 3 years. This is the result of creation of a national network to develop treatment for malignant skin tumors, and nivolumab, an anti-PD-1 antibody, was approved as a therapeutic agent for malignant melanoma in Japan for the first time in the world as a result of vigorous development of new drugs.

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

About 20 patients are hospitalized to undergo surgery, chemotherapy, or radiation therapy. In 2013, 233 operations were performed including 115 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.

Besides, we have treated advanced cases of mucosal melanoma patients in the nasal cavity, genital lesions, perianal lesions, and uveal melanoma even if our origins are “dermatologic”.

## Research activities

Malignant skin tumors are mainly treated by surgery (appended table). However, in recent years, several new drugs have been developed rapidly overseas for the treatment of malignant melanoma, and our Department is conducting many clinical studies and trials; the major ones are described below.

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

using molecular-targeted agents and skin care
- A retrospective study to clarify the outcomes of conventional treatment for cutaneous angiosarcoma of the head and neck
- A retrospective study of factors affecting failure to identify sentinel lymph nodes in sentinel lymph node biopsy using the indocyanine green (ICG) fluorescence method in patients with cutaneous malignant melanoma
- A profiling study of genes related to the therapeutic effects and toxicity using clinical specimens from cancer patients (Cancer Gene Profiling Study)
- A retrospective study on the efficacy of multiagent chemotherapy (FECOM therapy) for metastatic extramammary Paget's disease
- A retrospective study on the outcomes of TACE therapy using cisplatin for liver metastasis from primary ocular malignant melanoma
- Diagnosis and study of familial and juvenile cancers and hereditary tumors
- A clinical study on BRAF V600 mutations in Japanese patients with malignant melanoma
- A phase I/II clinical trial of vemurafenib in patients with recurrent malignant melanoma harboring BRAF V600 mutations who are not suitable candidates for curative resection
- A phase I/II trial of combined dabrafenib and trametinib in patients with BRAF V600E or V600K mutation-positive advanced solid cancer (for phase I trial) or cutaneous malignant melanoma (for phase II trial)
- A randomized phase III trial comparing the efficacy of an MEK inhibitor, MEK162, with that of dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive malignant melanoma
- A multicenter phase II trial on the effects of immune checkpoint inhibitors, such as nivolumab and ipilimumab, in patients with advanced malignant melanoma
- A multicenter, unblinded, uncontrolled phase I clinical trial of adjuvant therapy with PEG-modified IFNα-2b in patients with Stage II and III malignant melanoma
- An exploratory study on the usefulness of 18F-BPA PET/CT in diagnosing the Stage of malignancies
- Practical development of therapeutic agents for refractory skin cancer using innovative molecular-targeted agents inducing cancer-specific apoptosis through an investigator-initiated clinical trial

## Clinical trials

Table2 shows our clinical trials.

## Human resource development

Dr. Kenjiro Namikawa received the third 'My Oncology Dream' Award from the Japan Cancer Society and studied at MD Anderson Cancer Institute for a year.

Dr. Akira Takahashi has a doctorate in medicine.

## Perspectives

We are attempting to eliminate drug lag, which seems to exist between Western countries and Japan, and our goal is to achieve this in 3 years. Furthermore, we think that we can develop treatment for rare cancers, such as Merkel cell carcinoma, by sharing the current research infrastructure.

**Table 1. Number of New Patients**

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

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

| | |
|---|---|
| Wide local excision | 148 |
| Local excision | 41 |
| Sentinel node biopsy | 44 |
| Lymph node biopsy | 10 |
| Lymph node dissection | 36 |
| (neck) | 6 |
| (axilla) | 11 |
| (inguinal) | 8 |
| (groin) | 9 |
| (popliteal) | 0 |
| (epitrochlear) | 1 |
| Skin graft | 44 |
| Local flap | 15 |
| Free flap | 1 |
| Amputation | 5 |
| others (biopsy/debridement) | 5 |

**Table 3. New Agent Studies in 2014**

| Agent | Eligible Cancer Type | Trial Phase |
|---|---|---|
| Peg interferon alpha | Melanoma | I |
| MEK162 | Melanoma | I |
| LGX818 | Solid Tumors | I |
| Trametinib / Dabrafenib | Melanoma | I |
| MSB0010718C | Solid Tumors | I |
| ONO-4538 | Melanoma | II |
| Vemurafenib | Melanoma | I / II |
| Trametinib / Dabrafenib | Melanoma | II |
| Ipilimumab+DTIC | Melanoma | II |
| ONO-4538 | Melanoma | II |
| MEK162 / LGX818 | Melanoma | III |
| Ipilimumab (3mg) | Melanoma | II |
| MEK162 / LGX818 | Melanoma | III |
| MK-3475 | Melanoma | I |
| HVJ-E | Melanoma | I |

## List of papers published in 2014

## Journal


1. Gemma A, Kudoh S, Ando M, Ohe Y, Nakagawa K, Johkoh T, Yamazaki N, Arakawa H, Inoue Y, Ebina M, Kusumoto M, Kuwano K, Sakai F, Taniguchi H, Fukuda Y, Seki A, Ishii T, Fukuoka M. Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer. Cancer Sci, 105:1584-1590, 2014
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# Department of Hematology

**Kensei Tobinai, Yukio Kobayashi, Dai Maruyama, Tatsuya Suzuki, Wataru Munakata, Suguru Fukuhara, Hideaki Kitahara, Shinichi Makita**

## Introduction

The Department of Hematology is united with the Department of Hematopoietic Stem Cell Transplantation (HSCT), and the research and clinical activities in the Department of Hematology are devoted to the diagnosis and treatment of hematological malignancies. In the past, our Department introduced novel disease entities, including adult T-cell leukemia-lymphoma (ATL) (J Clin Oncol 2009;27:453-9) and angioimmunoblastic T-cell lymphoma (Blood 1988;72:1000-6). This Department is one of the leading hematology-oncology centers in the world, especially for lymphoid malignancies.

## Routine activities

The number of patients with newly diagnosed hematologic malignancies in the Division increased annually from 1997 to 2004, and then reached a plateau (Table 1). We hold a weekly case conference, where a summary of each hospitalized- or out-patient is presented. An educational cytology conference is held weekly for young doctors. Newly diagnosed lymphoma cases are presented at a weekly lymphoma case conference, where oncologists, pathologists, radiologists, and radiation oncologists discuss diagnosis and treatment plans. We also participate in weekly HSCT conferences, which deal with all HSCT cases.

In addition to patient care in the ward, our daily activities include management of hematology clinics and a diagnostic laboratory to perform bone marrow and peripheral blood microscopic examination, and flow cytometric and molecular-genetic analyses. Five staff physicians, two chief residents, and two to five 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), Flt3-ITD and so on. Our recent research has focused on indolent B-cell non-Hodgkin lymphoma (B-NHL). Clinical as well as molecular and cytogenetic analyses of ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma cases led to the discovery of a new tumor suppressor gene deleted at 6q23; we identified A20 gene as a tumor suppressor gene in various B-cell malignancies (Nature 2009;459:712-6). The gene is involved in NFκB signaling and its status would be a biomarker for BCR inhibitors.

This year, we authored or coauthored 17 articles related to hematological malignancies including 3 editorials or review articles. We have constructed tumor sample banking system, collecting the rest of sample taken as routine diagnostic procedures. The samples' DNA and RNAs are extracted and reserved for future use.

## Clinical trials

In 2014, we conducted 29 new-agent studies, including 8 international ones (Tables 2). The number is still increasing including domestic ones. Almost all the new agents that are developed against hematological malignancies in Japan have been evaluated in our Department, and many of them have been approved by the Ministry of Health, Labor and Welfare (MHLW).

A various phase I and II trials are ongoing on T cell malignancies. The agents include mogamulizumab, lenalidomide, romidepsin, forodesine, darinaparsin, chidamide and denileukin diftitox. Some of the agents are being evaluated

in international studies. For indolent ATL, we are evaluating interferon-alfa and AZT, as a phase III study (JCOG 1111).

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

For treatment of B-cell malignancies, patient enrolment into a phase III trial for newly diagnosed, diffuse large B-cell lymphoma (JCOG 0601) was completed. In this trial, a dose-intense schedule of rituximab was compared with that of a standard 3-weekly regimen. We also completed patient enrolment into a phase II study of a rituximab-incorporating dose-intensified chemotherapy for high-risk, untreated DLBCL (JCOG 0908), using high-dose chemotherapy with autologous stem cell transplantation. For symptomatic multiple myeloma patients ineligible for transplantation, we are conducting a randomized phase II trial to find a more suitable combination regimen of bortezomib, melphalan and prednisolone (JCOG 1105).

**Table 1. Newly diagnosed patients**

| Disease / Year | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|---|---|
| Acute myelocytic leukemia (AML) | 9 | 10 | 6 | 10 | 8 | 13 | 12 | 7 | 9 |
| Acute lymphocytic leukemia (ALL) | 4 | 9 | 8 | 2 | 2 | 1 | 1 | 6 | 3 |
| Chronic myelocytic leukemia (CML) | 10 | 11 | 3 | 3 | 2 | 2 | 2 | 2 | 3 |
| Myelodysplastic syndrome (MDS) | 3 | 9 | 8 | 20 | 9 | 3 | 3 | 6 | 3 |
| Hodgkin lymphoma (HL) | 21 | 11 | 12 | 7 | 11 | 16 | 15 | 13 | 9 |
| Non-Hodgkin lymphoma (NHL) | 265 | 210 | 208 | 151 | 185 | 243 | 172 | 193 | 151 |
| Adult T-cell leukemia-lymphoma (ATL) | 6 | 4 | 5 | 5 | 3 | 6 | 6 | 4 | 10 |
| Chronic lymphocytic leukemia (CLL) | 4 | 5 | 6 | 4 | 2 | 1 | 4 | 1 | 1 |
| Multiple myeloma (MM) | 9 | 8 | 10 | 12 | 9 | 10 | 7 | 8 | 3 |
| Waldenström macroglobulinemia (WM) | 0 | 2 | 3 | 1 | 2 | 2 | 1 | 0 | 0 |
| Total | 331 | 279 | 269 | 215 | 233 | 297 | 223 | 240 | 192 |

**Table 2. Clinical trials for new agents**

| Disease | Agents | Phase | Enrolment in 2014 | Total |
|---|---|---|---|---|
| CML | Nilotinib | III | 0 | 1 |
| | Bosutinib | I/II | 0 | 3 |
| | Ponatinib | I | 0 | 3 |
| MDS | Rigosertib | I | 1 | 2 |
| AML | WT1 (maintenance) | I | 0 | 4 |
| | Volasertib | I | 0 | 6 |
| | Volasertib | | 2 | 2 |
| ALL | Inotuzumab ozogamicin | I | 1 | 2 |
| MM | Carfilzomib | I | 0 | 1 |
| | Carfilzomib | III | 1 | 1 |
| | Pomalidomaide | II | 1 | 1 |
| PTCL | Forodesine | I/II | 4 | 6 |
| | Romidepsin | I/II | 4 | 10 |
| | Pralatrexate | I | 5 | 5 |
| | Denileukin diftitox (E7777) | I | 1 | 3 |
| FL | Ofatumumab vs. Rituximab | III | 5 | 40 |
| | Ofatumumab + Bendamustine | III | 0 | 4 |
| | Obinutuzumab | III | 0 | 16 |
| | R-B +/- Ibrutinib | III | 8 | 8 |
| | Rituximab + Lenalidomide (RELEVANCE) | | 2 | 2 |
| MCL | R-B +/- Ibrutinib | III | 0 | 1 |
| | VcR-CAP | III | 0 | 2 |
| DLBCL | Ofatumumab | III | 0 | 3 |
| | Everolimus | III | 0 | 1 |
| | Obinutuzumab | III | 0 | 2 |
| | Alisertib (MLN8237) | I | 0 | 5 |
| HL | SGN-35 | I | 1 | 3 |
| B-NHL | Ibrutinib | I | 0 | 7 |

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; PSL, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, PSL; R, rituximab

**Table 3. Cooperative group studies**

| Disease / Protocol | Phase | Year | No. of pts (a) | %CR (b) | OS (b) |
|---|---|---|---|---|---|
| AML | | | | | |
| 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 | 94.5% | 89%(5-yr) |
| JALSG-AML209 | IV | (11-) | 11 | NA | NA |
| JALSG-APL212 | II | (13-) | 1 | NA | NA |
| ALL/Lymphoblastic lymphoma | | | | | |
| 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 |
| JALSG-CML 212 | III | (13-) | 3 | NA | NA |
| Hodgkin lymphoma | | | | | |
| JCOG 9705 | II | (98-00) | 6 | 70% | 81% (5-yr) |
| Aggressive NHL | | | | | |
| JCOG 9809 | III | (99-02) | 55 | 62% | 56% (8-yr) |
| JCOG 0601 | III | (08-14) | 66 | NA | NA |
| JCOG 0406 | III | (08-13) | 5 | NA | NA |
| JCOG 0908 | III | (08-) | 21 | NA | NA |
| Indolent B-cell lymphoma | | | | | |
| JCOG 0203 | II/III | (02-07) | 52 | 77% | 88% (6-yr) |
| Adult T-cell leukemia-lymphoma | | | | | |
| JCOG 9801 | III | (98-03) | 6 | 33% | 19% (3-yr) |
| JCOG 0907 | II | (10-) | 3 | NA | NA |
| JCOG 1111 | III | (13-) | 4 | NA | NA |
| Nasal NK/T-lymphoma | | | | | |
| JCOG 0211-DI | I/II | (03-07) | 8 | 77% | 78% (2-yr) |
| Multiple myeloma | | | | | |
| JCOG 0112 | III | (02-05) | 9 | 46% (d) | 63% (2-yr) |
| JCOG 0904 | II | (09-14) | 7 | NA | NA |
| JCOG 1105 | III | (13-) | 2 | 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 2014

## Journal


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# Department of Hematopoietic Stem Cell Transplantation

**Takahiro Fukuda, Takuya Yamashita, Sung-Won Kim, Saiko Kurosawa, Shigeo Fuji, Yoshihiro Inamoto, Yoshitaka Inoue, Reiko Ito, Takashi Tanaka**

## Introduction

At the National Cancer Center Hospital, the Department of Hematopoietic Stem Cell Transplantation (HSCT) specializes in patients who undergo allogeneic or autologous HSCT. 26 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

6 staff physicians (Drs. Yamashita, Kim, Kurosawa, Fuji, Inamoto, and Fukuda) and 3 chief residents (Drs. Inoue, Ito, and Tanaka) participate in the transplant program. Children who have undergone HSCT are managed in collaboration with Dr. Ogawa, the chief of the Department of Pediatric Oncology, and transplant team. In 2014, a total of 103 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 2014 are shown in Tables 1 and 2, respectively. At the weekly conference on Monday afternoons, in collaboration with doctors of the Department of Hematology, about 30 hospitalized HSCT patients and those who have been referred for HSCT, are reviewed for clinical management and a decision regarding their eligibility for HSCT. The transplant unit is staffed by 24 nurses trained in oncology and specialized supportive care for HSCT patients. The nursing unit has been assuming leadership in an effort to facilitate improved care for skin and gut graft-versus-host disease (GVHD), and establishment of a Long-term Follow-up Unit (LTFU) for the education of patients and their family members. In 2014, 342 patients visited our LTFU clinic. At the weekly 12B ward meeting on Friday afternoons, all HSCT patients are reviewed in detail by all transplant team members including doctors, nurses, pharmacists, the nutritional support team, clinical research coordinators, and the transplant coordinator.

## Research activities and Clinical trials

Our transplant team has been focusing on the development of comprehensive cellular immunotherapy, including a reduced-intensity stem cell transplant for elderly patients. A clinical trial of post-transplant consolidation with the WT1 vaccine is also ongoing. A nationwide large survey of quality of life (QOL) in 576 patients with acute leukemia showed that the physical QOL in the allo-HCT patients without GVHD was comparable to that in the chemotherapy patients, and they experienced significantly better mental and general QOL than the chemotherapy patients. In 2014, we have published 23 articles in peer-reviewed international journals and 10 manuscripts have been accepted for E-pub before print or are in press for publication.

**Table 1. Newly diagnosed patients**

| Year | | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|---|
| Allogeneic | | 77 | 93 | 90 | 76 | 72 | 87 | 93 |
| Unrelated | BMT | 48 | 59 | 60 | 54 | 46 | 53 | 52 |
| | PBSCT | 1 | 0 | 0 | 0 | 3 | 5 | 6 |
| | CBT | 1 | 5 | 1 | 4 | 8 | 8 | 9 |
| Related | BMT | 5 | 2 | 5 | 2 | 0 | 1 | 2 |
| | PBSCT | 22 | 27 | 24 | 16 | 15 | 20 | 24 |
| Autologous | | 8 | 18 | 19 | 25 | 25 | 23 | 10 |
| Total | | 85 | 111 | 109 | 101 | 97 | 110 | 103 |

**Table 2. Number of patients who underwent HSCT between 2008 and 2014**

| Diagnosis | Allogeneic | Autologous |
|---|---|---|
| Acute myeloid leukemia | 225 | 1 |
| Myelodysplastic syndrome | 45 | 0 |
| Acute lymphocytic leukemia | 86 | 0 |
| Malignant Lymphoma (including ATL) | 216 | 74 |
| Multiple Myeloma | 0 | 26 |
| Solid tumors | 3 | 27 |
| Others | 13 | 0 |
| Total | 588 | 128 |

## List of papers published in 2014

## Journal


1. Hiramoto N, Kurosawa S, Tajima K, Okinaka K, Tada K, Kobayashi Y, Shinohara A, Inoue Y, Ueda R, Tanaka T, Kim S-W, Yamashita T, Heike Y, Fukuda T. Positive impact of chronic graft-versus-host disease on the outcome of patients with de novo myelodysplastic syndrome after allogeneic hematopoietic cell transplantation: a single-center analysis of 115 patients. Eur J Haematol, 92:137-146, 2014
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# Department of Blood Transfusion and Cellular Therapy

**Ryuji Tanosaki**

## Introduction

The missions of the Department of Blood Transfusion and Cellular Therapy are management of in-hospital transfusion and a support for the hematopoietic stem cell transplantation team in respect of providing safe and secure cellular products. In common with the Department of Clinical Laboratories, our blood transfusion examination laboratory received ISO 15189 accreditation, which certifies the quality and competence of a medical laboratory with regard to quality management and 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 6 specifically-engaged medical technologists (including 2 JSTMCT-accredited technologists) who come to us from the Department of Pathology and Clinical Laboratories. Most activities in our Department are undertaken in collaboration with the Department of Pathology and Clinical Laboratories.

The Transfusion Medicine Committee is held every month, the members of which consist of the deputy director in charge of safety management, chief doctors of our Department and clinical departments of surgery and internal medicine, chief of Department of Pharmacy, chief nurses of the Outpatient Treatment Center and the Hematopoietic Stem Cell Unit, and a secretary. An administrative meeting is also held weekly, the attendees consisting of 3 chief doctors and 2 head doctors of our Department and the Department of Pathology and Clinical Laboratories, and the head and vice-head medical technologists. All-staff meetings are held weekly in our Department and once a month in the Department of Clinical Laboratories, respectively.

As an in-hospital transfusion service section, we purchase blood products, which are required and ordered by clinicians, from the Red Cross, and examine and confirm the ABO blood type, and provide them for clinical use without any delay. In 2014, the total units of red cell concentrates (RCC), platelet concentrates (PC) and fresh frozen plasma (FFP), which were consumed in our hospital, were 10,667, 46,240 and 6,347, respectively, with wastage rate of 0.2% in total blood products. Thanks to the Tokyo Red Cross and the convenient location of our hospital, blood products are available within an hour almost every time when they are needed in an emergency.

We employ the Type & Screen and computer cross-match system, but a 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 sheet 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. Bar codes are used to match the patient and his or her designated blood product at each process during transfusion. Because the electronic medical record system was renewed since January 2014, the safety system for blood transfusion has also been strengthened and any case of incorrect blood transfusion has not been reported so far.

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, 15 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 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, Labor and Welfare of Japan, and a further analysis of the causative agents is then performed by the Red Cross laboratory.

Hematopoietic stem cells which are to be transplanted to the SCT patients, i.e. grafts, are also subject to the same safety and bio-vigilant system as other blood products. The SCT grafts include fresh harvested bone marrow or peripheral blood stem cells (PBSC), and thawed PBSC or cord blood which have been cryopreserved in liquid nitrogen. Each graft is registered and allotted its unique code number, which is recognized as its bar code. This bio-vigilant system is important for analyzing and improving practical aspects of transplantation because the incidence of adverse reactions associated with graft infusion is significantly high; 10.4% in 652 cases between January 2008 and October 2013 in our hospital.

Since October 2014, we started the management of processing, storage, and quality control of hematopoietic stem cells used for transplantation as a routine activity, which were formerly conducted in the Department of Hematopoietic Stem Cell Transplantation. We also indicate and inform other SCT-team members including medical engineers of the optimal timing for peripheral blood stem cell harvest (PBSCH) by monitoring counts of chemotherapy/G-CSF-mobilized progenitor cells. The management meeting is held once a month, the members of which consist of staff from the Department of Hematopoietic Stem Cell Transplantation, Medical Engineer Section, the head of technologist, and our members of our Department.

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

## Research activities

One of the Department's research projects is to develop a new enumeration technique of hematopoietic stem cells using an automated hematology analyzer (designated as 'HPC'), which started in 2006, in collaboration with a medical diagnostic company. We conducted a multicenter prospective study for evaluation of HPC with the support of JSTMCT, analysis of which is now underway.

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 with the support of Ministry of Health, Labor and Welfare. 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 and members of the hematology/oncology group at the Institute of Medical Science, the University of Tokyo.

## Education

The chief doctor supervises the education program of the Department of Clinical Laboratories for all medical technologists (MT). The education program consists of monthly educational meeting in which each MT gives presentations on his or her research, doctors' lectures, RCPC (twice a year). It also includes educational lectures concerning ISO 15189. We also support and facilitate academic presentations and publications by all the MT members.

## Future prospects

Since April 2015, National Cancer Center will start its way as one of the National Research and Development Agencies. We will contribute to our mission by continuing the project of establishing the nation-wide infrastructure of processing and management of cellular products used for hematopoietic stem cell transplantation with the continuing support of the Ministry of Health, Labor and Welfare.

We are starting a modified Cell-Free and Concentrated Ascites Reinfusion Therapy (KM-CART), with which we are providing another tool for the management of refractory ascites in addition of an on-going phase III study evaluating the efficacy of peritoneo-venous shunting by the Department of Diagnostic Radiology.

## List of papers published in 2014

### Journal

1. Tanosaki R, Kumazawa T, Yoshida A, Oguni S, Nakano A, Yamagata S, Takahashi N, Kurosawa S, Kim SW, Yamashita T, Mori S, Heike Y, Fukuda T, Hamaguchi Y, Tsuda H. Novel and rapid enumeration method of peripheral blood stem cells using automated hematology analyzer. Int J Lab Hematol, 36:521-530, 2014

# Department of Pediatric Oncology

**Chitose Ogawa, Hiroshi Kawamoto, Naoko Yasui, Hide Kaneda, Ako Hosono**

## Introduction

Pediatric oncology includes a wide variety of malignancies in children and adolescents such as acute leukemia and malignant lymphoma, as well as solid tumors including osteosarcoma, soft tissue sarcoma, neuroblastoma, liver tumor and retinoblastoma. Many diseases are usually chemo-sensitive and curable with appropriate treatment. The common approach to these diseases is a "risk-adapted therapy" strategy considering long-term life expectancy. In the Department of Pediatric Oncology, patients with pediatric malignancies are managed by 4 pediatric oncologists and 1 pediatric surgeon. Although pediatric oncologists mainly treat and manage patients, a multidisciplinary team approach including radiation oncologists, orthopedic surgeons, ophthalmologic surgeons and others is incorporated for the treatment. To achieve treatment completion and optimal quality of hospital life for children, pediatric nurse specialists, teachers, child life specialists, psychologists and psychiatrists also join our team. For young patients, educational opportunities ranging from elementary school to high school are available in the pediatric ward, where 7 teachers work daily.

## Routine activities

We deal with 60-80 new patients every year. Our daily activity in the pediatric outpatient clinic is to manage new patients, to treat patients with chemotherapy or blood transfusion and to provide follow-up care for patients who have completed intensive treatment. Patients receive multidisciplinary therapy, including surgical removal of the tumor, radiation therapy, chemotherapy, and sometimes SCT, as indicated.

A Pediatric Conference is held every morning, mainly to decide on individual treatment plans. The pediatric staff members and trainees discuss various issues regarding pediatric inpatients on daily rounds. Inter-department conferences in cooperation with orthopedics, radiation oncology, and palliative care are individually scheduled every 2 weeks.

## Research activities

1. For newly diagnosed patients, we participate in several multicenter studies, including those by the Japan Ewing Sarcoma Study Group (JESS), Rhabdomyosarcoma Study Group (JRSG) and Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG). In addition, we also conduct our own clinical trials.
2. For relapsed patients, we are actively involved in the development of new drugs and treatments including off-label and unapproved medications.
3. For the patients with veno-occlusive disease in stem cell transplantation and the patients with delayed excretion of methotrexate, a phase I registration trial of defibrotide and a phase II registration trial of glucarpidase are ongoing.
4. For the establishment of standard therapy in Japanese nationwide study groups, we support infrastructure building with the National Center for Child Health and Development.

## Clinical trials

In 2014, we conducted 16 trials, including early phase trials, an international study and cooperative studies. The 5 trials (3, 6, 8, 9, and 10) are investigator-initiated and 2 (15 and 16) are company sponsored registration-directed clinical trials conducted under the Pharmaceutical Affairs Law in Japan.

(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 crossover 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 II trial of glucarpidase for patients who were treated with high-dose methotrexate resulting in delayed excretion.
(4) A phase Ib study of $^{131}$I-metaiodobenzylguanidine (MIBG) therapy with valproic acid (VPA) for high risk or recurrent neuroblastoma.
(5) A phase Ib study of VPA and 13-cis-RA (isotretinoin) combination therapy for advanced and recurrent neuroblastoma.
(6) A feasibility trial of ch14.18 combined with IL-2 and various colony-stimulating factors for recurrent neuroblastoma.
(7) A phase I trial of immunotherapy using HLA-A2-and A24-restricted glypican-3 peptide vaccine for pediatric tumors.
(8) A phase I study of peptide cocktail vaccine for patients with refractory pediatric sarcoma.
(9) Efficacy and safety study of defibrotide (DF) for the treatment of veno-occlusive disease (VOD).
(10) Efficacy and safety study of defibrotide (DF) for the prophylaxis of veno-occlusive disease (VOD).
(11) Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) ALL-T11 and Japan Adult Leukemia Study Group (JALSG) T-ALL-211-U ALL-T11: A Multi-Center Phase II Study in Children and Adolescence with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia.
(12) Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) ALL-B12: A Multi-Center Phase II/III Study in Children with Newly Diagnosed B-cell Precursor Acute Lymphoblastic Leukemia.
(13) An International Study for Treatment of Standard Risk Childhood Relapsed ALL 2010 (IntReALL SR 2010): A randomized Phase III Study Conducted by the Resistant Disease Committee of the International BFM Study Group.
(14) A Multi-Center Seamless Phase II-III Randomized Trial of High-dose Cytarabine in Initial Induction with Evaluation of Flow-cytometry-based Minimal Residual Disease for Children with de Novo Acute Myeloid Leukemia (AML-12).
(15) A phase I trial of YHI-1003 for patients with relapsed /refractory neuroblastom.
(16) A Multi-Center trial of ONO-7847 for prophylaxis of nausea and vomiting during chemothrapy.

## Education

We provide personnel training and education for the skills of diagnosis for pediatric hematological malignancies and solid tumors. Residents also learn skills to treat not only newly diagnosed patients but also relapsed or refractory patients by the global standard therapy. In addition, senior residents acquire abilities to plan studies for new agents or new therapies, which we regard as an important role of this center.

## Future prospects

We promote development of therapies for pediatric malignancies as a top priority. For this mission, we lead to plan clinical or registration trials in cooperation with domestic and international centers as a core institution in Japan.

Our other mission is to provide a progressive model for medical care environment for children. Through the appropriate use of medical and social resources, patients get to be able to live in their local communities as long as possible even during treatment as before.

**Table 1. Number of patients**

| | |
|---|---|
| Acute lymphoblastic leukemia | 3 |
| Acute myeloid leukemia | 2 |
| Non-Hodgkin lymphoma | 2 |
| Hodgkin lymphoma | 0 |
| Other hematologic malignancies | 1 |
| Neuroblastoma | 14 |
| Retinoblastoma* | 13* |
| Osteosarcoma | 11 |
| Ewing sarcoma family | 7 |
| Rhabdomyosarcoma | 3 |
| Other soft tissue tumors | 1 |
| Germ cell tumor | 1 |
| Other solid tumors | 2 |
| Total | 61 |

*; advanced case only

**Table 2. Type of procedure**

| | |
|---|---|
| Tumor resection | 3 |
| retroperitoneum | 1 |
| abdominal wall (Lap) | 1 |
| omentum | 1 |
| Lung resection (Lap assist) | 8 |
| Surgery for pleural tumor (Lap assist) | 2 |
| Soft tissue tumor resection | 2 |
| Lymph node dissection | 2 |
| retroperitoneum | 1 |
| pelvic | 1 |
| Lymph node biopsy | 1 |
| Central venous (CV) port / catheter | 93 |
| placement | 50 |
| cutdown | 1 |
| remove | 42 |
| Total | 111 |

## List of papers published in 2014

### Journal


1. Kato M, Manabe A, Koh K, Inukai T, Kiyokawa N, Fukushima T, Goto H, Hasegawa D, Ogawa C, Koike K, Ota S, Noguchi Y, Kikuchi A, Tsuchida M, Ohara A. Treatment outcomes of adolescent acute lymphoblastic leukemia treated on Tokyo Children's Cancer Study Group (TCCSG) clinical trials. Int J Hematol, 100:180-187, 2014
2. Kobayashi S, Kikuta A, Ito M, Sano H, Mochizuki K, Akaihata M, Waragai T, Ohara Y, Ogawa C, Ono S, Ohto H, Hosoya M. Loss of mismatched HLA in myeloid/NK cell precursor acute leukemia relapse after T cellreplete haploidentical hematopoietic stem cell transplantation. Pediatr Blood Cancer, 61:1880-1882, 2014
3. Sekihara K, Okuma Y, Kawamoto H, Hosomi Y. Clinical outcome of thymic lymphoepitheliomalike carcinoma: Case report of a 14-year-old male. Oncol Lett, 8:2183-2186, 2014
4. Yasui N, Adachi N, Kato M, Koh K, Asanuma S, Sakata H, Hanada R. Cisplatin-induced hearing loss: the need for a long-term evaluating system. J Pediatr Hematol Oncol, 36:e241-245, 2014
5. Hoshino M, Sugito K, Kawashima H, Goto S, Kaneda H, Furuya T, Hosoda T, Masuko T, Ohashi K, Inoue M, Ikeda T, Tomita R, Koshinaga T. Prediction of contralateral inguinal hernias in children: a prospective study of 357 unilateral inguinal hernias. Hernia, 18:333-337, 2014
6. Araki Y, Kaneda H, Oashi K, Okada S, Tsutsumid A. Ovarian metastasis of malignant melanoma: The first pediatric case. J Pediatr Surg Case Rep, 2:473-475, 2014

# Department of General Internal Medicine/Oncologic Emergencies

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

## Introduction

The increasing numbers 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 field and provide comprehensive management of these issues.

## Routine activities

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

Cardiology:

Cardiologists take charge of ECG, echocardiography, 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 2,000 a year. When 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 600 diabetes consultations in 2014, 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 the NCCH.

Infectious diseases:

- Provide an infectious disease consultation service.
- Work with the infection control team.
- Investigated the cause of *Bacillus cereus* outbreak with a view to controlling and preventing further spreading.
- Analyzed the data obtained from the retrospective study of bacteremia among neutropenic cancer patients.
- Participated in the study of *Klebsiella pneumoniae* bacteremia, and provide information.
- Presented the cause and course of the *Bacillus cereus* outbreak at the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy and the 30th Annual Meeting of Japanese Society for Infection Prevention and

Control.

- Presented the characteristics of bacteremia among neutropenic cancer patients at the 62nd Annual Meeting of the Japanese Society of Chemotherapy.
- Presented the lectures on infectious disease and infection control.
- Provided training programs for two trainee doctors of other facilities.
- Continue to work towards improvements in the quality of care
- Continue to provide training programs for trainee doctors

# Department of Dentistry

**Takao Ueno, Wakao Yatsuoka, Kyoko Miyamoto, Natsumi Nakamura, Mayuko Watari**

## Introduction

Oral complications are common in patients receiving chemotherapy or undergoing radiation therapy of the head and neck.

Oral complications during cancer treatment are directly linked to ingestion problems, and may even serve as a source of various infections such as aspiration pneumonia, thereby exacerbating systemic conditions, and sometimes preventing the completion of cancer treatment with negative effects on treatment prognoses. Oral health status of patients with cancer is associated with the incidence rate and the degree of severity of oral complications. Effective oral hygiene management before initiating cancer treatment will contribute to the reduction of oral complications such as mouth sores, oral mucositis, or dental infections, and provide important support to facilitate smooth cancer treatment.

## Routine activities

To prevent or reduce oral complications, we check complication during cancer treatment oral conditions of the patients, identifying the patients at risk, start preventive measures before cancer therapy begins.

Our routine activities for cancer patient are below:

1) Management of oral complications of high-dose chemotherapy and/or stem cell transplant before treatment begins
2) Prevention and treatment of oral complications during chemotherapy and/or radiation therapy
3) Perioperative dental management for the prevention of postoperative pneumonia with oral, pharynx and esophageal surgery
4) Making prostheses for restoration of postoperative facial defects
5) Prevention and treatment of medication-associated osteonecrosis of the jaw (MRONJ)
6) Cooperation business of a medical department and dentistry for the solution to dental problem of the cancer patient

## Education

The lecture and the practice concerning the oral health care were regularly held for nurses and residents.

# Department of Genetic Counseling

**Teruhiko Yoshida, Kokichi Sugano, Takeshi Nakajima**

## Introduction

Approximately 5% of all cancer cases are considered to be caused by a highly penetrant monogenic mutation. Major causative genes for major hereditary cancer syndromes were identified in the 1990s, and since then, genetic diagnosis has been introduced as the standard medical care for some of the tumors. The National Cancer Center Hospital (NCCH) launched the Outpatient Genetic Counseling Clinic in 1998 as a part of collaboration with the Research Institute. However, cancer medical genetics still has a number of issues to be addressed as shown in Figure 1, which is again shown this year with some modification from the last year, because it has been the basic set of the agenda of the Clinic.

## Routine activities

As shown in the NCCH home page, the aim and mission of the clinical service of the Outpatient Genetic Counseling Clinic are:

#1/ to provide consultation and appropriate medical and genetic information (i.e., genetic counseling) to anyone who has a worry related to heredity of cancer.

#2/ to provide genetic testing when appropriate.

#3/ to support early diagnosis and treatment based on the family history and/or genetic test results.

In 2013, 113 patients and their relatives from 92 pedigrees visited the Clinic. In total, 1,242 clients from 834 families have visited the Clinic since its inception in 1998.

## Research activities

Among the Figure 1 research agenda, the staff of the Outpatient Genetic Counseling Clinic has been playing a leading role to organize and maintain a multi-institute collaborative research group based on the National Cancer Center Research and Development Fund and its predecessor. The group will identify the cases with hereditary cancer syndromes such as multiple endocrine neoplasias, hereditary breast and ovarian cancer syndrome, Lynch syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome and retinoblastoma to provide genetic tests for the known causative genes. However, in general, sensitivity of the current standard genetic tests remains approximately 70-80% even for the cases well-matched to the clinical criteria for hereditary cancer syndromes. Thus, a new common protocol has been established to perform a germline clinical sequencing by the next generation sequencers for those with negative test results, who would represent a part of the Undiagnosed Disease Patients. As a test run, whole exome sequencing (WES) and target deep sequencing were carried out for several cases with familial pancreatic cancers, and WES for familial gastric cancers.

## Clinical trials

The Outpatient Genetic Counseling Clinic has participated in a prospective clinical study to optimize BRCA1/2 genetic tests and clinical trials of PARP inhibitor for patients with ovarian or breast cancers both directed by the Departments of Breast and Medical Oncology and Breast Surgery.

## Education

Attendees of genetic counseling in the clinic would be certified as the trainees fulfilling the eligibility required to take the examination for clinical geneticist acknowledged by the Japanese Society of Human Genetics and the Japanese

Society of Genetic Counseling. In 2014, 6 doctors were registered as the trainee for the clinical geneticist in the education committee of the clinical geneticists.

## Future prospects

In Japan, most of the genetic tests are not covered by the mandatory health insurance, and the area clinical medical genetics has been in the transitional zone between the research and clinical practice. The well-publicized story by Ms. Angelina Jolie has increased the public awareness of the various issues on the hereditary cancer syndromes, as she disclosed in 2013 that she is a carrier of a pathogenic BRCA1 mutation with a family history of ovarian cancer and opted for Risk Reducing Mastectomy and Risk Reducing Salpingo-Oophorectomy. Moreover, on the technology side, the advent of the next generation sequencers has revolutionized medical sciences to herald the era of genomic medicine. Clinics of the hereditary cancer syndromes is expected to lead the germline part of the genomic medicine initiative in the oncology field, but the major agenda has been recognized already as Figure 1.

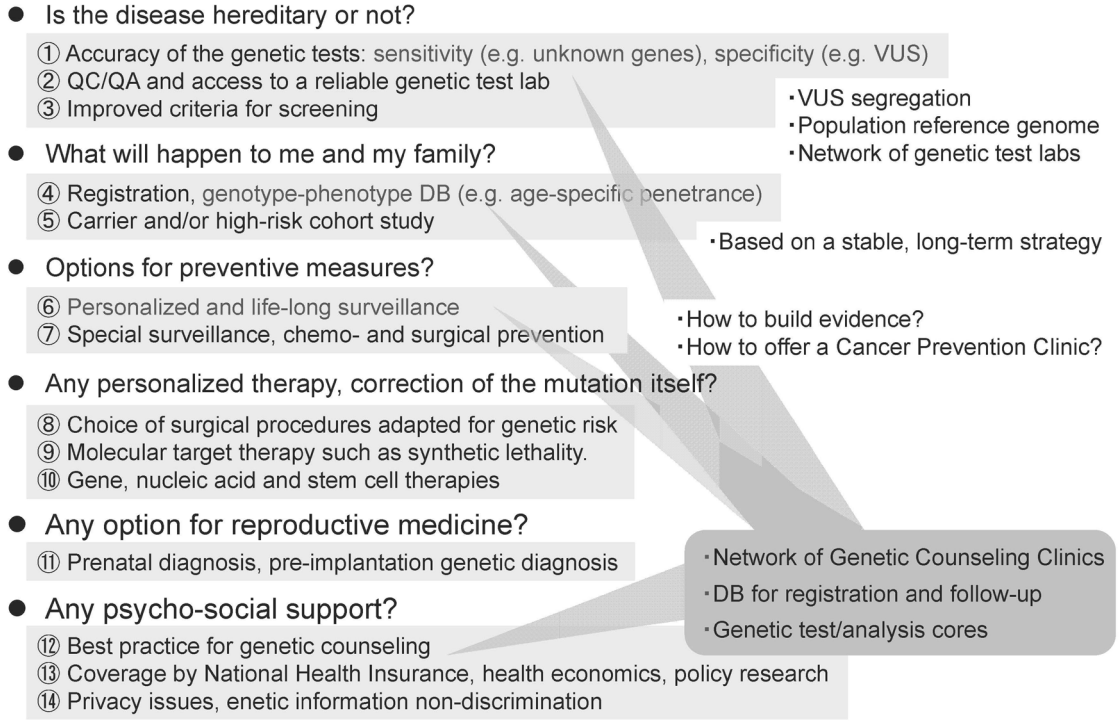


**Figure 1. Major Questions by the Patients and Families with Hereditary Cancer Syndromes**

**Table 1. Number of clients**

| | Proband | Relative | Total |
|---|---|---|---|
| Lynch syndrome (Hereditary Non-Polyposis Colon Cancer; HNPCC) | 11 | 4 | 15 |
| Familial Adenomatous Polyposis (FAP) | 4 | 3 | 7 |
| Retinoblastoma | 8 | 4 | 12 |
| Hereditary Breast and Ovarian Cancer Syndrome (HBOC) | 55 | 6 | 61 |
| MEN I (Multiple Endocrine Neoplasia Type I) | 0 | 0 | 0 |
| Other diseases | 14 | 4 | 18 |
| Total | 92 | 21 | 113 |

## List of papers published in 2014

## Journal


1. Yamada M, Fukagawa T, Nakajima T, Asada K, Sekine S, Yamashita S, Okochi-Takada E, Taniguchi H, Kushima R, Oda I, Saito Y, Ushijima T, Katai H. Hereditary diffuse gastric cancer in a Japanese family with a large deletion involving *CDH1*. Gastric Cancer, 17:750-756, 2014
2. Miyakura Y, Tahara M, Lefor AT, Yasuda Y, Sugano K. Haplotype defined by the MLH1-93G/A polymorphism is associated with MLH1 promoter hypermethylation in sporadic colorectal cancers. BMC Res Notes, 7:835, 2014
3. Tahara M, Inoue T, Sato F, Miyakura Y, Horie H, Yasuda Y, Fujii H, Kotake K, Sugano K. The use of Olaparib (AZD2281) potentiates SN-38 cytotoxicity in colon cancer cells by indirect inhibition of Rad51-mediated repair of DNA double-strand breaks. Mol Cancer Ther, 13:1170-1180, 2014

# Department of Anesthesia and Intensive Care

**Tetsufumi Sato, Yoko Kinoshita, Minako Arai, Jyunya Matsumi, Nobuko Yokokawa, Rie Suzuki, Yousuke Kawaguchi, Kazumasa Hiroi, Sayo Iwasaki, Kihoko Ichikawa, Rutesara Kyuragi**

## Introduction

Our Department provides anesthesia and intensive care. Anesthetic services are provided for 15 main operating theatres and sessions in endoscopy. There are about 4,000 operations per year. The Intensive Care Unit has 8 beds and provides care for all specialties including general medical and general surgical cases. There are over 500 admissions annually and the ICU is also responsible for resuscitation services within the hospital.

## Routine activities

The department of anesthesia and intensive care at the National Cancer Research Center Central Hospital is comprised of 12 staff anesthetists who are involved in critical care, education and research. Our Department provides perioperative care to all the patients require general anesthesia and spinal analgesia (Table1). Our operation theater performs approximately 4,000 surgical procedures per year, which include neurosurgical, orthopedic, plastics, ophthalmologic, gynecologic, urologic, and general surgery. 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 also has other clinical appointments including attending 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 closed-system, supported by two certificated intensivists and trainee. There are 8 operational ICU beds and over 500 admissions annually (Table2). The ICU is also responsible for resuscitation services within the hospital.

## Clinical trials

One of members is faculty of 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 were performed. To improve current care for perioperative patients, prospective studies are conducting.

**Table 1. Number of Patients for anesthesia**

| | |
|---|---|
| General Anesthesia | 1,957 |
| General Anesthesia + Epidural Anesthesia | 2301 |
| Spinal Anesthesia + Epidural Anesthesia | 4 |
| Epidural Anesthesia | 1 |
| Spinal Anesthesia | 59 |
| Others | 18 |
| Total | 4,340 |

**Table 2. Number of patients admitted to the ICU**

| | |
|---|---|
| Esophageal Surgery | 124 |
| Neurosurgery | 107 |
| Hepatobiliary and Pancreatic Surgery | 80 |
| Head and Neck Surgery | 63 |
| Musculoskelertal Oncology | 39 |
| Gastric Surgery | 33 |
| Colorectal Surgery | 33 |
| Thoracic Surgery | 31 |
| Urology | 18 |
| Hematopoietic Stem Cell Transplantation | 14 |
| Gastrointestinal Medical Oncology | 7 |
| Gynecology | 6 |
| Hematology | 5 |
| Dermatorogic Oncology | 4 |
| Hpatobiliary and Pancreatic Oncology | 3 |
| Breast and Medical Oncology | 2 |
| Radiation Oncology | 2 |
| Ophthalmic Oncology | 1 |
| Thoracic Oncoogy | 2 |
| Pediatric Oncology | 1 |
| Breast Surgery | 1 |
| Total | 576 |

# Department of Palliative Care

**Eriko Satomi**

## Introduction

Palliative care service has started as the palliative care team with multidiciplenary professionals (palliative care specialists, psyco-oncologists, certified nurses, pharmacists, psychologists) in the National Cancer Center Hospital (NCCH) since 1999 and the Department of Palliative Care and Psyco-oncology was established in 2010 when the reorganization of the NCCH. In 2013, the Department of palliative medicine has started. We provide palliative care to patients and families as members of palliative care team with primary doctors, nurses and other professionals to create an individualized palliative care plan. Our goals are:

- Relieve pain and other physical symptoms
- Focus patients' emotional and spiritual concerns, and those of their caregiver
- Coordinate patients' care
- Improve your quality of life with cancer
- Advance care planning

## Routine activities

Our missions are:

- Manage cancer-related pain and symptoms
- Collaborate other medical professionals and plan care plan
- Support patients' decision making and advance care planning
- Educate basic skill of supportive and palliative medicine to resident doctors
- Research about new treatment of supportive and palliative medicine

1) for hospitalized patients

We work as the palliative care team and provide consulting and follow-up services to hospitalized patients throughout the NCCH. A consultation request is made by a physician (doctors in charge) or the medical staff. We provide support to the primary team. We follow up about 25~30 pts every day.

2) for outpatients

Our outpatient clinic of palliative medicine is open on Monday through Friday. We can possibly see patients on demand.

## Research activities

We have just started to participate in some research groups for clinical trial about palliative care.

## Education

We have 2 training courses which are for doctors who will be palliative care specialist and for residents to learn primary palliative care. All the residents of surgical medical oncologist in the NCCH need knowledge and skill about primary supportive and palliative care in Oncology. They participate in our team for 4 weeks and on the job training for palliative medicine. It includes an opportunity to attend home hospice round in corporation to Chuou-ku medical association. 20 residents have finished 4-week palliative medicine course in 2014.

**Table 1. Number of patients for anesthesia**

| | | | |
|---|---|---|---|
| Cases | | 266 | |
| male/female | | 139 | 127 |
| age | | 55.6 (SD14.9) | |
| clinical stage | | | |
| | I | | 7 |
| | II | | 5 |
| | III | | 13 |
| | IV | | 69 |
| | reccurrence | | 136 |
| | others | | 25 |
| | unknown | | 11 |
| primary site of cancer | | | |
| | brain ,eyes | | 0 |
| | head and neck | | 9 |
| | esophagus | | 11 |
| | stomach | | 20 |
| | colorectal | | 26 |
| | hepatobiliary | | 3 |
| | pancreas | | 7 |
| | lung | | 40 |
| | breast | | 25 |
| | uterus,ovary | | 11 |
| | prostate | | 3 |
| | kidney,adrenal gland | | 5 |
| | thyroid | | 0 |
| | blood | | 42 |
| | bone | | 2 |
| | skin | | 23 |
| | soft tissue, methotelioma | | 28 |
| | unknown origin | | 7 |
| | others | | 4 |
| symptoms | pain | | 233 |
| | breathlessness | | 63 |
| | nausea/vomit | | 70 |
| | fatigue | | 82 |

## List of papers published in 2014

## Journal


1. Kokubun H, Yoshimoto T, Hojo M, Fukumura K, Matoba M. Pharmacokinetics of oxycodone after intravenous and subcutaneous administration in Japanese patients with cancer pain. J Pain Palliat Care Pharmacother, 28:338-350, 2014
2. Sakai H, Sagara A, Matsumoto K, Jo A, Hirosaki A, Takase K, Sugiyama R, Sato K, Ikegami D, Horie S, Matoba M, Narita M. Neutrophil recruitment is critical for 5-fluorouracil-induced diarrhea and the decrease in aquaporins in the colon. Pharmacol Res, 87:71-79, 2014
3. Sakai H, Sagara A, Arakawa K, Sugiyama R, Hirosaki A, Takase K, Jo A, Sato K, Chiba Y, Yamazaki M, Matoba M, Narita M. Mechanisms of cisplatin-induced muscle atrophy. Toxicol Appl Pharmacol, 278:190-199, 2014
4. Kosugi T, Hamada S, Takigawa C, Shinozaki K, Kunikane H, Goto F, Tanda S, Shima Y, Yomiya K, Matoba M, Adachi I, Yoshimoto T, Eguchi K. A randomized, double-blind, placebo-controlled study of fentanyl buccal tablets for breakthrough pain: efficacy and safety in Japanese cancer patients. J Pain Symptom Manage, 47:990-1000, 2014

# Department of Psycho-Oncology

**Ken Shimizu, Rika Nakahara, Yoshio Oshima, Masashi Kato, Chikako Dotani, Hironobu Inoguchi, Saran Yoshida, Satomi Kojima, Mariko Kobayashi, Chisato Kobayashi**

## Introduction

The Department of Psycho-Oncology was reestablished in September 1995, together with establishment of the Psycho-Oncology Division, National Cancer Center Research Institute East (reorganized to the Division of Psycho-Oncology, Research Center for Innovative Oncology in 2005). One of the most important clinical activities of the Department is the management of cancer patients' behavioral and social problems as well as their psychological distress. Furthermore, this Department's aim is to alleviate distress of patients, patients' families and our staff. Research activity is focused on studying the psychosocial influence of cancer on the quality of life of patients, their families, and oncology staff.

## Routine activities

The Department of Psycho-Oncology consists of four full-time staff psychiatrists, three full-time staff psychotherapists and three part-time psychotherapists. The department provides two major services; a clinic for outpatients (five days a week) and consultation for referred inpatients. The purpose of the psychiatric consultation is to diagnose and treat the mental distress and cancer related psychological problems of patients who have been referred by their attending physicians. Since 1999, the Department has played an active role as a member of the palliative care team. There is a palliative care team meeting with other members of the team every Tuesday. Additionally, a multicenter joint clinical teleconference to discuss difficult cases is held biweekly in Thursday evening with staff members from 6 cancer center hospitals and 4 university hospitals.

In 2014, a total of 827 patients were referred for psychiatric consultation (Table 1). The mean age was 50.7 years old and 17.3% percent of the referrals were outpatients. Three-hundred and forty three (41.5%) of the whole referred patients were males (Table 1). The most common cancer referrals were patients with sarcoma (17.4%), followed by hematological cancer (13.2%), breast cancer (10.2%), lung cancer (8.5%), and colorectal cancer (7.6%). The most common psychiatric diagnosis which is based on the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) was Delirium (22.9%), followed by Adjustment Disorders (22.1%), and major depressive disorder (12.8%), while 20.4% of the referrals had no psychiatric diagnosis. The three common mental disorders (delirium, adjustment disorders, and major depressive disorder) were responsible for half of the psychological problems.

## Research activities

We are now developing the psychosocial intervention for allogenic hematopoietic stem cell transplant survivors, the purpose of which is to improve the quality of life. This year, we have planned an observational study to decide the intervention components.

We also explored the contents of "posttraumatic growth" in Japanese cancer patients. Posttraumatic Growth is a positive dimension of patients' psychological change aftermath of trauma. There has been known little about the process in Japanese cancer patients, and this result will provide precious information to develop intervention to support patients' psychological adaptation after cancer diagnosis.

**Table 1. Psychiatric Consultation Data in 2014 (n=827)**

| | n | % |
|---|---|---|
| Age (years) | 50.7 | |
| Male | 343 | 41.5 |
| Inpatients | 684 | 82.7 |
| Top 5 of cancers by site | | |
| Sarcoma | 189 | 22.9 |
| Hematological | 183 | 22.1 |
| Breast | 84 | 10.2 |
| Lung | 70 | 8.5 |
| Colorectal | 63 | 7.6 |
| Psychiatric diagnoses | | |
| Delirium | 189 | 22.9 |
| Adjustment disorders | 183 | 22.1 |
| Major Depressive disorder | 106 | 12.8 |
| Others | 180 | 21.8 |
| No diagnosis | 169 | 20.4 |

## List of papers published in 2014

### Journal

1. Yoshida S, Shimizu K, Kobayashi M, Inoguchi H, Oshima Y, Dotani C, Nakahara R, Takahashi T, Kato M., Barriers of healthcare providers against end-of-life discussions with pediatric cancer patients, Jpn J Clin Oncol, 44(8), 729-735, 2014

### Book

1. Shimizu K, et al. Treatment of Anxiety and Stress-Related Disorders. Psychopharmacology in Oncology and Palliative Care, Springer, 129-144,2014

# Department of Diagnostic Radiology

**Yasuaki Arai, Ryutaro Kakinuma, Yasunori Mizuguchi, Gen Iinuma, Takashi Terauchi, Miyuki Sone, Hiroaki Kurihara, Nachiko Uchiyama, Hirokazu Watanabe, Minoru Machida, Seiko Kuroki, Mari Kikuchi, Tomoko Manabe, Mototaka Miyake, Hiroaki Ishii, Syunsuke Sugawara, Shinichi Morita, Masahiko Kusumoto, Yukio Muramatu**

## 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. This year, we launched the Center for Interventional Radiology to facilitate widespread proliferation of IR in Japan and to provide various IR treatments for the patients referred from other hospitals or clinics. We seek individuals with outstanding leadership capabilities, proven academic and administrative experience, the vision to build and sustain programs at the forefront of imaging research, and a commitment to clinical experience.

## Routine activities

| Modality | Number of examinations |
|---|---|
| 1 CT : | 42,453 |
| 2 MRI: | 8,248 |
| 3 IR: | 4,508 |
| 4 RI: | 4,363 |
| 5 Ultrasound: | 14,156 |
| 6 Radiograph: | 71,550 |
| 7 Gastrointestinal study: | 1,888 |

## Research activities

CT colonography (CTC) has been successfully introduced as an effective option for preoperative staging and colorectal screening in our center. Nearly 2000 patients and/or candidates have been examined with this modality in 2013. For the preparation of screening CTC, electronic cleansing with fecal barium tagging and automated $CO_2$ gas insufflation systems have been established in the formal National Cancer Center (NCC) collaboration studies with the associated companies. Furthermore, we are now developing computer-aided detection (CAD) for colorectal lesions, especially for flat lesions. The main purpose of our CTC research work is to conduct a multi-center trial to establish evidence regarding fully digitalized CTC for a colorectal screening system in Japan.

A multi tracer consisting of [18F]FDG, [18F] FBPA, [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 has been conducted in 22 cancer patients in this year. [11C]-choline and [11C]-methionine PET/CT examinations have been scheduled routinely two days per week. As for [64Cu]-DOTA-antibody PET imaging, [64Cu]-DOTA-trastuzumab PET/CT has been conducted in HER-2 positive breast cancer patients. Respiratory-gated PET/CT was evaluated to reduce breathing-induced artifacts using a four-dimensional PET/CT protocol. It provided better localization and quantification of tumors around the lower thorax to the upper abdomen. For cancer treatment, internal radiotherapy was carried out in 20 thyroid cancer patients with use of radioactive iodine (I-131) chloride and 2 neuroblastoma patients with I-131 MIBG.

In accordance with the achievement of collaborative research with the associated company since 2009, digital breast tomosynthesis (DBT) has been introduced as an effective routine option for preoperative evaluation since March2014. Up to Dec 2014, 271 patients were examined.

A multicenter study has started to establish

the CT classification of lung adenocarcinomas corresponding to the new IASLC/ATS/ERS pathological classification and to build the database of small adenocarcinomas. Digital Imaging and Communications in Medicine (DICOM) data of resected lung cancers from each institute have been accumulated and evaluated in collaboration to the Japanese Society of Thoracic Radiology.

The Japan Response Evaluation Criteria in Solid Tumors (RECIST) working group has developed a tumor response evaluation computer system, which is capable of semiautomatic RECIST evaluation and is compliant with DICOM data.

Image guided preoperative Breast Marking using ultrasound alone or combined with mammography has been performed for partial mastectomy cases which are difficult to determine the spread of disease. This technique makes it possible to resect abnormal lesion more precisely and assists to prevent both re-operation and local recurrence. Total 57cases were performed since January 2014 to December 2014.

We evaluated the usefulness of MRI for differentiation between Type I and Type II endometrial cancer.

## Clinical trials

A major departmental research theme is establishing an evidence base for interventional radiology. We have led a multi-institutional cooperative study group of interventional radiology (JIVROSG: Japan Interventional Radiology in Oncology Study Group) since 2002 as a steering organization of 90 participating domestic institutions. In this study group, we are investigating the efficacy of palliative interventional radiology in randomized controlled trials (RCTs) to compare it with other therapies. These palliative RCTs include: a phase III study evaluating the efficacy of peritoneo-venous shunting (JIVROSG-0803); a phase III study evaluating the efficacy of percutaneous vertebroplasty for painful bone metastases (JIVROSG-0804); a phase III study evaluating the efficacy of percutaneous trans-esophageal gastric tubing (JIVROSG-0805); a phase III study evaluating the efficacy of stenting for SVC/IVC syndrome (JIVROSG-0807) and JIVROSG-0807 completed patient enrollment in 2013. Other ongoing clinical trials are a phase I/II study of RFA for pelvic malignant tumors (JIVROSG-0204), a phase II study evaluating the efficacy of arterial infusion chemotherapy and radiotherapy for unresectable maxillary carcinoma (JIVROSG-0808) and a phase II study evaluating the efficacy and safety of n-butyl-2-cyanoacrylate (NBCA) in embolization (JIVROSG-0802).

## Education

The clinical education and training of young radiologists is an important part of our department's activities. During 2014, 6 residents and 5 short-term residents were trained with our Department. The educational opportunities to 4 overseas physicians from Philippines, Taiwan, German and Italy, were also provided. We have several clinical or educational conferences. A daily clinical IR case conference, a weekly educational case conference on diagnostic radiology, and a monthly IR research conference, are held.

## Future prospects

The Department of Radiology aims to strive for excellence in clinical care, education, and research. Our goal is to provide outstanding patient-centered radiology services and to establish evidence in this area. Future challenges include promoting the active role of the Center for Interventional Radiology opened this year and facilitating imaging as biomarkers for personalized cancer treatments such as molecular-targeted agents and boron neutron capture therapy.

## List of papers published in 2014

### Journal


1. Onoe S, Tsuda H, Akashi-Tanaka S, Hasebe T, Iwamoto E, Hojo T, Kinoshita T. Synchronous unilateral triple breast cancers composed of invasive ductal carcinoma, invasive lobular carcinoma, and Paget's disease. Breast Cancer, 21:241-245, 2014
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10. Johkoh T, Sakai F, Kusumoto M, Arakawa H, Harada R, Ueda M, Kudoh S, Fukuoka M. Association between baseline pulmonary status and interstitial lung disease in patients with non-small-cell lung cancer treated with erlotinib--a cohort study. Clin Lung Cancer, 15:448-454, 2014
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# Department of Radiation Oncology

**Jun Itami, Minako Sumi, Yoshinori Ito, Hiroshi Igaki, Madoka Morota, Naoya Murakami, Koichi Inaba, Kana Takahashi, Kotaro Yoshio, Shuhei Sekii, Hiroyuki Okamoto, Akihisa Wakita, Satoshi Nakamura**

## Introduction

The role of the Department is to provide the state-of-art radiation therapy to all relevant patients, to educate and develop the expertise of radiation oncologists, radiation technologists, and medical physicists, and to lead new developments in radiation oncology in Japan as well as worldwide. All departmental activities are dedicated to cancer patients. With a delay of as long as one-year, linear accelerator for the hospital-based boron neutron capture therapy (BNCT) was installed to the new facility and neutron beam will come in the summer of 2015. 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. Five linear accelerators, CyberKnife, one X-ray simulator, three XCT-simulators, and 15 treatment planning computers are working together under on-line networks to provide a state-of-art precision external beam radiation therapy. In addition to the conventional X-ray and electron therapies, stereotactic irradiations of brain and body tumors and intensity-modulated radiation therapy (IMRT) are employed routinely. Stereotactic brain irradiation is performed with CyberKnife in the treatment of metastatic as well as primary brain tumors. Stereotactic body tumor irradiation is performed in lung and liver tumors under respiratory gating in linear accelerators or CyberKnife. Four out of the 5 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. Gold marker fiducials have been implanted to improve geometric precision of radiation field reproducibility.

Brachytherapy is also performed very intensively to improve local control and many patients are referred to from all over Japan. For brachytherapy the following modalities are being employed, an Ir-192 high dose rate (HDR) afterloading system including dedicated CT simulator and fluoroscopy, an I-125 seed implantation system, and other low dose rate (LDR) brachytherapy systems using Au grains, Ir-thin wires, and ruthenium eye plaques. The number of patients undergoing HDR brachytherapy continued to rise constantly. This Department is the only 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 shortened fractionation regimen for various malignancies, especially for breast cancer and vocal cord cancer; 3) Image-guided HDR and LDR brachytherapy for genitourinary

and gynecologic cancers; 4) hypofractionated stereotactic irradiation of brain and body tumors; 5) adaptive radiation therapy in accordance with the intratherapeutic tumor and normal tissue change; and 6) development of accelerator based BNCT system.

## Clinical trials

Brain tumors: A multicenter phase II/III trial on interferon-beta and temozolomide combination therapy for newly diagnosed glioblastomas.

Lung cancer: Phase II trial on high dose thorax irradiation excluding prophylactic mediastinal lymph node radiation concurrent with CDDP+VNL in unresectable stage III non-small-cell lung cancers (NSCLCs).

Lung cancer: Stereotactic radiation therapy for histologically non-verified lung tumors.

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

Head and Neck cancers: Various JCOG studies including IMRT for nasopharyngeal and oropharyngeal cancers

Breast cancer: Phase II trial of SAVI applicator HDR brachytherapy after partial mastectomy.

Liver cancer: Phase I trial on stereotactic hypofractionated radiation to hepatocellular carcinoma.

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

Development of an Adaptive Radiation Therapy System

## Education

Five residents are trained in all fields of radiation oncology except particle beam therapy. Seminars about biology, physics, and clinical radiation oncology are regularly held in the evening time.

## Future prospects

With the introduction of BNCT, a new manpower will be required and research perspectives will be very widened.

**Table 1. Number of Patients**

| | |
|---|---|
| 1) New patients referred to the Department | 1,458 |
| 2) All patients undergoing radiation therapy | 2,063 |
| External Beam Radiation Therapy (EBRT) | |
| 1) New patients undergoing EBRT | 1,383 |
| 2) All patients undergoing EBRT | 1,976 |
| Brachytherapy (BT) and Radionuclide Therapy | |
| 1) All patients undergoing intracavitary radiation | 40 |
| 2) All patients undergoing interstitial radiation | 78 |
| 3) All patients undergoing prostate permanent seed implantation | 15 |
| 4) All patients undergoing I-131 therapy for thyroid cancer | 22 |
| 5) All patients undergoing Sr-89 therapy for bone metastasis | 2 |
| Other Special Radiation Therapy | |
| 1) All patients undergoing total body irradiation | 68 |
| 2) All patients undergoing stereotactic brain radiation | 247 |
| 3) All patients undergoing stereotactic body radiation | 49 |
| 4) All patients undergoing intensity modulated radiation therapy | 246 |

**Table 2. Number of New Patients according to the Primary Site**

| | |
|---|---|
| 1) CNS | 48 |
| 2) Head and Neck | 142 |
| 3) Esophagus | 117 |
| 4) Intrathoracic | 258 |
| 4)-a) Lung | 136 |
| 5) Breast | 296 |
| 6) Liver/Bile Duct/Pancreas | 88 |
| 7) Digestive Tracts | 252 |
| 8) GYN | 80 |
| 9) GU | 138 |
| 9)-a) Prostate | 102 |
| 10) Hematopoietic/Lymphatic | 88 |
| 11) Cutaneous/Bone/Soft Tissue | 110 |
| 12) Other Malignancies | 0 |
| 13) Benign | 2 |
| 14) Child Aged less than 15 Years | 19 |

**Table 3. Radiation Therapy of Brain or Bone Metastasis**

| | |
|---|---|
| 1) Brain metastasis | 266 |
| 2) Bone metastasis | 159 |

## List of papers published in 2014

### Journal


1. Harada K, Murakami N, Kitaguchi M, Sekii S, Takahashi K, Yoshio K, Inaba K, Morota M, Ito Y, Sumi M, Suzuki S, Tobinai K, Uno T, Itami J. Localized ocular adnexal mucosaassociated lymphoid tissue lymphoma treated with radiation therapy: a long-term outcome in 86 patients with 104 treated eyes. Int J Radiat Oncol Biol Phys, 88:650-654, 2014
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10. Fujibuchi T, Yonai S, Yoshida M, Sakae T, Watanabe H, Abe Y, Itami J. Measurement of activity distribution using photostimulable phosphor imaging plates in decommissioned 10 MV medical linear accelerator. Health Phys, 107:S158-162, 2014
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# Department of Pathology and Clinical Laboratories

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## Introduction

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

The Clinical Laboratories Division provides an important service as an in-hospital diagnostic unit by examining laboratory specimens and screening for disorders. All laboratory data are provided for clinicians under the strict internal and external quality control. The laboratories in this Department have 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

**Department of Pathology**: In 2014, a total of 13 board-certified pathologists, 7 residents and 12 medical technologists, including 9 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. Twelve pathologists working exclusively in the NCCH also shared management of the Department. We provided a total of 20,894 histological diagnoses consisting of 17,216 biopsy specimens including 1,917 intraoperative frozen sections and 3,678 surgically resected specimens (Table 1), a total of cytopathological diagnoses of 12,656 patients including 446 for intraoperative diagnoses (Table 2), and a total of 20 autopsies (Table 3). We also provided a total of 200 pathological diagnoses for outpatient clinic for pathology consultation (second opinion).

**Clinical Laboratories Division**: 52 full-time and 9 part-time medical technologists, 2 photographer and 5 assistants provide services. These staff work in the sections of 1) general laboratory medicine and hematology, 2) biochemistry, 3) endocrinology, immunology, and tumor markers, 4) bacteriology, 5) genetic diagnostics, 6) transfusion, 7) phlebotomy, 8) physiological examination, and 9) pathology in the NCCH, and in the sections of phlebotomy and physiological examination in the RCCPS. The sections of 1) to 5) are to be supervised by Dr. Koh Furuta, 6) and 7) by Dr. Ryuji Tanozaki (Transfusion Therapy), 8) by Dr. Yasunori Mizuguchi (Diagnostic Radiology), Drs. Masaaki Syoji and Takeshi Iwasa (General Internal Medicine), and Dr. Eriko Iwamoto (Breast Surgery), and 9) by doctors in the Department of Pathology. The bacteriology staff are the members of the Infection Control Team and participate in the activities of infection

management. The actual number of laboratory tests performed in this Division in 2014 is shown in Table 4.

## Research activities

1. Hepato-biliary pancreatic pathology

The gross appearance of pancreatic ductal adenocarcinoma, macroscopic necrosis and tube/branching structure were significantly correlated with patient outcome.

2. Gastrointestinal pathology

The roles of *GNAS* mutations in the tumorigenesis of gastrointestinal neoplasms were analyzed. HER2 expression was shown to be consistently absent in gastric neuroendocrine carcinomas, regardless of association with HER2-positive adenocarcinoma components.

3. Hematopathology

We reported prognostic significance of immunophenotypes and a nodular pattern in primary mediastinal large B-cell lymphoma and also case series of intrafollicular classical Hodgkin lymphoma mimicking nodular lymphocyte predominant Hodgkin lymphoma.

4. Pulmonary and mediastinal pathology

Clinical and molecular features of adenosquamous cell carcinoma, adenocarcinoma with morule-like components, or lung carcinoma with *RET* gene alterations were reported. Cytokeratin 19 or PAX8 expression was studied in lung carcinomas.

5. Bone and soft tissue pathology

We identified a unique and consistent mode of vascular involvement suggestive of an invasion-independent metastatic mechanism in alveolar soft part sarcomas. We demonstrated the utility of STAT6 immunohistochemistry for diagnosing solitary fibrous tumors and a value of SALL4 immunohistochemistry for differentiating malignant rhabdoid tumors from epithelioid sarcomas. Next generation sequencing of chondrogenic tumors identified recurrent mutations in *COL2A1* and other genes. We reported a benign metastasizing diffuse-type tenosynovial giant cell tumor.

6. Brain tumor pathology

We developed an optimal set of p53 immunohistochemistry interpretative criteria to predict *TP53* mutation in diffuse gliomas. We published a case of multinodular and vacuolating neuronal tumor of the cerebrum and a sclerosing variant of meningioma.

7. Breast and gynecological pathology

Wide local extension and higher proliferation indices were characteristic features of symptomatic lobular neoplasias and those with early invasive component. Lobular endocervical glandular hyperplasia was a neoplastic entity with frequent activating *GNAS* mutations.

8. Head and Neck pathology

A strong relationship between expression of CD326 and radiation response was demonstrated in early stage glottic cancer. We discovered a lack of SOX10 expression, high frequency of *BRAF* mutation and a lack of *GNAQ* or *GNA11* mutation in adenoma or adenocarcinoma of pigmented ciliary epithelium.

9. Clinical Laboratories

An in-hospital bio-bank has been maintained for use by various researchers, and more than 650,000 post-clinical-test blood samples have been stored at -20 °C as of the end of 2014. Three sections of hematology, biochemistry and endocrinology, immunology and tumor markers, participated in the external quality control program endorsed by the Japanese Society of Laboratory Medicine. Some Medical Technologists found interesting findings in their routine practice and made presentations at several domestic medical assemblies. At the molecular diagnostic section, mutation analyses of *EGFR*, *KRAS*, *NRAS*, and *BRAF* were provided as routine tests. At the cytogenetics section, using the Metafer system (an automated image analysis-assisted fluorescence *in situ hybridization* [FISH] system), the technique to evaluate the

FISH imaging of *HER2* gene amplification was established and maintained. These two sections provided data not only for clinical practices but also for research activities of doctors in the NCCH and/or the NCCRI.

**Table 1. Numbers of Histopathological Specimens Diagnosed in the Department of Pathology in 2014**

| Field | Number of specimens Total |
|---|---|
| Gastrointestinal tracts | 8,447 |
| Breast | 2,568 |
| Respiratory organs | 2,201 |
| Hematology | 1,422 |
| Gynecology | 1,294 |
| Urology | 785 |
| Hepatobiliary and Pancreas | 750 |
| Head and Neck | 941 |
| Dermatology | 639 |
| Orthopedics | 555 |
| Others | 342 |
| Research Center for Cancer Prediction and Screening | 570 |
| Total | 20,894 |

**Table 2. Numbers of Cytopathological Specimens Diagnosed in the Department of Pathology in 2014**

| Field | Number of specimens Total |
|---|---|
| Gynecology | 3,886 |
| Urology | 2,968 |
| Respiratory organs | 2,961 |
| Gastrointestinal tracts | 8,447 |
| Breast | 500 |
| Hepatobiliary and Pancreas | 544 |
| Hematology | 356 |
| Head and Neck | 274 |
| Radiation Oncology | 145 |
| Others | 196 |
| Research Center for Cancer Prediction and Screening | 0 |
| Total | 12,656 |

**Table 3. Numbers of Autopsies Performed in the Department of Pathology in 2014**

| Deaprtment/Division | Number |
|---|---|
| Hematology and Hematopoietic Stem Cell Transplantation | 6 |
| Thoracic Oncology | 6 |
| Hepatobiliary and Pancreas | 2 |
| Oncology | |
| Dermatology | 2 |
| Gastrointestinal Oncology | 1 |
| Endoscopy, Respiratory | 1 |
| Endoscopy Division | |
| Esophageal Surgery | 1 |
| Colorectal Surgery | 1 |
| Total | 20 |

**Table 4. Number of laboratory tests examined in the Clinical Laboratories Division in 2014**

| Section | Number |
|---|---|
| General laboratory medicine | 507,051 |
| Hematology | 1,308,384 |
| Biochemistry | 2,999,388 |
| Endocrinology, immunology, and tumor markers | 368,436 |
| Bacteriology | 49,126 |
| Physiology | 93,522 |
| Genetic diagnostics | 31981 |
| Total | 5,325,907 |

## List of papers published in 2014

## Journal


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# Office of Infection Control and Prevention

**Minoru Esaki, Keiji Okinaka, Noriko Wada, Keiichi Koido, Michi Shouji, Chiharu Miyamoto**

## Introduction

The Office of Infection Control and Prevention as a center of the infection control team consists of an infectious disease doctor (Infection Control Doctor), infection control nurse, board certified pharmacist in infection control, infection control microbiological technologist, office clerk, and director. The team works very closely with staff from all areas of the hospital to control and prevent infection. The annual activities of our team in 2014 were

- to announce the newest most up-to-date information and items for all clinical staff
- to reduce the risk of healthcare-associated infections among visitors, patients and staff by using the infection control management and workflow system "ICTweb"
- to collaborate with regional hospitals to keep cancer patient safe from healthcare-associated infections.
- to deliver the infection prevention education programs to all staff.

We hope to take on a role in improving the outcome of treatment for cancer patients through first class infection control and prevention.

## Routine activities and Education

Our team provides

- Advice about the prevention and management of outbreaks, and delivering education programs to all staff including lectures by staff or regional hospital, basic study session for infection and hand hygiene training.
- Implementation of antimicrobials stewardship based on the newest data. We use high-quality evidenced-based policies, guidelines and protocols as a reference to ensure care.
- Monitoring of environmental cleanliness and provide providing advice about building and refurbishment projects in the hospital from the infection control aspect.

## Research activities

1) In-Hospital Outbreaks of Bacillus cereus Bacteremia Associated with Reused Contaminated Bed Bath Towels (Washington DC)
2) The Efficacy of Certified Pharmacist in Infectious Diseases Region on Individualized Dosage Adjustment Concentrations of Vancomycin (in submission)

# Outpatient Treatment Center

**Kenji Tamura**

## Introduction

The Outpatients Treatment Center deals with all kinds of malignancies. Our mission is to provide safe, smooth and high quality of standard chemotherapies as outpatient style. There are 20 beds and 16 chairs (total 36) for chemotherapy. Several groups collaborate to ensure the best chemotherapies, consisting of medical oncologists, nurses, pharmacists, medical social workers (MSW) and clinical research coordinators (CRCs). Our visions are 1) to provide an evidence-based medicine, 2) to provide safe and efficient treatments, and 3) to keep quality of life of the patients.

## Routine activities

From January to December in 2014, the Outpatients Treatment Center supported a total of 26,383 patients who received anticancer drug (Table 1), that means around 2,200 per month, or 105 per month. The breakdown by department was Breast and Medical Oncology (36.6%), Gasrointestinal Medical Oncology (22.8%), Hepatobiliary and Pancreatic Oncology (11.6%), Hematology (8.4%), Thoracic Oncology (6.9%), and other department (13.7%). General infusions, general intramuscular or subcutaneous injections, blood transfusions, bone marrow puncture, lumbar puncture, intraperitoneal or chest drainage, blood gas analyses were conducted in the Center.

## Conference

The case conference is held on Tuesday biweekly with the participation of multidisciplinary specialists, including medical oncologists, nurses, and pharmacists. The monthly staff meeting is held on the second Tuesday every month with the participation of physicians and nurses who are the main members in the Center. The steering committee is held on the third Thursday every month.

## Research activities

- Treatment of platinum containing regime in outpatient style.
- Efficacy of frozen globe against nail toxicities by docetaxel.
- Efficacy of frozen cap against alopecia by chemotherapy
- Protection of allergic reaction by Oxaliplatin in out-patients.
- Management of skin toxicities as adverse event of molecular-targeted drug.
- Cosmetic support for women cancer patients
- Support for continuing job and circumstance of working in outpatients.
- Telephone hotline for emergency for out-patients who receive chemotherapy.

## Education

We provide educational opportunities for multidisciplinary specialists, including medical oncologists, nurses, and pharmacists. We also provide an educational program to hospitals outside the National Cancer Center, for medical oncologists, nurses, pharmacists and MSW in the designed hospital for cancer treatment in the each prefecture.

## Future prospects

We continue to propose a near-future model of the more clinical trials in outpatient style (the Clinical Trial Center in outpatient style). We aim at

shortening of waiting time, smooth administration of novel molecular targeted drugs for outpatients, and putting into practice multidisciplinary care for cancer patients who received chemotherapy in the Outpatients Treatment Center. We plan to install the 2nd Outpatients Treatment Center adding chairs/beds from the current total of 36 to 62 at the beginning of 2015.



**Table 1. Cumulative total number of patients who received anticancer drug by intravenous administration**

| Department | Jan. | Feb. | Mar. | Apr. | May | Jun. | Jul. | Aug. | Sep. | Oct. | Nov. | Dec. | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Breast and Medical Oncology | 727 | 730 | 772 | 860 | 789 | 750 | 851 | 844 | 847 | 903 | 787 | 802 | 9,662 |
| Gasrointestinal Medical Oncology | 434 | 473 | 491 | 540 | 563 | 434 | 542 | 476 | 493 | 568 | 499 | 512 | 6,025 |
| Hepatobiliary and Pancreatic Oncology | 223 | 203 | 232 | 250 | 258 | 246 | 294 | 257 | 277 | 283 | 255 | 282 | 3,060 |
| Hematology | 168 | 190 | 173 | 200 | 184 | 162 | 218 | 170 | 190 | 200 | 167 | 185 | 2,207 |
| Thoracic Oncology | 169 | 153 | 159 | 144 | 139 | 105 | 160 | 158 | 138 | 170 | 140 | 182 | 1,817 |
| Others | 259 | 235 | 252 | 264 | 267 | 275 | 313 | 312 | 370 | 361 | 336 | 368 | 3,612 |
| Total | 1,980 | 1,984 | 2,079 | 2,258 | 2,200 | 1,972 | 2,378 | 2,217 | 2,315 | 2,485 | 2,184 | 2,331 | 2,6383 |

# Consultation, Counseling and Support Service Center

**Masashi Kato, Kayoko Miyata, Rieko Shimizu, Naoko Goto, Miho Koitabashi, Natsuko Moroi, Yasuko Arimoto, Mariko Tsuchiya, Megumi Osuga, Yukiko Higuchi, Haruhiko Saijo, Mayumi Miura, Yuko Itakura, Atsuko Kawami, Tomoko Asayama, Kim Hyeon Ok**

## Introduction

The staff members referred to as "Cancer Counseling and Support Specialists" work mainly at the Consultation, Counseling and Support Service Center of the National Cancer Center Hospital (NCCH). The staff copes 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 cancer patients, their families and ordinary citizens solve their psychosocial problems through various social work skills, social recourses and cancer information. Furthermore, we have begun to offer support for job seekers in closer coorperation

with a "Hello Work Navigator" and Social Insurance Labor Consultants. 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.

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 class for job seekers

In the hospital, we discuss the patients with the doctors and medical staff, and 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 a 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 Administration of the patient library

## Research activities

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

## Education

We lecture and act as facilitators in seminars for education of Cancer Counseling and Support Specialists.

**Table 1. Number of cases (January 2014 – December 2014)**

| | | |
|---|---|---|
| 1 | Total | 11,800 |
| 2 | New cases | 6,428 |
| | New cases from NCCH | 3,122 |
| | New cases from other hospitals | 3,306 |

## Future prospects

We practice high quality cancer counseling and support, develop models and spread the results for the whole county.

# Appearance Support Center

**Keiko Nozawa, Naoya Yamazaki, Chikako Shimizu, Masahide Fujiki, Shoko Toma, Kazuko Aoki, Atsuko Ito, and Eriko Takahashi**

## Introduction

The Appearance Support Center aims to support patients to be able to 'live in society' and to 'live as a human' through clinical research and educational practices regarding patients' physical appearance.

## Routine activities

Our team consists of two clinical psychologists (1 full-time and 1 part-time) specialized in cosmetics, and they consult both in- and out-patients as well as their families for questions and concerns regarding physical appearance. Examples of issues are side effects of chemotherapy and radiotherapy on skin, nails, and hair, scarring and epithesis from surgeries, and breast surgery. In order to expand our practice beyond solely consultation, we are currently developing a new team in collaboration with a dermatologist, plastic surgeon, medical oncologist, pharmacist, and nurses.

The outpatient space is open to the public from Monday to Thursday between 12 am and 1 pm during which patients can try on different products and consult staff. Despite limited hours for security reasons, we had 897 users from January to December. Additionally, we conduct a patient support program titled "Cosmetic Information" every Tuesday and Thursday from 2 pm. Its main aim is to provide information to patients through group sessions. We had 95 sessions in which 381 patients participated. Forty-nine men participated in "Men's Consultation Day" held on the fourth Wednesday of every month from 1 to 3 pm. In addition, we offered long-term inpatients a special program at the transplantation ward twice this year, and a total of 15 men and women participated. The program had a good reputation which will be held regularly (the third Wednesday of every odd month) next year.

As for individual consultations for new patients, there were a total of 1248 consultations offered to 253 in- and out- patients. Patients' main concerns were coping strategies with specific symptoms. Reasons for consultations also included seeking stress relief, concerns over significant life events such as the coming-of-age ceremony, weddings, and graduations, questions regarding mortuary makeup, and concerns from family members.

## Research activities

One of the main purposes of this Center is information collection and active research due to lack of evidence regarding physical appearance. Current research projects are: the multi-faceted examination of the efficacy of support programs regarding physical appearance, the establishment of guidelines for support of cancer patients' appearance problems, the investigation and the development of the appearance-care educational training system, and the development of assessments and care methods for dermatological changes due to cancer treatment. In addition to examine the current situations and the issues of information for cancer patient regarding physical appearance, we found out that the appearance-related support program enhances psychological well-being of cancer patients. We also conducted research with business corporations and made the product called "wig na bousi (a cap looks like a wig)" based on patients' needs.

## Education

In order to support medical staff to practice appearance-care, "The Educational Workshop Regarding Appearance Care for Cancer Patients"

was held three times in a year (210 participants) for medical staff working at designated regional cancer centers and hospitals. Additionally, we welcomed visitors of our hospital and held a special educational workshop to offer the same program conducted at Shikoku Cancer Center.

## Future prospects

We anticipate emergence of new issues regarding physical appearance as the variety in treatment drugs increase, longer-survival rates increase, cosmetic surgeries develop, and cosmetic products continue innovations. Although responding to all patient needs is difficult as fulltime workers are scarce, we hope to expand human resources and develop this emerging field based on research.

## Conferences

| | |
|---|---|
| Sponsor: | The Appearance Support Center (Center Hospital) |
| Conference title: | The Educational Workshop on Appearance Care of Cancer Patients for Medical Staff: Basic course |
| | November 24th - December 21st, 2014 |
| Location (prefecture): | Tokyo |
| Sponsor: | The Appearance Support Center (Center Hospital) |
| Conference title: | The Educational Workshop on Appearance Care of Cancer Patients for Medical Staff: Advanced course |
| Date: | Date: October 18th, 2014 |
| Location (prefecture): | Tokyo |

## List of papers published in 2014

### Journal


1. Boku N, Sugihara K, Kitagawa Y, Hatake K, Gemma A, Yamazaki N, Muro K, Hamaguchi T, Yoshino T, Yana I, Ueno H, Ohtsu A. Panitumumab in Japanese patients with unresectable colorectal cancer: a postmarketing surveillance study of 3085 patients. Jpn J Clin Oncol, 44:214-223, 2014
2. Namikawa K, Tsutsumida A, Tanaka R, Kato J, Yamazaki N. Limitation of indocyanine green fluorescence in identifying sentinel lymph node prior to skin incision in cutaneous melanoma. Int J Clin Oncol, 19:198-203, 2014

# Rare Cancer Center

**(NCCH) Akira Kawai, Hirokazu Chuuman, Eisuke Kobayashi, Yoshikazu Tanzawa, Seiichi Yoshimoto, Motokiyo Komiyama, Tomoyasu Kato, Makoto Kodaira, Mayu Yunokawa, Shunsuke Kondo, Chitose Ogawa, Miyuki Sone, Shunsuke Sugawara, Hiroshi Igaki, Kana Takahashi, Akihiko Yoshida, Takuro Sakurai, Yoshitaka Narita, Naoya Yamazaki, Arata Tsutsumida, Satoshi Takahashi, Shigenobu Suzuki, Yoshitaka Honma, Tadashi Kondo, Koichi Ichikawa, Naohiro Higashi, Makiko Murase, Yoko Kato,**
**(NCCHE) Fumihiko Nakatani, Naoto Gotohda, Toshihiko Doi, Yoichi Naito, Ako Hosono, Tetsuo Akimoto, Junya Ueno**

## Introduction

The Rare Cancer Center was launched in December 2013 and officially opened in June 2014 as a multidisciplinary team to take measures against the innate problems associated with rare cancers. In the past decades, major cancers such as gastric, breast and colorectal cancers have been a public health priority at the national and international level, but at the same time little attention has been paid to the issue of rare cancers. There is still no generally agreed definition of rare cancers in Japan. Rare diseases are often defined as those with a prevalence of < 50/100,000. According to the definition of Rare Cancers in Europe (RARECARE), rare cancers are those with an incidence < 6/100,000/year. Although each rare cancer is rare by itself, when the number of each rare cancer is combined, it corresponds to up to 15% of all new cancer diagnoses. Information on rare cancers is scarce. Rare cancers are often inadequately diagnosed and treated in relation both to lack of knowledge and clinical expertise. Patients with rare cancers face great difficulty in having their diseases treated adequately.

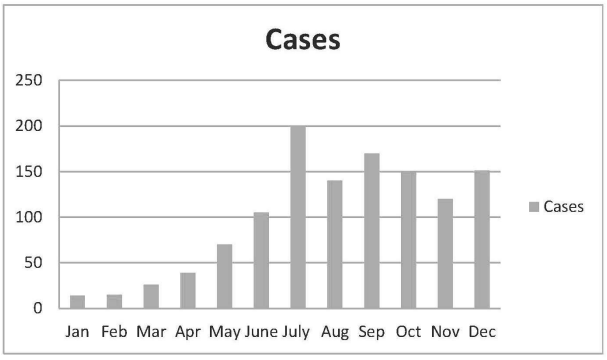


**Figure 1. The Number of telephone call to Rare Cancer Hotline in 2014**

## Routine activities

The Rare Cancer Center plays a central role in the treating and managing of rare cancers in National Cancer Center (NCC).

The mission statements of the Rare Cancer Center are as follows.

I. Establishing a vital network of diagnosis and treatment for rare cancers in the NCC Hospital and Hospital East.

II. Reviewing the problems associated with rare cancers in Japan and making proposals and taking up the issues as medical professionals.

To enable the Center to play its role, a total of 35 doctors, nurses and researchers dealing with rare cancers have joined as members of the Center. Each staff member of the Rare Cancer Center provides specialized, high-quality medical care to patients with rare cancers in cooperation with his/her Department staff.

The Rare Cancer Center provides consultation to the patients and relatives with rare cancers on the telephone (Rare Cancer Hotline). The number of telephone call was 1,200 cases in 2014 (Figure 1). The Center also provides comprehensive, scientifically based, up-to-date unbiased information about rare cancers to all patients, families and health professionals fighting against rare cancers via website (Rare Cancer Center Homepage).

## List of papers published in 2014

## Journal


1. Fukushima S, Narita Y, Yonezawa M, Ohno M, Arita H, Miyakita Y, Ichimura K, Yoshida A, Shibui S. Short communication: sclerosing meningioma in the deep sylvian fissure. Brain Tumor Pathol, 31:289-292, 2014
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3. Miyamoto S, Kayano S, Fujiki M, Chuman H, Kawai A, Sakuraba M. Early Mobilization after Free-flap Transfer to the Lower Extremities: Preferential Use of Flow-through Anastomosis. Plast Reconstr Surg Glob Open, 2:e127, 2014
4. Miyamoto S, Kayano S, Kamizono K, Fukunaga Y, Nakao J, Nakatani F, Kobayashi E, Sakuraba M. Pedicled superficial femoral artery perforator flaps for reconstruction of large groin defects. Microsurgery, 34:470-474, 2014
5. Trautmann M, Sievers E, Aretz S, Kindler D, Michels S, Friedrichs N, Renner M, Kirfel J, Steiner S, Huss S, Koch A, Penzel R, Larsson O, Kawai A, Tanaka S, Sonobe H, Waha A, Schirmacher P, Mechtersheimer G, Wardelmann E, Buttner R, Hartmann W. SS18-SSX fusion protein-induced Wnt/ β -catenin signaling is a therapeutic target in synovial sarcoma. Oncogene, 33:5006-5016, 2014
6. Nakamura T, Matsumine A, Uchida A, Kawai A, Nishida Y, Kunisada T, Araki N, Sugiura H, Tomita M, Yokouchi M, Ueda T, Sudo A. Clinical outcomes of Kyocera Modular Limb Salvage system after resection of bone sarcoma of the distal part of the femur: the Japanese Musculoskeletal Oncology Group study. Int Orthop, 38:825-830, 2014
7. Yoneda Y, Kunisada T, Naka N, Nishida Y, Kawai A, Morii T, Takeda K, Hasei J, Yamakawa Y, Ozaki T. Favorable outcome after complete resection in elderly soft tissue sarcoma patients: Japanese Musculoskeletal Oncology Group study. Eur J Surg Oncol, 40:49-54, 2014
8. Iwata S, Ishii T, Kawai A, Hiruma T, Yonemoto T, Kamoda H, Asano N, Takeyama M. Prognostic factors in elderly osteosarcoma patients: a multi-institutional retrospective study of 86 cases. Ann Surg Oncol, 21:263-268, 2014
9. Asano N, Yoshida A, Kobayashi E, Yamaguchi T, Kawai A. Multiple metastases from histologically benign intraarticular diffuse-type tenosynovial giant cell tumor: a case report. Hum Pathol, 45:2355-2358, 2014
10. Fujiwara T, Katsuda T, Hagiwara K, Kosaka N, Yoshioka Y, Takahashi RU, Takeshita F, Kubota D, Kondo T, Ichikawa H, Yoshida A, Kobayashi E, Kawai A, Ozaki T, Ochiya T. Clinical relevance and therapeutic significance of microRNA-133a expression profiles and functions in malignant osteosarcoma-initiating cells. Stem Cells, 32:959-973, 2014
11. Kubota D, Yoshida A, Kawai A, Kondo T. Proteomics identified overexpression of SET oncogene product and possible therapeutic utility of protein phosphatase 2A in alveolar soft part sarcoma. J Proteome Res, 13:2250-2261, 2014
12. Setsu N, Yoshida A, Takahashi F, Chuman H, Kushima R. Histological analysis suggests an invasion-independent metastatic mechanism in alveolar soft part sarcoma. Hum Pathol, 45:137-142, 2014
13. Totoki Y, Yoshida A, Hosoda F, Nakamura H, Hama N, Ogura K, Yoshida A, Fujiwara T, Arai Y, Toguchida J, Tsuda H, Miyano S, Kawai A, Shibata T. Unique mutation portraits and frequent COL2A1 gene alteration in chondrosarcoma. Genome Res, 24:1411-1420, 2014
14. Ueda T, Kakunaga S, Ando M, Yonemori K, Sugiura H, Yamada K, Kawai A. Phase I and pharmacokinetic study of trabectedin, a DNA minor groove binder, administered as a 24-h continuous infusion in Japanese patients with soft tissue sarcoma. Invest New Drugs, 32:691-699, 2014
15. Blay J-Y, Sleijfer S, Schoffski P, Kawai A, Brodowicz T, Demetri GD, Maki RG. International expert opinion on patient-tailored management of soft tissue sarcomas. Eur J Cancer, 50:679-689, 2014
16. Ogura K, Miyamoto S, Sakuraba M, Chuman H, Fujiwara T, Kawai A. Immediate softtissue reconstruction using a rectus abdominis myocutaneous flap following wide resection of malignant bone tumours of the pelvis. Bone Joint J, 96-B:270-273, 2014
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23. Kobayashi E, Satow R, Ono M, Masuda M, Honda K, Sakuma T, Kawai A, Morioka H, Toyama Y, Yamada T. MicroRNA expression and functional profiles of osteosarcoma. Oncology, 86:94-103, 2014
24. Odagiri H, Kadomatsu T, Endo M, Masuda T, Morioka MS, Fukuhara S, Miyamoto T, Kobayashi E, Miyata K, Aoi J, Horiguchi H, Nishimura N, Terada K, Yakushiji T, Manabe I, Mochizuki N, Mizuta H, Oike Y. The secreted protein ANGPTL2 promotes metastasis of osteosarcoma cells through integrin $\alpha^5\beta^1$, p38 MAPK, and matrix metalloproteinases. Sci Signal, 7:ra7, 2014

# 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.

## Routine activities

During 2014, the Surgical Center supported 4,708 surgical cases and 4,208 general anesthesia surgical cases, a 0.3% increase in the general anesthesia cases over 2013. Sentinel node navigation surgery in breast cancer, autonomic nerve preservation proximal gastrectomy with jejunal interposition in early gastric cancer, hepatectomy and pancreatectomy in patients with hepato-biliary and pancreas diseases, and placement of an artificial urinary sphincter for bladder incontinence after prostate cancer treatment are unique treatments in our institution, and 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 and are carried out in the Surgical Center.

Da Vinci robotic surgical system has been introduced to provide less invasive surgery to the patients for not only prostate cancer but also rectal cancer.

Post-anesthesia care unit has been a part of the Surgical Center during this year.

The multidisciplinary meeting has started in 2014. The multidisciplinary team includes medical doctors, nurses, and ME meets to plan the best surgical pathway during operation.

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 16 operating suites were evaluated to establish an optimal work flow, streamline room turnover, and improve start times.

Medical device nurse, who is engaged in equipment usage, has been assigned.

## Education and Training

All surgical oncology groups have their own training programs for their fellows with the support of the Surgical Center staff. Our center also provides virtual reality simulators to allow fellows to develop the skills used in laparoscopic and thoracoscopic surgery. About 50 foreign doctors have visited our surgical center.

**Table 1. Total number of operations**

| | Jan. | Feb. | March | Apr. | May | June | July | Aug. | Sep. | Oct. | Nov. | Dec. | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Anesthesia | | | | | | | | | | | | | |
| General | 123 | 145 | 142 | 147 | 142 | 162 | 165 | 154 | 126 | 171 | 155 | 136 | 1,768 |
| General and epidural | 202 | 193 | 188 | 210 | 207 | 199 | 205 | 200 | 206 | 226 | 193 | 199 | 2,428 |
| Epidural and lumbar | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Epidural and lumbar | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Lumbar | 1 | 3 | 9 | 12 | 6 | 3 | 7 | 4 | 0 | 1 | 9 | 5 | 60 |
| Local | 32 | 44 | 43 | 48 | 55 | 31 | 45 | 34 | 39 | 43 | 37 | 41 | 492 |
| Others | 8 | 8 | 7 | 5 | 7 | 7 | 10 | 7 | 6 | 7 | 8 | 4 | 84 |
| Total | 366 | 393 | 389 | 423 | 417 | 402 | 433 | 399 | 377 | 448 | 402 | 386 | 4,835 |

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

| | Jan. | Feb. | March | Apr. | May | June | July | Aug. | Sep. | Oct. | Nov. | Dec. | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Neurosurgery | 6 | 7 | 12 | 13 | 10 | 12 | 9 | 13 | 9 | 12 | 9 | 11 | 123 |
| Opthalmology | 23 | 24 | 25 | 20 | 25 | 28 | 25 | 24 | 25 | 29 | 22 | 29 | 299 |
| Head & Neck Surgery | 9 | 16 | 20 | 18 | 19 | 20 | 24 | 20 | 20 | 21 | 23 | 24 | 234 |
| Breast Surgery | 39 | 37 | 36 | 43 | 40 | 45 | 41 | 40 | 38 | 45 | 37 | 46 | 487 |
| Thoracic Surgery | 46 | 49 | 51 | 51 | 46 | 57 | 56 | 59 | 52 | 63 | 55 | 65 | 650 |
| Esophageal Surgery | 8 | 10 | 11 | 10 | 12 | 13 | 14 | 12 | 9 | 12 | 14 | 9 | 134 |
| Gastric Surgery | 36 | 42 | 34 | 39 | 32 | 33 | 38 | 34 | 37 | 36 | 41 | 36 | 438 |
| Colorectal Surgery | 34 | 37 | 44 | 39 | 38 | 52 | 45 | 43 | 42 | 44 | 34 | 45 | 497 |
| Hepatobiliary & Pancreatic Surgery | 22 | 19 | 23 | 25 | 19 | 26 | 28 | 29 | 24 | 30 | 19 | 29 | 293 |
| Gynecology | 17 | 18 | 16 | 13 | 18 | 19 | 23 | 19 | 17 | 21 | 16 | 20 | 217 |
| Urology | 20 | 22 | 23 | 23 | 25 | 23 | 26 | 23 | 23 | 33 | 26 | 18 | 285 |
| Dermatology | 8 | 4 | 8 | 11 | 9 | 11 | 13 | 10 | 8 | 9 | 7 | 11 | 109 |
| Orthopedic Surgery | 16 | 25 | 23 | 26 | 14 | 22 | 24 | 19 | 23 | 29 | 21 | 25 | 267 |
| Plastic and Reconstructive surgery | 9 | 10 | 10 | 4 | 3 | 4 | 3 | 7 | 5 | 8 | 8 | 12 | 83 |
| Endoscopy | 2 | 0 | 2 | 0 | 3 | 2 | 0 | 0 | 3 | 1 | 1 | 1 | 15 |
| Radiation oncology | 2 | 3 | 2 | 2 | 2 | 8 | 5 | 4 | 4 | 2 | 2 | 5 | 41 |
| Transplantation | 1 | 2 | 1 | 1 | 2 | 4 | 1 | 3 | 3 | 3 | 3 | 3 | 27 |
| Pediatric Surgery | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 2 | 0 | 1 | 1 | 9 |
| Total | 299 | 326 | 342 | 339 | 317 | 379 | 375 | 360 | 344 | 398 | 339 | 390 | 4,208 |

# Physician Referral Service Office

**Hidehito Horinouchi, Makiko Murase, Maya Ozawa, Yukiko Higuchi, Hisako Tanaka, Keiko Tsutsumi, Kayoko Yamada**

## Introduction

The Physician Referral Service Office was established as an independent section directly under the director of hospital. The mission of the Office is to provide appropriate access to the best cancer practice for more patients and their physicians. To help cancer patients with various needs to visit the National Cancer Center Hospital, the Physician Referral Service Office consists of a physician, a nurse, a medical social worker and 3 clerks. The Office also correspond inquiries for patients' medical records from their physician. Other important activity is to record and analyze the information concerning patients' referral to the National Cancer Center Hospital.

## Routine activities

1. Physician referral service

Under strong collaboration with the reservation center, the Office support patients and their physicians to select proper doctor promptly.

2. Inquiry for patients' medical record

We receive and correspond inquiries of medical records from physicians who see patients of our hospital.

3. Relationship with affiliated hospitals and clinics

We send reminder to patients' physician at the timing of patients' first visit to our hospital. To maintain relationship, we hold regular meetings and invite physicians from affiliated hospitals and clinics.

4. Record and analysis of clinical information

The information of all patients and their physicians is appropriately recorded in order to analyze and apply for next strategies for a better service.

5. Corporation with intramural departments and staff members

To provide best practice, we make great effort to collaborate with intramural departments, sections and staff members.

**Table 1. Total number of operations**

| | "Referral reply letters" | "Medical record inquiries" | "FAX Service" | "Reservation support" |
|---|---|---|---|---|
| January | 662 | 65 | 23 | 21 |
| February | 634 | 42 | 30 | 17 |
| March | 700 | 81 | 36 | 26 |
| April | 692 | 70 | 41 | 15 |
| May | 593 | 60 | 39 | 16 |
| June | 717 | 83 | 26 | 21 |
| July | 826 | 72 | 29 | 24 |
| August | 766 | 75 | 40 | 20 |
| September | 847 | 89 | 36 | 30 |
| October | 903 | 101 | 49 | 23 |
| November | 772 | 98 | 47 | 23 |
| December | 772 | 87 | 37 | 23 |
| Total | 8,884 | 923 | 433 | 259 |

# Clinical Trial Coordination (& Support) Office

**Noboru Yamamoto**

## 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 ("*Ishishudou-chiken*") and other clinical research studies (investigator-initiated trials). This Office consists of 2 Divisions (Clinical Research Coordinating Division and Administrating Division). The staff members, nurses, pharmacists and laboratory technologists, participate in these Divisions 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 27 CRCs (clinical research coordinators) are supporting these trials. The number of the industry-sponsored registration trials is increasing year by year, and we supported 269 registration-directed clinical trials including 17 physician-initiated registration directed clinical trials in 2014 (Table 1). 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. Supported Trials in Clinical Trial Coordination (& Support) Office in 2014**

| Phase | Ongoing | New (since 2013) | Total |
|---|---|---|---|
| I | 55 | 28 | 83 |
| I/II | 17 | 3 | 20 |
| II | 32 | 20 | 52 |
| II/III | 1 | 0 | 1 |
| III | 65 | 22 | 87 |
| POS | 5 | 1 | 6 |
| Medical device | 2 | 1 | 3 |
| In-vitro diagnostics | 0 | 0 | 0 |
| IITs | 12 | 5 | 17 |
| Total | 189 | 80 | 269 |

POS: post marketing study
IITs: physician-initiated registration directed clinical trials

# Nutrition Management Office

**Mayumi Miyauchi, Tomoko Suzuki, Hiroko Abe, Hiroko Takashima, Yasuko Muramatsu, Noriko Aoki, Moe Nishio, Maki Miura, Satoru Suzuki, Masato Fujii, Yasushi Ogaki, Nobuyuki Hirose, Masahiro Kikuchi, Kenichi Koshikawa, Takeshi Fujioka**

## Introduction

We aim to provide a highest quality food service for patients who are suffering from cancer, and therefore we have made efforts to prepare many kinds of meals appropriate for individual patients with allergic diseases. In addition, we strive to use seasonal menus, and meals for special occasions, as well as choice of special meals as an alternative to regular meals for pediatrics patients.

In the "taste-disorder restitution as an exploitation of a supportive treatment" research projects, in order to perform nutrition management which corresponds to the patient suffering from side effects and create an assessment sheet, Japan Society of Metabolism and Clinical Nutrition released this result.

Even a rookie dietitian, is able to offer adequate nutritional management in accordance with various status of the patients by using this sheet.

## Routine activities

The therapeutic diet, which is provided as part of nutritional therapy, was 429,912 meals. We also provided 1,379 dietary consultations. Nutrition Support Team (NST) accepted 931 patients; the average number of consultations was 78 cases per month.

In the Grant-in-Aid for carcinoma set up by Foundation for Promotion of Cancer Research, the survey on understanding of complementary and alternative medicine in cancer care by a hospital dietitian was conducted and the result was reported in the Cancer Patients Nutritional Management Study Group, the Japan Society of Metabolism and Clinical Nutrition, and the Carcinoma Patient Nutrition Management Society. We participated in the symposium voluntary as a lecturer and provided cancer survivorship support. The Research Department providing meal support to cancer patients was subjected to enlighten a regional movement.

In the field of education, we actively accept university students for training. We also put effort into cultivating human resources for registered dietitians.

## Research activities

1) The Nutritional Management Workshop for cancer patient has reached its 33rd anniversary, and “Nutrition past, present and future” was delivered as the president’s lecture in Yokohama.
2) Through the meal courses and cancer nutritional management courses being carried out at universities where cancer prevention is taught, cooperation with universities has been enhanced.
3) Research enterprise
   1. The factual survey of a taste disorder
   2. Studies on nutrition in surgical treatment of esophageal cancer.
   3. Prospective nutritional assessment after pancreaticoduodenectomy.

# 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. As the importance of providing drug information for patients has been widely acknowledged, clinical pharmacists visit inpatients and give advice on taking medicine, focusing especially on pain control with opioids, and participate in the palliative-care support team, while the Pharmacy provides outpatients with guidance in the proper use of opioids and anti-cancer agents. The Pharmacy also places pharmacists in every hospital ward to provide the medication reconciliation service for inpatients, with a view to enhance the quality of chemotherapy as well as to ease the burden of doctors and nurses.

Pharmacists collect, compile, and maintain a database of drug information and distribute pertinent information to the medical staff. Drug information is disseminated quickly throughout the hospital by paper distribution and/or on the in-hospital computer network. Pharmacists individualize dosage regimens for specified drugs such as tacrolimus, aminoglycosides, and vancomycin based on both measured blood concentrations and pharmacokinetic analysis to maximize their efficacy and minimize adverse events.

A physician places an order through the hospital's computerized electric medical record system. The prescription order is then redirected to the medicine-package-printing system 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.

**Table 1. Number of Prescriptions in 2014**

| | |
|---|---|
| 1) Oral and topical preparations | |
| Prepared in the hospital pharmacy | 142,675 |
| Inpatients | 132,559 |
| Outpatients | 10,116 |
| Taken to outside pharmacies | 74,744 |
| (% of prescription filled outside) | 88.1 |
| 2) Injections | |
| Inpatients | 352,391 |
| Outpatients | 39,575 |

**Table 2. Amounts of Drugs Consumed in 2014**

| | (including sales tax) | (%) |
|---|---|---|
| Total | 5,247,217 | 100.0 |
| Internal medicines | 408,944 | 7.8 |
| External | 47,385 | 0.9 |
| Injection | 3,823,835 | 72.9 |
| Narcotics | 124,007 | 2.4 |
| Blood | 494,016 | 9.4 |
| X-ray imaging | 218,276 | 4.2 |
| RI | 74,605 | 1.4 |
| Others | 56,149 | 1.0 |

Unit:1,000 yen

## Education and Training

The National Cancer Center Hospital offers a three-year postgraduate pharmacy residency training 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 will refine his/her clinical problem-solving skills in cancer management and patient education, as well as provide pharmaceutical care to ambulatory care patients and participate in an oncology-focused drug information program. In the third year, residents participate in specialized pharmaco-clinical practice and research activities, which may be tailored to the resident's goals. The hospital also provides a two-year chief residency program in which post-residency trainees may develop their clinical research capabilities to a higher level. Moreover, there are opportunities for educational activities, such as a training course for visiting expert pharmacists and post-graduate students of pharmacy, and participation in a multi-institutional TV conference.

**Table 3. Aseptic Preparation of Injectable Drugs in 2014**

| | |
|---|---|
| Anticancer Drugs | 58,632 |
| Others | 34,352 |

**Table 4. House Preparations in 2014**

| | |
|---|---|
| Sterilized | 67 |
| Non-sterilized | 119 |

**Table 5. Investigational Drugs**

| | |
|---|---|
| Newly registered | 71 |
| Ongoing study | 152 |
| Total | 223 |

## List of papers published in 2014

### Journal


1. Terazawa T, Nishitani H, Kato K, Hashimoto H, Akiyoshi K, Iwasa S, Nakajima TE, Hamaguchi T, Yamada Y, Shimada Y. The feasibility of a short bevacizumab infusion in patients with metastatic colorectal cancer. Anticancer Res, 34:1053-1056, 2014

2. Kiba T, Ito T, Nakashima T, Okikawa Y, Kido M, Kimura A, Kameda K, Miyamae F, Tanaka S, Atsumi M, Sumitani Y, Shitakubo Y, Niimi H. Bortezomib and dexamethasone for multiple myeloma: higher AST and LDH levels associated with a worse prognosis on overall survival. BMC Cancer, 14:462, 2014

# Department of Nursing

**Kazuko Nasu**

## Introduction

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

## Routine activities

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

We adopted the two-shift nursing system in 13 units, comprising an 8-hour day shift and a 16-hour night shift. Inpatient unit nurses work together more as closely than nurses in an outpatient clinic. Moreover, we have strengthened the support for the patient discharge process so that patients can return earlier to their own home or area.

We are accepting and meeting the challenge to provide many patient education programs produced by Certified Nurse Specialists and Certified Nurses. We have 5 patient education programs and consultation services, 3 outpatient clinics by nurses, and a support program for patients and their families. Many patients and families have participated in the educational program for their self-care and survivorship in their daily life.

## Research activities

We presented 20 studies on nursing at some annual conferences in 2014. 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 with 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.

## Education

1. Assist and support new nurses

We have worked to reduce the gap between the technical skill level of new nurses and the clinical nursing required for actual cancer care by carrying out practical nursing training. During the first month, we 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 an adverse a favorable work-related stress-free environment.

2. Development of knowledge and skills for cancer nursing

To develop the skills associated with of cancer nursing, the Department of Nursing is enhancing a system that can bring out individual expertise and an educational system to improve the careers of nurses. In particular, the interaction between a large-group training and a small-group training was increased to implement the knowledge and techniques acquired from years of continuing education, which resulted in improved patient care.

We have 11 specialized nurse training courses: Cancer chemotherapy nursing I and II; Clinical trial nursing; Palliative care nursing I and II; Lymphedema care; Wound and skin care; Dysphagia nursing; Radiotherapy and IVR nursing; Support for discharge and home care coordination nursing and nursing research. A total of 215 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, 10 certified nurse specialists and 34 certified nurses are working at the NCCH. 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, and respiratory support, these Certified Nurses contribute to effective cooperation. The identification of problems and discussions from the point of view of multidisciplinary teams serve as a good model for other nurses and provide an important educational role in the clinical setting.

Certified Nurse Specialists contribute to the education and coordination for ethical issues in the clinical setting. They support and empower not only patients and families, but also nursing staff.

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

## List of papers published in 2014

### Journal

1. Hiramatsu T, Sugiyama M, Kuwabara S, Tachimori Y, Nishioka M. Effectiveness of an outpatient preoperative care bundle in preventing postoperative pneumonia among esophageal cancer patients. Am J Infect Control, 42:385-388, 2014

# Hospital East

# Preface

Five years have passed since the National Cancer Center (NCC) was turned into an independent administrative institution, and this is the last year of the midterm plan. At the same year, the new vision of "Nobel Challenge and Changes" was indicated and, in the next year, the NCC shifts to a new research organization and a new medium term plan is launched.

In the East Hospital (NCCHE), the multidisciplinary supportive care center was founded in April 2014, and a new outpatient clinic has opened in August for an unexpectedly increased number of ambulant patients. Rehabilitation for cancer patients in the NCCHE has been greatly improved by opening of the rehabilitation center in the 9$^{th}$ floor and by regional cooperative alliances. To increase amenities for patients and families, the ambulant treatment ward has been expanded and ameliorated by the end of the year and private hospital rooms are renovated. With self-improvement and renovation of the Hospital where more than 20 years have passed since its establishment, we continuously provide cancer patients with high quality, specialized and advanced medicine with significant security and safety.

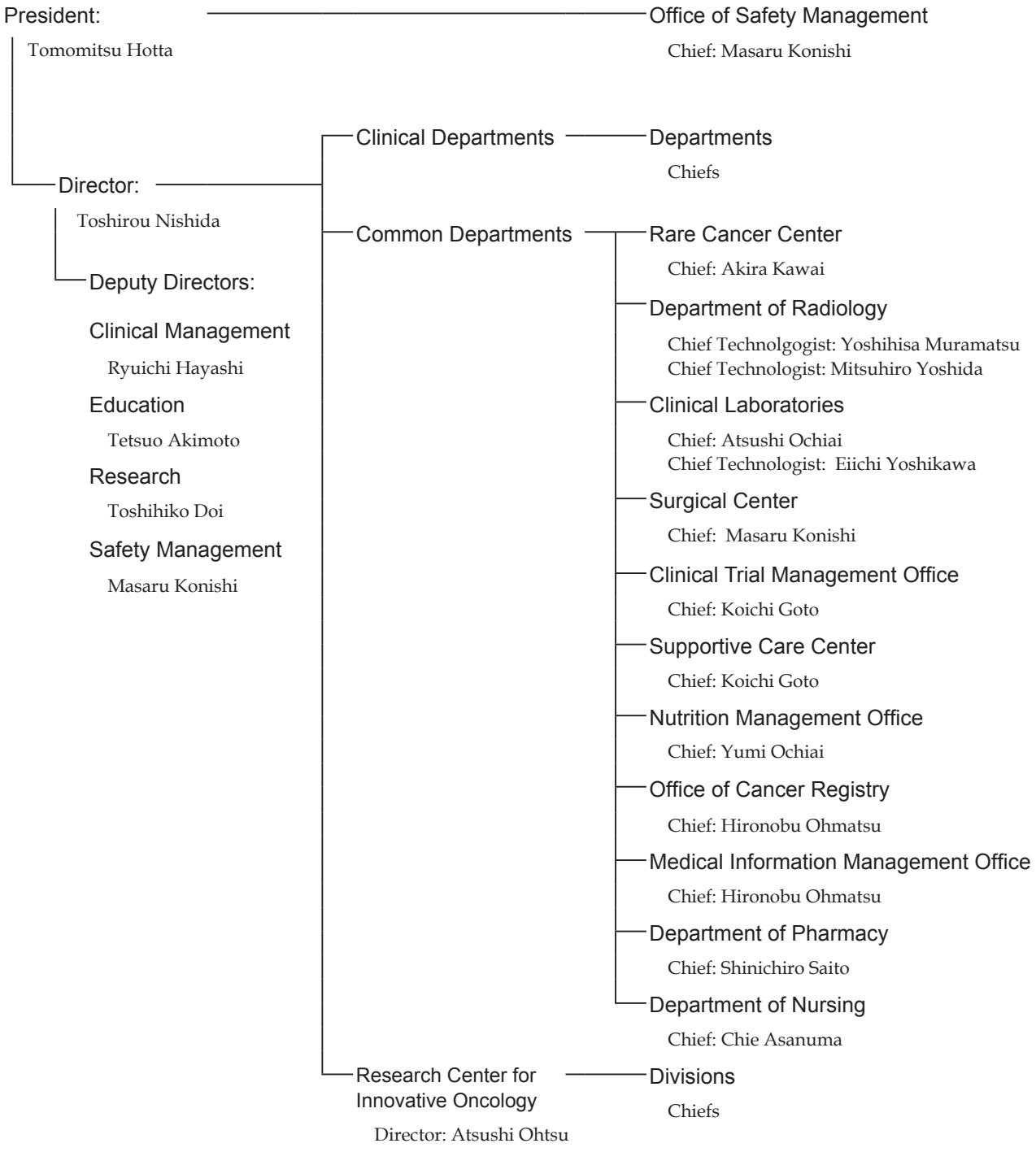
After increasing in the number of cancer patients visiting the NCCHE, there are significant limitations in hospital facilities, especially, of endoscopic examination and treatment as well as operating rooms. We have drawn the exciting and realistic future plan of the Kashiwa campus and, based on the plan, we have launched the project of NEXT (Institute of New Surgical and Endoscopic Development for Exploratory Technology), where we are planning a brand new surgical unit, intensive care unit (ICU) and an endoscopic ward based on ideas of future surgery and endoscopy. We also plan to set up the research laboratory for development of medical equipment and an educational center for minimally invasive surgery (MIS) in the NEXT.

In 2014, the NCCHE has been accredited by the Japan Council for Quality Health Care (JCQHC version 1.0) and also by the International Organization for Standardization (ISO15189, 2012). We have applied for the Advanced Treatment Hospitals in specific divisions and are going to apply for the Core Clinical Research Center. We have contended with improvement in hospital activity and business management for sustainable development in medical and research activities.

Lastly, we, the NCC, are re-organizing to maximize research outcomes, and the research center for innovative oncology is going to be incorporated into the Exploratory Oncology Research and Clinical Trial Center" (NCC-EPOC). In the Kashiwa campus, the NCCHE and EPOC are mutually collaborating in the clinical and translational research. We wish to make a significant and immense progress in health care research and development.

Toshirou Nishida, M.D., Ph.D.
Director, National Cancer Center Hospital East

## Organization



## Clinical Departments

Director:
Toshirou Nishida

Deputy Directors:

Clinical Management
Ryuichi Hayashi

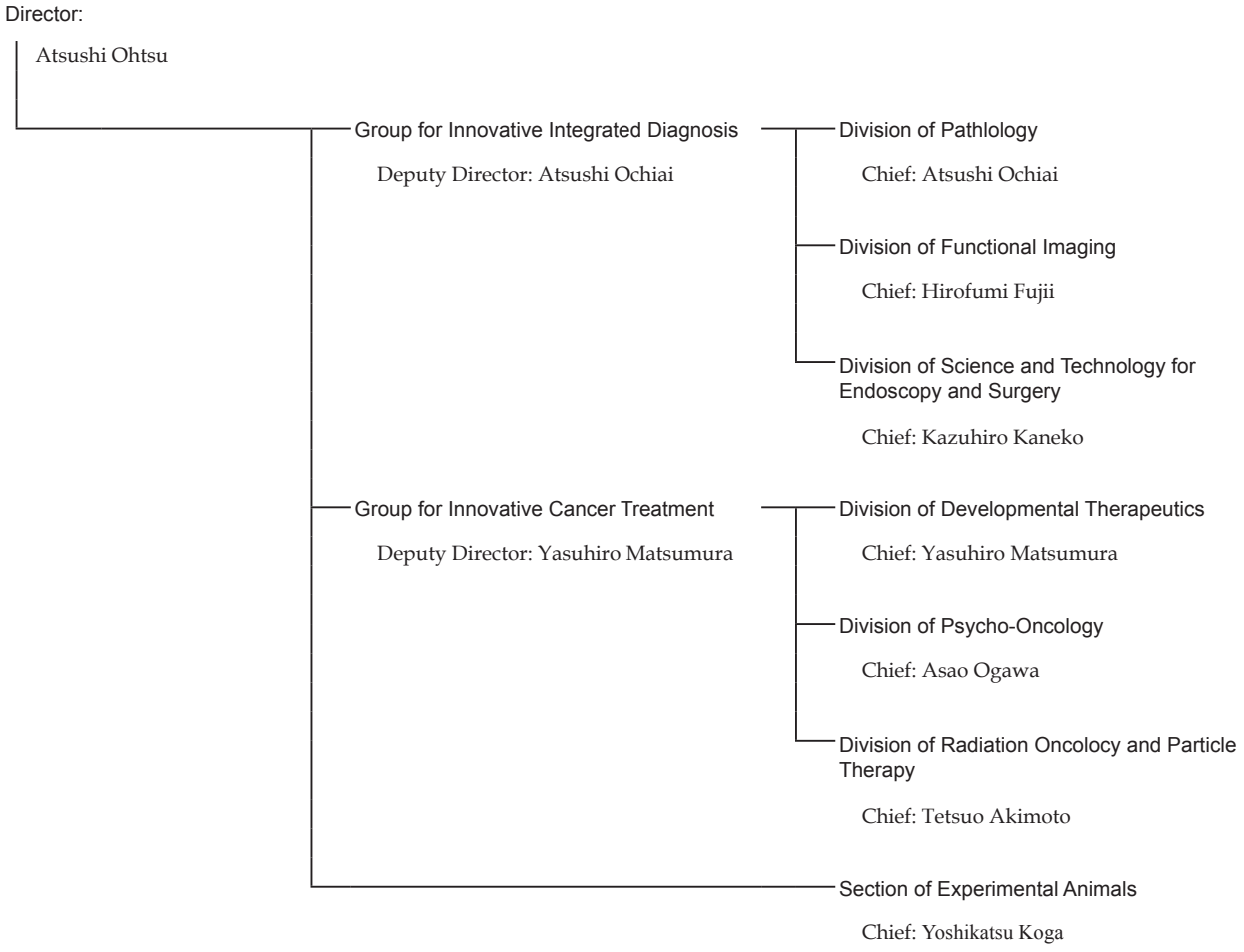
Education
Tetsuo Akimoto

Education
Toshihiko Doi

Safety Management
Masaru Konishi

- Department of Head and Neck Surgery
  Chief: Ryuichi Hayashi
- Department of Head and Neck Medical Oncology
  Chief: Makoto Tahara
- Department of Plastic and Reconstructive Surgery
  Chief: Minoru Sakuraba
- Department of Breast Surgery
  Chief: Noriaki Wada
- Department of Breast and Medical Oncology
  Chief: Tetsuo Akimoto
- Department of Thoracic Surgery
  Chief: Masahiro Tsuboi
- Department of Thoracic Oncology
  Chief: Koichi Goto
- Department of Esophageal Surgery
  Chief: Hiroyuki Daiko
- Department of Gastric Surgery
  Chief: Takahiro Kinoshita
- Department of Colorectal Surgery
  Chief: Norio Saito
- Department of Gastrointestinal Oncology
  Chief: Takayuki Yoshino
- Department of Digestive Endoscopy
  Chief: Kazuhiro Kaneko
- Department of Hepatobiliary and Pancreatic Surgery
  Chief: Masaru Konishi
- Department of Hepatobiliary and Pancreatic Oncology
  Chief: Masafumi Ikeda
- Department of Urology
  Chief: Norio Saito
- Department of Gynecology
  Chief: Ryuichi Hayashi
- Department of Musculoskeletal Oncology and Rehabilitation
  Chief: Ryuichi Hayashi
- Department of Hematology
  Chief: Kunihiro Tsukasaki
- Departments of General Internal Medicine, Dentistry, Cardiovascular Medicine, Pediatric Oncology
  Chief: Ryuichi Hayashi
- Department of Anesthesiology and Intensive Care Unit
  Chief: Vacant
- Department of Palliative Medicine
  Chief: Hiroya Kinoshita
- Department of Psycho-Oncology Service
  Chief: Asao Ogawa
- Department of Diagnostic Radiology
  Chief: Masahiko Kusumoto
- Department of Radiation Oncology
  Chief: Tetsuo Akimoto
- Department of Pathology and Clinical Laboratories
  Chief: Atsushi Ochiai

## Research Center for Innovative Oncology



# Activities of the Departments

# Department of Head and Neck Surgery

**Ryuichi Hayashi, Masakazu Miyazaki, Takeshi Shinozaki, Toshifumi Tomioka, Takashi Maruo, Hideaki Nishi, Takashi Mukaigawa, Kazuki Hashimoto**

## Introduction

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

## Routine activities

The current treatment policy for head and neck cancer is multimodal therapy. To effectively implement available therapeutic modalities, 5 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. The number of new cases who were treated in the hospital was 567 and the number operation was 472 cases. 111 cases of all underwent free flap reconstruction.

## Research activities

1. Gastrostomy Dependence in Head and Neck Carcinoma Patient Receiving Post-operative Therapy

Post-operative concurrent chemoradiotherapy significantly improves the rates of locoregional control and disease-free survival in high-risk patients but has significant adverse effects. Percutaneous endoscopic gastrostomy and opioid-based pain control increase treatment completion rates but can result in dysphagia. Prolonged percutaneous endoscopic gastrostomy use is not required in patients receiving post-operative chemoradiotherapy and will not lead to dysphagia.

## Clinical trials

1. Multicenter study to establish the indication of neck dissection for head and neck squamous cell carcinoma.

A prospective observation study is conducting and 199 cases have been enrolled to this study from 9 hospitals. Neck dissection at Level IIb and V areas influence the rate of postoperative accessory nerve palsy but the necessity of dissection of these areas is still controversial because of the low prevalence rate of lymph node metastasis. A randomized clinical trial will be run after evaluating the results of this study.

2. Evaluation of swallowing function related to the treatment for head and neck cancer

This prospective observation study is conducted to evaluate the swallowing function after treatment for oropharyngeal cancer. This study is related to standardizing the assessment of the swallowing function.

## Education

Two senior residents were recruited to our department in 2014. One head and neck surgeon from Sri Lanka visited to our department for his training. Our Division was assigned as one of observation centers of IFHNOS fellowship program from 2014.

## Future prospects

Transoral resection by using an endoscope will be one of the most important surgical procedures for pharyngeal cancer. We are going to get authorizations of insurance about endoscopic resection and planning to develop new surgical equipment in these operations.



**Table 1. Number of patients**

| | |
|---|---|
| Oral cavity | 133 |
| Nasopharynx | 23 |
| Oropharynx | 82 |
| Hypopharynx | 109 |
| Cervical esophagus | 28 |
| Larynx | 61 |
| Sino-nasal cavity | 45 |
| Thyroid gland | 40 |
| Major salivary glands | 28 |
| Cancer primary unknown | 13 |
| Others | 5 |
| Total | 567 |

**Table 2. Type of surgical procedures**

| | |
|---|---|
| General anesthesia | |
| Glossectomy | 50 |
| Resection of oral cancer (except for tongue ca.) | 71 |
| Nasopharyngectomy | 1 |
| Oropharyngectomy | 19 |
| Hypopharyngectomy | 44 |
| Cervical esophagectomy | 4 |
| Laryngectomy | 23 |
| Resection of the nasal cavity and/or paranasal sinuses | 12 |
| Resection of major salivary gland | 23 |
| Thyroidectomy | 42 |
| Parathyroidectomy | 3 |
| Endoscopic resection | 44 |
| Neck dissection | 56 |
| Others | 11 |
| Local Anesthesia | 69 |
| Total | 472 |

## List of papers published in 2014

### Journal

1. Shinozaki T, Hayashi R, Miyazaki M, Tomioka T, Zenda S, Tahara M, Akimoto T. Gastrostomy dependence in head and neck carcinoma patient receiving post-operative therapy. Jpn J Clin Oncol, 44:1058-1062, 2014

# Department of Head and Neck Medical Oncology

**Makoto Tahara, Tomoko Yamazaki, Tetsuro Wakasugi, Tomohiro Enokida**

## Introduction

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

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

## Routine activities

Our Department consists of 2 physicians, 1 senior resident and 1 resident. We manage the treatment of HNC patients who receive anticancer drug. An estimated 60% of HNC patients require a multidisciplinary approach, including surgery, radiotherapy, and chemotherapy. Furthermore, HNC patients are at risk of injury and impairment of vital organs both from the cancer itself and from the series of treatments provided to cure it. In treating patients, we therefore carefully assess both the curability of the condition and possible subsequent complications, such as swallowing dysfunction and cosmetic changes. Given the increasing complexity of the management of HNC, recommended treatment for patients who are referred to our institution is decided at weekly tumor board attended by a multidisciplinary team.

A total of 263 patients were referred to our department from Jan 2014 to Dec 2014 (Table 1). The outpatient service of our department is available from Monday to Friday. We carefully follow patients during and after treatment and provide palliative chemotherapy as an outpatient service.

## Research activities

Our research activity has focused on 2 areas, the development of new treatments in clinical trials for HNC and biomarker analysis in HNC.

1) Development of new treatments

Based on the results of our previously reported feasibility study (Kiyota N, Tahara M, et. al, 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 (SCCHN) (JCOG 1008) is now ongoing.

After the approval of cetuximab for HNC in Japan, the following multicenter clinical trials that we planned as primary investigator are ongoing: 1) CSPOR-HN01: The Phase II study of docetaxel, cisplatin and cetuximab (TPE) followed by cetuximab with concurrent radiotherapy in patients with local advanced SCCHN, 2) CSPOR-HN02: Phase II trial of combination with paclitaxel, carboplatin and cetuximab (PCE) as a first line treatment in patients with recurrent and/or metastatic SCCHN.

2) Biomarker analysis

An analysis of gene expression profiles in HNC is being carried out to determine the biomarker that can predict treatment outcomes. We then identified 27 genes with the most predictive value for recurrence, 5 genes highly expressed in the low-risk group and 22 highly expressed in the high-risk group. Clustering into high- and low-risk groups based on this 27-gene expression in a validation study also showed a significant association with recurrence. A prospective study to compare the miRNA expression patterns before and after completion of surgery in head and neck

cancer patients revealed that a total of 31 miRNAs was extremely changed.

## Clinical trials

A feasibility study of combination with docetaxel, cisplatin and 5-FU (TPF) as an induction chemotherapy (IC) for locally advanced SCCHN has been completed. A total of 48 patients accrued. 41 patients (85.4%) received the full course of IC and 33 patients (82.5%) received the planned CRT. To evaluate the feasibility of combination with paclitaxel, carboplatin and cetuximab (PCE) as IC, a feasibility study for unresectable locally advanced SCCHN is now ongoing.

To facilitate the timely approval of new drugs and eliminate the drug lag, we have also participated in the global phase trials. Our institution was ranked number one in the world for patient enrollment of SELECT study that is a randomized Phase III study of lenvatinib (E7080) compared to placebo in patients with locally advanced/metastatic RAI-refractory differentiated thyroid cancer. Lenvatinib demonstrated significantly improvement of progression-free survival compared with placebo (HR: 0.21,p<0.001), leading that FDA approved lenvatinib for RAI-refractory differentiated thyroid cancer. In Japan, a phase 2 study of lenvatinib for all histologic subtypes of advanced thyroid cancer is conducting for approval of all histologic subtypes of advanced thyroid cancer. The preliminary results was presented in last ESMO annual meeting and lenvatinib demonstrated promising activity in all histologic subtypes including anaplastic thyroid cancer with response rate of 27.3%.

## Education

We educate not only medical staff in our institute but also outside of our institute by conducting the following education program: 1) Seminar of Japan society of supportive care for patients with HNC and 2) Preceptorship in HNC. Furthermore, our Department is accepting trainees all the time.

## Future prospects

We hope that ongoing or planned clinical trials will change the standard of care for HNC and our biomarker analysis will lead to the development of new treatment strategy. Our education program will increase the number of medical oncologist who takes charge of treatment for HNC, leading to improving patient's quality of survival.

**Table 1. Number of patients according to sites**

| Primary site | No. of patients (N=263) |
|---|---|
| Nasal cavity | 26 |
| Nasopharynx | 22 |
| Oropharynx | 50 |
| Hypopharynx | 56 |
| Oral cavity | 41 |
| Larynx | 18 |
| Salivary | 14 |
| Thyroid | 26 |
| Other | 10 |

**Table 2. Number of patients according to procedure**

| Type of procedure | No. of patients (N=263) |
|---|---|
| Induction chemotherapy followed by CRT | 33 |
| CRT | 65 |
| Palliative chemotherapy | 41 |
| Study drug | 12 |
| Others | 112 |

## List of papers published in 2014

## Journal


1. Shinozaki T, Hayashi R, Miyazaki M, Tomioka T, Zenda S, Tahara M, Akimoto T. Gastrostomy dependence in head and neck carcinoma patient receiving post-operative therapy. Jpn J Clin Oncol, 44:1058-1062, 2014
2. Tahara M, Onozawa Y, Fujii H, Monden N, Yana I, Otani S, Hasegawa Y. Feasibility of cisplatin/5-fluorouracil and panitumumab in Japanese patients with squamous cell carcinoma of the head and neck. Jpn J Clin Oncol, 44:661-669, 2014
3. Machiels J-PH, Licitra LF, Haddad RI, Tahara M, Cohen EE. Rationale and design of LUX-Head & Neck 1: a randomised, Phase III trial of afatinib versus methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who progressed after platinum-based therapy. BMC Cancer, 14:473, 2014
4. Kunieda F, Kiyota N, Tahara M, Kodaira T, Hayashi R, Ishikura S, Mizusawa J, Nakamura K, Fukuda H, Fujii M. Randomized phase II/III trial of post-operative chemoradiotherapy comparing 3-weekly cisplatin with weekly cisplatin in high-risk patients with squamous cell carcinoma of head and neck: Japan Clinical Oncology Group Study (JCOG1008). Jpn J Clin Oncol, 44:770-774, 2014

# Department of Plastic and Reconstructive Surgery

**Minoru Sakuraba, Takuya Higashino, Azusa Oshima, Shogo Azumi, Shusaku Maeda, Yaso Saito**



## Introduction

The Department of Plastic and Reconstructive Surgery has mainly focused on surgical reconstruction following cancer ablation. In our institution, reconstructive procedures using free flap transfer with microvascular anastomosis are the most important operations. In addition, several methods such as tissue transfer with 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 ablative surgery. The quality of life (QOL) of the patient can be improved with the functional and morphological reconstruction.

## Routine activities

The Depart5 plastic surgeons cover reconstructive operations both in the NCCH East in Kashiwa and the NCCH in Tokyo, and train the residents in the 2 hospitals. These reconstructive surgeries are performed in cooperation with the surgeons of another department of the hospital, such as the Head and Neck Surgery, Breast Surgery, Orthopedic Surgery, Esophageal Surgery, Colorectal and Urological Surgery etc. In the NCCH East, Head and Neck reconstruction is the most frequently performed operation accounting for 65% of the reconstructive surgery. In head and neck region, a free jejunal graft and a rectus abdominis musculocutaneous flap are the most frequently used procedures. A weekly conference is held with doctors of the Department of Head and Neck Surgery, Radiation Oncology and Head and Neck Oncology. Breast reconstruction using autologous tissue transfer was employed in 2005, since then, patients' needs for breast reconstruction is increasing. And also, lymphatico-venulo anastomosis as a surgical treatment for lymphedema of the extremities was introduced since June 2013.

## Research activities

Plastic and reconstructive surgery has focused on the following four aspects in the surgical treatment of cancer, for the purpose of contributing to the improvement of the quality of life of patients.

1. Obtaining good functional recovery
2. Reduction of postoperative complications
3. Achieving less donor site morbidity
4. Treatment of postoperative complications after cancer ablation.

With the objective of addressing these four aspects, establishing a standard of reconstructive surgery and developing new techniques of reconstructive surgery are the most important aims of our studies. Multi institutional analysis of postoperative complication and swallowing function after total pharyngo laryngo esophagectomy and reconstruction with a free jejenal graft was performed continuously. This study was supported by a Grant in-Aid for Cancer Research. The aim of the study is to clarify the relationship between surgical procedures and postoperative complication and function.

Another multi institutional analysis of postoperative complication after microsurgical head and neck reconstruction was carried out to clarify the risk factor of postoperative vascular thrombosis. Data registration was closed and the data is now under evaluation.

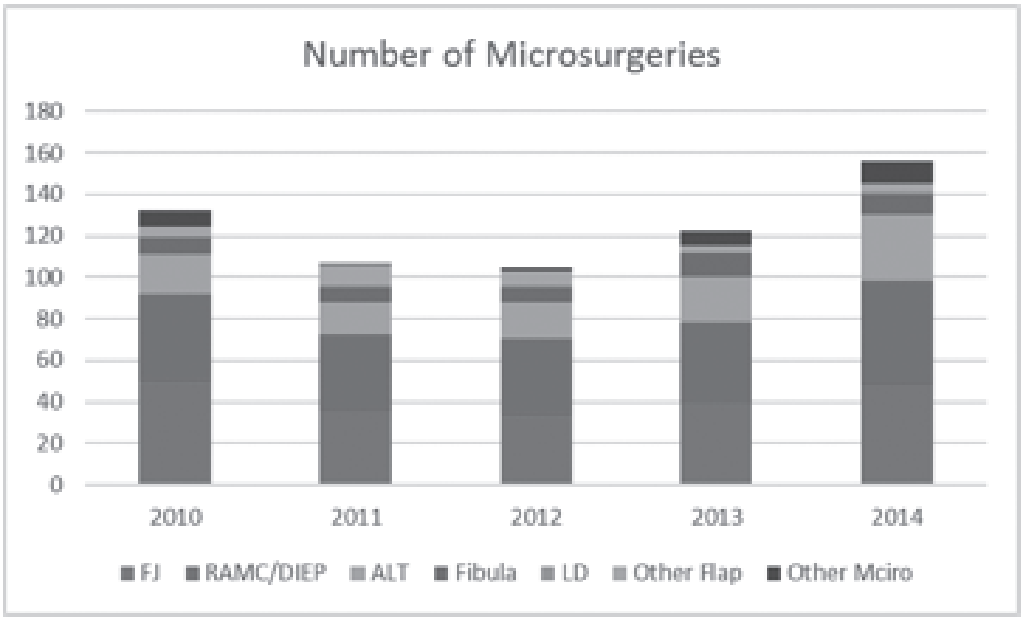



**Table 1. Cooperation with other divisions**

| NCCH East | No. of patients |
|---|---|
| Head & Neck surgery | 145 |
| Orthopedic surgery | 7 |
| Esophageal surgery | 6 |
| Breast surgery | 64 |
| Dermatology | ---- |
| Urologic surgery | 3 |
| HB&P surgery | 1 |
| Ophthalmic surgery | ---- |
| Colorectal surgery | 9 |
| Gastric surgery | 1 |
| Thoracic surgery | 6 |
| Gynecology | ---- |
| Plastic & Reconstructive | 8 |
| Total | 250 |

**Table 2. Operative procedures**

| NCCH East | No. of flaps |
|---|---|
| Microvascular free flap | 145 |
| Jejunum | 48 |
| RAMC (DIEP) | 50 (13) |
| Anterolateral thigh | 32 |
| Fibula bone | 10 |
| Latissimus dorsi | 1 |
| Radial forearm | 0 |
| Other flaps | 4 |
| Supercharge | 0 |
| Nerve graft | 1 |
| Limb salvage | 2 |
| Hepatic artery | 1 |
| Lymphatico-venulo anast | 6 |
| Others | 1 |
| Subtotal | 156 |
| Pedicled flaps | 19 |
| PMMC | 7 |
| Latissimus dorsi | 7 |
| RAMC | 4 |
| Other flaps | 1 |
| Other procedures | 39 |
| Total | 214 |

## List of papers published in 2014

### Journal

1. Kamizono K, Sakuraba M, Nagamatsu S, Miyamoto S, Hayashi R. Statistical analysis of surgical site infection after head and neck reconstructive surgery. Ann Surg Oncol, 21:1700-1705, 2014

# Department of Breast Surgery

**Noriaki Wada, Kimiyasu Yoneyama, Chisako Yamauchi**



## Introduction

We treat patients with operable malignant mammary glands. Diagnosis of breast disease, surgical treatment and follow-up for breast cancer patients are mainly our professional practice. The Division consists of 3 staff surgeons and 1 resident, and is committed to providing the latest, most comprehensive breast treatments for our patients. The multidisciplinary approach to the diagnosis and treatment of cancer are carried out under cooperation between related specialists: surgeons, radiologists, plastic surgeons, pathologists, medical oncologists, specialized nurses, and technicians.

The Division mainly focuses on "minimally invasive surgery" and performs a thorough investigation for an oncologically safe approach, less morbidity and good cosmesis. For example, although sentinel lymph node (SLN) biopsy has already been established as the standard care for clinical node negative patients, omitting axillary lymph node dissection (ALND) for positive SLNs with micro- or macrometastasis has started in clinical practice as an expanded indication. On the other hand, preoperative systemic therapy provides the opportunity for a curative operation or breast-conserving surgery to avoid mastectomy. Moreover, we can provide breast reconstructive surgery in collaboration with the Plastic Surgery Division. These procedures will contribute to a better quality of life for patients with breast cancer.

## Routine activities

For the regular activities of the Division, a daily morning routine round is scheduled for inpatients by all staff and residents. Moreover, our weekly preoperative diagnostic imaging conference on breast cancer is conducted on Monday evenings to discuss the surgical treatment planning for each patient. A clinical conference to decide on courses of treatment by multidisciplinary breast care team members is held twice a month. A monthly pathological conference on breast cancer is also conducted on the last Friday of each month. At those conferences, individual cases are presented to a team of highly trained cancer specialists, including radiologists, breast surgeons, pathologists, radiation oncologists, and medical oncologists. Our multidisciplinary team approach to breast cancer treatment sets the superior quality of care we provide for our patients.

Changes in the annual number of patients with breast cancer who underwent surgery are shown in Table 1. A total of 282 patients with primary breast cancer and 51 patients with recurrence or other breast disease were operated in 2014. 14 immediate breast reconstruction surgeries were included. Of the patients with primary breast cancer, 59 (21%) underwent primary systemic therapy. The types and number of operative procedures performed in 2014 are shown in Table 2. The rate of breast-conserving surgeries (including 8 radiofrequency ablation alone cases) was 57% (161/282). Sentinel node biopsy was performed in 218 patients, and 207 patients were spared from ALND.

## Research activities

1. Evaluation of the potential role of Ki67 as a biomarker for breast cancer patients.

The Ki67 index is a marker for cell proliferation. A retrospective search of a prospectively maintained clinical breast cancer database was performed. It was concluded that the pre-therapy Ki67 index was a useful predictor for the therapeutic response to neoadjuvant chemotherapy and Ki67 post-therapy was shown to predict outcomes for patients with residual invasive disease.

2. Long term results of patients treated with SNB omitting ALND.

In an observational study, there was not a significant difference in the overall survival and relapse free survival between SLN negative patients without ALND and those with ALND. We concluded that SLN biopsy without ALND is validated as a safe and effective method for regional node treatment of SLN negative breast cancer patients. We are going to omit ALND even in SLN positive patients under certain conditions.

3. In vivo cancer detection with a newly designed fluorescent probe.

γ-glutamyl hydroxymethyl rhodamine green (gGlu-HMRG) is a small-molecule aminopeptidase probe which was enzymatically cleaved, revealing a bright fluorescent region of cancer cells which overexpress the enzyme γ-glutamyltranspeptidase (GGT). Visualized tiny cancerous nodules may allow us to delineate the border of tumors and confirm that there are no residual tumors.

### Clinical trials

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

A Phase II study on RFA without resection was performed for T=<1.5 cm, N0 breast cancer patients with no extensive intraductal components using a Cool-tip electrode system. This study is certified as an advanced medical treatment by the Ministry of Health, Labour and Welfare.

2. Effectiveness of primary tumor resection for metastatic breast cancer (JCOG 1017).

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

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

This is a multi-center randomized Phase III trial which started in 2012. This clinical trial is to confirm the superiority of intensive follow-up to standard follow-up in terms of overall survival in high-risk breast cancer patients.

4. Postoperative therapy with endocrine and TS-1 (POTENT study)

This multi-center randomized trial started in 2012 and is a randomized, controlled study to determine whether S-1 combined with standard postoperative endocrine therapy more effectively inhibits recurrence than standard postoperative endocrine therapy alone in patients with estrogen receptor (ER)-positive, HER2-negative primary breast cancer.

5. Observational study of axilla treatment for breast cancer patients with SLN positive.

This multi-center study is designed to evaluate the outcome of no ALND in sentinel node-positive breast cancer using the propensity score. Patients with 1 to 3 positive micrometastases or macrometastases in sentinel lymph nodes are eligible. The primary endpoint is the recurrence rate of regional lymph nodes in patients treated with SNB. Patients treated with SNB followed by ALND are also registered simultaneously to compare the prognosis.

### Education

For residents in our Department, not only surgery residency training but also pre-and postoperative management of breast cancer patient, guidance of conference presentation and writing a paper are provided. Various clinical conferences of treatment, diagnostic imaging and pathology are conducted among doctors of cancer specialists, nurse and technicians.

### Future prospects

The future direction of breast cancer surgical treatment will be clearly a minimally invasive surgery.

An individualized treatment based on the biological properties is going to be performed without impairing the functional preservation and esthetic outcome, considering the minimal resection-dissection range, which does not affect the recurrence-survival.

**Table 1. Number of primary breast cancer patients operated on during 2005-2014**

| Clinical stage | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|---|---|---|
| Stage 0 | 29 | 34 | 27 | 23 | 38 | 39 | 43 | 28 | 25 | 29 |
| Stage I | 89 | 79 | 94 | 84 | 86 | 80 | 86 | 91 | 112 | 89 |
| Stage II | 94 | 103 | 87 | 87 | 122 | 137 | 112 | 128 | 138 | 122 |
| Stage III | 35 | 34 | 25 | 33 | 42 | 32 | 43 | 49 | 29 | 39 |
| Stage IV | 2 | 1 | 4 | 0 | 3 | 1 | 1 | 4 | 2 | 3 |
| Total | 249 | 251 | 237 | 227 | 291 | 289 | 285 | 300 | 306 | 282 |

**Table 2. Types of operative procedures**

| Type of operation | N |
|---|---|
| BT+SNB | 81 |
| BT+SNB→ALND | 5 |
| BT+ALND | 32 |
| BT alone | 3 |
| BP+SNB | 119 |
| BP+SNB→ALND | 5 |
| BP+ALND | 18 |
| BP alone | 11 |
| RFA+SNB | 7 |
| RFA+SNB→ALND | 1 |
| Total | 282 |

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

**Table 3. Overall survival (OS) rate**

**OP year: Jan 1993- Dec 2008**

| Clinical stage | N | 5 yr. OS | 10 yr. OS |
|---|---|---|---|
| Stage 0 | 227 | 98.7% | 96.5% |
| Stage I | 958 | 96.0% | 92.0% |
| Stage II | 1,521 | 90.9% | 81.6% |
| Stage III | 344 | 70.3% | 57.8% |
| Stage IV, unknown | 33 | 36.4% | 14.1% |
| Total | 3,083 | 90.0% | 82.5% |

Median follow up period: 110 months [0-261]



## List of papers published in 2014

## Journal


1. Observational study of axilla treatment for breast cancer patients with 1-3 Oba MS, Imoto S, Toh U, Wada N, Kawada M, Kitada M, Masuda N, Taguchi T, Minami S, Jinno H, Sakamoto J, Morita S, Japanese Society for Sentinel Node Navigation Surgery. Observational study of axilla treatment for breast cancer patients with 1-3 positive micrometastases or macrometastases in sentinel lymph nodes. Jpn J Clin Oncol, 44:876-879, 2014
2. Matsubara N, Mukai H, Masumoto M, Sasaki M, Naito Y, Fujii S, Wada N. Survival outcome and reduction rate of Ki-67 between pre- and post-neoadjuvant chemotherapy in breast cancer patients with non-pCR. Breast Cancer Res Treat, 147:95-102, 2014
3. Shibayama O, Yoshiuchi K, Inagaki M, Matsuoka Y, Yoshikawa E, Sugawara Y, Akechi T, Wada N, Imoto S, Murakami K, Ogawa A, Akabayashi A, Uchitomi Y. Association between adjuvant regional radiotherapy and cognitive function in breast cancer patients treated with conservation therapy. Cancer Med, 3:702-709, 2014

# Department of Breast and Medical Oncology

**Hirofumi Mukai, Nobuaki Matsubara, Yoichi Naito, Masaoki Sasaki, Mariko Masumoto, Mai Onomura, Yoko Yamada, Hiroaki Izumi, Tetsuya Urasaki, Yujiro Ueda, Takaaki Yokoyama, Naoka Okamura**

## Introduction

Patients with different types of cancers, 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 for 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 2014, 604 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 held on every morning. A weekly educational meeting is conducted on Thursday morning. Moreover, a biweekly joint conference is held on Wednesday evenings and on Monday evenings with breast surgeons and with urologists, respectively. Morning journal clubs also meet on Mondays and Fridays at the Division in collaboration with the Division of hematology.

## Research activities

Phase I studies of the following anticancer agents were conducted: K912 (epirubicin-incorporating micellar nanoparticle formulation) for patients with solid tumors for which standard chemotherapy was unavailable, and NK105 (paclitaxel-incorporating micellar nanoparticle formulation) for patients with advanced or metastatic cancer. Phase I/II studies of new anticancer agents for specific disease targets are conducted in collaboration with pharmaceutical companies.

In addition, many phase III studies are being conducted as follows: Randomized, optimal dose finding, Phase II Study of triweekly Abraxane in patients with metastatic breast cancer; Evaluation of Oral Care to Prevent Oral Mucositis in Estrogen Receptor Positive Metastatic Breast Cancer Patients Treated with Everolimus.(Oral Care-BC) : Randomized Controlled Phase III Trial; A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer; Intensive vs. standard post-operative surveillance in high risk breast cancer patients; Adjuvant Chemotherapy Trial of S-1 for breast cancer with ER-positive and HER2-negative; a randomized double-blind placebo-controlled trial of neratinib (an erbB1/2/4 inhibitor) after trastuzumab in women with early-stage HER-2 overexpressed/amplified breast cancer; a 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.



**Table 1. Number of new patients**

| | |
|---|---|
| Breast cancer | 265 |
| Genitourinary cancers | 201 |
| Gynecological cancers | 27 |
| Cancer of unknown primary | 57 |
| Sarcoma | 34 |
| Others | 20 |
| Total | 604 |

## List of papers published in 2014

### Journal


1. Matsubara N, Mukai H, Masumoto M, Sasaki M, Naito Y, Fujii S, Wada N. Survival outcome and reduction rate of Ki-67 between pre- and post-neoadjuvant chemotherapy in breast cancer patients with non-pCR. Breast Cancer Res Treat, 147:95-102, 2014
2. Ohsumi S, Mukai H, Ohashi Y. Factors affecting enrollment in a randomized controlled trial for Japanese metastatic breast cancer patients (SELECT BC-FEEL)--a prospective study. Jpn J Clin Oncol, 44:696-701, 2014
3. Tanioka M, Sasaki M, Shimomura A, Fujishima M, Doi M, Matsuura K, Sakuma T, Yoshimura K, Saeki T, Ohara M, Tsurutani J, Watatani M, Takano T, Kawabata H, Mukai H, Naito Y, Hirokaga K, Takao S, Minami H. Pathologic complete response after neoadjuvant chemotherapy in HER2-overexpressing breast cancer according to hormonal receptor status. Breast, 23:466-472, 2014
4. Mukai H, Takahashi S, Nozawa M, Onozawa Y, Miyazaki J, Ohno K, Suzuki K. Phase I dose-escalation and pharmacokinetic study (TED 11576) of cabazitaxel in Japanese patients with castration-resistant prostate cancer. Cancer Chemother Pharmacol, 73:703-710, 2014
5. Mukai H, Ohno S, Ohashi Y. Prospective cohort study: whether or not patients benefit from participation itself in randomized-controlled trials (SELECT BC ECO). Jpn J Clin Oncol, 44:296-299, 2014
6. Matsubara N, Uemura H, Satoh T, Suzuki H, Nishiyama T, Uemura H, Hashine K, Imanaka K, Ozono S, Akaza H. A phase 2 trial of abiraterone acetate in Japanese men with metastatic castration-resistant prostate cancer and without prior chemotherapy (JPN-201 study). Jpn J Clin Oncol, 44:1216-1226, 2014
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8. Niikura N, Hayashi N, Masuda N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M, Kondo N, Naito Y, Honda Y, Matsui A, Fujisawa T, Oshitanai R, Yasojima H, Tokuda Y, Saji S, Iwata H. Treatment outcomes and prognostic factors for patients with brain metastases from breast cancer of each subtype: a multicenter retrospective analysis. Breast Cancer Res Treat, 147:103-112, 2014
9. Noguchi S, Masuda N, Iwata H, Mukai H, Horiguchi J, Puttawibul P, Srimuninnimit V, Tokuda Y, Kuroi K, Iwase H, Inaji H, Ohsumi S, Noh W-C, Nakayama T, Ohno S, Rai Y, Park B-W, Panneerselvam A, El-Hashimy M, Taran T, Sahmoud T, Ito Y. Efficacy of everolimus with exemestane versus exemestane alone in Asian patients with HER2-negative, hormone-receptor-positive breast cancer in BOLERO-2. Breast Cancer, 21:703-714, 2014

# Department of Thoracic Surgery

**Masahiro Tsuboi, Junji Yoshida, Tomoyuki Hishida, Keiju Aokage, Nao Aramaki, Masahito Naitoh, Kanji Nagai**

## Introduction

The Department of Thoracic Surgery has three missions: surgical treatment, surgical resident training, and clinical research. Thoracic surgeries involve the treatment of thoracic neoplasms, primary and metastatic lung tumors, as well as mediastinal, pleural, and chest wall tumors. The Department specializes in the surgical treatment of pulmonary carcinomas. Routine surgical treatment modalities for carcinomas include limited resection (wedge or segmental resection) and simple resection (lobectomy or pneumonectomy) with or without systematic lymph node dissection. Thoracoscopic assistance is almost always used. Non-routine surgical procedures involve complex approaches, such as broncho-/angio-plasty, combined resection with adjacent structures, and perioperative adjuvant treatment.

Since its establishment in 1992, the Department has been one of the most active leaders in the field of lung cancer in Japan. Moreover, it has been an active participant in international and national scientific venues. In this year, in addition to 13 scientific papers published in English, the Department made 30 presentations: 4 international, 23 national, and 4 regional.

## Routine activities

The Department is presently composed of 4 consultant surgeons and 5 or 6 residents.

The Department has adopted a team approach for patient treatments and resident trainings. Potential surgical intervention candidate cases are presented every Tuesday evening at a multidisciplinary team conference of thoracic surgeons, oncology physicians, radiologists and residents. Each case is thoroughly and vigorously reviewed and discussed. To improve the English fluency of staff members and residents in preparation for international presentations, and to promote better involvement of visiting physicians from other countries, treatment modality discussions are conducted in English. Moreover, selected patients' records are radiologically and cytopathologically reviewed every Friday morning. These reviews aim to improve the interpretation of radiologic indications to pathology findings, accurately evaluate surgical indications, and upgrade knowledge on rare histologies. The Department believes that these activities improve the knowledge base, treatment indications, and surgical treatment.

For non-small cell histology, primary pulmonary carcinomas in clinical stages I/II and IIIA without bulky or multistation-involved mediastinal nodes, and primary pulmonary small cell carcinomas in clinical stage I, surgical resection is indicated for cure. Optimum treatment modalities are being sought via clinical trials with the aim of improving the poor prognosis of patients either with bulky or clinically and histologically proven multistation mediastinal lymph node metastases, with disease invading the neighboring vital structures, or with small cell cancers in clinical stage II and later.

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

The surgical procedures of the Department have generally remained similar for the past decade, but we have employed port-access thoracoscopic surgery more often for the last several years. Approximately 20% of the surgeries are completed via a 3-port access, and 70% of the surgeries are video-thoracoscopically assisted. To date, the average postoperative hospital stays of patients in the Department have improved and

become shorter: 3 days is the shortest and generally 7 days for primary lung cancer cases. These shorter hospital stays are realized with a slightly better complication rate than the normal rate. This year, 30-day operative mortality occurred in 2 patients undergoing surgery for primary lung cancer.

## Research activities

Research in the area of combined treatments, such as immunotherapy, in particular, has now advanced to clinical trials. It is a goal of researchers in the Department to acquire a basic understanding of the cellular and molecular mechanisms to lead the development and progression of lung cance,r and apply these findings to further the development of immunotherapy-based prevention and treatment strategies.

## Clinical trials

1. Surgical margin lavage cytology examination in limited resection for primary and metastatic lung cancer patients [observational].
2. Member of an organized trial of TS-1 vs. UFT adjuvant chemotherapy for completely resected pathologic stage I (> 2 cm) non-small cell lungcancer [phase III, patient accrual completed].
3. Member of an organized trial of sublobar resection for peripheral GGO dominant cT1aN0M0 lung adenocarcinomas [phase II, patient accrual completed].
4. Member of an organized trial of segmental resection vs. lobectomy for peripheral T1aN0M0 non-small cell lung cancers [phase III].
5. Member of an organized trial of pleurectomy for malignant pleural mesothelioma [feasibility study, patient accrual completed]

## Education

Our educational program is to expand residents' knowledge and technical skills in the treatment of lung cancer, other thoracic malignancies and benign tumors, such as hamartoma and mediastinal cystic lesion. In addition, we seek to instill into the trainee a motivation of continuous introspection and self-education and open communication between all health care providers while maintaining a respectful and professional demeanor.

## Future prospects

Treatment advances in thoracic cancers including lung, mesothelioma, thymic malignancies and lung metastases have been slow to develop, even though these cancers are among the most common clinical problems. This clinical and laboratory research is vital to making progress.

**Table 1. Number of patients**

| | |
|---|---|
| Lung cancer | 362 |
| Metastatic lung tumor | 78 |
| Mediastinal tumor | 22 |
| Others | 61 |
| Total | 523 |

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

| | |
|---|---|
| Pneumonectomy | 10 |
| Lobectomy | 268 |
| Segmentectomy | 39 |
| Wedge resection | 38 |
| (Combined resection) | 17 |
| Others | 7 |
| Total | 362 |

**Table 3. Survival rates of lung cancer**

| Diagnosis (primary lung cancer) | No. of pts | MST (mo) | 5-yr survival (%) |
|---|---|---|---|
| Pathologic stage | | | |
| IA | 1,376 | NR | 85.8 |
| IB | 571 | 102.9 | 67.8 |
| IIA | 347 | 68.9 | 55.2 |
| IIB | 241 | 42.8 | 41.8 |
| IIIA | 472 | 37.7 | 35.8 |

Data source from surgical records between 2000 and 2010;
Pathological stages according to the TNM Classification 7th edition;
NR: not reached.

## List of papers published in 2014

### Journal


1. Eba J, Kenmotsu H, Tsuboi M, Niho S, Katayama H, Shibata T, Watanabe S, Yamamoto N, Tamura T, Asamura H. A Phase III trial comparing irinotecan and cisplatin with etoposide and cisplatin in adjuvant chemotherapy for completely resected pulmonary high-grade neuroendocrine carcinoma (JCOG1205/1206). Jpn J Clin Oncol, 44:379-382, 2014
2. Kawano Y, Okamoto I, Fukuda H, Ohe Y, Nakamura S, Nakagawa K, Hotta K, Kiura K, Takiguchi Y, Saka H, Okamoto H, Takayama K, Semba H, Kobayashi K, Kenmotsu H, Tsuboi M, Yamamoto N, Nukiwa T, Nakanishi Y. Current status and future perspectives of cooperative study groups for lung cancer in Japan. Respir Investig, 52:339-347, 2014
3. Hishida T, Yoshida J, Ohe Y, Aokage K, Ishii G, Nagai K. Surgical outcomes after initial surgery for clinical single-station N2 nonsmall-cell lung cancer. Jpn J Clin Oncol, 44:85-92, 2014
4. Matsumura Y, Hishida T, Shimada Y, Ishii G, Aokage K, Yoshida J, Nagai K. Impact of extratumoral lymphatic permeation on postoperative survival of non-small-cell lung cancer patients. J Thorac Oncol, 9:337-344, 2014
5. Yamada E, Ishii G, Aramaki N, Aokage K, Hishida T, Yoshida J, Kojima M, Nagai K, Ochiai A. Tumor-size-based morphological features of metastatic lymph node tumors from primary lung adenocarcinoma. Pathol Int, 64:591-600, 2014
6. Hattori A, Suzuki K, Aokage K, Mimae T, Nagai K, Tsuboi M, Okada M. Prognosis of lung cancer patients with a past history of colorectal cancer. Jpn J Clin Oncol, 44:1088-1095, 2014
7. Matsuwaki R, Ishii G, Zenke Y, Neri S, Aokage K, Hishida T, Yoshida J, Fujii S, Kondo H, Goya T, Nagai K, Ochiai A. Immunophenotypic features of metastatic lymph node tumors to predict recurrence in N2 lung squamous cell carcinoma. Cancer Sci, 105:905-911, 2014
8. Neri S, Yoshida J, Ishii G, Matsumura Y, Aokage K, Hishida T, Nagai K. Prognostic impact of microscopic vessel invasion and visceral pleural invasion in non-small cell lung cancer: a retrospective analysis of 2657 patients. Ann Surg, 260:383-388, 2014
9. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and metaanalysis of individual participant data. Lancet, 383:1561-1571, 2014


### Book


1. Yoshida J. Open wedge resection. In: Dienemann HC, Hoffmann H, Detterbeck FC (eds), Chest Surgery, Germany, Springer-Verlag Berlin Heidelberg, pp 123-128, 2014

# Department of Thoracic Oncology

**Koichi Goto, Hironobu Ohmatsu, Seiji Niho, Kiyotaka Yoh, Shigeki Umemura, Shingo Matsumoto, Keisuke Kirita, Eri Sugiyama, Yoshitaka Zenke, Shinnosuke Ikemura**



## Introduction

The Department of Thoracic Oncology 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 and EBUS for diagnosis is performed on Monday, Tuesday, and Thursday afternoon. Fluoroscopic-CT guided needle lung biopsies is carried out on Tuesday afternoon. For patient management, we use approximately 70 beds in 8F, 6A, 5A and 5B wards.

Case conferences on thoracic surgery and medical oncology are scheduled on Tuesday evenings and Wednesday evenings, respectively. The staff members and residents of the 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 for chest X-ray and CT scan films.

## Research activities

Our research activities are focused on four areas: 1) development of new and effective diagnosis and treatment modalities; 2) detection, diagnosis, and treatment of peripheral-type minute lung cancers that are not visible in plain chest X-rays; 3) collaborative studies with the Research Center for Innovative Oncology in the following areas: detection of driver mutation for small cell lung cancer; development of new diagnostic method of rare driver gene aleration for lung cancer; correlation between gene abnormalities and clinical characteristics; correlation between sensitivity of EGFR-TKI and CAF (cancer-associated fibroblasts); and 4) translational research from bench to bed-side or from bed-side to bench for the development of innovative treatment strategies.

Especially, hole genome analysis of small cell cancer to detect new driver mutations and establishment of multiplex diagnosis methods for rare gene alteration of lung cancer such as ALK, RET and ROS1 fusion gene and BRAF mutation are under investigation as a collaboration with the Research Center for Innovative Oncology.

## Clinical trials

The Department of Thoracic Oncology is currently conducting and participating in multi-institutional Phase III studies to establish new standard treatments against lung cancer such as the Japan Clinical Oncology Group (JCOG) trials, West Japan Oncology Group (WJOG), Thoracic Oncology Research Group (TORG) and global trials conducted by pharmaceutical companies.

Recently, the usefulness of TS-1 and pemetrexed combined with thoracic dadiotherapy

has been reported for locally advanced NSCLC. Therfore, randomized Phase II study of cisplatin plus TS-1 vs. cisplatin plus pemetrexed combined with thoracic radiotherapy for stage III non-squamous NSCLC is now ongoing.

Alectinib is a newly developing selective ALK inhibitor and very effective for ALK fusion positive NSCLC, although 4-5% of NSCLC are positive for ALK fusion protein. Phase I /II study of alectinib demonstrated durable response and higher than 90% of response rate without severe toxicity. Currently, Phase III study of alectinib comparing with crizotinib is now ongoing. The Phase I study of AZD9291, 3rd generation EGFR-TKI which is also effective for T790M resistant mutation are ongoing. Patients were treated at a dose of 20mg to 240mg, upto 240mg no DLTs were observed. Very good response for T790M positive patients were observed with minimal toxicities. In addition, recent many clinical trials indicated that PD-1/PD-L1 immune checkpoint inhibitors showed remarkable clinical response against advanced NSCLC including squamous cell lung cancer.

LC-SCRUM-Japan (Lung Cancer Genomic Screening Project for Individualized Medicine in Japan), a nation wide genomic screening project of lung cancer with rare driver oncogenes, such as ALK, RET and ROS1 fusion, and BRAF mutation was stared in February 2013. As of March 6th 2015, 1,536 patients were enrolled and 34 (2%) RET and 61 (4%) ROS1 fusion gene positive were detected. Eighteen RET fusion positive, 26 ROS1 fusion positive, and 3 BRAF mutation positive patients were entered into clinical trial of vandetanib, crizotinib, or dabrafenib, respectively. Multiplex genomic screening by Oncomine® Cancer Pannel collaborating with 12 pharmaceutical companies was also started in LC-SCRUM-Japan from March 2015.

**Table 1. Number of patients in 2014**

| | |
|---|---|
| Lung Cancer | 452 |
| Small cell lung cancer | 71 |
| Adenocarcinoma | 253 |
| Squamous cell carcinoma | 73 |
| Large cell carcinoma | 2 |
| NSCLC NOS | 37 |
| Others | 16 |
| Thymic cancer | 8 |
| Thymoma | 0 |
| Malignant pleural mesothelioma | 3 |

**Table 2. Initial treatment of lung cancer in 2014**

| | |
|---|---|
| Chemotherapy | 267 |
| Chemoradiotherapy | 90 |
| Surgery followed by chemotherapy | 46 |
| Radiotherapy | 10 |
| Palliative care | 33 |
| Others | 6 |

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

| | | | | Survival rate (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| Disease | Stage | Treatment | N | 1y | 2y | 3y | 4y | 5y |
| NSCLC | III | Chemoradiotherapy | 221 | 79 | 54 | 39 | 32 | 26 |
| NSCLC | IV | Chemotherapy | 833 | 48 | 26 | 15 | 9 | 5 |
| SCLC | LD | Chemoradiotherapy | 96 | 82 | 41 | 27 | 20 | 20 |
| SCLC | ED | Chemotherapy | 192 | 39 | 7 | 2 | 0 | 0 |

## List of papers published in 2014

## Journal


1. Kenmotsu H, Niho S, Ito T, Ishikawa Y, Noguchi M, Tada H, Sekine I, Watanabe S, Yoshimura M, Yamamoto N, Oshita F, Kubota K, Nagai K. A pilot study of adjuvant chemotherapy with irinotecan and cisplatin for completely resected high-grade pulmonary neuroendocrine carcinoma (large cell neuroendocrine carcinoma and small cell lung cancer). Lung Cancer, 84:254-258, 2014
2. Eba J, Kenmotsu H, Tsuboi M, Niho S, Katayama H, Shibata T, Watanabe S, Yamamoto N, Tamura T, Asamura H. A Phase III trial comparing irinotecan and cisplatin with etoposide and cisplatin in adjuvant chemotherapy for completely resected pulmonary high-grade neuroendocrine carcinoma (JCOG1205/1206). Jpn J Clin Oncol, 44:379-382, 2014
3. Gemma A, Kudoh S, Ando M, Ohe Y, Nakagawa K, Johkoh T, Yamazaki N, Arakawa H, Inoue Y, Ebina M, Kusumoto M, Kuwano K, Sakai F, Taniguchi H, Fukuda Y, Seki A, Ishii T, Fukuoka M. Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer. Cancer Sci, 105:1584-1590, 2014
4. Kawano Y, Okamoto I, Fukuda H, Ohe Y, Nakamura S, Nakagawa K, Hotta K, Kiura K, Takiguchi Y, Saka H, Okamoto H, Takayama K, Semba H, Kobayashi K, Kenmotsu H, Tsuboi M, Yamamoto N, Nukiwa T, Nakanishi Y. Current status and future perspectives of cooperative study groups for lung cancer in Japan. Respir Investig, 52:339-347, 2014
5. Seto T, Kato T, Nishio M, Goto K, Atagi S, Hosomi Y, Yamamoto N, Hida T, Maemondo M, Nakagawa K, Nagase S, Okamoto I, Yamanaka T, Tajima K, Harada R, Fukuoka M, Yamamoto N. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncol, 15:1236-1244, 2014
6. Morise M, Niho S, Umemura S, Matsumoto S, Yoh K, Goto K, Ohmatsu H, Ohe Y. Low-dose irinotecan as a second-line chemotherapy for recurrent small cell lung cancer. Jpn J Clin Oncol, 44:846-851, 2014
7. Umemura S, Mimaki S, Makinoshima H, Tada S, Ishii G, Ohmatsu H, Niho S, Yoh K, Matsumoto S, Takahashi A, Morise M, Nakamura Y, Ochiai A, Nagai K, Iwakawa R, Kohno T, Yokota J, Ohe Y, Esumi H, Tsuchihara K, Goto K. Therapeutic priority of the PI3K/AKT/mTOR pathway in small cell lung cancers as revealed by a comprehensive genomic analysis. J Thorac Oncol, 9:1324-1331, 2014
8. Ando K, Takahashi F, Kato M, Kaneko N, Doi T, Ohe Y, Koizumi F, Nishio K, Takahashi K. Tocilizumab, a proposed therapy for the cachexia of Interleukin6-expressing lung cancer. PLoS One, 9:e102436, 2014
9. Murakami H, Yamamoto N, Shibata T, Takeda K, Ichinose Y, Ohe Y, Yamamoto N, Takeda Y, Kudoh S, Atagi S, Satouchi M, Kiura K, Nogami N, Endo M, Watanabe H, Tamura T. A single-arm confirmatory study of amrubicin therapy in patients with refractory small-cell lung cancer: Japan Clinical Oncology Group Study (JCOG0901). Lung Cancer, 84:67-72, 2014
10. Satouchi M, Kotani Y, Shibata T, Ando M, Nakagawa K, Yamamoto N, Ichinose Y, Ohe Y, Nishio M, Hida T, Takeda K, Kimura T, Minato K, Yokoyama A, Atagi S, Fukuda H, Tamura T, Saijo N. Phase III study comparing amrubicin plus cisplatin with irinotecan plus cisplatin in the treatment of extensive-disease small-cell lung cancer: JCOG 0509. J Clin Oncol, 32:1262-1268, 2014
11. Yoshida T, Niho S, Toda M, Goto K, Yoh K, Umemura S, Matsumoto S, Ohmatsu H, Ohe Y. Protective effect of magnesium preloading on cisplatin-induced nephrotoxicity: a retrospective study. Jpn J Clin Oncol, 44:346-354, 2014
12. Hishida T, Yoshida J, Ohe Y, Aokage K, Ishii G, Nagai K. Surgical outcomes after initial surgery for clinical single-station N2 non-small-cell lung cancer. Jpn J Clin Oncol, 44:85-92, 2014
13. Matsuwaki R, Ishii G, Zenke Y, Neri S, Aokage K, Hishida T, Yoshida J, Fujii S, Kondo H, Goya T, Nagai K, Ochiai A. Immunophenotypic features of metastatic lymph node tumors to predict recurrence in N2 lung squamous cell carcinoma. Cancer Sci, 105:905-911, 2014
14. Makinoshima H, Takita M, Matsumoto S, Yagishita A, Owada S, Esumi H, Tsuchihara K. Epidermal growth factor receptor (EGFR) signaling regulates global metabolic pathways in EGFR-mutated lung adenocarcinoma. J Biol Chem, 289:20813-20823, 2014
15. Naito T, Seto T, Takeda K, Goto K, Okamoto I, Nakagawa K, Ohba T, Murakami H, Takahashi T, Yamanaka T, Yamamoto N. Phase II clinical trial of S-1 plus oral leucovorin in previously treated patients with non-small-cell lung cancer. Lung Cancer, 86:339-343, 2014
16. Naito Y, Yasuno K, Tagawa H, Sakamoto N, Oue N, Yashiro M, Sentani K, Goto K, Shinmei S, Oo HZ, Yanagihara K, Hirakawa K, Yasui W. MicroRNA-145 is a potential prognostic factor of scirrhous type gastric cancer. Oncol Rep, 32:1720-1726, 2014
17. Sekine I, Okamoto H, Horai T, Nakagawa K, Ohmatsu H, Yokoyama A, Katakami N, Shibuya M, Saijo N, Fukuoka M. A randomized phase III study of single-agent amrubicin vs. carboplatin/etoposide in elderly patients with extensive-disease small-cell lung cancer. Clin Lung Cancer, 15:96-102, 2014

# Department of Esophageal Surgery

**Hiroyuki Daiko, Takeo Fujita**

## Introduction

The Department of Esophageal Surgery 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 establishment minimally invasive surgery which is consisted of neoadjuvant treatment followed by minimally invasive esophagectomy. The Division is conducting a study to define the role of surgery in the multimodal approach to the treatment of esophageal cancer, and aimed that thoracolaparoscopic esophagectomy consisted with thoracoscopic esophagectomy and laparoscopic reconstruction is to be become a standard surgical procedure.

## Routine activities

The Department of Esophageal Surgery consists of 2 staff surgeons and 4 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 2014, 156 patients underwent esophagectomy. Transthoracic esophagectomy with extended lymph node dissection was performed on 48 nontreated cases. Thoracoscopic esophagectomy in the prone position with radical lymph node dissection was undertaken in 108 cases. Two-stage surgical procedure divided into resection and reconstruction for more than 80 years old or multiple complicated patients was undertaken in 19 cases. Postoperatively, within 30 days, 1 patient died due to complications after a salvage operation.

## Clinical trials

Currently, the Department is examining the role of thoracolaparoscopic esophagectomy as a minimally invasive esophagectomy consisted with thoracoscopic esophagectomy and laparoscopic reconstruction. For patients without radical chemoradiotherapy, thoracoscopic esophagectomy in the prone position with radical lymph node dissection and laparoscopic reconstruction after esophagectomy for the patients without history of laparotomy are being attempted to become a standard surgical procedure for esophageal cancer.

For treating patients aged over 80 years or high risk, 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 going.

Since 2000, the Department 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 Department 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 | 137 |
| 2 stage operation | 19 |
| Total number of esophagectomy | 156 |
| | |
| Rt-transthoracic esophagectomy | 48 |
| Thoracoscopic esophagectomy | 108 |
| Emergency operation | 15 |
| Others | 32 |
| Total | 203 |

## List of papers published in 2014

## Journal


1. Fujita T, Daiko H. Efficacy and predictor of octreotide treatment for postoperative chylothorax after thoracic esophagectomy. World J Surg, 38:2039-2045, 2014
2. Hosokawa Y, Kinoshita T, Konishi M, Takahashi S, Gotohda N, Kato Y, Honda M, Kaito A, Daiko H, Kinoshita T. Recurrence patterns of esophagogastric junction adenocarcinoma according to Siewert's classification after radical resection. Anticancer Res, 34:4391-4397, 2014
3. Tsubosa Y, Sato H, Tachimori Y, Hokamura N, Hosokawa M, Kinoshita Y, Daiko H, Udagawa H, Ueno M, Seto Y, Jinbo K, Kitagawa Y, Takeuchi H, Park M, Nagasaka S, Yamada H, Ota Y. Multi-institution retrospective study of the onset frequency of postoperative pneumonia in thoracic esophageal cancer patients. Esophagus, 11:126-135, 2014

# Department of Gastric Surgery

**Takahiro Kinoshita, Hidehito Shibasaki, Naoki Enomoto, Toshirou Nishida**

## Introduction

Our Department consists of 2 staff surgeons, 1 senior resident and 5 resident surgeons. Our managing gastric tumors include not only common gastric adenocarcinoma but also adenocarcinoma of the esophagogastric junction (AEG), which is increasing recently, probably due to reduction of HP-infection rates, and gastric submucosal tumors (GIST etc.). Annually 260-300 patients are operated either by means of conventional laparotomy or laparoscopic surgery. Laparoscopic gastrectomy with radical LNs dissection was introduced in 2010 to pursue minimal invasiveness and better quality of life (QOL) for the patients, and in the latest guidelines it is recommended as an option for cStageI cancer. In 2014, about 80% of gastrectomy was performed under laparoscopy, and additionally robot-assisted surgery has been introduced as a clinical investigation. The basis of our surgery is radical extirpation of cancer lesion, but at the same time organ functions and better QOL should be maintained. In addition, we attempt to obtain favorable clinical outcomes for patients with disease with dismal prognoses (scirrhous gastric cancer or with progressive lymph nodes metastasis) by surgery combined with modern chemotherapy regimen, including molecular-targeting drugs.

## 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 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 optimal treatment strategy for each patient. In principle, patients with superficial gastric cancer lesions (cT1a) showing clear margin are treated by endoscopic submucosal dissection (ESD) according to the criteria of the guideline. Some are required to undergo subsequent completion laparoscopic surgery with nodal dissection based on pathological findings of specimen obtained by ESD. Not only distal gastrectomy but also total gastrectomy or function preserving procedures (pylorus-preserving gastrectomy or proximal gastrectomy) are performed laparoscopically. D2 dissection has been also commonly performed under laparoscopy; therefore its indication has been expanded to more advanced cancer. When the tumor infiltrates to adjacent organs (liver, pancreas, etc.), extended operations are chosen. Recently, due to progress of modern chemotherapy regimen, down-staging from cStageIV is sometimes seen. For such patients, we selectively perform conversion surgery to achieve favorable outcomes. For AEGs, transhiatal approach can be safely employed under laparoscopy with better surgical view. When the patients are diagnosed as p-Stage II or III in final pathological findings after operation, postoperative adjuvant chemotherapy with S-I are recommended to them according to the guidelines, but now its duration for p-StageII is investigated by phase-III 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 visited our Department to learn surgical techniques.

## Research activities & 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 Japan Clinical Oncology Group (JCOG)-Gastric Surgery Study Group or other organizations. Patients with gastric cancer are, if eligible to each study, invited to take part in one of the ongoing clinical trials. Current ongoing multi-institutional clinical trials, in which we participate, are below mentioned. A pilot study of robot assisted gastrectomy for clinical stage I gastric cancer using the da Vinci Si surgical system has been conducted as a single-center clinical trial.

1. JCOG 1001 Phase III randomized study to evaluate clinical benefits of bursectomy for patients with SS/SE gastric cancer
2. JCOG 1104 A phase II trial to define optimal period of adjuvant S-1 chemotherapy for pathological stage II gastric cancer patients who underwent D2 gastrectomy
3. JCOG1302-A Validity Study to Confirm the Accuracy of Preoperative Imaging Diagnosis for Stage III Gastric Cancer
4. A prospective cohort study to evaluate proper extent of lymph node dissection for esophagogastric junction cancer

**Table 1. Number of patients**

| | |
|---|---|
| Gastric cancer | 243 |
| Others (GIST etc.) | 28 |

**Table 2. Type of procedure**

| | |
|---|---|
| Open gastrectomy | 45 |
| Distal Gastrectomy | 19 |
| Pylorus-preserving Gastrectomy | 0 |
| Proximal Gastrectomy | 0 |
| Total Gastrectomy | 15 |
| Pancreaticoduodenectomy | 0 |
| Partial Gastrectomy | 2 |
| Others (bypass, exploration, etc.) | 9 |
| Laparoscopic Surgery (robot assisted surgery) | 226 (17) |
| Distal Gastrectomy | 127 (12) |
| Pylorus-preserving Gastrectomy | 2 |
| Proximal Gastrectomy | 16(1) |
| Total Gastrectomy | 33(4) |
| Partial Gastrectomy | 10 |
| Others (bypass, exploration, etc.) | 40 |

**Table 3. Survival rates of gastric cancer**

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

Op.year: 1995.1-2004.12

Stage: Japanese Classification (13th Ed.)

## List of papers published in 2014

### Journal


1. Takahari D, Hamaguchi T, Yoshimura K, Katai H, Ito S, Fuse N, Konishi M, Yasui H, Terashima M, Goto M, Tanigawa N, Shirao K, Sano T, Sasako M. Survival analysis of adjuvant chemotherapy with S-1 plus cisplatin for stage III gastric cancer. Gastric Cancer, 17:383-386, 2014
2. Hosokawa Y, Kinoshita T, Konishi M, Takahashi S, Gotohda N, Kato Y, Honda M, Kaito A, Daiko H, Kinoshita T. Recurrence patterns of esophagogastric junction adenocarcinoma according to Siewert's classification after radical resection. Anticancer Res, 34:4391-4397, 2014
3. Nishida T, Doi T. Improving prognosis after surgery for gastric cancer. Lancet Oncol, 15:1290-1292, 2014
4. Nishida T, Doi T, Naito Y. Tyrosine kinase inhibitors in the treatment of unresectable or metastatic gastrointestinal stromal tumors. Expert Opin Pharmacother, 15:1979-1989, 2014
5. Hosokawa Y, Konishi M, Sahara Y, Kinoshita T, Takahashi S, Gotohda N, Kato Y, Kinoshita T. Limited subtotal gastrectomy for early remnant gastric cancer. Gastric Cancer, 17:332-336, 2014
6. Nakayama Y, Gotohda N, Shibasaki H, Nomura S, Kinoshita T, Hayashi R. Usefulness of the neutrophil/lymphocyte ratio measured preoperatively as a predictor of peritoneal metastasis in patients with advanced gastric cancer. Surg Today, 44:2146-2152, 2014

# Department of Colorectal Surgery

**Norio Saito, Masaaki Ito, Akihiro Kobayashi, Yusuke Nishizawa, Yuji Nishizawa, Mitsuru Yokota, Yuichiro Tsukada, Kenichi Koushi**

## Introduction

The Department of Colorectal Surgery was established 16 years ago. Its main purpose is to bring together the Divisions that are composed of colorectal surgeons and urologists. Cooperation between these Divisions contributes not only to the establishment of effective operative techniques but also to an oncological consensus including consensus on the quality of life (QOL) and the various functions of patients with pelvic malignancies. New surgical procedures, such as nerve-sparing surgery, sphincter-saving surgery, bladder-sparing surgery, pouch surgery and minimally invasive surgery are being developed to prevent postoperative dysfunctions. These new approaches will contribute to better curability and QOL among patients with pelvic malignancies.

## Routine activities

The Department of Colorectal Surgery comprises 7 consultants (5 colorectal surgeons and 2 urologists) and 11 residents. The outpatient clinic is open 5 days a week. More than 360 new patients with colorectal carcinomas and more than 150 new patients with other pelvic malignancies visited this Department during the last year. Treatment plans are discussed at a weekly conference on GI malignancies and at another weekly conference on pelvic malignancies. Many treatment modalities, such as local excision with or without adjuvant chemo- or radiotherapy and other minimally invasive forms of surgery using laparoscopy, have been introduced for the treatment of patients in the early stages of cancer. Laparoscopy-assisted operations (Lap-Ops) with wider lymphadenectomy of up to more than D2 are also increasingly being performed in patients with advanced colorectal carcinomas. Abdominoperineal resection (APR) has, in the past, been the standard surgery in patients with very low rectal cancer; however, partial anal sphincter preserving surgery such as intersphincteric resection (ISR) and direct CAA have been performed in more than 500 patients with very low rectal tumors and has resulted in cure, preservation of anal function, and better QOL.

## Research activities

1) A prospective randomized trial for extending the indications for Lap-Op (JCOG0404 CRC Surg-LAP vs. Open). A total of 77 patients have been registered in this Department. This study has been completed.
2) Intersphincteric resection with or without neoadjuvant mFOLFOX6 study (NAIR Study)- A prospective multi-center trial -A Phase II/III randomized multicenter trial of intersphincteric resection (ISR) with or without preoperative chemotherapy for very low-lying rectal cancer. APR has been the standard surgery for very low rectal cancer located within 5 cm of the anal verge. However, a permanent colostomy causes severe impairment of QOL. This study was designed to evaluate the feasibility and the oncological and functional outcomes of ISR for treatment of very low rectal cancer. Curability with ISR was verified histologically, and acceptable oncological and functional outcomes were obtained in many patients. However, patients need to be informed preoperatively regarding the potential functional adverse effects after ISR. This study is in progress, and 50 patients have been registered.
3) Bladder-sparing surgery for locally advanced rectal cancer involving the prostate. Total pelvic exenteration (TPE) is the standard procedure in such patients. This study aims to evaluate the feasibility of bladder-sparing surgery as an alternative to TPE. This procedure has

been performed in 39 patients with primary or recurrent tumors and permits conservative surgery in selected patients with advanced rectal cancer involving the prostate without compromising local control. The QOL of these patients appears to be better. Evaluation on usefulness and safety of cysto-urethral anastomosis with additional ileal flap in patients with rectal cancer involving the prostate (Ileal flap study) is also in progress.

4) A prospective randomized trial for the feasibility and effect of lateral node dissection in low rectal cancer – (Total) Mesorectal Excision (ME) vs. Lateral Node Dissection with preservation of autonomic nerves (D3 with nerve-sparing) [JCOG0212 CRC Surg.]. In this study, 76 patients have been registered. The final results will be seen soon.
5) Local excision with postoperative chemoradiotherapy for T1・T2 rectal cancer. This study aims to evaluate preoperatively the feasibility and the oncologic outcome of local therapy for T1 and a part of T2 rectal cancer without lymph node metastases. In this study, 82 patients have been registered. The final results will be made clear soon.
6) A prospective cohort study of Reduced Port Surgery for colorectal cancer. This study is currently in progress, 66 patients have been registered.
7) Study on Robotic surgery for rectal cancer. This study is currently in progress, 12 patients have been registered.

## Clinical trials

Other clinical trials are also in progress as follows.

- A Phase I/II trial of chemoradiotherapy concurrent with S-1 plus MMC in patients with clinical stage II/III squamous cell carcinoma of the anal canal (JCOG0903)
- A randomized study of conventional technique vs. no-touch isolation technique (JCOG1006)
- A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer (JCOG1007)
- A randomized Phase III study of mFOLFOX7 or CAPOX plus bevacizumab versus 5-fluorouracil/leucovorin or capecitabine plus bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer (JCOG1018)
- A randomized controlled trial comparing laparoscopic surgery with open surgery in palliative resection of primary tumor in incurable Stage IV colorectal cancer (JCOG1107)
- A Prospective Phase II Trial of Laparoscopic Surgery for Ultra-low Rectal Cancers within Five Centimeters from the Anus or Three Centimeters from the Dentate Line. Under the Japanese Society for Cancer of the Colon and Rectum (JSCCR)
- A prospective study of urinary and sexual dysfunction after surgery for rectal cancer
- A Phase II study of neoadjuvant mFOLFOX6 (+ cetuximab) in patients with resectable pelvic recurrences after rectal cancer surgery
- T-REX Study; the International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer (JSCCR)
- Development of LAP-instruments for colorectal surgery

## Education

- Guiding university students in their studies
- Guiding colorectal surgeons for obtaining medical specialist

## Future prospects

Establishment of less-invasive surgery for cure and function-preserving in cancer patients with colorectal malignances.

**Table 1. Number of patients**

| Primary colorectal canter | | | Other cases |
|---|---|---|---|
| Colon | Rectum | Sub-total | |
| 160 | 216 | 376 | 123 |

**Table 2. Type of procedure**

Operative Procedures (2014.1-2014.12)

| Colon N=160 Laparoscopic(LAP) : 121 Open : 39 | | |
|---|---|---|
| Sigmoidectomy | 59 | (LAP:54) |
| Right (hemi) colectomy | 31 | (LAP:27) |
| Ileocecal resection | 19 | (LAP:18) |
| Limited colectomy | 23 | (LAP:18) |
| Hartmann procedure | 2 | |
| High anterior resection | 2 | (LAP:1) |
| Low anterior resection | 1 | (LAP:1) |
| Left (hemi) colectomy | 3 | (LAP:2) |
| Total pelvic exenteration | 2 | |
| Stoma | 13 | |
| Other | 5 | |

| Rectum N=216 Laparoscopic (LAP) : 141 Robot : 10 Open : 65 | | | |
|---|---|---|---|
| Low anterior resection | 89 | (LAP:75) | (Robot:8) |
| Abdomino Anal resection(AAR)* | 68 | (LAP:51) | |
| High anterior resection | 11 | (LAP:7) | (Robot:2) |
| Abdominoperineal resection (APR) | 8 | (LAP:8) | |
| Hartmann procedure | 2 | | |
| Local excision | 2 | | |
| Total pelvic exenteration | 4 | | |
| Stoma | 25 | | |
| Others | 7 | | |

*Conventional coloanal anastomosis : 21
Partial intersphincteric resection (ISR) : 22
Subtotal ISR : 18
Total ISR : 5
Partial external sphincter resection (ESR) : 2

**Table 3. Survival rates**

| Stage | Colon | | | Rectum | | |
|---|---|---|---|---|---|---|
| | No. of pts | 5-yr survival (%) | | No. of pts | 5-yr survival (%) | |
| | | overall | cancer specific | | overall | cancer specific |
| Stage0 | 10 | 100 | 100 | 14 | 100 | 100 |
| Stage I | 210 | 95.2 | 100 | 171 | 93.6 | 97.6 |
| Stage II | 286 | 90.3 | 84.8 | 215 | 84.5 | 89.4 |
| Stage IIIa | 194 | 82.1 | 86.5 | 179 | 79.3 | 82.0 |
| Stage IIIb | 63 | 71.9 | 74.5 | 123 | 60.5 | 64.1 |
| Stage IV | 167 | 22.0 | 23.2 | 102 | 23.8 | 24.0 |

OP: 2000.1.1-2007.12

## List of papers published in 2014

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# Department of Gastrointestinal Oncology

**Takayuki Yoshino, Atsushi Ohtsu, Toshihiko Doi, Takashi Kojima, Wataru Okamoto, Kohei Shitara, Hideaki Bando, Nozomu Fuse, Yusuke Hashimoto, Ken Hatogai, Sawako Miyoshi**

## Introduction

In 2014, approximately 630 gastrointestinal (GI) cancer patients were treated by staff oncologists and skilled residents in the Department of GI Oncology, which focuses on the optimal chemotherapy W/ or W/O radiation for the treatment of GI cancers.

## Routine activities

Inter-Divisional tumor board conferences with the Surgical/Radiation Oncology Divisions are held regularly to review the current treatment for each patient and to discuss the further treatment strategies. Basically, routine chemotherapy is done on an outpatient basis, and there are approximately 1,900 selected patients who need the hospitalization for the purpose of planned therapy with chemotherapy or palliation. Our activities for each type of GI cancer in 2014 are shown in Table 1 (Number), Table 2 (Treatment), and Table 3 (Efficacy). There are 77 ongoing clinical trials which consisted of 42 Phase I trials including globally first-in-class (FIC), first-in-human (FIH), investigational new drugs (INDs) and 35 Phase II/III clinical trials to approve the INDs.

## Research activities

### Phase I

Our Department has focused more on early stage clinical development of INDs. The number for patient enrolled for Phase I trials have been increasing recently. During April to December 2014, 149 patients were enrolled for Phase I trials. Importantly, the number of FIH trials and trials around the same time as Western countries is increasing. Several results of Phase I trials, such as a HSP90 inhibitor (AUY922), IgG1 monoclonal antibody of PDGFRα (Olaratumab, IMC-3G3), PI3K inihibitor (buparlisib, BKM120), anti-HGF monoclonal antibody (Rilotumumab) as monotherapy or combination with capecitabine+cisplatin, were published or presented at international meetings. Notably, international Phase 1 study of a potent and selective inhibitor of focal adhesion kinase (BI 853520) was selected for oral presentation in 26th EORTC–NCI–AACR Symposium on Molecular Targets and Cancer Therapeutics 2014.

### Esophageal Cancer (EC)

A non-randomized confirmatory study of definitive chemoradiotherapy including salvage treatment in patients with clinical stage II/III esophageal carcinoma (JCOG 0909) was completed. Surgical safety results from JCOG0502 to compare thoracoscopic esophagectomy versus traditional thoracotomy were reported. And the result of JCOG0604: Phase I/II trial of chemoradiotherapy concurrent with S-1 and cisplatin in patients with clinical stage II/III esophageal carcinoma was presented in ASCO-GI 2014. And sub-analysis of the study of JCOG9907 were published or presented at international meeting.

### Gastric Cancer (GC)

The results of a global randomized Phase III trial comparing lapatinib with paclitaxel to placebo with paclitaxel alone (TyTAN) and a multicenter Phase III trial (G-SOX) comparing S-1 plus oxaliplatin to S-1 plus cisplatin were published. We have investigated if each HER2, EGFR and c-Met status is an independent prognostic factor for advanced GC patients who received standard chemotherapy, which indicated poor prognosis of MET positive gastric cancer. Results of other study of comprehensive molecular profiling of advanced gastric cancer using NGS (Next Generation Sequencing) and immunohistochemistry was presented in Poster Highlights Session in ASCO

2014, which identified several possible candidate genes that could be targets for precision medicine. Results of Phase 1 trial of sulfasalazine (SSZ) for 11 patients with gastric cancer were also presented in ASCO 2014. Retrospective analysis of clinical outcomes in 66 patients with advanced gastric cancer treated in Phase I trials was also presented in GI cancer symposium in 2015.

**Colorectal Cancer (CRC)**

Based on the result of prospective multicenter clinical validation study of a multiplex kit for all RAS mutations (RASKET), the Japanese authority approved all RAS testing for the use of anti-EGFR monoclonal antibodies. We have established the nationwide cancer genome screening project (GI-SCREEN 2013-01) to detect the upfront identification of NRAS, BRAF, and PIK3CA mutations, and have moved forward to the SCRUM-Japan GI-screen (UMIN000016343). As the part of BREAC trial, we reported in GI cancer symposium in 2015, the association between the expanded RAS and BRAF non-V600E mutations and lack of the efficacy on anti-EGFR antibody. Based on the results, we are planning the new clinical trial which targets patients with BRAF non-V600E mutations. We also have conducted a confirmatory study called SUNRISE trial of Oncotype 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. The results of SUNRISE will be presented in upcoming international meeting in 2015. Notably, international Phase III study of TAS-102 over placebo (RECOURSE) was selected for oral presentation in ESMO World Congress on GI Cancer 2014.

## Clinical trials

**Esophageal Cancer (EC)**

Three-arm randomized phase III study comparing preoperative CDDP+5-FU (CF) versus docetaxel+CF versus CF-radiation followed by esophagectomy with D2-3 lymphadenectomy for locally advanced esophageal squamous cell cancer (JCOG1109) is going. And a multicenter phase II trial of BKM120 in patients with advanced esophagus cancer is going. As in the single institutional clinical study, Phase II trial of definitive chemoprotontherapy in patients with clinical stage I/II/III esophageal carcinoma is going.

**Gastric Cancer (GC)**

The enrollment for multicenter global trial (JACOB, GATSGY) was completed. A multicenter global phase III trial (ENRICH, ABSOLUTE, BRIGHTER) is ongoing. Several phase 1 or 2 studies of newer agents including c-MET tyrosine kinase inhibitor of MET high GC, FGFR-inhibitor for FGFR high GC as well as immune check point inhibitor are ongoing. The enrollment for a phase II trial of adjuvant chemotherapy with capecitabine plus oxaliplatin and with S-1 plus oxaliplatin has been completed. Several investigator initiated trials of a multicenter phase III trial comparing DCS to cisplatin plus S-1 (JCOG 1013), a multicenter phase II trial comparing 12 months of S-1 to 6 months of S-1 as an adjuvant chemotherapy (JCOG 1104) are ongoing. After confirmation of mode of action of SSZ as cancer stem cell inhibitor, we began phase1 trial of SSZ in combination of cisplatin for cisplatin refractory GC patients.

**Colorectal Cancer (CRC)**

The results of an international phase III trial comparing TAS-102 with BSC (best supportive care) (RECOURSE) were presented in ESMO World Congress on GI Cancer 2014. We have completed the phase1b/2 trial of the novel combination of TAS-102 plus bevacizumab as an investigator-initiated trial (IIT). An international phase III trial which investigate the survival benefits of oral multi-target kinase inhibitor, nintedanib with placebo in a salvage setting (LUME-COLON 1) is ongoing. We are participating two different international phase 1b/2 trials which target the patients with BRAF V600E mutated CRC, whose results of phase 1b part were reported in Poster Highlights Session of ASCO 2014. We have conducted two randomized, multicenter, phase III studies called ACHIEVE and ACHIEVE-2 trial, together with other nations' collaborative groups in US, UK/Australia, Italy, Greece and France.

## Education

Our residents learn the latest evidence-based medicine and apply this knowledge pragmatically to enhance care for patients with GI cancers, and eventually have qualifications as a comprehensive GI oncologist through the daily practice and the direct training from our staffs. Accordingly, our staffs actively provide a pile of valuable opportunities to polish the skill of various chemotherapies, especially in collaboration with Department of Experimental Therapeutics as well as diagnostic & therapeutic endoscopies collaborated with Department of Digestive Endoscopy. We regularly held tumor board meetings and frequently do numerous face-to-face opportunities with experts in different specialties. We instruct them how to conduct valuable clinical trials, the chance to attend international academic conferences, and the best way to present the academic meeting and work on many high-impact articles in scholarly journals. To date, our department has led many residents to become 'true' skilled GI oncologists who play major roles at leading cancer centers across the country

## Future prospects

We continue to provide the best treatment for cancer patients, the best education for residents, and aim to perform the following activities:

1) To provide more the latest, cutting-edged medicine to cancer patients and to foster more the next generation of skilled GI oncologists.
2) To achieve medical innovation from Japan, we aim to play leading roles in the clinical developments of INDs by contributing to various types of clinical trials including FIC, FIH early trials, IITs with proof-of-concept, and international clinical trials.
3) To enhance our research activity, we will establish the research networks with cutting-edged researchers in Japan as well as globally.

**Table 1. Number of new patients**

| | |
|---|---|
| Esophageal | 295 |
| Gastric | 217 |
| Colorectal | 215 |
| Other type of tumors | 54 |
| Total | 746 |

**Table 2. Treatment**

| | | |
|---|---|---|
| Esophageal Cancer | Chemotherapy (include CRT*) | 248 |
| Gastric Cancer | Chemotherapy | 180 |
| Colorectal Cancer | Chemotherapy | 194 |

## List of papers published in 2014

## Journal


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# Department of Digestive Endoscopy

**Kazuhiro Kaneko, Tomonori Yano, Hiroaki Ikematsu, Yasuhiro Oono**

## Introduction

The Department of Digestive Endoscopy covers the fields of the gastrointestinal (GI) tract and head and neck regions. In 2014, over 10,000 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. In addition, Blue LASER imaging (BLI) system was equipped in 2013. Furthermore, endoscopic treatments such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), percutaneous endoscopic gastrostomy (PEG), endoscopic balloon dilation (EBD), radial incision and cutting (RIC), and photodynamic therapy (PDT) have been performed.

In addition, research studies have been conducted in various fields: endoscopic diagnosis and treatment, or prevention for cancer patients in the GI tract and head and neck. Many of the research projects are conducted as prospective clinical studies either in a single institution or in collaboration with other institutions. The present research activities mainly focus on the development of new instruments for endoscopic diagnosis and new endoscopic treatment modalities. In addition, molecular biology research is also performed using blood and tissues samples of patients in order to examine strategies to enable the early detection, prevention, or prediction of prognosis for treatment. These projects are conducted in collaboration with not only commercial companies but also the faculties of Technology and Science of the university.

## Routine activities

Routine endoscopic examinations including magnifying NBI and endoscopic ultrasound are presently used for head and neck, esophageal, gastric, and colorectal cancers, and the NBI or BLI systems have become essential in detecting very early cancer in these areas. With the NBI or BLI systems, a differential diagnosis between neoplasia and non-neoplasia can be performed without the need for any dye solution. Single-balloon enteroscopy and capsule endoscopy are performed for examinations of the small intestine. Follow-up examinations after endoscopic treatment and chemotherapy are also performed in many cases, in addition to routine examinations.

With the recent progress in instruments and techniques, the number of endoscopic treatments has been increasing. EMR is indicated routinely for early GI tract cancers, and ESD is basically used not only for gastric cancers but also for esophageal or colorectal cancers. For the colon and rectum, colonoscopic day surgeries such as polypectomy and EMR are currently performed in one-third of all examinations. Furthermore, EMR and PDT are sometimes indicated as salvage treatments for local residual/recurrent tumors after chemoradiotherapy for esophageal cancer. PEG and EBD are valuable supporting techniques during the treatments of patients with head and neck, and esophageal cancers.

## Research activities

Furthermore, molecular biological analysis of cancers of the esophagus, head and neck, stomach, and colorectum is underway. Importantly, analysis of the genetic polymorphism in the genes coding for alcohol dehydrogenase (ADH 1B) and aldehyde dehydrogenase (ALDH 2) regarding alcohol metabolism is performed as a useful novel strategic approach in the prevention of upper aerodigestive tract cancers. In addition, the relationships between the production of acetaldehyde and oral microflora after consumption of alcohol are being investigated in our study group.

In contrast, developing research into novel endoscopy systems is being performed. Hypoxia imaging is detected for neoplastic lesions of the head and neck and alimentary tracts, with blue visualized images. First in-human clinical trial of hypoxia imaging was finished. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and nanoparticles of the rare earth, doped yttrium oxide. This system is capable of penetrating through the intestinal wall and obtaining images. Furthermore, molecular imaging endoscopy for the use of this system with InGaAs CCD has been developed, since nanoparticles of rare earth act as fluorescent agents. With a low-temperature atmospheric pressure plasmas system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnosis system using photosensitizing agents, such as hypericin and 5ALA, has been constructed. Moreover, a new clinical trial of biodegradable (BD) stent has been performed for patients with benign esophageal stricture after curative treatment, such as ESD, surgery, and chemoradiotherapy.

## Clinical trials

A wide range of many prospective clinical trials is ongoing into the endoscopic treatment of cancers of the esophagus, stomach, and colorectum, as follows: first in-human clinical trial of hypoxia imaging for neoplasia of alimentary tract in a single unit; phase II clinical trial for BD stent implantation for benign esophageal stricture; 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 II trial of combined treatment of endoscopic mucosal resection and chemoradiotherapy for clinical stage I esophageal carcinoma (JCOG0508); a multicenter clinical study for enrollment of early gastric cancer following endoscopic treatment for enrollment system using the Web; a multicenter clinical trial of ESD for undifferentiated gastric cancer (JCOG1009); a multicenter clinical study regarding residual/recurrent rates and observation periods of endoscopic piecemeal mucosal resection (EPMR) for colorectal neoplastic lesions; and the Japan Polyp Study (JPS) for determination of observation periods after endoscopic treatment for colorectal polyps.

## Education

The aim is to cultivate human resources specializing in endoscopic diagnosis and treatment for alimentary tract cancer. Staff supervises individual residents. Positiveness is made importance in a periodic case conference and joint conferences among internal medicine, surgery and radiology. Staff supervises in congress presentation and writing manuscripts after decision of individual themes, and much discussion is made in the department conference. For residents interested in development research, their opportunity to study is supported after graduation.

## Future prospects

Existing endoscopic diagnosis for neoplasia of alimentary tract is performed on the basis of morphological feature of tumor. A molecular imaging endoscopy is a novel system to visualize cancer using specific laser sources under phosphor combined with cancer specific agents. We can obtain a new imaging, since function or metabolic state in cancer cells is visualized. In additional modalities, there are photodynamic diagnosis, endomicroscopy, and hypoxia imaging endoscopy. These modalities will be expected as a next generation endoscopy, and we try innovative development to produce all new endoscopy.

# Department of Hepatobiliary and Pancreatic Surgery

**Masaru Konishi, Shinichiro Takahashi, Naoto Gotohda, Yuichiro Kato, Kazuhiko Kitaguchi**

## 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 hemotherapy for malignancies with dismal prognoses have been conducted.

With the refinements in laparoscopic instruments and advances in surgical experience, laparoscopic surgery is a safe alternative for selected patients with hepatobiliary pancreatic neoplasms, and has fulfilled its indications. In our division, laparoscopic hepatectomy has been performed since 2002, and laparoscopic distal pancreatectomy since 2011.

## Routine activities

Our group is composed of 4 attending surgeons, 1 chief resident, and 5 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 2014, 250 patients with hepatobiliary and pancreatic diseases underwent surgical treatment including 56 laparoscopic hepatectomies and 5 laparoscopic distal pancreatectomies.

## Research activities

We studied the safety margin afforded by the use of stroke volume variation (SVV), in place of central venous pressure (CVP), in the circulatory management during liver resection. The purpose of this study is to conduct a new circulatory management using the Flo Trac ™ system in liver resection and evaluate specific fluctuations of SVV.

## Clinical trials

- JASPAC04 is a randomized Phase II study on neoadjuvant chemotherapy using combination therapy with gemcitabine and S-1 vs. S-1 and concurrent radiotherapy in patients with resected pancreatic cancer. Recruitment started in 2014.
- JASPAC05 is a Phase II study on neoadjuvant S-1 and concurrent radiotherapy for patients with borderline resectable pancreatic cancer. Recruitment started in 2012.
- JCOG1202 (ASCOT) is a Phase III study to compare S-1 with surgery alone as adjuvant chemotherapy for patients with curatively resected extrahepatic bile duct cancer. Recruitment started in 2013.
- JCOG0605 is a randomized Phase III trial to compare FOLFOX with surgery alone as adjuvant chemotherapy for patients with curatively resected liver metastasis from colorectal cancer. Recruitment is on-going.
- EXPERT trial is a randomized Phase III trial of surgery followed by mFOLFOX6 as adjuvant chemotherapy versus peri-operative mFOLFOX6 plus cetuximab for KRAS wild type resectable liver metastases of colorectal cancer.
- COAST 15983 is a global Phase III trial studying adjuvant Regorafenib in patients with colorectal cancer after surgical removal of liver metastases and completion of all planned chemotherapy.

- Recruitment in a Phase III trial on adjuvant chemoprevention with Peretionin for HCC patients following curative local treatment is ongoing.

## Education

'Board certified expert surgeons' is a high level of skill in the field of hepatobiliary-pancreatic surgery. To be qualified as a board certified surgeon, surgeons are required to perform a prescribed number of operations under the guidance of a board certified instructor. The residents of our department are training to get the certifications until the end of the chief resident course.

**Table 1. Number of new patients**

| | |
|---|---|
| Invasive pancreatic cancer | 46 |
| Other pancreatic neoplasms | 11 |
| Hepatocellular carcinoma | 42 |
| Hepatic metastases | 53 |
| Intrahepatic cholangiocarcinoma | 11 |
| Perihilar cholangiocarcinoma | 11 |
| Distal bile duct cancer | 24 |
| Ampullary cancer | 3 |
| Gallbladder cancer | 6 |

**Table 2. Type of procedure**

| | |
|---|---|
| Hepatectomy and pancreaticoduodenectomy | 2 |
| Pancreaticoduodenectomy | 59 |
| Distal pancreatectomy | 14 |
| Total pancreatectomy | 7 |
| Laparoscopic distal pancreatectomy | 5 |
| Hapatectomy with biliary reconstruction | 11 |
| Hapatectomy without biliary reconstruction | 54 |
| Laparoscopic hepatectomy | 56 |
| Others | 42 |
| Total | 250 |

**Table 3. Survival rates**

| Diagnosis | No. of pts | 5-yr survival(%) |
|---|---|---|
| Invasive pancreatic cancer | 367 | 17.7 |
| Hepatocellular carcinoma | 350 | 48.5 |
| Hepatic metastases | 575 | 51.7 |
| Intrahepatic cholangiocarcinoma | 60 | 39.0 |
| Perihilar cholangiocarcinoma | 121 | 42.0 |
| Distal bile duct cancer | 97 | 45.6 |
| Ampullary cancer | 68 | 52.1 |
| Gallbladder cancer | 82 | 47.1 |

## List of papers published in 2014

### Journal


1. Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Gotohda N, Konishi M. Surgical procedure depending on the depth of tumor invasion in duodenal cancer. Jpn J Clin Oncol, 44:224-231, 2014
2. Komai Y, Sakai Y, Gotohda N, Kobayashi T, Kawakami S, Saito N. A novel 3-dimensional image analysis system for case-specific kidney anatomy and surgical simulation to facilitate clampless partial nephrectomy. Urology, 83:500-506, 2014
3. Sugimoto M, Takahashi S, Kojima M, Gotohda N, Kato Y, Kawano S, Ochiai A, Konishi M. What is the nature of pancreatic consistency? Assessment of the elastic modulus of the pancreas and comparison with tactile sensation, histology, and occurrence of postoperative pancreatic fistula after pancreaticoduodenectomy. Surgery, 156:1204-1211, 2014
4. Sugimoto M, Mitsunaga S, Yoshikawa K, Kato Y, Gotohda N, Takahashi S, Konishi M, Ikeda M, Kojima M, Ochiai A, Kaneko H. Prognostic impact of M2 macrophages at neural nvasion in patients with invasive ductal carcinoma of the pancreas. Eur J Cancer, 50:1900-1908, 2014
5. Oba A, Takahashi S, Kato Y, Gotohda N, Kinoshita T, Shibasaki H, Ikeda M, Konishi M. Usefulness of resection for hepatocellular carcinoma with macroscopic bile duct tumor thrombus. Anticancer Res, 34:4367-4372, 2014

# Department of Hepatobiliary and Pancreatic Oncology

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

## Introduction

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

## Routine activities

Our Department is composed of 5 staff oncologists, 1 senior resident and 2 residents, with 35-50 beds in the hospital and conduct clinical rounds for admitted patients every morning and evening. Most new patients with unresectable hepatobiliary and pancreatic tumors are hospitalized for the diagnosis and treatment of tumors. The treatment strategies on individual patient are discussed in weekly tumor board conferences attended by medical oncologists, surgeons, radiologists, radiation oncologists, and pharmacists. Furthermore, we are also responsible for external or endoscopic abdominal ultrasonographic examinations, percutaneous or endoscopic ultrasound-guided biopsies of abdominal masses, percutaneous local ablative therapy for liver tumors, percutaneous or endoscopic biliary drainage and stenting for obstructive jaundice.

## Research activities

Hepatocellular carcinoma (HCC)

The following clinical studies have been investigated for advanced HCC patients: the efficacy and adverse events of sorafenib as a first line chemotherapy in patients with advanced HCC, the prognostic factors in patients with HCC refractory or intolerant to sorafenib and the efficacy and safety of hepatic arterial infusion chemotherapy with cisplatin after sorafenib treatments, etc.

Pancreatic cancer (PC)

FOLFIRINOX has been established as a standard chemotherapy for advanced PC, but the myelosuppression and gastrointestinal toxicities have been reportedly high frequencies. In our hospital, modified regimen of FOLFIRINOX has been adapted and it became easy to manage the toxicities. The number of patients who treated with this regimen was No.1 in Japan. The treatment efficacy and adverse events of modified FOLFIRINOX on clinical practice have been reported, and the efficacies have been clarified to be comparable on each subgroup of patient characteristics to those of original FOLFIRINOX.

Hepatitis B viral (HBV) reactivation following chemotherapy

In a multicenter retrospective cooperative study of patients who developed HBV reactivation following chemotherapy, the clinical features of HBV reactivation and the patient outcomes after HBV reactivation have been clarified. A prospective study has been also conducted to investigate the incidence and outcome of the patients in whom the HBV reactivation developed among the patients with solid tumors receiving first line chemotherapy, and no clinically significant HBV reactivation has been reported to be developed by periodical measurement of HBV DNA and proper management at the reactivation.

## Clinical trials

42 clinical trials (sponsored: 28 trials, investigator-initiated: 21 trials) are ongoing, and 8 clinical trials (sponsored: 4 trials, investigator-initiated: 4 trials) are being planned for the upcoming year.

HCC

A randomized Phase II trial comparing sorafenib vs. observation in combination with TACE is ongoing. Some sponsored trials of lenvatinib, sorafenib plus resminostat, and sorafenib plus TGF-β inhibitor (LY2157299) are ongoing as the first line chemotherapy. As the second line setting, the enrollment of some clinical trials of ALK-1 inhibitor (PF-03446962), rafametinib, nintedanib, pimasertib, a stat 3 inhibitor (AZD9150), etc. have been finished, but some clinical trials of tivantinib, regorafenib, a peptide vaccine including glypican-3 (ONO-7268MX1), etc. are ongoing. As the adjuvant setting after resection or ablation, phase III trials of peretinoin vs. a placebo is also underway.

Biliary tract cancer (BTC)

A randomized Phase III trial comparing adjuvant S-1 with observation in patients with resected BTC (JCOG1202) is ongoing. And a randomized Phase III trial comparing Gemcitabine (Gem) plus S-1 with Gem plus cisplatin (JCOG1113) and a Phase I trial of Gem, cisplatin plus MEK inhibitor (AZD6244) for first line chemotherapy and some sponsored trials of trametinib, and PD-L1 inhibitor for advanced BTCs refractory to Gem are underway.

PC

A multicenter Phase II trial of neoadjuvant S-1 and concurrent radiotherapy for borderline resectable PC (JASPAC05) is ongoing. A Phase III trial of Gem plus TH-302 vs. Gem+Placebo in chemo-naive PC patients has been finished on the enrollments. A randomized Phase II trial of mixed agents of S-1 plus leucovorin (TAS-118) vs. S-1 in Gem refractory PC patients is underway. A multicenter investigators-initiated Phase II trial of GBS-01, which is an orally administered drug rich in arctigenin and has been reported to exert antitumor activity by attenuating the tolerance of cancer cells to glucose deprivation has been conducted in PC patients who are refractory to Gem and fluoropyrimidine therapy.

## Education

For our resident and senior residents, one-to-one training is provided on the daily practice of management of inpatients and outpatients. And they can learn all cancer treatments from local treatments to systemic chemotherapy for hepatic, biliary, and pancreatic cancer patients and the accompanied procedures to make a diagnosis, drainage for obstructive jaundice and management of the adverse events. In addition, they can make a presentation of their research in the domestic and overseas meetings and make a paper in English under the instruction of staff physicians.

## Future prospects

The prognosis of patients with hepatic, biliary, and pancreatic cancers remains dismal and standard treatments for these cancers are limited. In Japan, the incidences of these cancers, especially HCC and BTC, are higher than those in western countries. Therefore, we must conduct a lot of novel and promising clinical trials and researches which take a lead worldwide. And it is necessary to develop the biomarker research as accompanied with cancer treatment in cooperated with our cancer research center and pharmaceutical companies to identify the more effective and less toxic patients subgroups.

**Table 1. Number of new patients**

| | |
|---|---|
| Hepatocellular carcinoma | 82 |
| Biliary tract cancer | |
| Intrahepatic cholangiocarcinoma | 28 |
| Extrahepatic cholangiocarcinoma | 24 |
| Gallbladder cancer | 35 |
| Papilla of vater carcinoma | 5 |
| Pancreatic cancer | |
| Locally advanced disease | 42 |
| Metastatic disease | 154 |
| Other | 15 |
| Total | 385 |

**Table 2. Type of procedure**

| | |
|---|---|
| Hepatocellular carcinoma | |
| Radiofrequency ablation | 82 |
| Transarterial chemoembolization | 196 |
| Intra-arterial chemotherapy | 47 |
| Systemic chemotherapy | 47 |
| Proton beam radiotherapy | 30 |
| Biliary tract cancer | |
| Systemic chemotherapy | 118 |
| Radiotherapy | 7 |
| Pancreatic cancer | |
| Systemic chemotherapy | 264 |
| Chemoradiotherapy | 8 |
| Total | 799 |

## List of papers published in 2014

## Journal


1. Sunakawa Y, Furuse J, Okusaka T, Ikeda M, Nagashima F, Ueno H, Mitsunaga S, Hashizume K, Ito Y, Sasaki Y. Erratum to: Regorafenib in Japanese patients with solid tumors: phase I study of safety, efficacy, and pharmacokinetics. Invest New Drugs, 32:104-12, 2014
2. Okusaka T, Ojima H, Morizane C, Ikeda M, Shibata T. Emerging drugs for biliary cancer. Expert Opin Emerg Drugs, 19:11-24, 2014
3. Hagihara A, Ikeda M, Ueno H, Morizane C, Kondo S, Nakachi K, Mitsunaga S, Shimizu S, Kojima Y, Suzuki E, Katayama K, Imanaka K, Tamai C, Inaba Y, Sato Y, Kato M, Okusaka T. A phase I study of sorafenib combined with transcatheter arterial infusion of cisplatin for advanced hepatocellular carcinoma. Cancer Sci, 105:354-8, 2014
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5. Shoji H, Morizane C, Hiraoka N, Kondo S, Ueno H, Ohno I, Shimizu S, Mitsunaga S, Ikeda M, Okusaka T. Twenty-six Cases of Advanced Ampullary Adenocarcinoma Treated with Systemic Chemotherapy. Jpn J Clin Oncol, 44:324-30, 2014
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7. Okusaka T, Ikeda M, Fukutomi A, Kobayashi Y, Shibayama K, Takubo T, Gansert J. Safety, Tolerability, Pharmacokinetics and Antitumor Activity of Ganitumab, an Investigational Fully Human Monoclonal Antibody to Insulin-like Growth Factor Type 1 Receptor, Combined with Gemcitabine as First-line Therapy in Patients with Metastatic Pancreatic Cancer: A Phase 1b Study. Jpn J Clin Oncol, 44:442-7, 2014
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12. Ikeda M, Shiina S, Nakachi K, Mitsunaga S, Shimizu S, Kojima Y, Ueno H, Morizane C ,Kondo S, Sakamoto Y, Asaoka Y, Tateishi R, Koike K, Arioka H, Okusaka T. Phase I study on the safety, pharmacokinetic profile, and efficacy of the combination of TSU-68, an oral antiangiogenic agent, and S-1 in patients with advanced hepatocellular carcinoma. Invest New Drugs, 32:928-36, 2014
13. Kudo M, Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, Yamakado K, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T, Minami T; Liver Cancer Study Group of Japan. Transarterial chemoembolization failure/refractoriness: JSHLCSGJ criteria 2014 update. Oncology, 87 Suppl 1:22-31, 2014
14. Shiba S, Okusaka T, Ikeda M, Saito H, Ichida T. Characteristics of 18 patients with hepatocellular carcinoma who obtained a complete response after treatment with sorafenib. Hepatol Res, 44:1268-76, 2014
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# Department of Urology

**Yasuyuki Sakai, Yoshinobu Komai**

## Introduction

The Department of Urological Surgery has existed as part of the Department of Pelvic Surgery at the National Cancer Center Hospital East from 2003. This Department mainly treats diseases of the pelvic organs, including urogenital cancer, with the aim of preserving the sexual and/or voiding functions under minimally invasive surgery.

## Routine activities

Outpatient activities: An outpatient clinic is open 2 days a week as a Urology Department. Flexible cystoscopy, abdominal ultrasonography, retrograde pyelography and some prostate biopsies are performed in the outpatient clinic. Superficial bladder cancer (G3, cis, or recurrent tumor) after

TUR-Bt is treated by instillation of BCG into the bladder. Advanced urogenital cancers including stage D2 prostate cancer are referred to the Medical Oncology Division for chemotherapy or hormonal therapy. Extrinsic obstructions of the upper urinary tract that directly result from invasion of an adjacent malignancy or peritoneal metastasis are also treated. In most cases, internal stenting is better tolerated than percutaneous nephrostomy. 67 patients newly received ureteral stents and 25 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 about 28 combination surgeries with colorectal surgeons. In the Department of Urology, 102 general anaesthesia surgeries, 77 spinal anesthesia surgeries and 39 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 muscle invasive bladder cancer, combination therapy of hormone and radiation for prostate cancer, treatment strategies for metastatic renal cell carcinoma and testicular cancer, and so on, are determined in the meeting.

## Research activities

In recent years, partial nephrectomy has become the standard treatment of T1 renal cell carcinoma instead of radical nephrectomy. We reported on the Synapse Vincent 3D image analysis system for kidney surgery. Its 3D images and surgical simulation helped not only surgeons in their performance of clampless partial nephrectomy but also patients in their understanding of the operation. Total pelvic exenteration (TPE) is the standard procedure for locally advanced rectal cancer involving the prostate and seminal vesicles. We evaluated the feasibility of bladder-sparing surgery as an alternative to TPE. We performed concomitant prostatectomy and cysto-urethral anastomosis.

## Clinical trials

1. A retrospective study of perioperative results in partial nephrectomy for renal cell carcinoma
2. An estimate of the prevalence of Lynch syndrome in upper urinary tract urothelial cancer
3. Development and validation of a nomogram to predict recurrences of upper urinary tract urothelial cancer in Japanese patients
4. A Phase II clinical study of robotic assisted radical prostatectomy by da Vinci S/Si Surgical System
5. A Phase III study: BCG instillation for high grade T1 bladder cancer (JCOG1019)

**Table 1. Number of new patients**

| | |
|---|---|
| Renal cell carcinoma | 20 |
| Upper urinary tract urothelial carcinoma | 18 |
| Bladder cancer | 45 |
| Prostate cancer | 51 |
| Testicular cancer | 3 |

**Table 2. Type of procedure**

| | |
|---|---|
| Radical nephrectomy | 4 |
| Partial nephrectomy | 16 |
| Nephroureterectomy | 18 |
| Radical cystectomy | 15 |
| TURBT | 69 |
| Radical prostatectomy (RARP) | 34 (31) |

## List of papers published in 2014

## Journal


1. Komai Y, Sakai Y, Gotohda N, Kobayashi T, Kawakami S, Saito N. A novel 3-dimensional image analysis system for case-specific kidney anatomy and surgical simulation to facilitate clampless partial nephrectomy. Urology, 83:500-506, 2014
2. Kihara K, Saito K, Komai Y, Fujii Y. Integrated image monitoring system using head-mounted display for gasless single-port clampless partial nephrectomy. Wideochir Inne Tech Malo Inwazyjne, 9:634-637, 2014
3. Ishioka J, Masuda H, Kijima T, Tatokoro M, Yoshida S, Yokoyama M, Matsuoka Y, Numao N, Koga F, Saito K, Fujii Y, Sakai Y, Arisawa C, Okuno T, Nagahama K, Kamata S, Yonese J, Kageyama Y, Noro A, Morimoto S, Tsujii T, Kitahara S, Gotoh S, Kihara K. Bimodal pattern of the impact of body mass index on cancer-specific survival of upper urinary tract urothelial carcinoma patients. Anticancer Res, 34:5683-5688, 2014
4. Fukushima H, Saito K, Ishioka J, Matsuoka Y, Numao N, Koga F, Masuda H, Fujii Y, Sakai Y, Arisawa C, Okuno T, Yonese J, Kamata S, Nagahama K, Noro A, Morimoto S, Tsujii T, Kitahara S, Gotoh S, Higashi Y, Kihara K. Equivalent survival and improved preservation of renal function after distal ureterectomy compared with nephroureterectomy in patients with urothelial carcinoma of the distal ureter: a propensity score-matched multicenter study. Int J Urol, 21:1098-1104, 2014

# Department of Musculoskeletal Oncology and Rehabilitation

**Fumihiko Nakatani**

## Introduction

The Department of Musculoskeletal Oncology and Rehabilitation of the National Cancer Center Hospital East is a team consisting of a panel of orthopedic surgeons and rehabilitation professionals starting from 2012. We strive to provide expert interdisciplinary care for a variety of benign and malignant bone and soft tissue tumors and tumor-like conditions, and we also provide comprehensive rehabilitation services. Currently, we have a chief orthopedic surgeon and 2 rehabilitation staff engaging in the treatment of a variety of patients with the aid of other orthopedic staff from the National Cancer Center Hospital (NCCH).

## Routine activities

Our outpatient service is open 3 days a week (Mondays, Wednesdays and Fridays) for patients with a variety of musculoskeletal tumors or cancer patients who need rehabilitation care. We also manage the patients who suffer bone metastases, other orthopedic diseases, consulted form other cancer specialists on a daily basis. To provide the prosthetic and orthotic care for our patients, a special outpatient service is open every Friday. In cases patients who need multidisciplinary approaches to the treatments, we offer appropriate referral to the NCCH for further treatments.

In 2014, we have conducted 43 operations in total, consisted of twenty resections of soft tissue tumors, 17 osteosyntheses of pathological fractures form bone metastases and 5 operations for bone tumors.

On September 2014, we have opened the spacious rehabilitation unit with adequate equipment for the aim to reduce the common side effects of cancer treatment, including fatigue, weakness, poor endurance, pain, nausea, anxiety, depression and loss of confidence. As a result, we have conducted rehabilitation of 493 patients in 2014 (Table 1).

## Research activities

We have been focusing on regional cooperation with the local physiotherapists of the Kashiwa-city for the aim to provide cancer patients of the community with seamless rehabilitation care after the invasive cancer operations. Until now, we have established the standard methods of physiotherapy and functional evaluations in common.

## Clinical trials

We have been focusing on the standardization of multidisciplinary treatment for bone and soft tissue sarcomas cooperated with the Musculoskeletal Oncology Department of the NCCH. Two multi-institutional clinical trials are active as follows:

1. A multi-institutional Phase III clinical trial of multidrug adjuvant chemotherapy for osteosarcoma (JCOG 0905) has been ongoing since 2010.
2. A multi-institutional Phase III clinical trial of adjuvant chemotherapy for high-grade soft part sarcoma (JCOG 1306) has started in February 2014.

## Education

We have been engaging in several educational lectures for the medical staff to prevail the importance of rehabilitation for cancer treatment. We also provide some instructive lectures for the medical staff of the community.

## Future prospects

Recent evolution of the cancer treatment increases the demands for the orthopedic care and rehabilitation of cancer survivors. We must consistently focus on the standardization for the methodology of rehabilitation for all the cancer patients, which will be beneficial for the augmentation of quality of life for the cancer patients.

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

| Department | 2012 | 2013 | 2014 |
|---|---|---|---|
| Hematology | 39 | 24 | 11 |
| Thoracic oncology | 35 | 44 | 54 |
| Thoracic surgery | 29 | 13 | 30 |
| Head and neck oncology | 21 | 10 | 5 |
| Gastrointestinal oncology | 21 | 23 | 59 |
| Esophageal surgery | 19 | 34 | 60 |
| Musculoskeletal oncology | 17 | 52 | 23 |
| Palliative medicine | 15 | 18 | 2 |
| Colorectal surgery | 13 | 2 | 42 |
| Hepatobiliary and pancreatic oncology | 12 | 15 | 24 |
| Breast and medical oncology | - | 27 | 34 |
| Head and neck surgery | - | 13 | 97 |
| Others | 24 | 19 | 52 |
| Total | 146 | 245 | 493 |

## List of papers published in 2014

### Journal


1. Miyamoto S, Kayano S, Kamizono K, Fukunaga Y, Nakao J, Nakatani F, Kobayashi E, Sakuraba M. Pedicled superficial femoral artery perforator flaps for reconstruction of large groin defects. Microsurgery, 34:470-474, 2014
2. Nishida Y, Kobayashi E, Kubota D, Setsu N, Ogura K, Tanzawa Y, Nakatani F, Kato Y, Chuman H, Kawai A. Chronic expanding hematoma with a s igni f i cant ly high fluorodeoxyglucose uptake on $^{18}$F-fluorodeoxyglucose positron emission tomography, mimicking a malignant soft tissue tumor: a case report. J Med Case Rep, 8:349, 2014

# Department of Hematology

**Kunihiro Tsukasaki, Masahiko Nezu, Sachiko Seo, Kuniaki Itou**



## Introduction

The staff physicians and residents of the Department of Hematology carry out clinical and research activities related to multi-disciplinary treatment of patients with hematological malignancies which consists of more than 100 disease entity in the WHO classification (version 2008). Our Department focuses on early and late phases of clinical trials in collaboration with Research Center for Innovative Oncology and Japan Clinical Oncology Group (JCOG), respectively, especially on lymphoid malignancies.

## Routine activities

The number of patients with newly diagnosed hematologic malignancies in our Department is increasing, and approximately 250 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. Morning case conference on inpatient care of our Department is held from Mondays to Friday, and a weekly case conference on new patients visiting our clinic is held on Thursday evenings. On Wednesday evenings, a weekly joint conference on lymphoid malignancies with expert pathologists and an educational cytology conference on bone marrow specimens are held. Joint morning journal club of Departments of ours and Breast and Medical Oncology is held on Mondays and Fridays.

## Research activities

Ancillary studies associated with retrospective case series and clinical trials at this Department have been continuously conducted focusing on several kinds on hematological malignancies and their complications. Recently, nation-wide survey of human T-lymphotropic virus type I (HTLV-1) associated adult T-cell leukemia-lymphoma (ATL) is ongoing by us under a grant for Cancer Research from the Ministry of Health to elucidate the pathophysiology including geographical findings as compared to those surveys in 1980' to 1990'.

## Clinical trials

Clinical trials on hematological malignancies performed by our Department comprise protocols prepared in-house and participation in the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG-LSG), the Japan Adult Leukemia Study Group (JALSG) and others. The Department participated in pharmaceutical company-sponsored 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 melpharan, cyclophosphamide, etoposide and dexamethasone (LEED) with APBSCT in patients with newly diagnosed poor risk CD20+ DLBCL (JCOG0908); a randomized Phase II study of two induction treatments of melphalan, prednisolone, plus bortezomib, JCOG-MPB versus modified PETHEMA-MPB, in elderly patients or non-elderly patients refusing transplant with untreated symptomatic myeloma (JCOG1105); and a Phase II study of mLSG15 chemotherapy followed by allo-HSCT, comparing the results with historical control 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 (JCOG0907). A Phase III study evaluating the efficacy of combination of interferon-alpha (IFN) and zidovudine (AZT) as compared to watchful-waiting for indolent ATL (JCOG1111) is ongoing under the highly advanced medical technology assessment system because IFN and AZT are not covered for ATL by the National Health Insurance in Japan.

**Table 1. Number of new patients**

| | |
|---|---|
| Non-Hodgkin's lymphoma | 155 |
| Hodgkin's lymphoma | 7 |
| Multiple myeloma | 25 |
| Acute leukemia | 2 |
| Chronic leukemia | 10 |
| Others | 48 |
| Total | 247 |

**Table 2. Type of procedure**

| | |
|---|---|
| PBSCT for non-Hodgkin's lymphoma in relapse | 2 |
| PBSCT for myeloma in remission | 5 |
| Total | 7 |

## List of papers published in 2014

### Journal


1. Yamaguchi M, Takata K, Yoshino T, Ishizuka N, Oguchi M, Kobayashi Y, Isobe Y, Ishizawa K, Kubota N, Itoh K, Usui N, Miyazaki K, Wasada I, Nakamura S, Matsuno Y, Oshimi K, Kinoshita T, Tsukasaki K, Tobinai K. Prognostic biomarkers in patients with localized natural killer/T-cell lymphoma treated with concurrent chemoradiotherapy. Cancer Sci, 105:1435-1441, 2014
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4. Tsukasaki K, Tobinai K. Human T-cell lymphotropic virus type I-associated adult T-cell leukemia-lymphoma: new directions in clinical research. Clin Cancer Res, 20:5217-5225, 2014
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7. Taniguchi H, Hasegawa H, Sasaki D, Ando K, Sawayama Y, Imanishi D, Taguchi J, Imaizumi Y, Hata T, Tsukasaki K, Uno N, Morinaga Y, Yanagihara K, Miyazaki Y. Heat shock protein 90 inhibitor NVP-AUY922 exerts potent activity against adult T-cell leukemialymphoma cells. Cancer Sci, 105:1601-1608, 2014
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### Book


1. Tsukasaki K, Watanabe T, Tobinai K. Adult T-cell Leukemia-Lymphoma. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE (eds), Abeloff's Clinical Oncology, 5th Edition, USA, Churchill Livingstone, an imprint of Elsevier, pp 2076-2091, 2014
2. Tsukasaki K, Tobinai K. Adult T-cell Leukemia- Lymphoma. In: Dreyling M, Williams ME (eds), Rare Lymphomas, Germany, Springer-Verlag Berlin Heidelberg, pp 99-110, 2014

# Department of Dentistry

**Tetsuhito Konishi, Toshiro Miyata, Tomoko Kaneda**

## Introduction

We are attempting to cope with the diverse intraoral complications associated with cancer treatment and to maintain and improve the patients' quality of life (QOL) in the field of dentistry.

Cancer treatment is frequently associated with a variety of intraoral complications, such as mucositis, taste disorder, dry mouth, pain, and infection. In particular, in patients undergoing treatment for head and neck cancer (chemoradiotherapy, surgery) and hematopoietic stem cell transplantation, severe intraoral symptoms may occur, and strict infection control measures are needed.

When such measures are inadequate, composite complications may result in secondary complications such as eating disorders and undernutrition, and the oral cavity may serve as a source of systemic infections; these may lead to the need for deferring or discontinuing treatment, making continuation and completion of cancer treatment difficult.

To manage and prevent intraoral complications, we evaluate and stabilize the oral status before the initiation of cancer treatment. Proactive intervention by dentists or dental hygienists to educate the patients, their families, and the attending medical staff is extremely important.

## Routine activities

We undertake efforts to prevent infection of wounds and aspiration pneumonia and to reduce other complications by oral hygiene management before and after surgery. To maintain postoperative functions of jaw defects, we are attempting to correct speech-language and eating functions by preparing appropriate artificial dentition and prostheses at an early stage, thereby improving the QOL of patients after treatment. For patients receiving chemotherapy and radiotherapy, we are supporting continuation and completion of treatment by taking measures to prevent infections arising from the dentistry realm and mucositis and by reducing pain. In regard to delayed complications, we are undertaking preventive and treatment activities for multiple dental caries, osteomyelitis of the jaw, and necrosis of the jaw bone. Patients treated over the long-term with zoledronic acid or denosumab may develop Medication-Related Osteonecrosis of the Jaw(MRONJ) as a result of contamination of the oral cavity and tooth extraction; thus, we are undertaking measures to prevent/ treat this complication.

By participating in multidisciplinary conferences, we apply prevailing practices and information updates to future medical care support. In 2014, the numbers of new and revisiting patients were 874 and 7,491, respectively, and the total number of patients was 8,365. These numbers represent an approximately 1.5-fold increase as compared to those in the first year when dentists at the National Cancer Center Hospital East began to hold full-time positions. We believe that the importance of supportive care in cancer has been recognized.

## Research activities

We are participating in a multicenter study being conducted to evaluate the effectiveness of proactive use of supportive care for preventing serious oral mucositis in patients with head and neck cancer undergoing chemoradiotherapy.

We are carrying out a study on multiple dental caries and radiation-induced osteomyelitis developing after radiotherapy for head and neck cancers. In addition, we are a part of the nutrition support team.

We cooperate with other facilities for the establishment of oral care programs for patients with head and neck cancers receiving chemoradiotherapy.

# Department of Pediatric Oncology

**Ako Hosono**



## 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 overburdening 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.

One clinical trial described below is currently active.

A Phase I trial of immunotherapy using HLA-A2 and A24-restricted glypican-3 peptide vaccine for pediatric tumors.

**Table 1. Number of new patients**

| | |
|---|---|
| Benign bone tumors | 12 |
| Soft tissue sarcoma | 3 |
| Rhabdomyosarcoma | 1 |
| Ewing sarcoma | 2 |
| Leiomyosarcoma | 2 |
| Synovial sarcoma | 1 |
| Hepatoblastoma | 1 |

# Department of Anesthesiology and Intensive Care Unit

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

## Introduction

The Department of Anesthesiology and Intensive Care Unit (ICU) consists of 4 staff members (3 Japan Society of Anesthesiologists Board Certified Anesthesiologists and a JSA Qualified Anesthesiologist) and 2 or 3 rotating residents. Each year, we provide more than 2,500 anesthesia services in 8 operating rooms and over 1,200 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. 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

4 staff members (2 full-time and 2 visiting anesthesiologists), 3 rotating residents and 12 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 problem and strategy for patients with various complications. In 2014 we provided 2,697 anesthesia services (Table 1). Annual number of patients admitted to the ICU was 1,458, and more than 95% of them were postsurgical patients (Table 2).

## Education

The Department of Anesthesiology and Intensive Care Unit has no resident. For rotating residents we provide opportunities of epidural anesthesia, one lung ventilation technique for thoracotomy, and difficult airway management including fiberoptic intubation. A Journal club is also held once a week other than everyday morning conference. We support residents who hope to obtain the qualification of anesthesiologist or JSA Qualified Anesthesiologist during rotation periods.

## Future prospects

In 2015 one staff anesthesiologist increases and a senior resident belonging to a surgical division is to be assigned to our Department for the study of hemodynamic change during liver resection. With these additional members the increase of 100-150 operations are expected next year. Under the NEXT project a construction plan of new surgical and endoscopic center which has 12 operating rooms has been launched. We are going to be involved in the design of operating rooms.

**Table 1. Number of anesthesia cases**

| Type of Surgery | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| Head and Neck | 515 | 424 | 454 | 423 | 409 |
| Thoracic | 488 | 466 | 473 | 501 | 520 |
| Esophageal | 137 | 126 | 182 | 201 | 215 |
| Gastric, Hepatobiliary, Pancreatic | 542 | - | - | | |
| Hepatobiliary and Pancreatic | - | 269 | 231 | 282 | 253 |
| Gastric | - | 286 | 308 | 292 | 268 |
| Colorectal | 491 | 426 | 453 | 479 | 550 |
| Urology | 88 | 78 | 107 | 114 | 111 |
| Orthopedic | - | - | 22 | 43 | 34 |
| Breast | 297 | 291 | 309 | 325 | 315 |
| Plastic and Reconstructive | - | - | 3 | 8 | 20 |
| Others | - | - | - | - | 2 |
| Total | 2,558 | 2,366 | 2,542 | 2,668 | 2,697 |

**Table 2. Number of patients admitted to the ICU**

| | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| Number of Patients | 1,435 | 1,228 | 1,412 | 1,458 | 1,348 |

# Department of Palliative Medicine

**Hiroya Kinoshita, Yoshihisa Matsumoto, Hideaki Hasuo, Tomofumi Miura, Kazuaki Hiraga, Keita Tagami, Hanako Iwamoto, Yoriko Herai**

## Introduction

The purpose of our Department is to improve the quality of life in the cancer patients and their family caregivers by management of irritable symptom burden and establishment of a regional palliative care system. Therefore, we provide 3 palliative care services; 1) outpatient clinic, 2) supportive care team and 3) palliative care unit.

## Routine activities

1) Outpatient clinic

Patients with or without anti-cancer therapy consult our outpatient clinic for management of their devastating symptoms or support to decide where and how spend their lives. The concept of early palliative care gradually spread, the consultations of patient undergoing anti-cancer therapy have been increasing.

2) Supportive care team

This team consist of physician, psycho-oncologist, nurse, dietician, physiotherapist speech-language-hearing therapist. Our supportive care team performs a multidisciplinary approach for inpatients with various sufferings in the oncology floor.

3) Palliative care unit

Our palliative care unit is Japanese version of acute palliative care unit (APCU). The features of APCU are multidimensional assessment, rapid symptom control and intensive psychosocial care with shorter length of stay and lower death rate than in traditional PCU. Medical social worker greatly contributes to a transition to palliative home care and a transfer to other hospital.

## Research activities

The aim of research in our Division is to establish the regional palliative care system and to integrate the early palliative care with oncology. Following researches are conducted;

1. A system construction of counseling-and-support centers and regional palliative care in a disaster stricken area.
2. An application of "Information and Communication Technology" for regional palliative care system.
3. A feasibility study of the integration of early palliative care in metastatic lung cancer.
4. A prospective cohort study about end of life care discussions and informal caregiver's burdens.
5. A registration for Japanese multicenter cohort studies and international multicenter project.

## Education

The purpose is to promote understanding about palliative care in cancer patients and their families for residents. Residents can train in home palliative care on request. To spread the knowledge of primary palliative care, we held several workshops for medical staff in the NCCHE and for regional palliative care staff.

## Future prospects

Our Department will continue above activities and develop new researches to improve QOL in cancer patients and their family caregivers.

## List of papers published in 2014

## Journal


1. Morita T, Sato K, Miyashita M, Yamagishi A, Kizawa Y, Shima Y, Kinoshita H, Suzuki S, Shirahige Y, Yamaguchi T, Eguchi K. Does a regional comprehensive palliative care program improve pain in outpatient cancer patients? Support Care Cancer, 22:2445-2455, 2014
2. Yamagishi A, Sato K, Miyashita M, Shima Y, Kizawa Y, Umeda M, Kinoshita H, Shirahige Y, Akiyama M, Yamaguchi T, Morita T. Changes in quality of care and quality of life of outpatients with advanced cancer after a regional palliative care intervention program. J Pain Symptom Manage, 48:602-610, 2014
3. Imura C, Morita T, Kato M, Akizuki N, Kinoshita H, Shirahige Y, Suzuki S, Takebayashi T, Yoshihara R, Eguchi K. How and why did a regional palliative care program lead to changes in a region? A qualitative analysis of the Japan OPTIM study. J Pain Symptom Manage, 47:849-859, 2014
4. Sasahara T, Watakabe A, Aruga E, Fujimoto K, Higashi K, Hisahara K, Hori N, Ikenaga M, Izawa T, Kanai Y, Kinoshita H, Kobayakawa M, Kobayashi K, Kohara H, Namba M, Nozaki-Taguchi N, Osaka I, Saito M, Sekine R, Shinjo T, Suga A, Tokuno Y, Yamamoto R, Yomiya K, Morita T. Assessment of reasons for referral and activities of hospital palliative care teams using a standard format: a multicenter 1000 case description. J Pain Symptom Manage, 47:579-587 e576, 2014
5. Miura T, Matsumoto Y, Motonaga S, Hasuo H, Abe K, Kinoshita H. Dyspnea, relative youth and low daily doses of opioids predict increased opioid dosage in the last week of a terminal cancer patient's life. Jpn J Clin Oncol, 44:1082-1087, 2014

# Department of Psycho-Oncology Service

**Asao Ogawa, Yosio Iwata, Daisuke Fujisawa, Hiroyuki Nobata, Kensuke Higa, Lina Orikabe, Daisuke Fujisawa, Junko Ueda, Natsuki Hori, Rina Kakinuma**

## Introduction

The Department of Psycho-Oncology (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, 3 clinical psychologists, and 2 psychiatry residents. The clinical activities include psychiatric consultation, involving comprehensive assessment and addressing of psychiatric problems of cancer patients. The patients are either self-referred or referred by their oncologists in charge. The consultation data are shown in the Table. Psychiatric diagnosis is based on the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria. Consultation data also includes individuals who are family members of cancer patients.

A conference with the Supportive Care Team is held on Wednesdays, and a multicenter joint clinical teleconference involving 6 cancer center hospitals and 3 university hospitals is held on Thursdays. In 2014, the Supportive Care Center was developed. This center is the multi professional attention to the individual's overall physical, psychosocial, and social needs, cooperate with the Department of Psycho-Oncology.

**Table 1. Psychiatric consultation data (n=973; January-December, 2014)**

| Section | | N (%) |
|---|---|---|
| Age | Mean ± SD (median, range) (yr) | 64.4±12.6 (67,15 ～ 92) |
| Gender | (male/female) | 599 (61.6%) / 374 (38.4%) |
| Inpatient / Outpatient | | 685 (70.4%)/288 (29.6%) |
| Cancer patient / Family member | | 939 (96.5%) / 34 (3.5%) |
| Cancer site | Head and Neck | 192 (19.7%) |
| | Lung | 178 (18.3%) |
| | esophagus | 99 (10.2%) |
| Stage | I/II/III/IV/Recurrent | 82 (8.4%) / 70 (7.7%) / 120 (12.3%) / 410 (42.1%) / 143 (14.7%) / |
| PS | 0/1, 2/3, 4 | 288 (29.6%) / 516 (53.0%) / 16 (17.4%) |
| Psychiatric diagnosis | Delirium | 247 (25.4%) |
| | Adjustment disorders | 169 (17.4%) |
| | Major depression | 26 (2.7%) |
| | Dementia | 90 (9.2%) |
| | No diagnosis | 139 (14.3%) |

## List of papers published in 2014

### Journal


1. Shibayama O, Yoshiuchi K, Inagaki M, Matsuoka Y, Yoshikawa E, Sugawara Y, Akechi T, Wada N, Imoto S, Murakami K, Ogawa A, Akabayashi A, Uchitomi Y. Association between adjuvant regional radiotherapy and cognitive function in breast cancer patients treated with conservation therapy. Cancer Med, 3:702-709, 2014
2. Nakanotani T, Akechi T, Takayama T, Karato A, Kikuuchi Y, Okamoto N, Katayama K, Yokoo M, Ogawa A. Characteristics of elderly cancer patients' concerns and their quality of life in Japan: a Web-based survey. Jpn J Clin Oncol, 44:448-455, 2014
3. Yokoo M, Akechi T, Takayama T, Karato A, Kikuuchi Y, Okamoto N, Katayama K, Nakanotani T, Ogawa A. Comprehensive assessment of cancer patients' concerns and the association with quality of life. Jpn J Clin Oncol, 44:670-676, 2014

# Supportive Care Team

**Hiroya Kinoshita, Yoshihisa Matsumoto, Hideaki Hasuo, Tomofumi Miura, Asao Ogawa, Yoshio Iwata, Naoko Kobayashi, Chiyuki Sasaki, Shinya Motonaga, Jyunya Ueno, Yoshie Iino, Kazuaki Hiraga, Daisuke Fujisawa, Hiroyuki Nobata, Keita Tagami, Hanako Iwamoto, Kensuke Higa, Lina Orikabe, Kentaro Abe, Junko Ueda, Natsuki Hori, Rina Kakinuma, Hideo Uesugi, Kumi Nakamura, Kentaro Abe, Taichi Watanabe, Hatoe Sakamoto**

## Introduction

The Supportive Care Team (SCT), established in October 2005, primarily aims to improve care for cancer patients and families facing a life-threatening illness. The role of the SCT is to implement comprehensive cancer care by assessing unrelieved symptoms (physical and psychiatric) and unattended needs, as well as efficiently managing physical symptoms, providing psychological support, and coordinating services.

## Routine activities

The SCT is an interdisciplinary team composed of palliative care physicians, psychiatrists, certified nurse specialists, certified nurses, clinical psychologists, pharmacy practitioners, registered dietitians and social workers. The SCT keeps regular contact with clinician-teams in charge, discusses patients' needs, and refers patients and families to the appropriate services. Interdisciplinary team conferences and SCT rounds are held on Wednesdays. The SCT consultation data are shown in the table.

## Clinical trials

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

**Table 1. Supportive Care Team consultation data (n =929; January-December, 2014)**

| | | N (%) |
|---|---|---|
| Age | Mean ± SD (range) (yr) | 64.3±12.4 |
| | (male/female) | 599 (61.6%) / 374 (38.4%) |
| Gender | (male/female) | 612 (66%) / 317 (34%) |
| Service | Palliative care/ Psycho-oncology | 244 / 685 |
| Performance status | 0/ 1/ 2/ 3/ 4 | 127 (14%) / 246 (27%) / 247 (27%) / 214 (23%) / 95 (10%) |
| Physical symptoms | Pain | 452 (49%) |
| (moderate - severe) | Appetite loss | 411 (44%) |
| | Fatigue | 518 (58%) |
| | Respiratory distress | 238 (26%) |
| Psychiatric diagnosis | Delirium | 234 (25%) |
| (primary diagnosis) | Adjustment disorders | 81 (9%) |
| | Dementia | 61 (7%) |
| | Major Depressive Disorder | 9(1%) |
| Outcome | Discharge/ Hospital transfer | 812 (87%) / 114 (12%) |

## List of papers published in 2014

### Journal

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

# Department of Diagnostic Radiology

**Masahiko Kusumoto, Mitsuo Satake, Ryoko Iwata, Yoshihiro Nakagami, Tatsushi Kobayashi, Hirohumi Kuno, Kaoru Shimada**

## Introduction

The Department of Diagnostic Radiology is committed to improving health through excellence in image-oriented patient care and research. Our Division performs more than 94,000 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 Department has four multi-slice CT scanners, including one area detector CT scanner and one Dual Source CT, two MRI systems (one is 1.5 T, the other is 3 T) one interventional radiology (IVR) CT system, one 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 18F-FDG (fluorodeoxyglucose) has been performed. These all-digital image systems enhance the efficacy of routine examinations.

This Department has 7 consulting radiologists and 22 technologists. As part of our routine activities, every effort is made to produce an integrated report covering almost all examinations, such as MMG, contrast radiologica1 procedures, CT, MRI, RI, PET, angiography and IVR, mainly transarterial chemoembolization (TACE).

The number of cases examined in 2014 is shown in the Table below. Several conferences are routinely held at our division, including pre-and postoperative conferences.

## Research activities

The Research activities of the Department of Diagnostic Radiology focus on Diagnostic imaging and IVR. 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 were added to poly adenines 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 genesilencing 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/MRI technology

For evaluation of head and neck cancer, dual-energy CT images have revealed tumor invasion within the cartilage as red color-coded areas of the iodine distribution, resulting in contrast enhancement between the tumor and non-

calcified cartilage. Preliminary evidence suggests that dual-energy CT can improve interobserver reproducibility and diagnostic performance for the evaluation of laryngeal cartilage invasion and deserve the assessment of extralaryngeal spread in laryngeal and hypopharyngeal cancer patients.

In 320-row area-detector CT, newly-developed single-energy metal artifact reduction (SEMAR) algorithm applied to images acquired on a 320-MDCT volume scanner reduces image artifacts from dental metal without increasing the radiation dose. Metal artifacts due to dental restorations considerably deteriorate the quality of computed tomography (CT) images of the head and neck region. Our study has been performed to clarify this influence. A novel phantom comprising the jaws, gingiva, and replaceable teeth with and without amalgam restorations were used. Twelve models with single to multiple restorations based on the tooth decay rate were scanned using a 320 detector row CT scanner. The results of this preliminary study have suggested that the location of dental amalgam restorations has a greater influence on the SEMAR effect compared with the number of restorations, with the presence of multiple restorations in the same axial plane being the most important factor.

In 3-Tesla MR images, mandibular cross-sectional multiplanar reconstruction (CS-MPR) using 3D sequences are applied for the preoperative evaluation of mandibular bone marrow invasion in patients with oral carcinomas. Diagnosis on Mandibular CS-MPR images showed significantly higher specificities with no compromise to the sensitivity for bone marrow invasion. High diagnostic performance could be achieved because Mandibular CS-MPR images taken with 3T-MRI visualized the longitudinal section of the mandible, delineating the relationship between the tumor lesion, cortical bone and mandibular marrow, thus enabling verification of the presence/absence of mandibular invasion and detailed assessment of the continuity with the main tumor. This is of the utmost importance for the selection of appropriate surgical techniques.

**Table 1. Number of cases examined**

| | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| Plain X-ray examination | 34,330 | 35,032 | 39,128 | 38,722 | 39,802 |
| Mammography (MMG) | 2,595 | 2,434 | 2,380 | 2,354 | 2,664 |
| Fluoroscopic Imaging (GI-series, etc.) | 3,478 | 3,903 | 4,029 | 4,628 | 5,358 |
| CT | 21,128 | 21,967 | 24,101 | 28,963 | 34,918 |
| MRI | 5,830 | 5,708 | 5,619 | 5,657 | 6,546 |
| RI | 1,676 | 1,582 | 1,586 | 1,363 | 1,623 |
| PET | 2,048 | 2,239 | 2,284 | 2,208 | 2,695 |
| Angiography | 728 | 656 | 742 | 511 | 800 |
| Total | 71,813 | 73,521 | 79,869 | 84,406 | 94,406 |

## List of papers published in 2014

## Journal


1. Yanagawa M, Tanaka Y, Leung AN, Morii E, Kusumoto M, Watanabe S, Watanabe H, Inoue M, Okumura M, Gyobu T, Ueda K, Honda O, Sumikawa H, Johkoh T, Tomiyama N. Prognostic importance of volumetric measurements in stage I lung adenocarcinoma. Radiology, 272:557-567, 2014
2. Gemma A, Kudoh S, Ando M, Ohe Y, Nakagawa K, Johkoh T, Yamazaki N, Arakawa H, Inoue Y, Ebina M, Kusumoto M, Kuwano K, Sakai F, Taniguchi H, Fukuda Y, Seki A, Ishii T, Fukuoka M. Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer. Cancer Sci, 105:1584-1590, 2014
3. Ikeda M, Mitsunaga S, Shimizu S, Ohno I, Takahashi H, Okuyama H, Kuwahara A, Kondo S, Morizane C, Ueno H, Satake M, Arai Y, Okusaka T. Efficacy of sorafenib in patients with hepatocellular carcinoma refractory to transcatheter arterial chemoembolization. J Gastroenterol, 49:932-940, 2014
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5. Yoshizawa K, Mukai HY, Miyazawa M, Miyao M, Ogawa Y, Ohyashiki K, Katoh T, Kusumoto M, Gemma A, Sakai F, Sugiyama Y, Hatake K, Fukuda Y, Kudoh S. Bortezomib therapyrelated lung disease in Japanese patients with multiple myeloma: incidence, mortality and clinical characterization. Cancer Sci, 105:195-201, 2014
6. Fujimoto K, Hara M, Tomiyama N, Kusumoto M, Sakai F, Fujii Y. Proposal for a new mediastinal compartment classification of transverse plane images according to the Japanese Association for Research on the Thymus (JART) General Rules for the Study of Mediastinal Tumors. Oncol Rep, 31:565-572, 2014
7. Watanabe Y, Tsuta K, Kusumoto M, Yoshida A, Suzuki K, Asamura H, Tsuda H. Clinicopathologic features and computed tomographic findings of 52 surgically resected adenosquamous carcinomas of the lung. Ann Thorac Surg, 97:245-251, 2014
8. Komai Y, Sakai Y, Gotohda N, Kobayashi T, Kawakami S, Saito N. A novel 3-dimensional image analysis system for case-specific kidney anatomy and surgical simulation to facilitate clampless partial nephrectomy. Urology, 83:500-506, 2014
9. Kuno H, Onaya H, Fujii S, Ojiri H, Otani K, Satake M. Primary staging of laryngeal and hypopharyngeal cancer: CT, MR imaging and dual-energy CT. Eur J Radiol, 83:e23-35, 2014
10. Ishihara T, Kobayashi T, Ikeno N, Hayashi T, Sakakibara M, Niki N, Satake M, Moriyama N. Evaluation of a near-infrared-type contrast medium extravasation detection system using a swine model. J Comput Assist Tomogr, 38:285-292, 2014
11. Endou M, Aoki H, Kobayashi T, Kunisada T. Prevention of hair graying by factors that promote the growth and differentiation of melanocytes. J Dermatol, 41:716-723, 2014
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# Department of Radiation Oncology

**Tetsuo Akimoto, Naoki Nakamura, Sadatomo Zenda, Masakatsu Onozawa, Satoko Arahira, Masamichi Toshima, Atsushi Motegi, Yasuhiro Hirano**

## Introduction

Radiotherapy (RT) plays an essential role in the management of cancer patients. It is used as (1) a curative treatment for many patients with loco-regional localized malignant disease, (2) integrated therapy combined with chemotherapy and/or surgery, and (3) palliative treatment for patients in whom curative treatment is not a treatment option. In radiotherapeutic approaches, the radiation dose to the loco-regional tumor must be as high as possible, while dose to the surrounding normal tissues should be kept as low as possible in order to maintain severity of radiation-related complications within 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 body RT (SBRT) and proton beam therapy (PBT) and establish the definitive role of RT in cancer treatment. Another important goal is to establish standard treatments for various cancers and optimal irradiation techniques including total dose, fractionation and radiation fields.

## Routine activities

At present, the staff of the Radiation Oncology Division is consisted from 7 consultant physicians (radiation oncologist), 19 radiation technologists, 4 medical physicists, 1 nurse, and 1 clerk. We have more than 1,000 new cases for conventional RT and 300 or more new patients for proton beam therapy in every year, and quality assurances of both conventional RT and PBT are performed by medical physicists and radiation technologists, and the conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. RT and PBT are routinely based on three-dimensional radiation therapy planning and PBT using RT-dedicated multi-detector-row helical computed tomography (CT) scanning in order to confirm precise radiation dose to the targeted tumors. Respiratory-gating has been applied especially in radiotherapeutic management for patients with lung, esophagus and liver cancers.

Selection of treatment approaches is determined through clinical conferences between radiation oncologist, surgical oncologists and medical oncologists. More than 20 clinical trials involving RT as the sole or a combined treatment modalities for various cancers are in progress.

The Section is responsible for conventional (photon-electron) RT that is consisted from 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 that is composed of 7 operating staff members and 1 technician for fabricating the compensator and aperture; they are sent from manufacturing companies and work in collaboration with the other staff members of the Division. PBT is consisted from 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 under progress.

1) Establishment of optimal combined approaches including RT and chemotherapy for locally advanced head and neck cancer, non-small cell lung cancer and esophageal cancer, and so on.
2) Establishment of clinical usefulness of IMRT for head and neck cancer, localized prostate cancer and cervical esophageal cancer.
3) Hypofractionated IMRT for localized prostate cancer.

4) Hypofractionated PBT for localized prostate cancer.
5) Evaluation of feasibility of PBT combined with chemotherapy for inoperable locally advanced non-small cell lung cancer and locally advanced esophageal cancer.
6) Evaluation of long-term complications after PBT for pediatric malignancies.
7) The role of gene polymorphism in development of acute and late radiation-related complications.
8) Exploration of biomarker for head and neck cancer.
9) Radiobiological investigation of cellular response to radiation and proton beam.

## Clinical trials

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

1) JCOG0701: Accelerated fractionation vs. conventional fractionation radiation therapy for glottic cancer of T1-2N0M0 Phase III study.
2) JCOG0701-A1: Evaluation of single-nucleotide polymorphisms (SNPs) in development of acute and late complications after accelerated fractionation and/or conventional fractionation radiation therapy for glottic cancer of T1-2N0M0.
3) JCOG1015: A phase II study of intensity modulated radiation therapy (IMRT) with chemotherapy for loco-regionally advanced nasopharyngeal cancer (NPC).
4) Phase II study of PBT for malignant melanoma of nasal cavity.
5) Phase II trial of concurrent chemoradiotherapy with 5-FU plus cisplatin for resectable squamous cell carcinoma of cervical esophagus.
6) JROSG Phase II trial of IMRT with concurrent chemoradiotherapy for resectable squamous cell carcinoma of cervical esophagus.
7) JCOG1208: A non-randomized confirmatory study of intensity modulated radiation therapy (IMRT) for T1-2N0-1M0 oropharyngeal cancer.
8) JCOG1008: Phase II/III Trial of Postoperative Chemoradiotherapy Comparing
   3-Weekly Cisplatin with Weekly Cisplatin in High-risk Patients with Squamous Cell Carcinoma of Head and Neck



**Table 1. The changes in the number of patients treated with RT**

Number of patients treated with rdiation therapy during 2010-2014

| | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| New patients | 1,039 | 1,074 | 1,058 | 1,148 | 1,082 |
| IMRT | 98 | 122 | 218 | 243 | 258 |

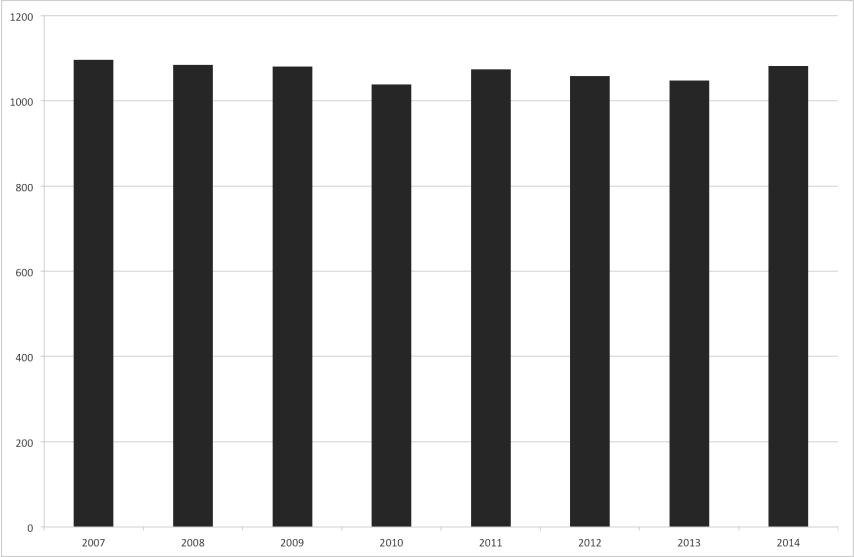


**Figure 1.**

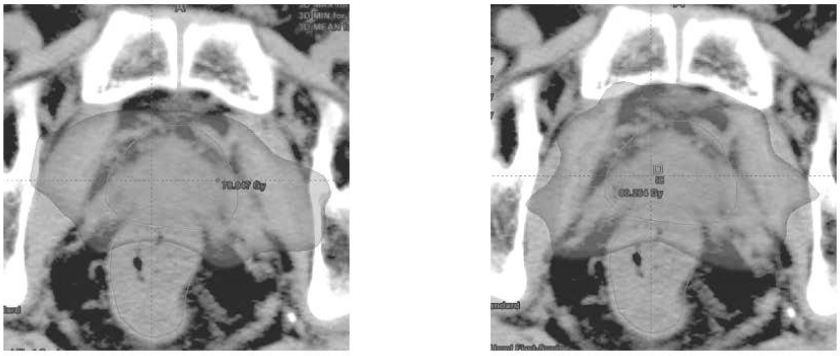

**Figure 2.**

## List of papers published in 2014

## Journal

1. Maebayashi T, Ishikawa H, Yorozu A, Yoshida D, Katoh H, Nemoto K, Ishihara S, Takemoto S, Ishibashi N, Tokumaru S, Akimoto T; Working Subgroup of Urological Cancers in Japanese Radiation Oncology Study Group. Patterns of Practice in the Radiation Therapy for Bladder Cancer: Survey of the Japanese Radiation Oncology Study Group (JROSG). Jpn J Clin Oncol 44(11): 1109-15, 2014.
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# Department of Pathology and Clinical Laboratories

**Atsushi Ochiai, Takeshi Kuwata, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Chisako Yamauchi, Eiichi Yoshikawa, Naoki Maezawa, Masahiro Inoue, Masahiro Karibe, Seiji Iwasaki, Miki Gotou, Masaki Takeda, Satoru Sunohara, Hiromi Kimura, Hiroyuki Shimada, Yasuharu Hashimoto, Yukihiro Okano, Akiko Yamada, Mari Hisano, Shinya Yanagi, Takuya Yamaguchi, Takuya Aiba, Keiko Nakai, Ayumi Setsuta, Mayumi Motohashi, Miwa Kanehira, Aya Koike, Sayuri Shibayama, Yasuko Yoshihara, Kazumi Yamaguchi, Rie Taniguchi, Izumi Suzuki, Eriko Iwamoto, Michiteru Yamagishi, Nagisa Bouno, Kasumi Tamura, Tomomi Sekine, Noriko Motono, Yuki Soeda, Rie Kuroiwa, Masayuki Ito, Iida Michiko, Chizuru Asanuma, Akiko Matsumoto, Megumi Michikawa, Emiko Yoshikawa, Yoshiko Ohtake, Miwa Yamada, Megumi Yamaguchi, Tomoko Hirasawa**



## Introduction

The Department of Pathology and Clinical Laboratories (DPCL) has 2 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 (NCCHE).

The DPCL received ISO15189:2007 accreditation in 2012, and successfully transit to the newest version (ISO15189:2012) in 2014, ensuring quality control and quality assurance of the testing, including the one for clinical trials, performed in the departments.

## Routine activities

Primarily of routine activities at the PD is surgical pathology. The number of samples examined at the Department in 2014 is listed in Table1.

The Clinical Laboratory Division consists of 7 sections; i) General laboratory medicine, ii) Hematology, iii) Biochemistry/serology, iv) Physiology, v) Bacteriology ,vi) Blood transfusion and vii)Supporting laboratory testing in clinical studies. Numbers of testing performed in each division are listed in Table 2 and 3. The total number of testing performed in the DPCL in 2014 increased 11.5% from the previous year; including 64.3% and 11.3% increase in the Serology and Bacteriology Sections, respectively.

## Research activities

All of the pathologists were involved in research activities at the RCIO. All the technologists working at the Department were also highly motivated to develop advanced diagnostic technology and some results were presented in several meetings.

## Clinical trials

Practically the CLD participated in all of clinical trials operated at the NCCHE by providing laboratory data. The section for supporting laboratory testing in clinical studies has been transferred to the DPCL since Jun, 2014. The section, coordinated with pathology and physiology sections, reinforces quality control and quality assurance for clinical testing performed in clinical trials at the NCCHE.

## Education

Clinicopathological conferences were held regularly with each clinical department/section. In the PD, conference-style training sessions were open weekly for the residents.

## Future prospects

Pathological diagnosis and laboratory testing play fundamental role not just in routine hospital works but also in medical researches. As an ISO15189-certified clinical laboratory, the DPCL will be continuously involved in investing new diagnostic technologies, developing new drugs and conducting translational /clinical researches in the NCCHE with our slogan “all the activities for cancer patients.”

**Table 1. Number of pathology and cytology samples examined at Pathology Division in 2014**

| Department | Biospy | Surgical | Cytology | Autopsy |
|---|---|---|---|---|
| Digestive Endoscopy | 5,036 | 1 | 2 | 0 |
| Gastrointestinal Oncology | 144 | 4 | 75 | 1 |
| Breast Surgery | 482 | 327 | 117 | 0 |
| Head and Neck Surgery | 604 | 362 | 404 | 0 |
| Thoracic Surgery | 453 | 488 | 558 | 1 |
| Thoracic Oncology | 651 | 3 | 817 | 0 |
| Hematology and medical oncology | 450 | 3 | 132 | 1 |
| Hepatobiliary and Pancreatic Oncology | 443 | 1 | 407 | 1 |
| Urology | 251 | 99 | 817 | 0 |
| Upper Abdominal Surgery | 181 | 453 | 190 | 0 |
| Radiation Oncology | 147 | 0 | 4 | 0 |
| Lower Abdominal Surgery | 88 | 352 | 40 | 0 |
| Orthopedics | 51 | 24 | 6 | 0 |
| Ambulant Treatment Center | 0 | 0 | 0 | 0 |
| Esophageal Surgery | 7 | 197 | 14 | 0 |
| Head and Neck Oncology | 23 | 0 | 8 | 0 |
| Obstetrics and Gynecology | 33 | 0 | 221 | 0 |
| Dental division | 12 | 0 | 0 | 0 |
| Anesthesiology | 0 | 0 | 0 | 0 |
| Dermatology | 19 | 0 | 0 | 0 |
| Plastic Surgery | 6 | 4 | 4 | 0 |
| Palliative medicine | 2 | 0 | 5 | 0 |
| Others | 16 | 0 | 5 | 0 |
| Total | 9,099 | 2,318 | 3,826 | 4 |

**Table 2. Number of laboratory tests examined at Clinical Laboratory Division in 2013&2014**

| | 2013 | 2014 |
|---|---|---|
| General laboratory medicine | 47,980 | 48,199 |
| Hematology | 276,610 | 302,752 |
| Biochemistry | 1,834,169 | 1,970,515 |
| Serology | 164,382 | 270,112 |
| Blood transfusion | 10,720 | 11,438 |
| Bacteriology | 26,870 | 29,917 |
| Physiology | 22,730 | 24,703 |
| total | 2,383,461 | 2,657,636 |

**Table 3. Number of case and samples prepared in Clinical Laboratory Division for clinical trials in 2014**

| | Cases | Samples |
|---|---|---|
| General Laboratory test | 3,733 | 6,336 |
| ECG | 867 | 1,128 |
| Pathology | 156 | 996 |

# Rare Cancer Center

**(NCCH) Akira Kawai, Hirokazu Chuuman, Eisuke Kobayashi, Yoshikazu Tanzawa, Seiichi Yoshimoto, Motokiyo Komiyama, Tomoyasu Kato, Makoto Kodaira, Mayu Yunokawa, Shunsuke Kondo, Chitose Ogawa, Miyuki Sone, Shunsuke Sugawara, Hiroshi Igaki, Kana Takahashi, Akihiko Yoshida, Takuro Sakurai, Yoshitaka Narita, Naoya Yamazaki, Arata Tsutsumida, Satoshi Takahashi, Shigenobu Suzuki, Yoshitaka Honma, Tadashi Kondo, Koichi Ichikawa, Naohiro Higashi, Makiko Murase, Yoko Kato,**
**(NCCHE) Fumihiko Nakatani, Naoto Gotohda, Toshihiko Doi, Yoichi Naito, Ako Hosono, Tetsuo Akimoto, Junya Ueno**



## Introduction

The Rare Cancer Center was launched in December 2013 and officially opened in June 2014 as a multidisciplinary team to take measures against the innate problems associated with rare cancers. In the past decades, major cancers such as gastric, breast and colorectal cancers have been a public health priority at the national and international level, but at the same time little attention has been paid to the issue of rare cancers. There is still no generally agreed definition of rare cancers in Japan. Rare diseases are often defined as those with a prevalence of < 50/100,000. According to the definition of Rare Cancers in Europe (RARECARE), rare cancers are those with an incidence < 6/100,000/year. Although each rare cancer is rare by itself, when the number of each rare cancer is combined, it corresponds to up to 15% of all new cancer diagnoses. Information on rare cancers is scarce. Rare cancers are often inadequately diagnosed and treated in relation both to lack of knowledge and clinical expertise. Patients with rare cancers face great difficulty in having their diseases treated adequately.

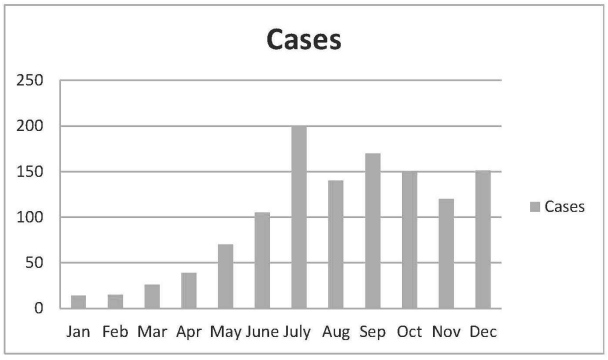


**Figure 1. The Number of telephone call to Rare Cancer Hotline in 2014**

## Routine activities

The Rare Cancer Center plays a central role in the treating and managing of rare cancers in National Cancer Center (NCC).

The mission statements of the Rare Cancer Center are as follows.

I. Establishing a vital network of diagnosis and treatment for rare cancers in the NCC Hospital and Hospital East.

II. Reviewing the problems associated with rare cancers in Japan and making proposals and taking up the issues as medical professionals.

To enable the Center to play its role, a total of 35 doctors, nurses and researchers dealing with rare cancers have joined as members of the Center. Each staff member of the Rare Cancer Center provides specialized, high-quality medical care to patients with rare cancers in cooperation with his/her Department staff.

The Rare Cancer Center provides consultation to the patients and relatives with rare cancers on the telephone (Rare Cancer Hotline). The number of telephone call was 1,200 cases in 2014 (Figure 1). The Center also provides comprehensive, scientifically based, up-to-date unbiased information about rare cancers to all patients, families and health professionals fighting against rare cancers via website (Rare Cancer Center Homepage).

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## Journal


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# Department of Radiology

**Yoshihisa Muramatsu, Mitsuhiro Yoshida, Yutaka Ohnuma, Kazuyoshi Yamano, Kazutoshi Yokoyama, Koichi Nemoto, Takaki Ariji, Kuniji Naoi, Keisuke Takahashi, Naotaka Yamazawa, Satoe Kito, Hajime Ohyoshi, Kaoru Ikeno, Tsunemichi Akita, Keiichi Nomura, Hiroyuki Shitara, Daiki Kumagai, Shogo Amano, Fuminori Shimizu, Noriko Nishikawa, Asami Tanaka, Ryuzo Uehara, Tatsuya Mogaki, Hiromi Baba, Shota Hosokawa, Kaori Yanagisawa, Syun Aoyagi, Yukihiro Matsukawa, Yuto Iwabuchi, Yuki Ito, Toshiyuki Shibuya, Kazuto Kano, Hikaru Sugahara, Hiroyuki Asai, Fumiya Tanaka, Toshiya Rachi, Daiki Kanke, Taku Tochinai, Yohei Takeda, Makoto Gohdo, Tomohiro Ohishi, Hiroshi Tsuruoka, Hikari Inagawa**



## Routine activities and research activities

The number of radiographic examination and radiation therapy in 2014 was increasing, as it shown in Table 1.

Related to radiological diagnosis; inquiry, injection and contrast radiography assistance by interventional radiology specialized nurses have been launched, and a regulation of peripheral intravenous injection was stipulated with the cooperation of Department of Nursing. Thus enabled to improve the percentage of radiographic image interpretation by radiologists, providing them more time spending on image reading. Certified radiological technologists participated in primary image reading on low-dose lung cancer CT screening in cooperation with certified radiologists. A sequence which visualizes tumors and blood vessels on plain head and neck MRI examinations without contrast media has been designed and clinically applied. Taking part in clinical trial on a cancer pain palliative using alpha-emitting nuclide which is Phase III study in progress.

Number of intensity-modulated radiation therapy (IMRT), which has lower risk of side effects by irradiation, was applied in photon radiation therapy. IMRT requires complex treatment planning and verification, hence it takes 1 to 2 weeks before launching a treatment in general, although, according to coordination between each staff and reinforcing the educational system for long years, have been achieved less than 3 days for preparation. Furthermore, image guided radiation therapy which compensates millimeter measures of irradiation positions has been applied to the most of the cases. When it comes to proton therapy, patch field irradiation has been applied that enabled to treat over 20 centimeters size of nidus. Also, scanning irradiation which enables much more complicated dose distribution is heading toward to its final phase of the practical use.

## Clinical trials

Participating in Ishigaki section (Rikuta Ishigaki: the Ministry of Education, Culture, Sports, Science and Technology, Japan and Kyoto College of Medical Science.) A software managing dose of radiological examinations is in under development. Related to this, a research on CT radiation dose simulation has been proceeded. These productions have been reported in international conferences, domestic conferences and published in academic journals.

## Education

For the purpose of learning National Cancer Center Hospital East's particular radiation technology, technics have been documented by each type of the cancer classification. By discussing with other staffs belong to different modalities, it is expected to develop better understanding between each staff and to improve clinical technique, in the process of documentation.

Owing to the numbers of MRI accidents, such as projectile related or carrying in ferromagnetic objects, were reported recent years, a magnetic field experience program was carried out with new employees to be targets.

4 of the radiological technologists learned in master's course of graduate schools in this year,

and 2 of them received the master's degree. In addition to that, accepted and educated 12 trainees from 3 universities in radiological technology.

## Future prospects

Therefore the Department of Radiology consists of multidisciplinary staffs, ensuring medical safety with close cooperation and effective management are work in progress. Refining clinical trials, research activities and education, the Department of Radiology will continue striving to provide benefit to other clinical departments in the next year.

**Table 1. Transition of number of radiological examination and radiation therapy by year.**

| | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| Plain X-ray examination | 34,330 | 35,032 | 39,128 | 38,722 | 39,802 |
| Mammography (MMG) | 2,595 | 2,434 | 2,380 | 2,354 | 2,664 |
| "Fluoroscopic Imaging (GI-series, etc.)" | 3,478 | 3,903 | 4,029 | 4,628 | 5,358 |
| CT | 21,128 | 21,967 | 24,101 | 28,963 | 34,918 |
| MRI | 5,830 | 5,708 | 5,619 | 5,657 | 6,546 |
| RI (Scintiscan) | 1,676 | 1,582 | 1,586 | 1,363 | 1,623 |
| PET | 2,048 | 2,239 | 2,284 | 2,208 | 2,695 |
| Angiography | 728 | 656 | 742 | 511 | 800 |
| Radiation therapy | 15,120 | 16,798 | 19,254 | 32,453 | 29,524 |
| Proton therapy | 2,888 | 4,941 | 5,910 | 11,460 | 9,513 |
| Total | 71,813 | 73,521 | 79,869 | 84,406 | 94,406 |

# Clinical Trial Management Office

**Koichi Goto, Yumiko Uchiyama**



## Introduction

The Clinical Trial Management Office (CTMO) 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 mission of the CTMO is to facilitate the conduct of quality clinical trials at the National Cancer Center Hospital East (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.

All staff work with investigators, co-medicals (including out/inpatient divisions, wards for clinical research, the nursing division and pharmacy), they also collaborate with pharmaceutical personnel and regulatory authorities, and they always contribute to "Chiken" based on best practice.

## Routine activities

The CTMO 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. Our role is critical in helping to ensure that assigned studies are conducted in accordance with human subjects' federal regulations/guidelines regarding human subjects, and meet good clinical practice (GCP) standards. The number of the industry-sponsored registration trials is increasing year by year, and the increase in the rate of phase 1 trial is particularly striking. We supported 176 registration-directed clinical trials including 11 phase1 trials in 2014 (Table 1). These early clinical trials need more complicated and specific management rather than conventional trials. With the increasing number of phase1 trials as previously described, the supporting area covered by the CRCs will expand to encompass registration trials. All members of the CTMO will work together to contribute to reinforcing the clinical research capabilities and to making the CTMO a valuable unit for all members of our hospital. An operational committee is 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. Furthermore, we will contribute to the worldwide network system for phase 1 trials to establish the acceleration of the preclinical and clinical development of investigational anti-cancer agents.

**Table 1. Supported trials in clinical trial management office in 2014**

| Phase | New (since 2014) | Ongoing |
|---|---|---|
| I | 11 | 60 |
| I/II | 2 | 7 |
| II | 5 | 37 |
| II/III | 1 | 2 |
| III | 15 | 62 |
| POS | 2 | 8 |
| Total | 36 | 176 |

POS: post marketing study

# Supportive Care Center

**Koichi Goto, Miho Kurihara, Hiroya Kinoshita, Hatoe Sakamoto**

## Introduction

Our Department was established as an organization to provide, in addition to conventional consultation support, positive and comprehensive support from a variety of professional occupations for actual or potential, physical, mental, and social problems that cancer patients and their families have to confront. The main activities are establishment of a continuous support system for the patients' families, enhancement of a home care support system, and promotion of community cooperation for establishing early palliative care.

## Routine activities

1. Consultation support/community medicine cooperation

In 2014, we received 5,115 new consultations. Among them, 3,849 (75.2%) were from patients who had received medical treatment from our hospital or their families, and 1,266 (24.8%) were from patients who had received medical treatment at other medical institutions or their families, or local medical welfare workers (Table 1).

In the same year, we started new services such as an educational program for patients with esophageal cancer, a cancer patient support group for children, and a program for providing cosmetic camouflage. We provide the new services taking into account the difficulties faced by the patients.

As part of the activities for acquiring new patients, we have started to collect information and to adjust schedules of the participants in case conferences held in communities in order to build face-to-face relationships between the physicians of our hospital and local physicians.

2. Continuous nursing support

For outpatients, we provide continuous nursing support. In fiscal year 2014, we provided continuous support and consultation services to about 3,300 patients, mainly in the areas of thoracic and gastrointestinal oncology.

In order to promote acquisition of self-care by inpatients and/or their families, as well as to secure appropriate social resources, we provide medical and social supports with a view to home care even from an early timing of hospitalization. We carried out a screening program about 1,700 patients who needed any social support and provided them the appropriate support.

In order to sustain seamless medical and social supports, we strengthen cooperation with home-visit nursing stations to deal with the problems faced by home care patients and/or their families, mainly related to medical management. In fiscal year 2014, we carried out interventions such as approximately 980 phone-calls and face-to-face consultations.

**Table 1. Details of the consultation support provided in 2014**

| | Number | % |
|---|---|---|
| New consultation | 5,115 | |
| Total number | 16,495 | |
| Purpose of new support request | | |
| Support for nursing hospital selection | 3,036 | 59.4 |
| Consultation about treatment and diagnosis | 570 | 11.1 |
| Consultation about social problems | 565 | 11.0 |
| Consultation about physical symptoms | 116 | 2.3 |
| Consultation for the caregiver | 65 | 1.3 |
| Mental problems | 42 | 0.8 |
| Others | 721 | 14.1 |
| Responsible hospital | | |
| Our hospital | 3,849 | 75.2 |
| Other hospitals | 1,117 | 21.8 |
| Others (no treatment, etc.) | 149 | 2.9 |
| Treatment state | | |
| Before the diagnosis | 201 | 3.9 |
| Before the first treatment | 1,125 | 22.0 |
| During chemotherapy | 1,356 | 26.5 |
| After treatment/under follow-up | 840 | 16.4 |
| Only palliative care | 1,352 | 26.4 |
| Dead (Bereaved family) | 17 | 0.3 |
| Others | 224 | 4.4 |

# Office of Cancer Registry

**Hironobu Ohmatsu, Takashi Kojima, Tokiko Inagaki, Yumi Ishii, Chie Ogura, Maiko Miura, Yayoi Ohtsuka**

## Introduction

In September 2014, the "Health Information Management Office" was separated into the Medical Information Management Office and the Office of Cancer Registry. The Office of Cancer Registry is a department for executing a hospital-based cancer registry.

## Routine activities

Diagnostic cases registered in 2013 in the hospital cancer registry (the first visit of cancer patients diagnosed from January to December in our hospital) were 6,039 (of which, an initial treatment conducted in our hospital: 3,923 cases: in our hospital diagnosis only: 161 cases; after the start of treatment in another hospital: 985 cases; and diagnosis and treatment in another hospital (including a second opinion): 970 cases).The number of new registrations shows that the number of female patients has been consistently less with time than male patients due to uneven situations by department, but the number of diagnosis cases in our hospital has increased steadily since 2010 (see Table 1).

**Table 1. The number of cancer registries of the NCCH-East**

| year | male | female | Total |
|---|---|---|---|
| 2000 | 3,054 | 1,625 | 4,679 |
| 2011 | 3,145 | 1,733 | 4,878 |
| 2012 | 3,435 | 1,749 | 5,184 |
| 2013 | 3,996 | 2,043 | 6,039 |

# Medical Information Management Office

**Hironobu Ohmatsu, Tokiko Inagaki, Setsuko Mori**



## Introduction

In September 2014, the "Health Information Management Office" was separated into the Medical Information Management Office and the Office of Cancer Registry. The Medical Information Management Office is a department for managing the medical records of hospital by professional medical information management officers.

## Routine activities

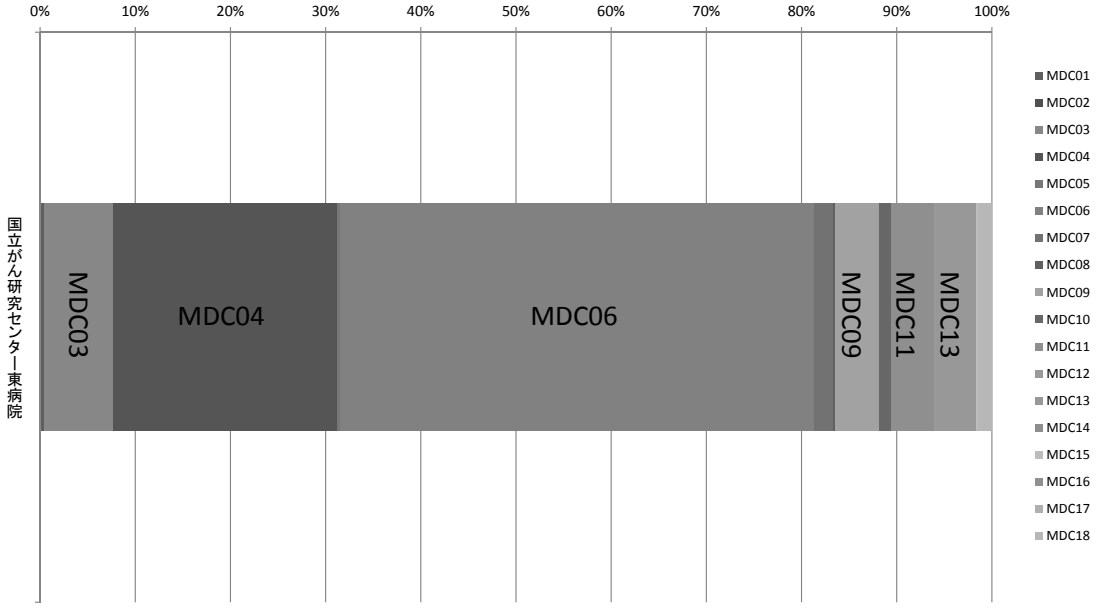
- Auditing Discharge Summary (quantitative inspection)
  Data on discharge summaries should be entered by attending physician. We inspected and checked the summaries and, where required, gave some advice for correct input.
- Maintenance of disease codes based on ICD-10
- Analysis of medical contents on DPC (Diagnostic Procedure Combination) and recommendation for efficiency.

## Future prospects

Approved discharge summaries within 2 weeks after patient's discharge should be held over 95%.

**Table 1. Submitting rate of dischage summary**

| 2012 | 2013 | 2014 |
|---|---|---|
| 79% | 81% | 97% |




| | | | | | |
|---|---|---|---|---|---|
| MDC01 | Nervous System | MDC07 | Hepatobiliary System And Pancreas | MDC13 | Blood and Blood Forming Organs and Immunological Disorders |
| MDC02 | Eye | MDC08 | Musculoskeletal System And Connective Tissue | MDC14 | Newborn And Other Neonates |
| MDC03 | Ear, Nose, Mouth And Throat | MDC09 | Skin, Subcutaneous Tissue And Breast | MDC15 | Childhood disease |
| MDC04 | Respiratory System | MDC10 | Endocrine, Nutritional And Metabolic System | MDC16 | Injuries, Poison And Burns |
| MDC05 | Circulatory System | MDC11 | Kidney And Urinary Tract | MDC17 | Mental Diseases |
| MDC06 | Digestive System | MDC12 | Female Reproductive System | MDC18 | Others |

**Figure 1. Ratio of Major Diagnostic Category in our Hospital**

# Department of Pharmacy

**Shinichiro Saito, Kunio Takahashi, Yasuhiko Ichida, Tomoyuki Akimoto, Reiko Matsui, Hisanaga Nomura, Yasuaki Ryushima, Naoko Yoshino, Minako Yoshida, Yoshiki Kojima, Daisuke Kanou, Yosuke Maki, Nobuo Mochizuki, Kenji Kawasumi, Tomoka Okano, Shinya Motonaga, Ryoko Udagawa, Hiroko Ouchi, Tomoko Morita, Mai Itagaki, Shinya Suzuki, Takeshi Koike, Misaki Kobayashi, Motoko Kaneko, Akira Shinohara , Asuka Iwamoto, Akihito Kibune, Sonoko Kobayashi**

## Introduction

The main objectives of the Department of Pharmacy are: (1) To promote clinical studies to create new evidence-based data; (2) To provide chemotherapy based on the most updated evidence-based data; and (3) To pursue patient-centered pharmaceutical care.

Our residents' training program started in 2006. In 2014, 8 residents joined our department. Presently, we have a total of 21residents. In addition, our department has accepted 4 trainees from other institutions for our oncology pharmacist training programs. Through 2014, 3 terms of the training courses, we have educated 8 pharmacy students and 2 advanced-training pharmacy students.

The Department of Pharmacy provides various important services: controlling inventory; dispensing medications; preparing i.v. solutions for chemotherapy, which include the aseptic mixing of antineoplastic agents; collecting and providing drug information; managing therapeutic drug monitoring; checking treatment regimens for each patient's chemotherapy; and providing pharmaceutical management and counseling.

Our Department reviews the drugs taken by patients before and during their hospitalization. In inpatient care, the Department assigns pharmacists to provide medication counseling and drug information for healthcare providers and patients, to pursue effective pharmaceutical care. In outpatient care, the Department provides a pharmacy outpatient service in which pharmacists check patients for adverse reactions and doses of antineoplastic agents, especially in the case of oral anticancer medications. We then assess the necessity of supportive-care medications and suggest them to physicians. The pharmacy outpatient service also reviews the drugs taken by all patients to evaluate when patients have to stop their anticoagulants before their operation or when they have to stop to take metformin before examinations with iodinated-contrast material. Pharmacists are on duty at the Outpatient Chemotherapy Center as dedicated staff members. The pharmacists provide the Chemotherapy Hotline Service, which is a direct line for our outpatients who have any problems concerning their chemotherapy treatment. In the Outpatient Chemotherapy Center, pharmacists are always available to provide drug information for healthcare providers and patients. We also manage investigational drugs.

## New developments

In the research activities, we lunched the Clinical Pharmacokinetics Unit, and the unit has analyzed pharmacokinetics data in clinical studies. In the education, we have started 2-year chief pharmacy resident program. This year, one pharmacist was selected as a chief resident pharmacist in the department.

**Table 1. Pharmacy Achievement**

| | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| Chemotherapy hotline service | 980 | 1,468 | 1,665 | 2,087 | 2,258 |
| Pharmacy outpatient service | 479 | 738 | 1,782 | 2,375 | 3,493 |

## List of papers published in 2014

## Journal

1. Suzuki S, Enokida T, Kobayashi T, Yajima Y, Ishiki H, Izumi K, Endo K, Tahara M. Evaluation of the impact of a flow-chart-type leaflet for cancer inpatients. SAGE Open Medicine, 2:2014

# Department of Nursing

**Chie Asanuma**

## Introduction

The Department of Nursing promoted several actions such as taking part in the hospital's administration through collaboration with departments concerned, preparation of providing system of medical and nursing service, improvement of routine activities of staff, Team health care, public health cooperation, and human resource development.

We could prepare a new framework of outpatient system in the new building constructed in 2004 through reorganization of outpatient booth including emergency room and reallocation of staff, and it contributed to operate outpatient services more safely and effectively.

The 13th Open Nursing Seminar "A delirium Care" was took place with 102 participants, and we also managed several training programs such as (1) a delirium Care Assessment course for palliative care nurse team, (2) communication skill training course for leader nurse (3) a delirium care program training for leader nurse of other institutions. In an educational course for certification of palliative care nurses opened in 2013, 12 attendees were completed of the course, and 11 of them were passed in a certification exam authorized by the Japan Nursing Association. The course was opened with 18 new participants in July 2014. In the certified expert nurse course in the hospital for intravenous anticancer drug delivery, 34 nurses were certified, and a framework of new training "intravenous radiological examination" was established.

While the average hospitalization term was shortened from November 2014, the number of outpatients has been increasing, so we need to work on functional development of the supportive care center and strategic collaboration system with regional institutions in order to promote "Regional care" which is provided home care continuously for outpatient after they leave hospital, and we also promote increase of the number of inpatients and new patients, and it has been planned to be expanded and advanced at the clinical research and medical treatment fields in the National Cancer Center Hospital East, so we try to prepare appropriate staff allocation, to develop of nursing and research skills, and to manage educational training for human resource development.

Stable management of institution is indispensable for realization of our mission, so we also take part in the hospital's administration in order to implement strategic hospital management.

## Routine activities

In 2014, the number of nurses newly employed was doubled and the ratio of separated nurse among the current 370 nurses was 8.1 % (13.8% in 2013) through promotion of recruitment and improvement of routine activities and it has been continued to strengthen nursing system.

The number of patients has been increasing on an annual basis. In 2014, the number of outpatients per day was 995.7 while that of impatient was 382.4. The average hospitalization term was 13.4 days and the occupancy rate of bed was 90.0%. The number of operations conducted per day was 12.0. The number of chemotherapy treatments in the Medical Treatment Center per day was 115. The number of consultations for support of decision making of patient has been increasing dramatically.

We gave 43 presentations at academic conferences in 2014 including one at an international conference. Increase in the number of them were contributed by support system by expert nurse and certified expert nurse and financial back up from the hospital and nursing association. The number of contributions to journal was 17 and of 145 expert nurses and certified expert nurses were dispatched as a lecturer.

# Certified Nurse Curriculum

**Asuko Sekimoto, Yuko Tanaka**

## The educational program for certified palliative care nurse in the NCCHE

The certified nurse course of palliative care was prepared and organized in the National Cancer Center Hospital East (NCCHE) in July 2012, and it was accredited by the Japanese Nursing Association (JNA) on Dec. 21, 2012. The first-year program was launched with 12 applicant nurses in July 2013. All trainees had successfully completed the required whole program, and 11 applicant nurses passing the credentialing examination have been certified by JNA. In the second year, the course was started with 18 applicant nurses out of 22 passing the admission test of the NCCHE, and all 18 nurses finished the required program in March 2014. They are going to have the credentialing examination this summer. This year, we welcome 22 nurses out of 26 applicants into our educational program, and it will be started in upcoming May. The surveillance of JNA have recognized and validated our program.

The certified nurse system has been established by JNA to provide high level of nursing practice and to improve nursing expertise in specific nursing areas. We are ready to expand our educational programs for other nursing fields depending on requirement of neighboring hospitals and prefectures.

# Preface

The Research Center for Innovative Oncology (RCIO) was originally funded as the branch of the Research Institute in 1994 at Kashiwa campus. For the purpose of more focusing on translational researches (TR) and mutual collaborations between basic and clinical researchers, the National Cancer Center Kashiwa campus was reorganized, which made the RCIO belong to the Hospital East in 2005. With the launch of the Exploratory Oncology Research & Clinical Trial Center (EPOC), some divisions in the RCIO were included into the EPOC. A large number of studies in collaborations with the Hospital East, EPOC, and Research Institute have been conducted for TR and support for hospital services.

In the Pathology Division, the investigators play a central role in bio-bank system, various types of TR and standardization of a procedure in pathological sample analysis. With many collaboration studies with the EPOC and industries for establishing companion diagnosis, they are acting as a central pathology diagnosis in an international IND registration trial. Various TRs are also on-going in collaboration with TR division in the EPOC. Large molecular epidemiologic data in lung, colorectal, and gastric cancer have already been published, which will become a landmark in the development of molecular targeting agents. A project for making patient-derived xenograft in combination with genome profiling is also underway.

Several new drug-delivery system (DDS) agents based on cutting-edge nanotechnology have originally been developed in the Developmental Therapeutics Division and one of them is now under evaluation in an international phase III trial. The division has also yielded some antibody-drug-conjugates for innovative targets including anti-tissue factor antibody, which are now being optimized for preclinical study and will be implicated into clinical study within a few years. They are participating the "Center of Innovation for nanotechnology" at Kanagawa prefecture designated by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) as an antibody yielding laboratory.

In 2012, our hospital was also selected as "a designated center for new endoscopic instrument development" by the Ministry of Health, Labour and Welfare and several exploratory studies with new diagnostic instruments/devices have been initiated. Several studies for new endoscopic/surgical instruments development were conducted in the Division of Science and Technology for Endoscopy and Surgery. A first in human clinical trial of hypoxia imaging they conducted was finished into the endoscopic diagnosis of neoplasia of the esophagus, stomach, and colon/rectum. Preclinical studies, such as a low-temperature atmospheric pressure plasmas system and photodynamic diagnosis of hypericin, are performed using animal model. Furthermore, clinical trial for biodegradable (BD) stent implantation for benign esophageal stricture after curative treatment, and clinical trial for photodynamic diagnosis using 5ALA has been started. A new generation surgical device/technique development (NEXT) project is also being planned for establishing new surgical techniques. 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. Clinical trials of hypoxia PET tests are ongoing using Cu-62 labeled diacetyl methyl-thiosemicarbazone (ATSM). Patients with lung cancer or 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.

We are also pioneers of proton-beam therapy, new imaging instruments such as super-MRI, and psycho-oncology, in which our researchers are leading. In the Particle Therapy Division, the investigator experimentally evaluated the proton beam dose reproducibility, sensitivity, angular dependence and depth-dose relationships for a new Metal Oxide Semiconductor Field Effect Transistor (MOSFET) detector. The detector was fabricated with a thinner oxide layer and was operated at high-bias voltages. In order to accurately measure dose distributions, they developed a practical method for correcting the MOSFET response to proton beams. The number of patients who received proton-beam irradiation has been rapidly increasing in recent years and multi-institutional clinical trials with proton beam radiation has been started. The Psycho-oncology 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. Supportive care center with a collaboration of psycho-oncology, palliative care, nursing, pharmacy, and social worker divisions has also been organized for various patient supports. With these activities, we eagerly establish a top innovative cancer center with best amenities for cancer patients in the world.

Atsushi Ohtsu, M.D., Ph.D.
Director, Research Center for Innovative Oncology
National Cancer Center Hospital East

# Division of Pathology

**Atsushi Ochiai, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Takeshi Kuwata, Syuichi Mitsunaga, Akiko Nagatsuma, Chisako Yamauchi, Kazuyoshi Yanagihara, Yuka Nakamura, Shinya Neri, Tomofumi Miura, Eiji Higaki, Akiko Takahashi, Kenji Sakai, Ken Hatogai, Mitsuru Yokota, Masayuki Ishibashi, Kouji Ikeda, Shingo Kawano, Hiroko Hashimoto, Sachiko Fukuda, Tamae Hanai, Ayumi Iwaya, Aya Endo, Natsuko Maruyama, Yuki Iino, Masaaki Sato, Motoko Suzaki, Yoshiko Onuma, Youichi Higuchi, Anna Abe, Kei Natori, Yoshitaka Suda, Tomoyuki Miyashita, Ukyo Inaba, Yusuke Asai**

## 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 in the NCCH-E; 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 in the NCCH-E with the collaboration of the staff pathologists of the Department of Pathology and Clinical Laboratories of the NCCH-E. 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 conferences and research meetings between the NCCH-E and the RCIO.

## Research activities

The goal of the research at the Division of Pathology is to explore the cause of the cancer and to develop novel diagnostic and therapeutic methods for cancer patients. The research activities of the Division of Pathology start with the detection of cancer specific pathological conditions closely associated with clinical outcomes. The appropriate *in vitro* and *in vivo* models are required to solve molecular mechanism of the relevant issues. Researches are further confirmed in final validation studies using human samples. Followings are major research results of this year.

1) Podoplanin-positive cancer associated fibroblasts play an important role in primary resistance to EGFR-TKIs and may be an ideal therapeutic target in EGFR mutated lung adenocarcinoma patients.
2) Basal cell hyperplasia detected in superficial-type esophageal or head and neck squamous cell carcinoma was an independent entity in terms of not only pathological findings, but also endoscopic findings observed using narrow-band imaging (25).
3) Peritoneal invasion in colon cancer is an important prognostic factor and cancer microenvironment formed by the peritoneal invasion is involved in the promotion of tumor growth and metastasis (8,20).
4) Approximately two-thirds of patients with gastric adenocarcinoma exhibited the expression of at least one tyrosine kinase receptors and would be candidates for targeted therapies (14,16).
5) Higher number of CD204(+) macrophage at extrapancreatic nerve plexus invasion of pancreatic ductal carcinoma was associated with shortened OS and DFS and early recurrence in the peritoneal cavity and locoregional space (11).

Prognostic factors and clinicopathological characteristics of various cancers have also been investigated in collaboration with the NCCH-E Diagnostic Pathology Section and other institutions.

These include lung cancers (1,2,4,5,6,7,19), colon cancers (8,9,13,17,20,21,23), gastric cancers (14,15,16,18,22), pancreatic cancers (10,11), breast cancers (3) and head and neck cancers (12,25).

## Education

The Division participates in the pathological training of clinical residents in NCCH-E. Moreover staff members give professional guidance for doctoral students of Juntendo University, Keio University, Tokyo Medical and Dental University and Graduate School of Frontier Sciences, The University of Tokyo.

## Future prospects

As a research institution, we are strengthening particularly in 1) collecting fundamental pathological information for cancer diagnosis and treatment, 2) promotion of translational research and 3) promotion of basic research of cancer biology.

## List of papers published in 2014

## Journal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25. Yagishita A, Fujii S, Yano T, Kaneko K. Endoscopic findings using narrow-band imaging to distinguish between basal cell hyperplasia and carcinoma of the pharynx. Cancer Sci, 105:857-861, 2014

# 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 to develop new kinds of radiopharmaceuticals and these new compounds were examined *in vivo* using a single photon emission computed tomography (SPECT) scanner. Recently, dual modality probes of radionuclides and optical dyes are also under investigation. 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 the field of nuclear medicine, imaging probes including multimodality ones were investigated.

Since *in vivo* visualization of tumor hypoxia can greatly contribute to the optimization of cancer therapy, we are developing new hypoxia imaging probes. We proposed $^{99m}$Tc-labeled ones that can be used more widely than PET probes in the light of feasibility of tests. These probes also had unique retention mechanism that was different from conventional hypoxia imaging agents. We synthesized many candidates of this kind of hypoxia imaging probes and obtained some promising results. *In vivo* imaging tests using tumor-bearing mice indicated that some candidates of our unique probes accumulated in hypoxic cells well after the successful delivery to tumors.

To improve the detectability of sentinel lymph nodes (SLNs) in head and neck cancer, multimodality imaging probes of radionuclides and optical dyes are under investigation. The combination of indocyanine green (ICG) and $^{99m}$Tc-phytate are attractive because both of them have been already covered by health insurance. We found that ICG-colloid mixture showed good optical signal of near-infrared lights for a longer period than ICG alone, improving the accuracy for the detection of true SLNs. In experimental studies using mice, fusion images of radionuclides and optical ones confirmed that gamma rays and optical signals were emitted from the same node. Multimodal imaging of SLN would contribute to improved sentinel node navigation surgery.

In boron neutron capture therapy (BNCT), 4-borono-L-phenylalanine (BPA) is an important $^{10}$B carrier and its concentration of target tumors is a key to successful treatment. $^{18}$F-FBPA is an analog of BPA and it can be visualized by PET. We examined $^{18}$F-FBPA would be a useful PET tracer to predict the sensitivity to BNCT using BPA. We investigated the transport mechanism of $^{18}$F-FBPA using human glioma cell lines and transport inhibitors. 2-aminobicyclo-(2.2.1)-heptane-2-carboxylic acid (BCH) drastically inhibited the uptake of $^{18}$F-FBPA, indicating that system L amino acid transporter was dominantly involved in the uptake of $^{18}$F-FBPA. In addition, the inhibition study using BPA indicated that 1 mM of BPA reduced the uptake of $^{18}$F-FBPA to 2-7% of control. This result suggested that the transport mechanism of $^{18}$F-FBPA would be similar to that of BPA and $^{18}$F-FBPA PET would be useful to predict the sensitivity to BNCT using BPA.

In the field of magnetic resonance (MR) imaging, ferucarbotran-enhanced MR imaging, which is currently covered by health insurance, was investigated to precisely visualize the margins of treated areas of hepatic tumors after radiofrequency ablation (RFA) as well as radiation therapies. Our experimental studies using rats revealed that iron ions derived from ferucarbotran

remained for a long time in damaged liver tissues due to RFA or radiotherapy and these iron ions successfully delineated the margin of treated areas on MR images. We expect that the sustained signal reduction in ferucarbotran-accumulated liver tissues can be utilized to visualize ablative margins after RFA as well as target volumes in radiation therapy, both of which help clinicians to evaluate the risk of recurrence and enhance the curability of liver tumors.

## Clinical trials

The effects of systemic chemotherapy on the cerebral metabolism and cognitive function in breast cancer patients were evaluated with MR spectroscopy.

## Education

Some graduate school students took part in our studies and received degrees of doctor or master in the field of medicine and related sciences.

## Future prospects

We will develop our research projects to translate our research products into clinical practice.

## List of papers published in 2014

### Journal


1. Tani H, Kurihara H, Hiroi K, Honda N, Yoshimoto M, Kono Y, Murakami R, Kumita S, Arai Y, Itami J. Correlation of $^{18}$F-BPA and $^{18}$F-FDG uptake in head and neck cancers. Radiother Oncol, 113:193-197, 2014
2. Takeda A, Sanuki N, Fujii H, Yokosuka N, Nishimura S, Aoki Y, Oku Y, Ozawa Y, Kunieda E. Maximum standardized uptake value on FDG-PET is a strong predictor of overall and disease-free survival for non-small-cell lung cancer patients after stereotactic body radiotherapy. J Thorac Oncol, 9:65-73, 2014
3. Ogawa M, Umeda IO, Kosugi M, Kawai A, Hamaya Y, Takashima M, Yin H, Kudoh T, Seno M, Magata Y. Development of 111In-labeled liposomes for vulnerable atherosclerotic plaque imaging. J Nucl Med, 55:115-120, 2014
4. Yoshii Y, Matsumoto H, Yoshimoto M, Furukawa T, Morokoshi Y, Sogawa C, Zhang M-R, Wakizaka H, Yoshii H, Fujibayashi Y, Saga T. Controlled administration of penicillamine reduces radiation exposure in critical organs during $^{64}$Cu-ATSM internal radiotherapy: a novel strategy for liver protection. PLoS One, 9:e86996, 2014
5. Yoshimoto M, Hirata M, Kanai Y, Naka S, Nishii R, Kagawa S, Kawai K, Ohmomo Y. Monitoring of gefitinib sensitivity with radioiodinated PHY based on EGFR expression. Biol Pharm Bull, 37:355-360, 2014
6. Nakagami R, Yamaguchi M, Ezawa K, Kimura S, Hamamichi S, Sekine N, Furukawa A, Niitsu M, Fujii H. Recovery correction technique for NMR spectroscopy of perchloric acid extracts using DL-valine-2,3-d2: validation and application to 5-fluorouracil-induced brain damage. Magn Reson Med Sci, 13:145-153, 2014
7. Inoue K, Gibbs SL, Liu F, Lee JH, Xie Y, Ashitate Y, Fujii H, Frangioni JV, Choi HS. Microscopic validation of macroscopic in vivo images enabled by same-slide optical and nuclear fusion. J Nucl Med, 55:1899-1904, 2014
8. Furuta T, Yamaguchi M, Nakagami R, Akahane M, Minami M, Ohtomo K, Fujii H. Delayed hepatic signal recovery on ferucarbotranenhanced magnetic resonance images in a rat model with regional liver irradiation. MAGMA, 27:501-508, 2014


### Book


1. Iimoto T, Fujii H, Someya S, Iizumi S, Ebisawa T, Hirose S, Furuta E, Kusama K, Nogawa N, Mitani H, Kamiko M, Kutsuna N, Watanabe Y, Suzuki T. Environmental Radiation Status In and Around Tokyo Immediately After the TEPCO Fukushima Dai-ichi Nuclear Power Plant Disaster. In: Takahashi S (ed), Radiation Monitoring and Dose Estimation of the Fukushima Nuclear Accident, Japan, Springer Verlag Tokyo, pp 49-57, 2014

# Division of Science and Technology for Endoscopy and Surgery

**Kazuhiro Kaneko, Tomonori Yano, Mari Takahashi, Atsushi Yagishita**



## Introduction

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

One of the characteristic natures of the early cancer is the growth of blood vessels (neovascularity). Using two narrow wave bands of light (blue: 390-445 nm; green: 530-550 nm) that can be absorbed by circulating hemoglobin, narrow band imaging (NBI) endoscopy may provide better images of the capillaries in the mucosal surface.

Another characteristic 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 spatial distribution of tumor hypoxia, such as fluorescent labeling techniques or hemoglobin absorption-based techniques. However, these methods are limited because of low spatiotemporal resolution. We developed an imaging technology that can derive the oxygen saturation ($StO_2$) images from small numbers of wavelength measurements. Thus, novel endoscopy of next generation would be required to be visible to specific function in cancerous tissue. To progress the technology, laser light and near-infrared light would be necessary.

## 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 the Endoscopy Division. Therefore, endoscopic diagnoses are routinely performed for cancer patients, endoscopic treatments, 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 of Technology and Science of the university.

## Research activities

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. In addition, the present researches are to develop new devices or procedures in innovative less invasive laparoscopic surgery for gastrointestinal malignancies. These projects are conducted as prospective clinical studies and preclinical studies in collaboration with not only commercial companies but also the faculties of Technology and Science of the university.

Developing research into novel endoscopy systems is being performed. Hypoxia imaging is detected for neoplastic lesions of the head and neck and alimentary tracts, with two types of visualized images, such as pseudocolour $StO_2$ image and a $StO_2$ overlay image. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and nanoparticles of the rare earth, doped yttrium oxide. This system is capable of penetrating through the gastrointestinal

wall and obtaining images. Furthermore, a preclinical study of molecular imaging endoscopy using small molecular was planed in this year. With a low-temperature atmospheric pressure plasmas system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnosis system using photosensitizing agents, such as hypericin, has been constructed. A novel tattooing system under endoscopy has been developed. Now, this system is applied for a patent. Ongoing projects are to develop needle graspers, needle ultrasonic coagulator in surgical field. Clinical trial regarding confocal laser endocytoscopy using fluorescein was planned. This type of endocytoscopy is classified into a new category.

## Clinical trials

A first in-human clinical trial of hypoxia imaging was finished into 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 a $StO_2$ overlay image that overlapped StO2 levels in blue on a white light illumination image to detect background mucosa. In a system of near-infrared light with nanoparticles, nanoparticles of rare earth act as fluorescent agents. Nanoparticles attached probe excite due to emission of near-infrared light, when probe attaches surface of cancer cells. Now, molecular imaging endoscopy for the use of this system with InGaAs CCD has been developed in collaboration with Technology of University. Preclinical studies, such as a low-temperature atmospheric pressure plasmas system and photodynamic diagnosis of hypericin, are performed using animal model. Furthermore, clinical trial for biodegradable (BD) stent implantation for benign esophageal stricture after curative treatment, and clinical trial for photodynamic diagnosis using 5ALA are on going.

## Education

The aim is to cultivate of human resources specializing in endoscopic diagnosis and treatment for alimentary tract cancer. Staff supervises individual residents. Positiveness is made importance in a periodic case conference and joint conferences among internal medicine, surgery and radiology. Staff supervises in congress presentation and writing manuscripts after decision of individual themes, and much discussion is made in the department conference. For residents interested in development research, their opportunity to study is supported after graduation.

## Future prospects

Existing endoscopic diagnosis for neoplasia of alimentary tract is performed on the basis of morphological feature of tumor. A molecular imaging endoscopy is a novel system to visualize cancer using specific laser source under phosphor combined with cancer specific agents. We can obtain a new imaging, since function or metabolic state in cancer cells is visualized. In additional modalities, there are photodynamic diagnosis, endomicroscopy, and hypoxia imaging endoscopy. These modalities will be expected as a next generation endoscopy, and we try innovative development to produce all new endoscopy.

# Division of Developmental Therapeutics

**Yasuhiro Matsumura, Masahiro Yasunaga, Yoshikatsu Koga**



## Introduction

Our Division has been involved in basic research on drug delivery systems (DDS) and antibody therapeutics including anticancer agent incorporating micelle system, monoclonal antibody development (mAb), and antibody drug conjugate. We also investigate a mechanism of cancer induced blood coagulation and are developing a new cancer diagnosis based on the cancer specific mAb. In addition to the research works, we are operating the Japan Clinical Oncology Group Tumor Repository.

## Routine activities

Examination of clinical trials as an IRB member
Operation of the JCOG Tumor Repository
Management of personal information protection in the NCC East Hospital

## Research activities

(DDS in Cancer Chemotherapy)

Tumor-targeted delivery of therapeutic agents is a longstanding pharmacological goal to improve the treatment selectivity and therapeutic index. Most scientists have sought to use 'active' receptor-mediated tumor-targeting systems. However, the 'passive' targeting afforded by the "Enhanced Permeability and Retention (EPR) effect" provides a versatile and non-saturable approach for tumor-selective delivery. Polymeric micelles are ideally suited to exploit the EPR effect, and have been used for the delivery of a range of anticancer drugs in preclinical and clinical studies.

We showed the stronger antitumor effect and lower toxicity of the combination of the epirubicin-incorporating polymeric micelle and DACHP (oxaliplatin parent complex)-incorporating polymeric micelle in a human gastric cancer model than that of epirubicin and oxaliplatin.

(Cancer Stromal Targeting Therapy)

In spite of recent success of antibody drug conjugate (ADC) therapy in patients with hypervascular and special tumors recognized by a particular mAb, there are several issues to be solved for ADC counted as universal therapy for any types of cancer. Especially most human solid tumors possess abundant stroma that hinders the distribution of ADC. To overcome these drawbacks, we developed a unique strategy that the cancer-stromal targeting (CAST) therapy by cytotoxic immunoconjugate bound to the collagen 4, tissue factor (TF), or fibrin network in the tumor stroma from which the payload released gradually and distributed throughout the tumor, resulting in the arrest of tumor growth due to induced damage to tumor cells and tumor vessels. During this study, we found that anti-TF scFv may be suitable as an imaging probe for the diagnosis of solid tumors.

(Infrastructure for the mAb development)

We have established an infrastructure for antibody development including antigen production, animal immunization, hybridoma production, antibody expansion and purification, SPR characterization, and ELISA development. Simultaneously, we have found various cell surface molecules specific to colorectal cancer and succeeded in developing the one of those molecules.

(Noninvasive Diagnostic Test for Colorectal Cancer)

Regarding colorectal cancer (CRC), we investigated the applicability of the fecal miRNA test (FmiRT) to fecal samples used for previous fecal occult blood test (FOBT) stored under various conditions.

## Education

(Doctoral student)
Graduate School of Frontier Science, The University of Tokyo: 5 students
Juntendo University Graduate School of Medicine: 2 students
Department of Gastroenterology and Hepatology, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba: 1student
Department of Neurosurgery, Kumamoto University Graduate School of Medical Science: 1 student

(Master course student)
Graduate School of Frontier Science, The University of Tokyo: 5 students

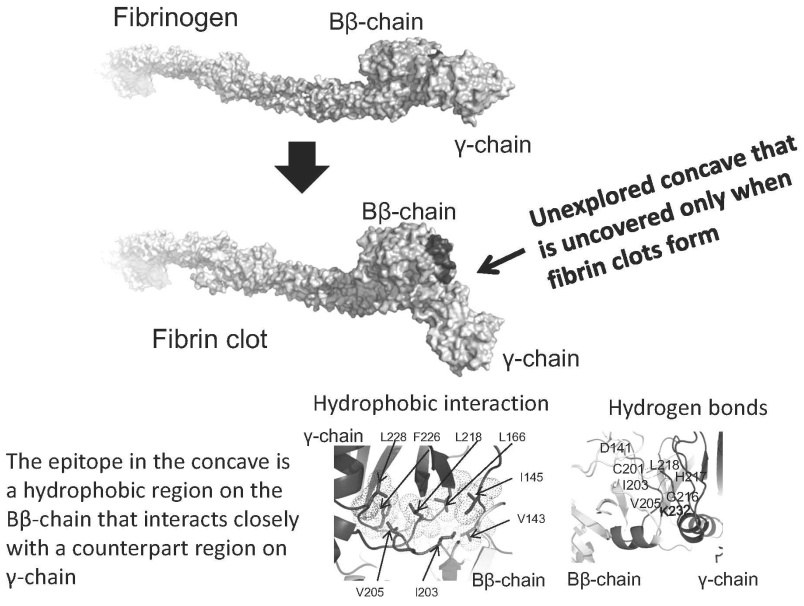



**Figure 1. Image of structural change from fibrinogen to fibrin clot and discovery of unique concave in fibrin clot**

## List of papers published in 2014

### Journal


1. Yanagihara K, Takigahira M, Kubo T, Ochiya T, Hamaguchi T, Matsumura Y. Marked antitumor effect of NK012, a SN-38-incorporating micelle formulation, in a newly developed mouse model of liver metastasis resulting from gastric cancer. Ther Deliv, 5:129-138, 2014
2. Koga Y, Yamazaki N, Takizawa S, Kawauchi J, Nomura O, Yamamoto S, Saito N, Kakugawa Y, Otake Y, Matsumoto M, Matsumura Y. Gene expression analysis using a highly sensitive DNA microarray for colorectal cancer screening. Anticancer Res, 34:169-176, 2014
3. Koga Y, Yamazaki N, Matsumura Y. New molecular diagnosis and screening methods for colorectal cancer using fecal protein, DNA and RNA. Expert Rev Mol Diagn, 14:107-120, 2014
4. Yamamoto Y, Hyodo I, Takigahira M, Koga Y, Yasunaga M, Harada M, Hayashi T, Kato Y, Matsumura Y. Effect of combined treatment with the epirubicin-incorporating micelles (NC-6300) and 1,2-diaminocyclohexane platinum (II)-incorporating micelles (NC-4016) on a human gastric cancer model. Int J Cancer, 135:214-223, 2014
5. Matsumura Y. The drug discovery by nanomedicine and its clinical experience. Jpn J Clin Oncol, 44:515-525, 2014
6. Yasunaga M, Matsumura Y. Role of SLC6A6 in promoting the survival and multidrug resistance of colorectal cancer. Sci Rep, 4:4852, 2014
7. Sato R, Obonai T, Tsumura R, Tsumoto K, Koga Y, Yasunaga M, Matsumura Y. Preparation and characterization of anti-tissue factor singlechain variable fragment antibody for cancer diagnosis. Cancer Sci, 105:1631-1637, 2014

# Division of Psycho-Oncology

**Asao Ogawa, Hiroya Kinoshita, Ken Shimizu**

## Introduction

The aim of the Division is to develop mind-centered interventions to restore, maintain, and improve the quality of life of patients and their families 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

Consent capacity and associated risk factors in patients with lung cancer

Little is known regarding consent capacity in patients newly diagnosed with as having lung cancer and clinical factors associated with incapacity. Over an 11-month period, we recruited 135 newly diagnosed patients newly diagnosed as having with lung cancer. All patients were receiving a combination of treatments (e.g., chemotherapy, chemoradiotherapy, or targeted therapy). Participants were administered the MacArthur Competence Tool for Treatment was administered to participants, in addition to a neurocognitive test battery, to help us identify clinical factors associated with incapacity in lung cancer patients. 27 (24%, 95% CI, 16–31%) patients were judged to not to have consent capacity. Logistic regression identified vulnerability (odds ratio, 3.51; 95% CI, 1.13 to 10.8) and cognitive impairment (odds ratio, 5.45; 95% CI, 1.26 to 23.6) as the factors associated with mental incapacity.

Place of death and the differences in patient quality of death

Little is known regarding the associations between place of death and quality of death and dying and caregiver burden in terminally ill patients with cancer and their families. Two bereavement surveys were conducted in October 2008 and October 2011. A total of 2,247 family caregivers of patients with cancer who were deceased responded to the mail surveys (response rate, 67%). Family members reported patient quality of death and dying and caregiver burden by using the Good Death Inventory and Caregiving Consequences Inventory. Patient quality of death and dying was significantly higher at home relative to other places of dying after adjustment for patient and/or family characteristics (adjusted means): 5.0 (95% CI, 4.9 to 5.2) for home, 4.6 (95% CI, 4.5 to 4.7) for palliative care units, and 4.3 (95% CI, 4.2 to 4.4) for hospitals. Home was superior to palliative care units or hospitals with respect to "dying in a favorite place," "good relationships with medical staff," "good relationships with family," and "maintaining hope and pleasure" ($P < .001$ for all combinations of home v palliative care units and home v hospitals). Home death was significantly associated with a lower overall ($P = .03$) and financial caregiver burden ($P = .004$) relative to hospital death. Dying at home may contribute to achieving good death in terminally ill patients with cancer without causing remarkably increased caregiver burden. Place of death should be regarded as an essential goal in end-of-life care.

## List of papers published in 2014

### Journal

1. Shibayama O, Yoshiuchi K, Inagaki M, Matsuoka Y, Yoshikawa E, Sugawara Y, Akechi T, Wada N, Imoto S, Murakami K, Ogawa A, Akabayashi A, Uchitomi Y. Association between adjuvant regional radiotherapy and cognitive function in breast cancer patients treated with conservation therapy. Cancer Med, 3:702-709, 2014
2. Morita T, Sato K, Miyashita M, Yamagishi A, Kizawa Y, Shima Y, Kinoshita H, Suzuki S, Shirahige Y, Yamaguchi T, Eguchi K. Does a regional comprehensive palliative care program improve pain in outpatient cancer patients? Support Care Cancer, 22:2445-2455, 2014
3. Yamagishi A, Sato K, Miyashita M, Shima Y, Kizawa Y, Umeda M, Kinoshita H, Shirahige Y, Akiyama M, Yamaguchi T, Morita T. Changes in quality of care and quality of life of outpatients with advanced cancer after a regional palliative care intervention program. J Pain Symptom Manage, 48:602-610, 2014
4. Imura C, Morita T, Kato M, Akizuki N, Kinoshita H, Shirahige Y, Suzuki S, Takebayashi T, Yoshihara R, Eguchi K. How and why did a regional palliative care program lead to changes in a region? A qualitative analysis of the Japan OPTIM study. J Pain Symptom Manage, 47:849-859, 2014
5. Sasahara T, Watakabe A, Aruga E, Fujimoto K, Higashi K, Hisahara K, Hori N, Ikenaga M, Izawa T, Kanai Y, Kinoshita H, Kobayakawa M, Kobayashi K, Kohara H, Namba M, Nozaki-Taguchi N, Osaka I, Saito M, Sekine R, Shinjo T, Suga A, Tokuno Y, Yamamoto R, Yomiya K, Morita T. Assessment of reasons for referral and activities of hospital palliative care teams using a standard format: a multicenter 1000 case description. J Pain Symptom Manage, 47:579-587 e576, 2014
6. Miura T, Matsumoto Y, Motonaga S, Hasuo H, Abe K, Kinoshita H. Dyspnea, relative youth and low daily doses of opioids predict increased opioid dosage in the last week of a terminal cancer patient's life. Jpn J Clin Oncol, 44:1082-1087, 2014
7. Nakanotani T, Akechi T, Takayama T, Karato A, Kikuuchi Y, Okamoto N, Katayama K, Yokoo M, Ogawa A. Characteristics of elderly cancer patients' concerns and their quality of life in Japan: a Web-based survey. Jpn J Clin Oncol, 44:448-455, 2014
8. Yokoo M, Akechi T, Takayama T, Karato A, Kikuuchi Y, Okamoto N, Katayama K, Nakanotani T, Ogawa A. Comprehensive assessment of cancer patients' concerns and the association with quality of life. Jpn J Clin Oncol, 44:670-676, 2014

### Book

1. Shimizu K, Yoshiuchi K, Onishi H. Treatment of Anxiety and Stress-Related Disorders. In: Grassi L, Riba M (eds), Psychopharmacology in Oncology and Palliative Care: A Practical Manual, Germany, Springer-Verlag Berlin Heidelberg, pp 129-144, 2014

# Division of Radiation Oncology and Particle Therapy

**Tetsuo Akimoto, Sadatomo Zenda, Teiji Nishio, Hidenobu Tachibana, Ryosuke Kohno, Tomoko Miyagishi, Kenji Hotta**

## Introduction

The aim of research in the Radiation Oncology and Particle Therapy Division at the National Cancer Hospital East is to study and develop innovative treatment techniques and pilot clinical trial for proton beam therapy (PBT). Medical physicists mainly perform development and verification of the systems for beam irradiation, dose calculation system, dose measurement and imaging of PBT. Radiation oncologists mainly perform studies on the clinical trials, efficacy and side effects of PBT.

## Routine activities

At present, the staff of the Radiation Oncology and Particle Therapy Division is consisted from 7 consultant physicians (radiation oncologist), 6 radiation technologists, 4 medical physicists, 1 nurse, and 1 clerk. We have more than 300 or more new patients for PBT in every year, and quality assurances of PBT are performed by medical physicists and radiation technologists, and the conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. PBT are routinely based on three-dimensional radiation therapy planning and PBT using RT-dedicated multi-detector-row helical computed tomography (CT) scanning in order to confirm precise radiation dose to the targeted tumors. Respiratory-gating has been applied especially in radiotherapeutic management for patients with lung, esophagus and liver cancers. The Section is responsible for PBT that is composed of 7 operating staff members and 1 technician for fabricating the compensator and aperture; they are sent from manufacturing companies and work in collaboration with the other staff members of the Division. PBT is consisted from 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

1) PBT as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study.
2) Phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.
3) Phase I/II study of dose escalated PBT combined with chemotherapy for esophageal cancer.
4) Establishment of feasibility and effectiveness of line scanning for localized prostate cancer.
5) Proton dose distribution measurements using a MOSFET detector with a simple dose-weighted correction method for LET effects.
6) Radiobiological evaluation of cellular response to PBT.
7) Radiobiological evaluation of combined effect of chemotherapeutic agents on enhancement of PBT.
8) Standardization of methods of PBT and quality assurance of PBT among Japanese proton beam facilities.
9) Establishment of infrastructure for multi-institutional study of PBT for various cancers.
10) Technical development of intensity modulated proton beam therapy (IMPT).

## Clinical trials

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

1) Phase II study of PBT for malignant melanoma of nasal cavity.
2) Phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.

3) Phase I/II study of dose escalated study of PBT combined with chemotherapy for esophageal cancer.

4) Phase I/II study of line scanning for localized prostate cancer.

**Table 1. The changes in the number of patients treated with PBT**

Number of patients treated with PBT during 2010-2014

| | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| New patients | 107 | 200 | 245 | 378 | 331 |
| Head and neck cancers | 39 | 49 | 45 | 35 | 33 |
| Lung and mediastinal cancers | 12 | 24 | 76 | 101 | 82 |
| Hepatocellular carcinoma | 12 | 27 | 35 | 38 | 21 |
| Prostate cancer | 42 | 93 | 79 | 143 | 111 |
| Others | 2 | 7 | 17 | 45 | 54 |

## List of papers published in 2014

## Journal


1. Hatanaka S, Miyabe Y, Tohyama N, Kumazaki Y, Kurooka M, Okamoto H, Tachibana H, Kito S, Wakita A, Ohotomo Y, Ikagawa H, Ishikura S, Nozaki M, Kagami Y, Hiraoka M, Nishio T. Dose calculation accuracies in whole breast radiotherapy treatment planning: a multi-institutional study. Radiol Phys Technol. 2015.
2. Matsumoto Y, Matsuura T, Wada M, Egashira Y, Nishio T, Furusawa Y. Enhanced radiobiological effects at the distal end of a clinical proton beam: in vitro study. J Radiat Res. 55(4): 816-22, 2014.
3. Nishio T, Shirato H, Ishikawa M, Miyabe Y, Kito S, Narita Y, Onimaru R, Ishikura S, Ito Y, Hiraoka M. Design, development of water tank-type lung phantom and dosimetric verification in institutions participating in a phase I study of stereotactic body radiation therapy in patients with T2N0M0 non-small cell lung cancer: Japan Clinical Oncology Group trial (JCOG0702). J Radiat Res. 55(3): 600-7, 2014.
4. Motegi K, Kohno R, Ueda T, Shibuya T, Ariji T, Kawashima M, Akimoto T. Evaluating positional accuracy using megavoltage conebeam computed tomography for IMRT with head-and-neck cancer. J Radiat Res, 55:568-574, 2014
5. Aoki-Nakano M, Furusawa Y, Uzawa A, Matsumoto Y, Hirayama R, Tsuruoka C, Ogino T, Nishio T, Kagawa K, Murakami M, Kagiya G, Kume K, Hatashita M, Fukuda S, Yamamoto K, Fuji H, Murayama S, Hata M, Sakae T, Matsumoto H. Relative biological effectiveness of therapeutic proton beams for HSG cells at Japanese proton therapy facilities. J Radiat Res, 55:812-815, 2014
6. Zenda S, Nakagami Y, Toshima M, Arahira S, Kawashima M, Matsumoto Y, Kinoshita H, Satake M, Akimoto T. Strontium-89 (Sr-89) chloride in the treatment of various cancer patients with multiple bone metastases. Int J Clin Oncol, 19:739-743, 2014

# Section of Experimental Animals

**Yoshikatsu Koga, Kimie Iijima, Taeko Aruga, Aki Kawaida**



## Introduction

The basic and translational researches investigated in the Research Center for Innovative Oncology (RCIO) and the Exploratory Oncology Research & Clinical Trial Center (EPOC) are aimed toward a future clinical use. To develop anti-cancer drugs based on a novel concept or a novel imaging technology, the animal experiments are necessary. The Section of Experimental Animals supports the animal experiments conducted in RCIO and EPOC.

## Routine activities

- Health management of the experimental animals and maintenance of the animal laboratories.
  - Animal-breeding rooms: specific pathogen-free (SPF) rooms (8 rooms for mice and 1 room for rats), conventional rooms (1 room for mice, 1 room for rats, hamsters, and rabbits, and 1 room for pigs), and P2 animal laboratory.
- Approval of animal experiments and gene recombinant experiments in accordance with the regulations.
  - In 2014, 62 studies involving animal experiments and 25 studies with gene recombinant experiments were approved by the Committee of Experimental Animals and Gene Recombination.

## List of papers published in 2014

### Journal

1. Koga Y, Yamazaki N, Takizawa S, Kawauchi J, Nomura O, Yamamoto S, Saito N, Kakugawa Y, Otake Y, Matsumoto M, Matsumura Y. Gene expression analysis using a highly sensitive DNA microarray for colorectal cancer screening. Anticancer Res, 34:169-176, 2014
2. Koga Y, Yamazaki N, Matsumura Y. New molecular diagnosis and screening methods for colorectal cancer using fecal protein, DNA and RNA. Expert Rev Mol Diagn, 14:107-120, 2014
3. Yamamoto Y, Hyodo I, Takigahira M, Koga Y, Yasunaga M, Harada M, Hayashi T, Kato Y, Matsumura Y. Effect of combined treatment with the epirubicin-incorporating micelles (NC-6300) and 1,2-diaminocyclohexane platinum (II)-incorporating micelles (NC-4016) on a human gastric cancer model. Int J Cancer, 135:214-223, 2014
4. Sato R, Obonai T, Tsumura R, Tsumoto K, Koga Y, Yasunaga M, Matsumura Y. Preparation and characterization of anti-tissue factor singlechain variable fragment antibody for cancer diagnosis. Cancer Sci, 105:1631-1637, 2014

Research Institute

# Preface

For more than 50 years since its establishment in 1962 as a department of the National Cancer Center (NCC), the National Cancer Center Research Institute (NCCRI) has been the leading cancer research institute. The NCCRI is now internationally recognized for its major contributions to various aspects of cancer research. Its mission 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 the NCC Hospitals, the Exploratory Oncology Research & Clinical Trial Center (EPOC), the Research Center for Cancer Prevention and Screening and the Research Institute, is highly encouraged.

The NCCRI consists of the Advanced Biomedical Research Faculty and the Fundamental Innovative Oncology Core (FIOC). The former body now comprises 18 divisions which are sub-grouped into four major Research Groups and one Project Group, that is, the Group for Cancer Development and Progression, the Group for Research into Molecular Functions and Targets, the Group for Development of Molecular Diagnostics and Individualized Therapy and the Group for Translational Research and Project Group. On the other hand, the FIOC is established in 2014 as a core facility to bridge the gap between preclinical and clinical studies for efficient drug development. It consists of 5 cores comprising 15 departments and provides several kinds of technical support for molecular biology, high-throughput omics-type analyses, biological analysis and animal experiments to researchers in both the Research Institute and Hospitals in order to further encourage and facilitate the development of translational-type studies in the Institute.

Currently, there are approximately 80 research staff and around 30 postdoctoral fellows in the NCCRI with over 230 supporting staff members. Foreign scientists and research fellows also visit the NCCRI on a regular basis.

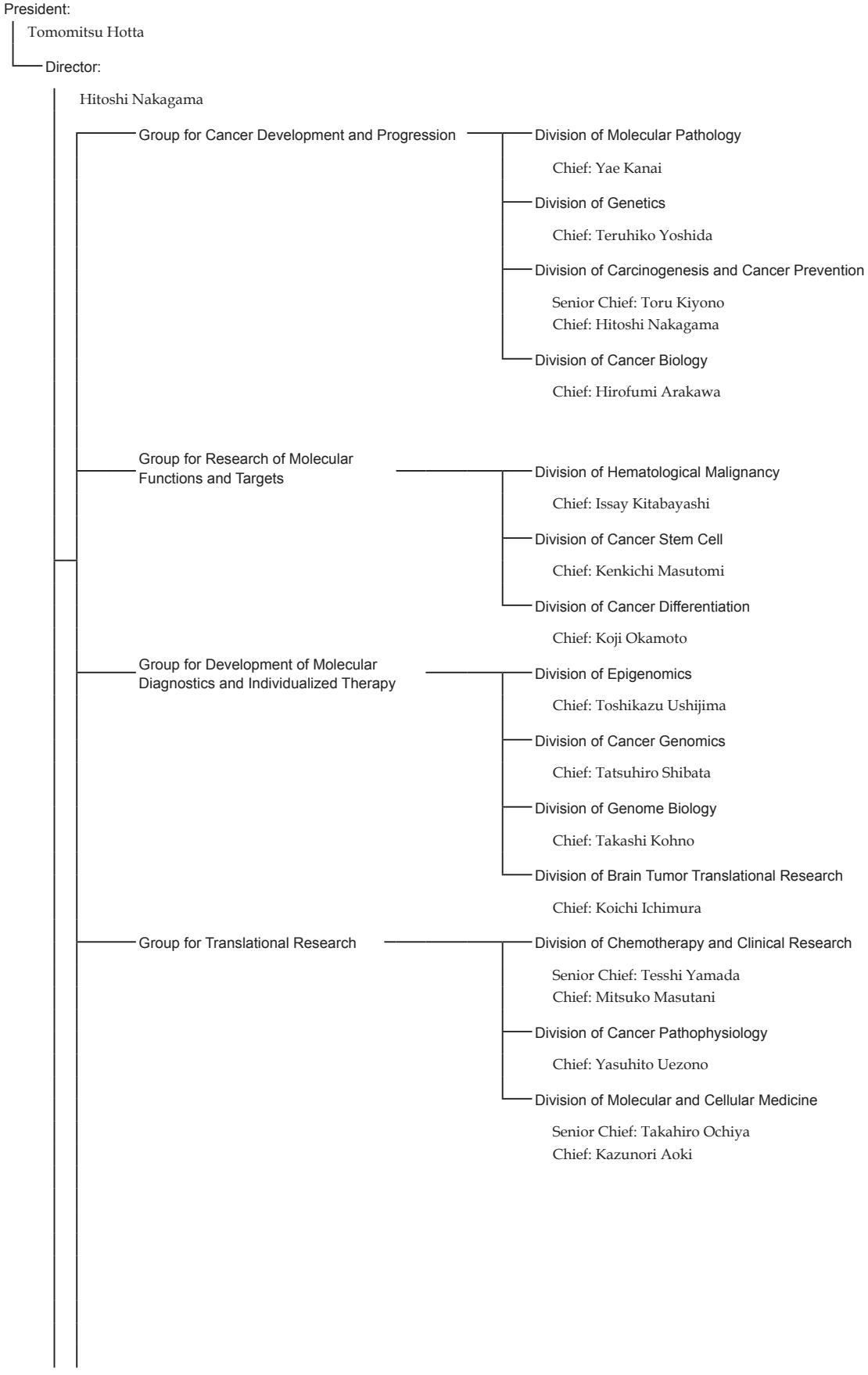
The "Annual Report" of the NCCRI summarizes the recent research activities of each division. Our recent major accomplishments are as follows:

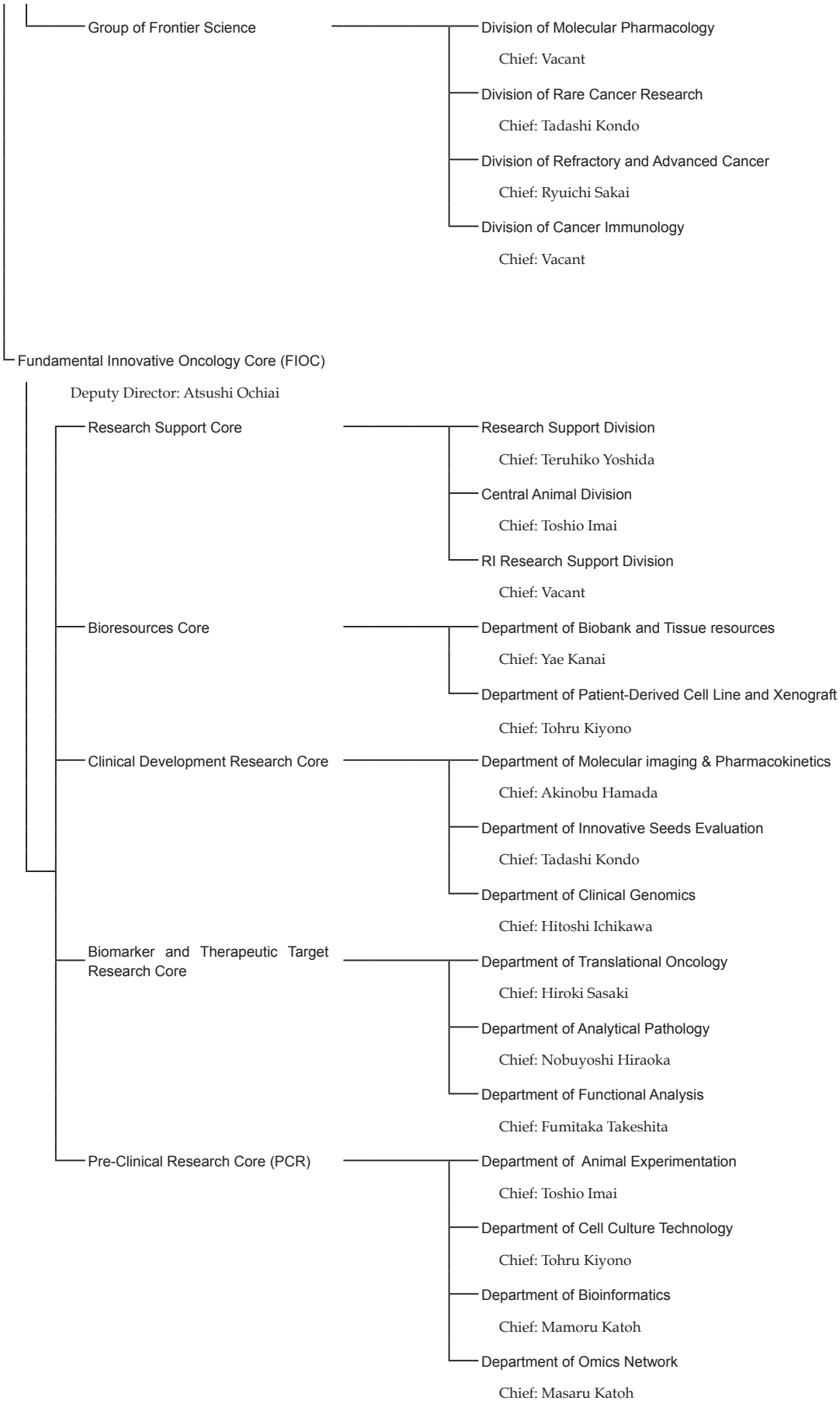
(i) Identification of novel fusion genes in lung cancers, and characterized mutations in hepatitis C-associated liver cancers;
(ii) Identification of novel druggable targets, such as TNIK, RPN2, and GLIS2;
(iii) Establishment of the concept of epigenetic field for cancerization; and
(iv) Development of markers for patient stratification in multiple types of cancers.

We have participated in worldwide research consortia, such as the International Cancer Genome Consortium (ICGC) and International Human Epigenome Consortium (IHEC), and joined the Early Detection Research Network (EDRN) of the National Cancer Institute (NCI), the National Institutes of Health (NIH). In addition to further encouraging collaborative research with NIH, we are now developing international collaborative research projects in other various areas. Information on research activities of NCCRI is also available on the website: http://www.ncc.go.jp/en/nccri/index.html.

Hitoshi Nakagama, M.D., D.M.Sc.
Director, National Cancer Center Research Institute

# Organization




Group of Frontier Science
Division of Molecular Pharmacology
Chief: Vacant
Division of Rare Cancer Research
Chief: Tadashi Kondo
Division of Refractory and Advanced Cancer
Chief: Ryuichi Sakai
Division of Cancer Immunology
Chief: Vacant
Fundamental Innovative Oncology Core (FIOC)
Deputy Director: Atsushi Ochiai
Research Support Core
Research Support Division
Chief: Teruhiko Yoshida
Central Animal Division
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Department of Functional Analysis
Chief: Fumitaka Takeshita
Pre-Clinical Research Core (PCR)
Department of Animal Experimentation
Chief: Toshio Imai
Department of Cell Culture Technology
Chief: Tohru Kiyono
Department of Bioinformatics
Chief: Mamoru Katoh
Department of Omics Network
Chief: Masaru Katoh

# Activities of the Divisions

# Division of Molecular Pathology

**Yae Kanai, Eri Arai, Masahiro Gotoh, Ying Tian, Hidenori Ojima, Takuya Yotani, Yuriko Yamada, Ayako Shibuya, Nanako Itoh, Michiko Suzuki**

## Introduction

Research in the Division of Molecular Pathology is based on a combination of clinicopathological observations and molecular pathological analyses.

## Routine activities

Staff scientists of the Division of Molecular Pathology are also Japanese Board-certified pathologists, who are engaged in routine pathology work involving diagnosis of biopsy and surgically resected materials at the National Cancer Center Hospital. On the basis of findings from our routine diagnostic work, we develop scientific ideas and follow them up using a molecular pathological approach, which can yield potential benefits for patients with cancer.

## Research activities

Multilayer omics analysis in human cancers for personalized medicine

We have participated in the Research Project, "Comprehensive Exploration of Drug Targets Based on Multilayer/Integrative Disease Omics Analyses," as a PI supported by the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation. In March 2015, "Multilayer/Integrative Disease Omics Database" will be launched to disclose data obtained from this project.

To reveal the molecular pathways significantly participating in CpG-island methylator phenotype (CIMP)-positive renal carcinogenesis, genome (whole-exome), transcriptome and proteome analyses were performed in the collaborative project study. A signaling pathway most frequently affected by multilayer omics abnormalities in CIMP-positive clear cell renal cell carcinomas (RCCs), which are characterized by accumulation of DNA hypermethylation of CpG islands, clinicopathological aggressiveness and poor patient outcome, was identified as the potential therapeutic target. The effectiveness of the inhibitor of the identified pathway has been revealed in CIMP-positive RCC cell lines.

In order to make DNA methylation diagnosis, such as prognostication of patients with RCCs using RCC-specific CIMP marker genes, widely applicable for clinical use in each hospital and clinic, we are now innovating a Scaled-Down, Methylated DNA Detection Device in collaboration with a medical device company. We have made patent publications (JP2014-514703, US14/399591, EP13787593.6, CN201380036415.8, KR10-2014-7032254) and put out a media release.

The whole transcriptome analysis (RNA sequencing) and exploration of candidate chimeric transcripts using the deFuse program were performed on cancerous tissue specimens obtained from patients with clear cell RCCs. After verification by reverse transcription-PCR and Sanger sequencing, 26 novel chimeric transcripts were identified in 25% of the examined clear cell RCCs. Genomic breakpoints were determined in the chimeric transcripts. Quantitative RT-PCR analysis revealed that the mRNA expression levels for the MMACHC, PTER, EPC2, ATXN7, FHIT, KIFAP3, CPEB1, MINPP1, TEX264, FAM 107A, UPF3A, CDC16, MCCC1, CPSF3 and ASAP2 genes, being partner genes involved in the chimeric transcripts in the initial cohort, were significantly reduced in cancerous tissue samples relative to the corresponding non-cancerous renal cortex tissue samples in the second cohort. Moreover, the mRNA expression levels for the above partner genes in cancerous tissue samples were significantly correlated with tumor aggressiveness and poorer patient outcome, indicating that reduced expression

of these genes may participate in malignant progression of RCCs. As is the case when their levels of expression are reduced, these partner genes also may not fully function when involved in chimeric transcripts. These data suggest that generation of chimeric transcripts may participate in renal carcinogenesis by inducing dysfunction of tumor-related genes.

Activities in the International Human Epigenome Consortium (IHEC)

We have participated in the IHEC as a PI supported by the Core Research for Evolutional Science and Technology (CREST) project by the Japan Science and Technology Agency (JST). In collaboration with research groups in Kyushyu University and the University of Tokyo, we perform whole-genome bisulfite sequencing using the post-bisulfite adaptor-tagging method, chromatin immunoprecipitation-sequencing and RNA-sequencing of various cell lineages of the gastrointestinal and urinary systems. Epigenome maps of hepatocytes purified from normal liver tissue and diseased liver tissue with hepatitis C virus (HCV) or hepatitis B virus (HBV) infection have been deposited in the National Bioscience Database Center supported by the JST. In addition to standard protocols recommended by the IHEC, the whole genome sequencing was performed in purified hepatocytes and genome-epigenome crosstalk was examined. Our data indicated that genomic variations, such as single-nucleotide polymorphisms, insertions and deletions, may induce personal variations of DNA methylation status in cis-acting manner.

Clinicopathological studies of human cancers based on the practice of diagnostic pathology

Using morphological, histological, immunohistochemical and molecular pathological approaches, diagnostic and prognostic criteria which are applicable to histological specimens were explored. We collect tissue samples for the National Cancer Center Biobank and contribute to collaboration researches through providing clinicopathological information.

## Future prospects

We will perform joint researches with users of "Multilayer/Integrative Disease Omics Database" among government, industry and academia. We will hold the sixth annual meeting of the IHEC in next November in Tokyo. Accurate standard epigenome profiles of digestive and urogenital organ epithelilal cells obtained through IHEC activities will be used to explore more useful biomarkers and drug targets of cancers.

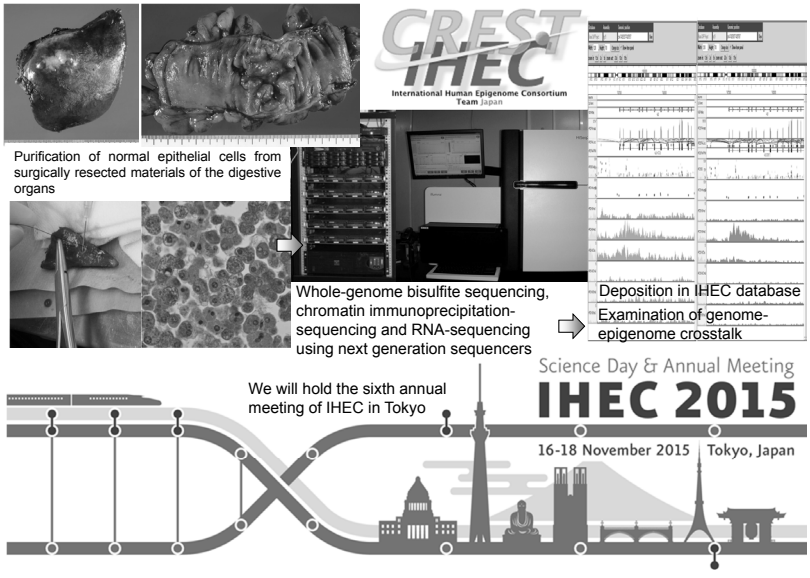


**Figure 1. Activities in The International Human Epigenome Consortium**

## List of papers published in 2014

## Journal


1. Arai E, Sakamoto H, Ichikawa H, Totsuka, H Chiku S, Gotoh M, Mori T, Nakatani T, Ohnami S, Nakagawa T, Fujimoto H, Wang L, Aburatani H, Yoshida T, Kanai Y. Multilayer-omics analysis of renal cell carcinoma, including the whole exome, methylome and transcriptome. Int J Cancer, 135:1330-1342, 2014

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21. Okusaka T, Ojima H, Morizane C, Ikeda M, Shibata T. Emerging drugs for biliary cancer. Expert Opin Emerg Drugs, 19:11-24, 2014

22. Arai Y, Totoki Y, Hosoda F, Shirota T, Hama N, Nakamura H, Ojima H, Furuta K, Shimada K, Okusaka T, Kosuge T, Shibata T. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. Hepatology, 59:1427-1434, 2014

# Division of Genetics

**Teruhiko Yoshida, Hiromi Sakamoto, Hitoshi Zenbutsu, Norihisa Saeki, Fumiaki Koizumi, Misuzu Okuyama, Yoko Odaka, Mineko Ushiama, Masumi Shimizu, Sayaka Mito, Hitomi Gunji, Tomoko Ikegami, Hiroe Ishii, Norie Kowatari, Misaki Ono, Sumiko Ohnami**

## Introduction

In 2014, the Division continued to pursue its ongoing research agenda except the departure of a laboratory head, Dr. Koizumi in March 2014. Dr. Zenbutsu has joined the Division as a new laboratory head. The 3 major research themes of the Division were #1) molecular understanding of cancer susceptibility; #2) development of personalized cancer diagnosis and treatment and #3) pharmacogenomics research on cancer treatment.

## Research activities

#1) The Division has been engaged in the studies on prostate stem cell antigen (PSCA) gene related to cancer susceptibility identified by a genome-wide association studies. The Division demonstrated previously that the T allele of a single nucleotide polymorphism (SNP) rs2294008 (T/C) in the gene is associated with gastric cancer, and that the T allele significantly suppresses the transcriptional activity of the PSCA promoter. Replacing the C allele of rs2294008 to the T generates a binding consensus for Yin Yang 1 (YY1), a multifunctional zinc-finger transcription factor member of the Polycomb Group protein family, suggesting that YY1 contributes to PSCA promoter suppression. The PSCA protein is thought to be involved in some form of intracellular signaling. Gene-expression profiling on tumors with and without expression of PSCA unveiled several immune-related genes down-regulated by PSCA, including IL1RN and S100A9.

#2) The Division has continued the Integrated Disease Omics Project to explore target candidates for drug and biomarker development on 13 diseases supported by NiBio (National Institute of Biomedical Innovation). Dr. Sakamoto is in charge of the genomics core facility of the project and contributed to the construction of the Integrated Omics Database. Moreover, as a collaborative study with Drs. Hiroki Sasaki and Hitoshi Ichikawa, who were laboratory heads of the Division by 2013, Dr. Sakamoto performed SNP array and whole exome sequence analyses on diffuse-type gastric cancer and identified several new therapeutic target candidates (Figure 1).

#3) In 2014, Dr. Zenbutsu published in the following research on pharmacogenomics of breast cancer: CYP2D6 genotype and adjuvant tamoxifen (Figure 2): meta-analysis of heterogeneous study populations, Polygenic inheritance of paclitaxel-induced sensory peripheral neuropathy driven by axon outgrowth gene sets in CALGB 40101, VAV3 mediates resistance to breast cancer endocrine therapy.

## Clinical trials

#3) CYP2D6 is well-known to be a key enzyme in the generation of the endoxifen which is a principal active metabolite of tamoxifen, and the genetic polymorphisms of CYP2D6 have been extensively investigated in association with the plasma endoxifen concentrations and clinical outcome of tamoxifen therapy. To prospectively investigate the effects of CYP2D6 genotype on the response of patients with hormone receptor-positive breast cancer, prospective clinical trial is ongoing using the patients receiving the preoperative tamoxifen therapy.

## Education

Dr. Zenbutsu contributed to the pharmacy residency program in the NCC.

## Future prospects

#1) Elucidation of the mechanism of carcinogenic effect of the genes identified by a hypothesis-free observational study on human clinical cancers is critically important for the translation of the scientific findings to the medical and health care of the society. It could be, however, a high-risk research, and PSCA seems to be a difficult case to dissolve its mystery. The Division highly appreciates Dr. Saeki for his remarkable perseverance and effort even in the limited research resource allocation.

#2) As in the case with #1), observational study should be followed by a functional exploration to identify an actionable drug target. The gastric cancer genome project by the Division has an advantage in that context, because it has entailed the establishment of primary culture cell lines, which have turned out to be precious resource for drug screening.

#3) The genome information-based companion diagnostics (CDx) could be one of the most important devices for precision medicine. The Division keeps working on the establishment of prediction system for the efficacy and adverse events of cancer chemotherapy through pharmacogenomics study.

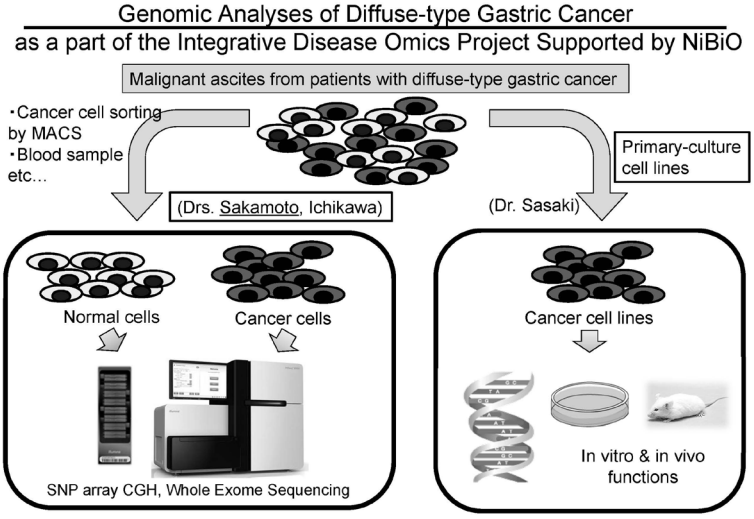


**Figure 1. Genomic analyses of diffuse-type gastric cancer**

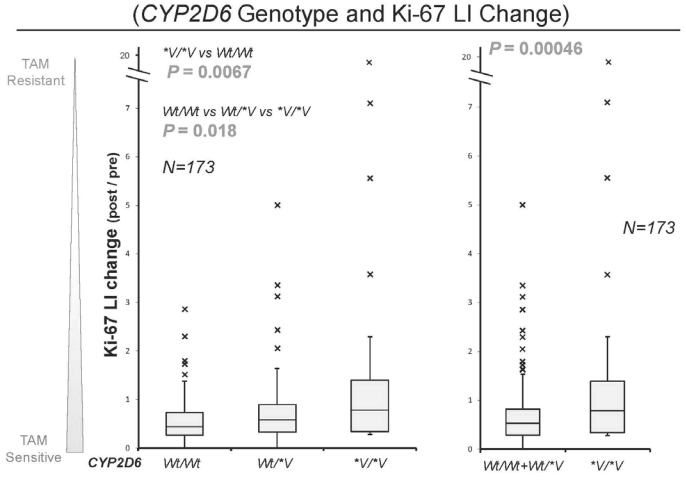


**Figure 2. Clinical research on CYP2D6 polymorphism and personalized tamoxifen treatment**

## List of papers published in 2014

### Journal


1. Nakaoku T, Tsuta K, Ichikawa H, Shiraishi K, Sakamoto H, Enari M, Furuta K, Shimada Y, Ogiwara H, Watanabe S, Nokihara H, Yasuda K, Hiramoto M, Nammo T, Ishigame T, Schetter AJ, Okayama H, Harris CC, Kim YH, Mishima M, Yokota J, Yoshida T, Kohno T. Druggable oncogene fusions in invasive mucinous lung adenocarcinoma. Clin Cancer Res, 20:3087-3093, 2014
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# Division of Carcinogenesis and Cancer Prevention (Viral Carcinogenesis and Prevention Group)

**Tohru Kiyono, Takashi Yugawa, Tomomi Nakahara, Kenji Yamada, Satomi Kikawa, Yuki Inagawa, Takako Ishiyama, Katsuyuki Tanaka, Shin-ichi Ohno, Kasumi Ohtsubo, Kazuki Shimomura, Shotaro Tsunoda, Akiko Noguchi, Etsuko Kabasawa**

## Introduction

Approximately 15% of human cancers have a viral etiology, and seven viruses have been elucidated as being associated with human cancers. Among these recognized viruses, research in the Division of Carcinogenesis and Cancer Prevention is mainly focused on the molecular mechanisms of oncogenesis by human papillomaviruses (HPVs). A subset of HPVs including types 16 and 18 are closely associated with human cancers and have thus been called high-risk HPVs (HR-HPVs). The E6 and E7 proteins of HR-HPVs are known to inactivate the major tumor 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).

## Routine activities

To clarify molecular mechanisms of oncogenesis by viral and cellular oncogenes and inactivation of tumor suppressors, we are establishing ex vivo carcinogenesis models for cervical cancer and other cancers by transducing abnormalities of genes found in cancer into normal cells-of-origin of each cancer.

## Research activities

1. HPV-induced carcinogenesis and its prevention

A subset of HPVs including types 16 and 18 are closely associated with human cancers and have thus been called high-risk HPVs (HR-HPVs). Persistent infection of the HR-HPVs is a major cause of cervical cancer. About 50 to 100 copies of HPV genome are maintained in basal cells of the infected lesions such as cervical intraepithelial neoplasm (CIN). We demonstrated previously that the viral helicase E1 is dispensable for maintenance replication of the HPV genome in basal cell layer but indispensable for the initial amplification of the genome soon after primary infection and productive amplification in suprabasal layer. We previously established a human cervical keratinocyte cell line that harbors about 50 copies of episomal HPV16 genome. By using the tetON system, we transduced E1 and E2 in the cells where these two genes were induced upon doxycycline (DOX) treatment. These cell lines showed robust amplification of the HPV genome upon induction of E1 and E2 by DOX treatment. With this newly developed cell lines, we are analyzing the mechanism of transition from initial amplification to maintenance replication. We also study what facilitates loss of episomal HPV and emergence of viral genome integration which potentiates cancer progression. Once HPV genome is integrated in the form that E6 and E7 genes can be highly expressed in the basal cells, these oncogenes cooperatively immortalize and transform cells so as to induce CIN2/3 lesions. Recent genome editing technology with nucleases such as Zinc finger nuclease and CRISPR/Cas made it possible to directly target HPV genome whether or not it is integrated. With the CRISPR/Cas system, we are developing targeting vector to knock down E6/E7 regions of HPV16 and 18.

2. Human cancer xenograft model utilizing normal pancreatic duct epithelial cells

Pancreatic ductal adenocarcinomas (PDACs) are considered to arise through neoplastic transformation of human pancreatic duct epithelial cells (HPDECs). In order to evaluate the biological significance of genetic and epigenetic alterations in PDACs, we isolated primary HPDECs and established an in vitro carcinogenesis model.

Firstly, lentivirus-mediated transduction of $KRAS^{G12V}$, MYC and human papillomavirus 16 (HPV16) E6/E7 under the control of a tetracyclin-inducible promoter efficiently immortalized and transformed primary HPDECs, which gave rise to adenocarcinomas subcutaneously in an immune-deficient mouse xenograft model, depending on expression of the four genes. The tumors regressed promptly upon shutting-off the oncogenes, and the remaining tissues showed histological features corresponding to normal ductal structures with simple columnar epithelium. Re-expression of the oncogenes resulted in development of multiple PDACs through pancreatic intraepithelial neoplasia-like structures (Fig 1). We also succeeded in efficient immortalization of primary HPDECs with transduction of mutant CDK4, cyclin D1 and TERT. In combination with p53 silencing, $KRAS^{G12V}$ alone was sufficient to fully transform the immortalized HPDECs, and MYC markedly accelerated the development of tumors.

## Education

Five undergraduate and graduate students in local universities worked as trainees in our lab and had cancer research training.

## Future prospects

The current HPV vaccines have no therapeutic effect upon pre-existing CIN lesions. To clear HPV infection from CIN lesions, possible strategy is eradication of HPV genome with specific inhibitor of HPV replication or elimination of HPV-infected cells with surgery or by induction of cell death with drug or therapeutic vaccine. Elucidation of the transition mechanism from initial amplification to maintenance replication will facilitate development of such drugs. If such drugs are developed, prevention of cervical cancer will be much easier.

The in vitro carcinogenesis model with reversible control of oncogene expression enabled de novo development of PDAC from quasi-normal human tissues pre-formed subcutaneously in mice and might be applicable to carcinogenesis models in many organ sites. These models will be useful for preclinical assessment of new cancer therapies.



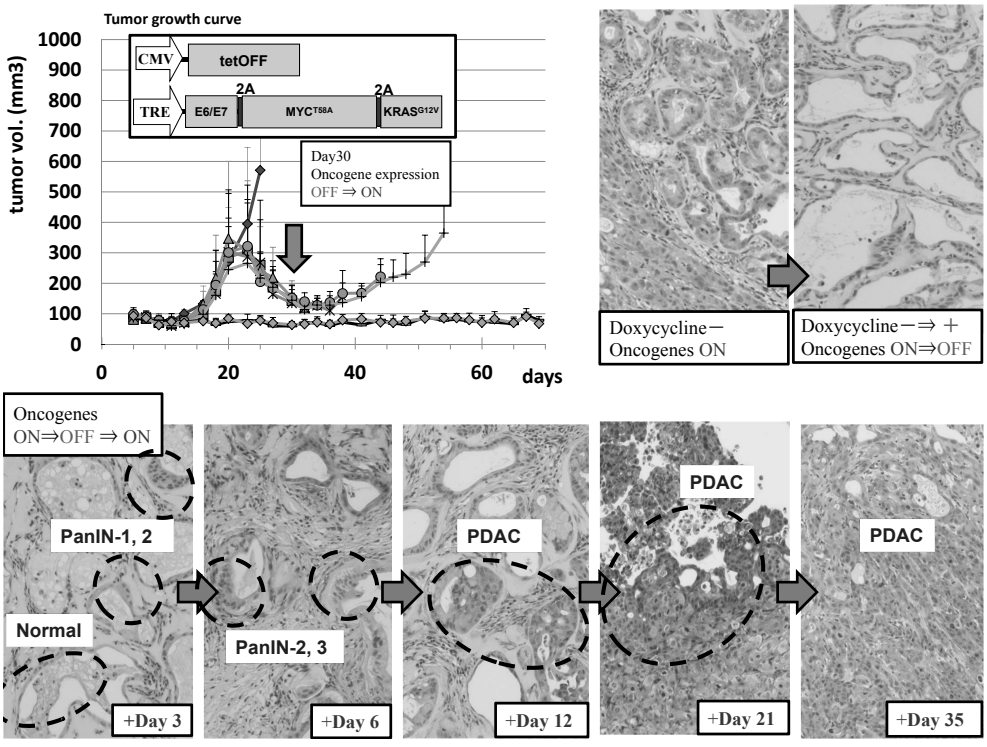


**Figure 1. Ex vivo Pancreatic Carcinogenesis Model**

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# Division of Carcinogenesis and Cancer Prevention (Chemical Carcinogenesis and Prevention Group)

**Hitoshi Nakagama, Yukari Totsuka, Ken-ichi Yoshioka, Sachiko Dobashi, Kazuhiro Shiizaki, Masanori Goto, Michihiro Mutoh, Gen Fujii, Satomi Shimizu, Wakana Onuma, Takahiro Hamoya, Masahiro Ishikawa**

## Introduction

Cancer is a disease associated with environmental factors and aging. Most of them are developed without particular backgrounds that risk genomic destabilization, such as repair deficiency. This poses multiple questions, including how genomic instability is developed in association with aging and how genomic instability drives cancer development. To address these questions, we are studying environmental and aging-associated risk factors of genomic instability and cancer. We are also evaluating the usefulness and safety of thorough endoscopic polypectomy and of cancer chemopreventive agents in familial adenomatous polyposis (FAP) patients.

## Routine activities

To clarify cancer risks, we are studying DNA adducts and damages and genomic instabilities that are triggered by those DNA lesions and cause cellular transformation. In addition, we are also studying DNA damage response and repair mechanisms, which can neutralize the cancer risks.

## Research activities

1. DNA damage repair study in senescent cells

Senescent cells are defective in DNA damage repair, hence usually accumulating unrepairable DNA lesions. Here we showed such repair deficiency was partly because of the decrease of histone H2AX that was required for DNA repair. Intriguingly, such cells still can repair DNA double strand breaks (DSBs) because H2AX transiently expresses in response to DSBs.

2. Study of genomic instability development

Mismatch repair deficient cancer cells generally show microsatellite instability (MSI). Here we have observed that such MSI induction was triggered by DNA replication stress.

3. Identification of novel mutagens/carcinogens

A new mutagenic Maillard reaction product formed from glucose and L-tryptophan, an aminobenzoazepinoquinolinone derivative (ABAQ) was identified. To investigate *in vivo* mutagenicity of ABAQ, *gpt* delta transgenic mice were treated with five consecutive administrations of ABAQ by gavage at doses of 25 or 50 mg/kg per week for 3 weeks. *gpt* mutation frequencies (MF) in the liver of mice treated with ABAQ significantly increased in a dose-dependent manner. Mutation spectra analysis showed that G:C to A:T transition and A:T to C:G transversion were the most significant. Moreover, we determined the tumor-initiating potency of ABAQ using an inflammation-related, two-stage mouse colon carcinogenesis model. Male Crj: CD-1 (ICR) mice were treated with the single intragastric administration (100 or 200 mg/kg body weight) of ABAQ followed by subsequent 1-week oral exposure to 2% dextran sodium sulfate (DSS) in drinking water. The ABAQ treatment alone resulted in high-grade dysplasia, which is a precursor to colorectal cancer, in the colon. Following the administration of DSS after ABAQ treatment, the incidence and frequency of high-grade dysplastic lesions increased. These findings indicate that ABAQ is mutagenic, and might contribute to cancer development in animal models.

Reports related to other environmental mutagens/carcinogens can be found in the attached list of references.

4. Prevention of colorectal cancer

FAP patients are a well-known high risk group of colorectal cancer (CRC). We are evaluating the usefulness and safety of thorough endoscopic polypectomy and of cancer chemopreventive

agents in FAP patients. Based on these findings, we are trying to clarify the underlying mechanism of colorectal carcinogenesis in laboratory study. Moreover, we are searching for novel chemopreventive agents against CRC using animal models of FAP.

## Education

Six undergraduate and graduate students in local universities worked as trainees in our lab and had cancer research training.

## List of papers published in 2014

### Journal


1. Hori M, Takahashi M, Hiraoka N, Yamaji T, Mutoh M, Ishigamori R, Furuta K, Okusaka T, Shimada K, Kosuge T, Kanai Y, Nakagama H. Association of pancreatic Fatty infiltration with pancreatic ductal adenocarcinoma. Clin Transl Gastroenterol, 5:e53, 2014
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## Future Prospects

Our challenge is to characterize the risk factors of cancer and the regulation to control those risks. As a future direction, we are trying to establish the strategies to prevent cancer.

### Book


1. Mutoh M, Takahashi M and Wakabayashi K. Chapter 20 ”Chemoprevention of colorectal cancer by anti-inflammatory agents”. In: Hiraku Y, Kawanishi S, Ohshima H (eds), Cancer and Inflammation Mechanisms: Chemical, Biological, and Clinical Aspects, First edition, USA, John Wiley & Sons, Inc., 2014

# Division of Cancer Biology

**Hirofumi Arakawa, Yasuyuki Nakamura, Noriaki Kitamura, Masayuki Tsuneki, Sayaka Yasuda, Saori Morota, Hiroki Kamino, Yoko Sagami, Ruri Nakanishi, Yoko Takahashi**

## 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 line, a new p53-target gene was identified, and designated Mieap for mitochondria-eating protein, reflecting its unusual function of the protein. Surprisingly, the function of Mieap is involved in mitochondrial quality control (MQC).

Mieap-induced accumulation of lysosome-like organelles within mitochonria

Mieap controls mitochondrial quality via two distinct novel mechanisms. One of the mechanisms has been designated MALM for Mieap-induced accumulation of lysosome-like organelles within mitochondria (*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 MALM plays a role in repairing unhealthy mitochondria.

BNIP3 and NIX, mitochondrial outer membrane proteins, two Mieap-interacting proteins mediate the translocation of lysosomal proteins from cytosol into mitochondria during MALM by forming an unknown pore in the mitochondrial double membrane (*PLoS ONE* 7: e30767, 2012). 14-3-3γ mediates the degradation of oxidized mitochondrial proteins within mitochondria during MALM (*Scientific Reports* 2: 379, 2012).

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. The Mieap-regulated MQC is frequently inactivated by p53 mutations or Mieap-methylation or BNIP3 methylation in more than 80% primary colorectal and pancreatic cancer tissues. In order to further 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 many primary

cancer tissues including breast and gastric cancer patients.

To clarify the in vivo role of Mieap in tumorignenesis, the Mieap knockout mice were generated in the Division. Using the Mieap knockout mice, the Mieap-deficient $Apc^{MIN/+}$ mice were also generated and being analyzed in order to elucidate the role of Mieap in colorectal cancer tumorigenesis. In addition, the Mieap-deficient pancreatic and gastric cancer models are being prepared at the Division.

Aerobic glycolysis is a common feature of human cancers, which is also known as the Warburg effect. The p53-Mieap pathway is frequently inactivated in human cancers because of p53 mutations and/or Mieap methylation. This leads to accumulation of unhealthy mitochondria and consequently the Warburg effect (Figure 2). The accumulated unhealthy mitochondria in cancer cells also produce high level of reactive oxygen species (ROS). The increased mitochondrial ROS dramatically enhance cancer migration and invasion (Figure 2).

## Education

To acquire knowledge and skills for cancer research, students attend lectures and seminars, and attend and/or practice research meeting, journal club, scientific meeting, etc. These practices will enable students to develop an ability to conduct their studies as an independent cancer researcher in the future. To obtain good skills to carry out experiments that are required for cancer research, students belong to one of our research groups, and conduct their own studies under the guidance of the instructor and/or staff. Students perform various experiments involved in genetics, gene technology, biochemistry, cellular biology, molecular biology, physiology, experimental animal, pathology, genomic/epigenomic/proteomic analysis, imaging, next generation sequencing, etc.

## Future prospects

Analyses of clinical cancer tissues and various cancer-mouse models enable us to understand the actual role of the Mieap-regulated mitochondrial quality control in human cancer formation, progression, invasion and metastasis. Finally, we will be able to establish a solid foundation for development of new strategies for cancer prevention, diagnosis, and therapy in the future.

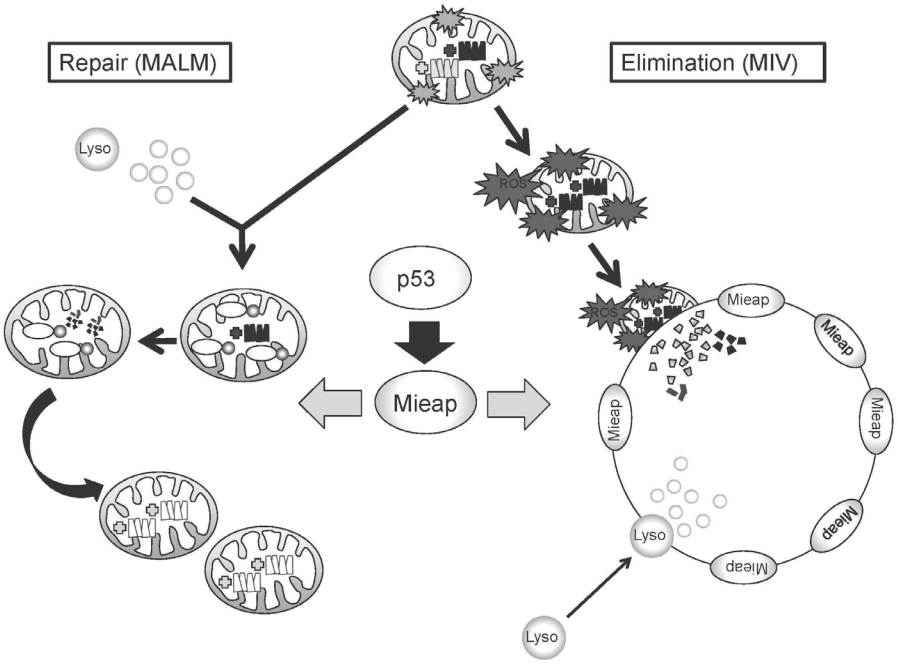


**Figure 1.**

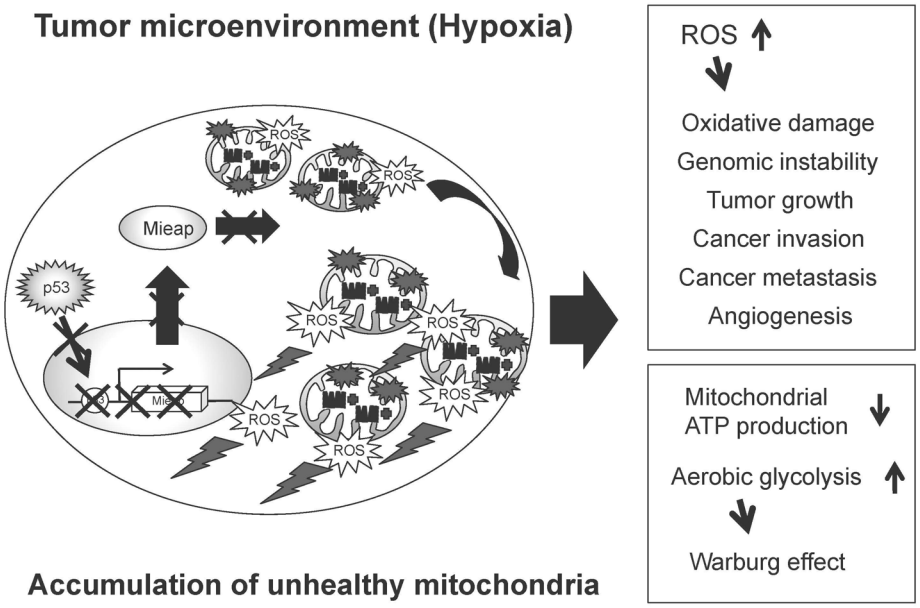
Tumor microenvironment (Hypoxia)
ROS
Mieap
p53
Mieap
Accumulation of unhealthy mitochondria
ROS
Oxidative damage
Genomic instability
Tumor growth
Cancer invasion
Cancer metastasis
Angiogenesis
Mitochondrial ATP production
Aerobic glycolysis
Warburg effect

**Figure 2.**

# Division of Hematological Malignancy

**Issay Kitabayashi, Kazutsune Yamagata, Takuo Katsumoto, Yutaka Shima, Yoko Ogawara, Emi Takamatsu, Yuuki Kagiyama, Mai Suzuki, Shuhei Fujita, Yukiko Aikawa, Mika Shino, Rieko Furuya**

## Introduction

AML is the most common leukemia in Japan and 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 patients relapse AML and only 25-30% of young adults and fewer than 10% of older patients survive longer than 5 years, suggesting presence of AML stem cells that are resistant to chemotheraphy. Thus, AML stem cell eradication is thought to be crucial for cure of AML. Chromosome abnormalities, which result in generation of specific fusion genes, are observed in ~50% of AML patients. AML associated with fusion genes involving MLL, MOZ, CALM or NUP98 have an extremely poor outcome. Normal cytogenetics portend average-risk AML. Recent genome analysis revealed that mutations in NPM, IDH1/IDH2/TET2, DNMT3a and FLT3 genes are often simultaneously observed in patients with normal cytogenetics. Our research purpose is to establish new therapeutic methods by identifying molecular targets that is essential for maintenance of AML cells, especially AML stem cells.

## Research activities

Chromosomal translocations that involve the monocytic leukemia zinc finger (MOZ) gene are typically associated with human acute myeloid leukemia (AML) and often predict a poor prognosis. Overexpression of HOXA9, HOXA10, and MEIS1 was observed in AML patients with MOZ fusions. To assess the functional role of HOX upregulation in leukemogenesis by MOZ-TIF2, we focused on bromodomain-PHD finger protein 1 (BRPF1), a component of the MOZ complex that carries out histone acetylation for generating and maintaining proper epigenetic programs in hematopoietic cells. Immunoprecipitation analysis showed that MOZ-TIF2 formed a stable complex with BRPF1, and chromatin immunoprecipitation analysis showed that MOZ-TIF2 and BRPF1 interacted with HOX genes in MOZ-TIF2-induced AML cells. Depletion of BRPF1 decreased the MOZ localization on HOX genes, resulting in loss of transformation ability induced by MOZ-TIF2. Furthermore, mutant MOZ-TIF2 engineered to lack histone acetyltransferase activity was incapable of deregulating HOX genes as well as initiating leukemia. These data indicate that MOZ-TIF2/BRPF1 complex upregulates HOX genes mediated by MOZ-dependent histone acetylation, leading to the development of leukemia. We suggest that activation of BRPF1/HOX pathway through MOZ HAT activity is critical for MOZ-TIF2 to induce AML.

The CALM-AF10 fusion gene, which results from a t(10;11) translocation, is found in a variety of hematopoietic malignancies. Certain HOXA cluster genes and MEIS1 genes are upregulated in patients and mouse models that express CALM-AF10. Wild-type clathrin assembly lymphoid myeloid leukemia protein (CALM) primarily localizes in a diffuse pattern within the cytoplasm, whereas AF10 localizes in the nucleus; however, it is not clear where CALM-AF10 acts to induce leukemia. To investigate the influence of localization on leukemogenesis involving CALM-AF10, we determined the nuclear export signal (NES) within CALM that is necessary and sufficient for cytoplasmic localization of CALM-AF10. Mutations in the NES eliminated the capacity of CALM-AF10 to immortalize murine bone-marrow cells in vitro and to promote development of acute myeloid leukemia in mouse models. Furthermore, a fusion of AF10 with the minimal NES can immortalize bone-marrow cells and induce leukemia in mice.

These results suggest that during leukemogenesis, CALM-AF10 plays its critical roles in the cytoplasm.

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# Division of Cancer Stem Cell

**Kenkichi Masutomi, Yoshiko Maida, Satoko Yamaguchi, Mami Yasukawa, Marco Ghilotti, Yosuke Satomura**

## Introduction

Research in the Division of Cancer Stem Cell is focused on deciphering the mechanisms that establish and maintain cancer stem cells and developing novel therapeutic approaches to treat cancer stem cells. In particular, the Division studies the molecular links between a) telomerase and RNA-dependent RNA polymerase (RdRP); b) telomerase and cancer stem cells; and c) RdRP and anticancer drugs.

### Telomerase and RNA-dependent RNA polymerase

Telomerase is a ribonucleoprotein complex that elongates telomeres. Human TERT is known as the catalytic subunit of the enzyme. TERT acts as an RNA-dependent DNA polymerase (RdDP) and synthesizes telomere DNA from a non-coding RNA template human TERC. Although the major function of TERT is believed to be telomere elongation, emerging evidence indicates that TERT exhibits various functions beyond telomere maintenance. We reported that TERT has an RdRP activity and mediates post-transcriptional gene silencing through the production of endogenous siRNAs[1] (Figure 1). To further investigate biological functions of TERT-RdRP, we generated a new anti-TERT monoclonal antibody and established an RdRP assay using TERT immune complexes isolated from cell lysate (IP-RdRP assay). We confirmed that both TERT levels and TERT-associated RdRP activity are increased during mitosis while telomerase activity is upregulated in S phase[2]. These observations indicate a non-telomere directed function of TERT during mitosis.

RdRPs in yeast and worm regulate centromeric heterochromatin formation, and RdRPs are required for proper chromosome segregation during mitosis in these organisms. The RNA-directed RNA polymerase complex (RDRC) contributes to the regulation, and the complex contains RdRP and RNA helicase. In our study, TERT assembles with BRG1 and nucleostemin (NS) in mitotic cells, and the TERT/BRG1/NS complex (TBN complex) exerts RdRP activity. Because TERT has RdRP activity, and BRG1 has helicase activity, we speculated that the TBN complex might have similar functions with the RDRC. We confirmed that TERT-RdRP suppresses transcription from heterochromatic regions at centromeres and transposons, and suppression of TERT-RdRP complex results in the increase of the cells arrested in mitosis, binucleate cells and the heterochromatic transcription[2]. These observations indicate that TERT-RdRP contributes to mitotic progression through the regulation of heterochromatin maintenance (Figure 2). Our findings suggest that inhibitors for the novel functions of TERT may prove useful in targeting cancer cells.

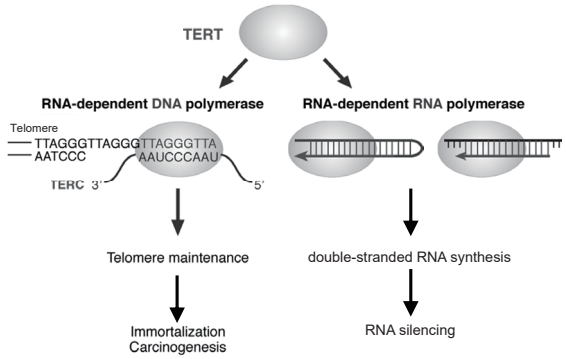


**Figure 1. TERT exerts RdRP activity**

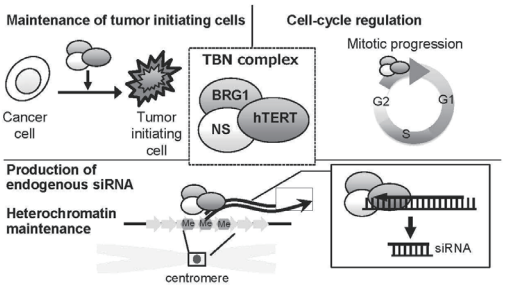


**Figure 2. Various functions of the TBN complex**

**Telomerase and cancer stem cells**

Previous studies indicated that TERT has activities beyond telomere maintenance, and it is speculated that the constitutive expression of TERT not only stabilizes telomere length and facilitates cell immortalization but also contributes to tumor susceptibility and alters stem cell cycling in vivo even when telomere lengths are not limited. As mentioned above, we found that TERT forms a protein complex with the SWI/SNF component (BRG1) and the nucleolar GTP-binding protein (NS); the TBN complex participates in the regulation of tumor initiating cells (TICs) phenotypes through telomere-independent mechanisms[3] (Figure 2). We also confirmed that the cells that constitutively express NS exhibited increased beta-catenin signaling and elevated MYC, OCT3/4, KLF4 and TWIST (master regulator of epithelial mesenchymal transition [EMT]) expression. Moreover, cells that constitutively express elevated levels of TERT, BRG1 and NS exhibit increased CD133 and CD44 expression and enhanced tumorigenicity at limiting cell numbers. These observations indicate that the TBN complex is essential for the maintenance of TICs.

**RdRP and anticancer drugs**

Ovarian cancer is the most lethal of all gynecological malignancies in Japan. The majority of ovarian cancers are diagnosed at an advanced stage. Currently, platinum-based chemotherapy is the standard first-line treatment for advanced ovarian cancer patients; however, chemoresistance is a major obstacle for long-term survival after initial treatment. Using platinum-sensitive and platinum-resistant ovarian cancer cell lines, we screened a series of anti-cancer compounds for growth suppression of platinum-resistant ovarian cancer cell lines[4]. We found that eribulin mesylate (eribulin) effectively inhibits growth of platinum-resistant ovarian cancer cells. Eribulin is available for the treatment of breast cancer in Japan. Although, it has been confirmed that eribulin exerts its anticancer effect by blocking the elongation of microtubules, we found that eribulin specifically inhibits the RdRP activity of TERT in vitro, suggesting TERT-RdRP as a novel molecular target of the drug beyond tubulin. This hypothesis was further supported by the results showing that 1) eribulin-sensitive ovarian cancer cell lines express high levels of TERT, and 2) suppression of TERT expression reduced sensitivity to erilubin. The eribulin-sensitive cell lines have enhanced cancer stem cell (CSC)-like traits, the characteristics related to TERT, as well. Our study demonstrated that eribulin may be a promising therapeutic agent for platinum-resistant ovarian cancer.

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# Division of Cancer Differentiation

**Koji Okamoto, Daisuke Shiokawa, Hirokazu Ohata, Su Youn Chung, Noriyuki Yokomichi, Hirokazu Takahashi, Waka Kato, Naoko Osada, Kenta Takahashi, Rie Uchino, Ai Sato, Hiroaki Sakai**

## Introduction

Cancer stem cells (CSCs) are likely to be responsible of malignant traits of refractory cancer, i.e. ability to generate metastatic foci and chemoresistance. Our group mainly focuses on studying CSCs from colon cancer and serous ovarian cancer. We aim to investigate biological feature of CSCs by cultivating them *in vitro* from various clinical specimens. In addition, we use the established CSCs to generate patient-derived xenograft tumor by injecting them into immuno-compromized mice. As an alternative approach to understand cancer metastasis, we have performed functional screening using lentivirus libraries of shRNAs and miRNAs.

## Routine activities

A weekly conference is held with members of the Division of Cancer Differentiation.

## Research activities

Biological studies of cancer stem cells *in vitro* from human refractory cancer

Recently, by performing spheroid culture in the presence of an inhibitor of Rho-associated protein kinase (ROCK), we isolated and expanded cancer stem cells *in vitro* from human colon cancer and serous ovarian cancer. In addition, we successfully cultivated CSCs from metastatic foci in liver. We are comparing the metastatic and non-metastatic CSCs through microarray analyses and metabolome analyses. These investigations revealed several specific genes and metabolites that are specifically expressed at high levels in metastatic liver. We are now examining if they are linked to any functional roles in liver metastasis of colon cancer.

In our previous studies, we demonstrated that, in colon CSCs, CD44 induction after suppression of ROCK is associated with the maintenance of stemness of colon CSCs. We demonstrated that activation of mTORC1 by reactive oxygen species (ROS) is responsible for the induction of CD44 and the stemness of colon CSCs. Furthermore, we revealed that NADPH oxidase is responsible for ROS production in colon CSCs.

In addition to colon CSCs, we also looked for the crucial regulatory pathways for proliferation of ovarian CSCs. We showed that ALDH, one of the established CSC markers for various types of CSCs, is specifically expressed in ovarian CSCs. Further, ALDH activity is functionally important for their proliferation.

Functional identification and characterization of regulatory factor of cancer metastasis

Through functional screening of miRNA lentivirus library, we previously identified miR-493 as metastasis-inhibitory miRNA, and demonstrated that up-regulation of miR-493 during carcinogenesis may prevent liver metastasis via the induction of cell death of metastasized cells, through inhibition of its targets, i.e. IGF-1R and MKK7. We also performed the functional screening of shRNA lentivirus library and identified several metastasis-suppressive shRNA. Characterization of the corresponding genes is under way.

## Education

Teaching students (2 undergraduate students, 2 graduate students)

## Future prospects

We will pursue the basic research on CSCs derived from refractory cancer. In future, we aim to translate the acquired knowledge for CSCs into clinical purposes.

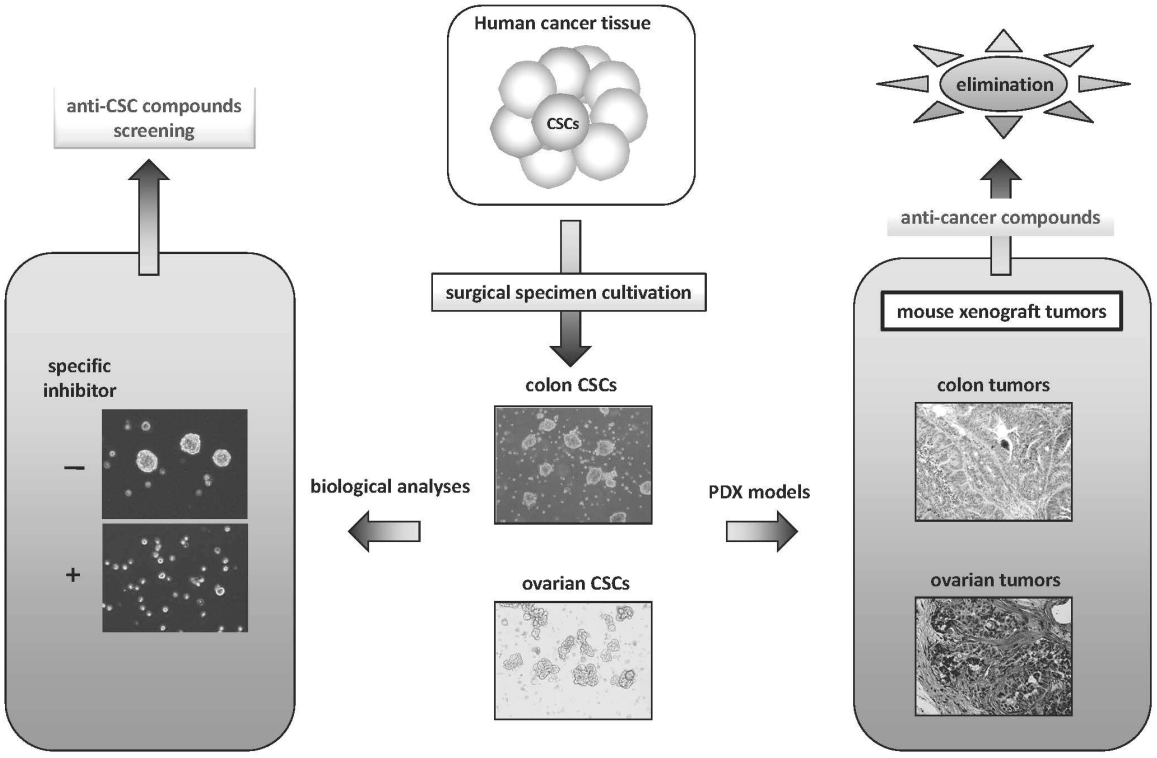


**Figure 1. Experimental platforms for identification of novel anti-cancer compounds**

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# Division of Epigenomics

**Toshikazu Ushijima, Satoshi Yamashita, Kiyoshi Asada, Hideyuki Takeshima, Naoko Hattori, Takayoshi Kishino, Yuka Takeuchi, Yukie Yoda, Takamasa Takahashi, Satoshi Yoshida, Masahiro Maeda, Zong Liang, Akiko Mori, Kana Kimura, Naoko Kobayashi, Yuko Miyaji, Aya Nakajima**

## Introduction

This Division has been focusing on the epigenetic mechanisms of carcinogenesis, and has identified many aberrantly methylated CpG islands (CGIs) in various cancers, including gastric cancers, esophageal squamous cell carcinomas (ESCCs), neuroblastomas, breast cancers, pancreatic cancers, lung cancers, ovarian cancers, and melanomas. This has led to identification of novel tumor-suppressor genes in various cancers, development of a powerful prognostic marker in neuroblastomas, and establishment of the concept of an "epigenetic field for cancerization (field defect)." This Division continues its activity in 1) developing clinically useful biomarkers, a novel approach of cancer prevention, and epigenetic therapy, and 2) in revealing molecular mechanisms of aberrant DNA methylation induction.

## Research activities

1. Identification of Novel Epigenetic Alterations

Identification of tumor-suppressor genes silenced by aberrant DNA methylation is important. This year, *ANGPTL4* was identified as a tumor-suppressor gene inactivated by either aberrant DNA methylation or genetic alteration, namely a somatic 21-bp deletion. It was also revealed that ANGPTL4, which is a secreted protein, functions as a tumor-suppressor by suppressing the proliferation of human vascular endothelial cells and vascular tube formation. This showed that ANGPTL4 is a secreted tumor-suppressor that inhibits tumor angiogenesis inactivated by both genetic and epigenetic alterations.

The recent development of personal sequencers and bead array technology has made it possible to conduct integrated analysis of genetic and epigenetic alterations in multiple cancer samples. This year, integrated analysis was conducted in 50 primary gastric cancers, and it was revealed that epigenetic alterations were more frequently observed than genetic alterations in gastric cancers.

2. Development of Biomarkers

This Division previously revealed that neuroblastomas with the CpG island methylator phenotype (CIMP) have a worse prognosis than those without. This year, a diagnostic assay based on pyrosequencing technology was developed for clinical practice in collaboration with a diagnostic company, SRL, Inc (Figure 1). Now, the clinical usefulness of CIMP in neuroblastomas is being analyzed using primary neuroblastoma samples collected in a prospective manner. A pre-clinical study using a combination of a DNA demethylating drug, 5-aza-2'-deoxycytidine (decitabine), and a differentiation-inducing drug, tamibarotene, is also being conducted for the development of epigenetic therapy in neuroblastomas.

In gastric cancers, the degree of accumulated aberrant DNA methylation in normal-appearing gastric mucosae is expected to be a useful diagnostic marker to predict a gastric cancer risk. To bring this concept into clinical practice, a multicenter prospective cohort study has been conducted for the prediction of metachronous gastric cancer risk after endoscopic resection. This year, an intermediate analysis was conducted, and it was suggested that cases with higher DNA methylation levels of *miR-124a-3* had a higher risk of metachronous gastric cancers.

## Future Prospects

Based on these results, this Division will conduct 1) a multicenter prospective cohort study for the prediction of gastric cancer risk in

healthy volunteers who underwent eradication of *Helicobacter pylori*, the almost exclusive cause of gastric cancers, and 2) the development of epigenetic therapy in gastric cancers and neuroblastomas.

## Other Activities

This Division assisted with 1) epigenetic and genetic analyses of primary cancer samples in several translational researches that are being conducted in the National Cancer Center and other institutions, and 2) epigenetic analysis in various animal models.

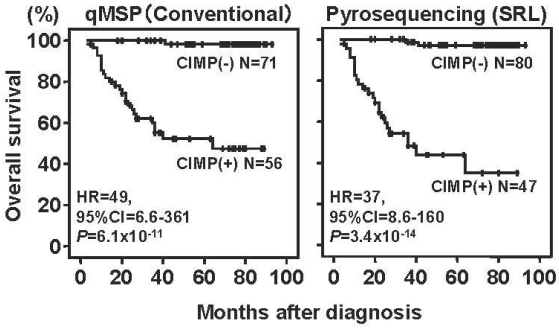


**Figure 1. Diagnosis of prognosis in neuroblastoma by pyrosequencing**

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# Division of Cancer Genomics

**Tatsuhiro Shibata, Fumie Hosoda, Yasushi Totoki, Mamoru Kato, Shinichi Yachida, Yasuhito Arai, Natsuko Hama, Hiromi Nakamura, Isao Kurosaka, Masami Suzuki, Hirofumi Rokutan, Erina Takai, Ogura Koichi, Tomoko Urushidate, Akiko Kokubu, Hiroko Shimizu, Shoko Ohashi, Wakako Mukai, Momoko Nagai, Erika Arakawa, Chika Shima, Keiko Igarashi, Hiroki Sato, Asmaa Elzawahry, Machiko Watanabe**

## Introduction

The Division of Cancer Genomics focuses on comprehensive characterization of the cancer genome on the basis of tumor pathology and aims to make a "breakthrough" by identifying novel cancer-related genes, including potential therapeutic targets and biomarkers, and to understand the cancer genome as heterogeneous but *intervention-able* "biological systems" that contribute to the pathogenesis of cancer. This Division has also been participating in the international consortium (International Cancer Genome Consortium; ICGC), contributed to the core facility of the center, and developing new informatics tools for the data analysis from various types of next-generation high-performance sequencers (NGS).

## Research activities

To elucidate genetic diversities in liver cancer with regards to ethnic and epidemiological differences, we have conducted the trans-ethnic cancer genome research under the umbrella of ICGC and US-based The Cancer Genome Atlas. We performed whole exome sequencing and copy number analysis of 619 pairs of liver cancers, which overrides in several ethnic populations (424 cases from the Japanese cohort and 195 from the US cohort) with various etiological backgrounds. Principal component analysis of six substitution patterns demonstrated that diversity of somatic substitution patterns existed among ethnic groups, which was not associated with known etiological backgrounds. Non-negative matrix factorization analysis extracted unique combinations of mutation signatures in each ethnic group. Trans-ethnic cancer genome sequencing first uncovered the existence of ethnicity-related mutagenesis processes in common human cancer (published in *Nature genetics*).

Whole genome sequencing of chondrosarcoma, rare bone cancer subtype, identified somatic alterations of the COL2A1 gene, which encodes an essential extracellular matrix protein in chondroskeletal development, in 19.3% of chondrosarcoma and 31.7% of enchondroma cases. Furthermore, a novel FN1-ACVR2A fusion transcript was observed in both chondrosarcoma and osteochondromatosis cases. We also found that mutational signature of chondrosarcoma shares significant commonalities with that of prostate cancer (published in *Genome Research*).

Biliary tract cancer (BTC) is an intractable cancer, with limited therapeutic options, in which the molecular mechanisms underlying tumor development remain poorly understood. To find out cancer driver alterations and biomarkers for personalized therapy, we performed whole exome and transcriptome sequencing analyses of BTCs (manuscript in revision). FGFR2 fusion kinase genes we identified are one of the high-potential therapeutic targets of BTC (published in *Hepatology*).

Whole exon sequencing and copy number analysis of rare hepato-biliary pancreatic tumors were conducted. "Liquid Clinical Sequencing" project in which digital PCR or NGS analysis of cell-free DNA from blood samples is used for molecular diagnosis, especially identification of actionable mutations, has been actively conducted in our group. We also launched the cancer-metagenomics project: establishment of the Japanese gut metagenomics database and exploring roles of gut microbiome in human carcinogenesis.

To understand the genetic basis of developing gastric cancer and to identify new drug targets for malignant gastric cancer, transcriptome sequence analysis of 200 gastric cancers has been performed.

Paired-end RNA sequence analysis detected thousands of abnormal structural variations and a verification experiment identified a hundred of fusion genes including protein kinase fusions. Further molecular and functional studies on oncogenic properties of these fusions promise to identify novel therapeutic targets.

## Education

Three young research residents have been trained in this Division.

## Future prospects

By utilizing current and cutting-edged sequencing technologies (e.g. single cell sequencing), this Division will actively investigate the cancer genomics from both basic (new biomarkers including therapeutic targets, epigenomics, metagenomics and immune-genomics) and translational research (preclinical research and liquid clinical sequencing) viewpoints. This Division will also contribute to the development of bioinformatics tools and human resources for analyzing the large cancer genomics data.



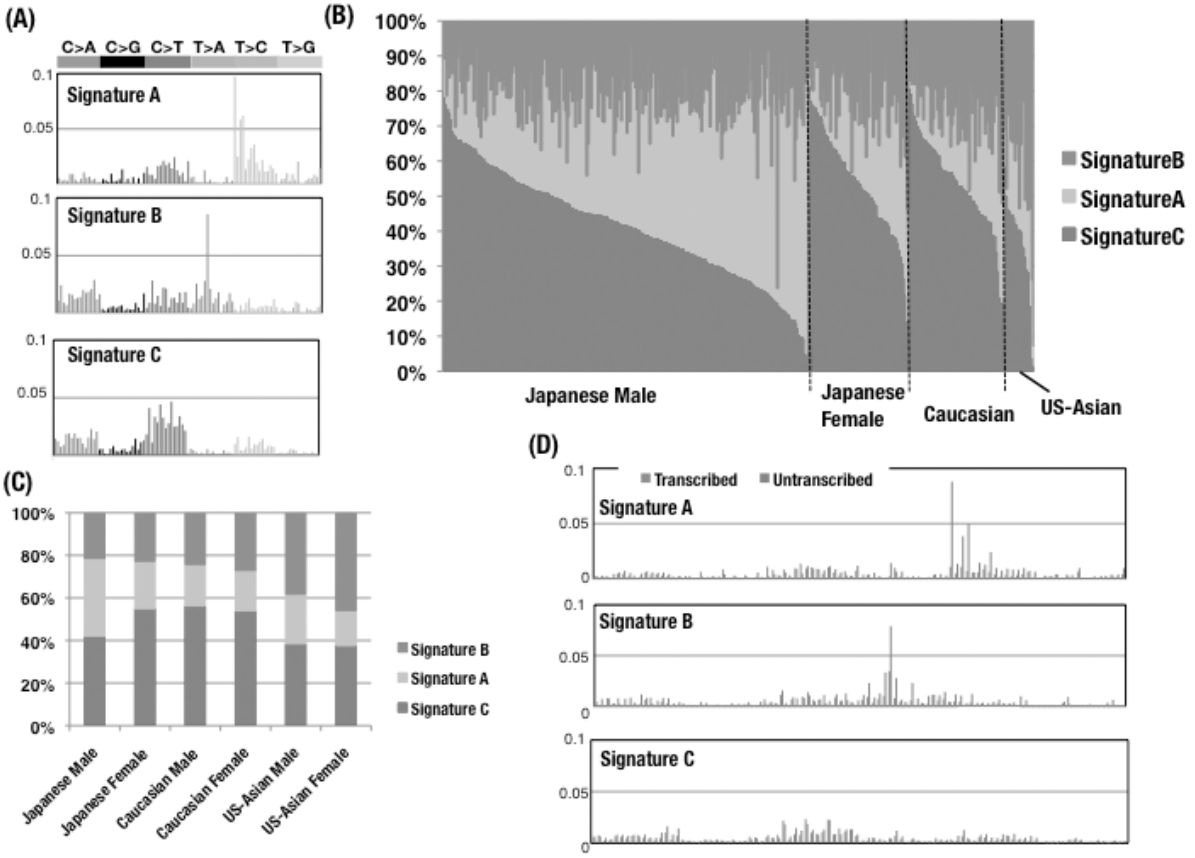


**Figure 1.**

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23. Ogura K, Yasunaga H, Horiguchi H, Fushimi K, Kawano H. What is the effect of advanced age and comorbidity on postoperative morbidity and mortality after musculoskeletal tumor surgery? Clin Orthop Relat Res, 472:3971-3978, 2014
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# Division of Genome Biology

**Takashi Kohno, Naoto Tsuchiya, Hideaki Ogiwara, Kouya Shiraishi, Motonobu Saito, Yoko Shimada, Mariko Sasaki, Ayaka Ohtsuka, Yuko Fujiwara, Keiko Igarashi, Reika Iwakawa-Kawabata, Takashi Nakaoku, Yoshitaka Seki, Kazuaki Takahashi, Kuniko Sunami, Takashi Mitachi, Yujin Ishihara, Keisuke Sugiyama, Daisuke Kurioka, Yoshiaki Onozato, Mei Tanabe, Ryo Okada**

## Introduction

Somatic mutation in the cancer genome and inter-individual variations in the human genome are crucial keys to improve cancer clinics. The aim of our Division is to find "seeds" that are expected to drastically improve treatment and prevention of cancer through identifying and understanding the biological significances of somatic mutations of their seeds in cancer genomes and genetic polymorphisms of cancer patients. To this end, we are working together with NCC staff from hospital, 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 worldwide.

## Routine activities

Weekly research seminar and journal club are held with all members of the Division.

## Research activities

1. Genes for personalized cancer medicine

Oncogenic fusion of the RET gene was recently identified as a novel driver gene aberration in lung adenocarcinoma (LADC) by us. Mouse transgenic model demonstrated that expression of *RET* fusion gene promotes tumor development in the lung. Treatment of the transgenic mice with RET inhibitor, vandetanib, showed marked reduction in the number of lung tumors. The results indicate that *RET* fusion functions as a driver for the onset of LADC. Furthermore, molecular mechanism for rearrangement of RET locus was addressed through the structural analysis of breakpoints and it was revealed that oncogenic RET fusion in LADC occurs through multiple pathways of illegitimate repair of DNA strand breaks. Whole RNA sequencing of 32 invasive mucinous adenocarcinomas (IMAs), including 27 cases without KRAS mutations, led us to identify the NRG1/neuregulin fusion gene as a novel druggable oncogenic fusion in IMA (Figure 1A). We proposed a synthetic lethality therapy approach using synthetic lethal relationship between two paralogous genes, based on our finding that BRG1-deficient cancer cells are susceptible to depletion of its paralogue, BRM. Microarray-based screening of microRNAs (miRNAs) was performed to identify miRNA species that are differentially expressed in chemotherapy responders and non-responders, and demonstrated that the three-miRNA signature in surgically resected primary LADC tissues could be clinically useful for predicting responsiveness to platinium-based doublet chemotherapy in recurrent LADC patients. Genome-wide association study (GWAS) led us to identify a novel LADC susceptibility locus. International and pan-Japan collaborative GWAS are underway to further identify genetic factors involved not only in susceptibility but also in prognosis of lung cancer.

2. Basic research for the development of miRNA drugs

Tumor-suppressive miRNA, miR-22, is a regulator for p53 tumor-suppressor network. By the miR-22 target screening, we identified NIMA-related kinase 9, NEK9, as a novel factor required for cell cycle progression in p53-inactivated cancer cells. NEK9 repression inhibited cell proliferation selectively in p53-deficient cancer cells in vitro and in vivo. Lung adenocarcinoma patients with positive staining for NEK9 and mutant p53 proteins exhibited significantly poorer prognosis, suggesting

that expression of both proteins promotes tumor growth. Collectively, these results provided possibility that NEK9 inhibition could be a novel strategy for development of cancer therapy (Figure 1B). In addition, we have successfully identified 6 circulating serum exosomal miRNAs as promising diagnostic biomarkers for the detection of colon cancer patients.

## Clinical trials

A phase II clinical trial, which investigates the therapeutic effect of a RET-tyrosine kinase inhibitor, vandetanib, has been started by us in Japan in Q1 of 2013. For the purpose, >1500 non-small cell lung carcinoma cases have been screened by an all-Japan consortium consisting of 190 hospitals, LC-SCRUM-Japan (Lung Cancer Genomic Screening Project for Individualized Medicine in Japan), using RT-PCR and FISH assays developed by us. More than 10 RET fusion-positive cases are being treated with vandetanib.

## Education

Supervising for the investigation and presentation skills of students and young researchers

## Future prospects

Our Division aims to contribute for establishment of novel strategies of personalized cancer medicine, including prevention, diagnosis and therapy, through the finding of unique "seeds". A clinical trial, which investigates the therapeutic effect of a RET-tyrosine kinase inhibitor, will be expected to be a good response. Furthermore, identification and understanding biological roles of novel molecular targets, which are screened by synthetic lethality, provide unique and/or novel concepts for development cancer therapy. Furthermore, practical applications of miRNAs as a diagnostic biomarker for cancer detection will be expected in the near future.

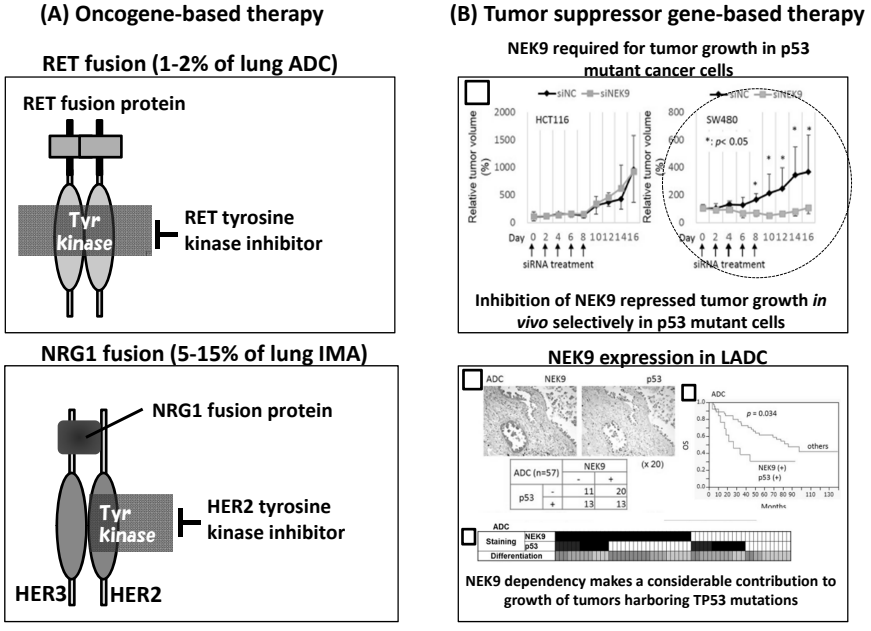


**Figure 1. Div. Genome Biol.**

## List of papers published in 2014

## Journal


1. Saito M, Shiraishi K, Matsumoto K, Schetter AJ, Ogata-Kawata H, Tsuchiya N, Kunitoh H, Nokihara H, Watanabe S, Tsuta K, Kumamoto K, Takenoshita S, Yokota J, Harris CC, Kohno T. A three-microRNA signature predicts responses to platinum-based doublet chemotherapy in patients with lung adenocarcinoma. Clin Cancer Res, 20:4784-4793, 2014
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# Division of Brain Tumor Translational Research

**Koichi Ichimura, Shintaro Fukushima, Kai Yamasaki, Taishi Nakamura, Hirokazu Takami, Emiko Yamamoto, Kohei Fukuoka, Yuko Matsushita, Hideyuki Arita, Motoki Yonezawa**

## Introduction

Our laboratory focuses on translational research on various types of malignant brain tumor, which remains one of the most difficult cancer to cure in humans. There are more than 130 different types of brain tumors, each developing through distinct molecular pathogenesis. Morphological ambiguity across some tumor types makes accurate diagnosis sometimes challenging. To develop a novel molecular diagnostics and an effective personalized therapy, we set our aim to investigate the molecular pathogenesis of key malignant brain tumors including adult gliomas, primary central nervous system lymphomas (PCNSL) and pediatric brain tumors, in particular intracranial germ cell tumors (iGCT), to identify novel tumor markers to aid making diagnosis, to establish a novel molecular classification and an optimal assay for the molecular tests, and to more accurately predict outcome of the patients as well as novel therapeutic targets. For this purpose, we have organized nationwide multicenter collaborations to collect a large number of cases. The results will be applied to clinical trials and a routine clinical practice. The details of selected projects are described below.

## Research activities

1. Development of a novel molecular classification and optimal molecular tests for adult gliomas

In 2013, we discovered that hotspot mutations in the promoter region of TERT, the reverse transcriptase subunit of human telomerase, were very common in oligodendrogliomas and glioblastomas however rare in astrocytomas. We are now conducting a multicenter study to develop a novel molecular classification scheme utilizing the statuses of the TERT promoter, IDH1/2, chromosomal arms 1p/19q and MGMT methylation. More than 800 adult glioma cases have been collected from 13 centers and a central pathology diagnosis is being carried out. They will be classified according to the molecular profiles and compared with the survival data to validate the efficacy of the system.

2. Development of a novel targeted therapy for glioblastoma

A novel therapy for glioblastoma targeting TERT is being developed in collaboration with the Division of Cancer Stem Cell. Pre-clinical experiments are currently being carried out. The initial results showed that the compound significantly suppressed growth of cultured or transplanted glioblastoma cell lines, indicating a strong anti-tumor activity. A successful result will lead to a clinical trial.

3. Genomic analysis of intracranial germ cell tumors

Intracranial germ cell tumors are the second most common pediatric brain tumors in Japan. We have established the Intracranial Germ Cell Tumor Genome Analysis Consortium, a nationwide collaborative network to study germ cell tumors, through which tumor samples of more than 170 cases from 22 centers have been so far collected. A whole exome sequencing was performed for 41 tumors and a targeted sequencing for further 91 intracranial and 65 testicular germ cell tumors. The results showed a high prevalence of mutations affecting the MAPK pathway, most notably in KIT, which appear to be one of the main driving forces of germ cell tumorigenesis. A genome-wide DNA methylation analysis, hCG expression in the tumor tissues, tumor-infiltrating lymphocytes in germinomas are also being investigated to elucidate the pathogenesis of these tumors with the aim for better prognostication and treatment.

4. Molecular diagnosis of pediatric brain tumors

In order to establish a central molecular diagnostic system, we have established the Japan Pediatric Molecular Neuro-oncology Group (JPMNG) to collect pediatric brain tumor samples nationwide and offer various molecular tests according to the internationally accepted procedures. More than 100 ependymomas have been collected through JPMNG, 70 of which have been subjected to a genome-wide methylation analysis using an Illumina HumanMethylation 450 BeadChip. The results were comparable to those published, indicating the accuracy of the method. An integrated protocol to genotype pediatric low-grade gliomas is also being developed.

## Clinical trials

We continue to offer a MGMT methylation test for the patients enrolled in the EGGTRIAL, a clinical trial to evaluate the feasibility of the treatment strategy for elderly (70 or older) glioblastoma patients based on the MGMT status, in which those with methylated MGMT will be given TMZ chemotherapy alone while those with unmethylated MGMT will receive radiation alone. During 2014, 30 tumors from 28 patients were tested for MGMT methylation, 9 of which were judged methylated. The trial continues in 2015.

## Education

Two postgraduate students, 3 Research Residents, 2 Clinical Residents were conducting research during 2014.

## Future prospects

We aim to establish ourselves as a translational research center on malignant brain tumors in Japan through setting up efficient molecular tests and a molecular classification system, applying them for clinical trials and other clinical studies, developing novel therapeutic strategy for glioblastomas, educating young researchers and organizing a multicenter collaboration. Our goal is to contribute to facilitate brain tumor research and to provide better clinical management of malignant brain tumors in Japan.

## List of papers published in 2014

### Journal


1. Fukushima S, Otsuka A, Suzuki T, Yanagisawa T, Mishima K, Mukasa A, Saito N, Kumabe T, Kanamori M, Tominaga T, Narita Y, Shibui S, Kato M, Shibata T, Matsutani M, Nishikawa R, Ichimura K. Mutually exclusive mutations of KIT and RAS are associated with KIT mRNA expression and chromosomal instability in primary intracranial pure germinomas. Acta Neuropathol, 127:911-925, 2014
2. Fukushima S, Narita Y, Yonezawa M, Ohno M, Arita H, Miyakita Y, Ichimura K, Yoshida A, Shibui S. Short communication: sclerosing meningioma in the deep sylvian fissure. Brain Tumor Pathol, 31:289-292, 2014
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# Division of Chemotherapy and Clinical Research

**Tesshi Yamada, Mitsuko Masutani, Masaya Ono, Kazufumi Honda, Mari Masuda, Hiroaki Fujimori-Sakuma, Nami Miura, Ayako Mimata, Masahiro Kamita, Shoji Imamichi, Yuka Sakaki, Hiromi Harada, Naoko Goto, Hiroko Ito, Junhui Wang, Haruyo Tozaki, Yuko Miyamoto, Nobuhiko Nishijima, Takanori Kakuya, Makoto Kobayashi, Kengo Inoue, Takahisa Hirai, Tasuku Itoh, Miyuki Hozumi, Sota Kikuhara, Gui Zhen Chen**

## Introduction

Advances in so-called "-omics" technologies have contributed tremendously to the discovery of therapeutic target molecules and diagnostic biomarkers. The Division has been devoted to the clinical application/translation of basic research findings obtained through the comprehensive genomics and proteomics approaches.

### Signaling pathway profiling by reverse-phase protein arrays

Sorafenib monotherapy is the current standard treatment for unresectable hepatocellular carcinoma (HCC). However, not all HCC patients receive therapeutic benefits. Some tumors show marked shrinkage after short-term administration of sorafenib, but many others show no response. Sorafenib is a multi-kinase inhibitor, and its precise target molecule/pathway has not been established. We newly developed fluorescence reverse-phase protein arrays and profiled the phosphorylation status of signaling molecules in 23 HCC cell lines with different sensitivities to sorafenib. We found that sorafenib-resistant HCC cells showed constitutive activation of mammalian target of rapamycin (mTOR) signaling, and that increased expression of ribosomal protein S6 phosphorylated at serine residues 235/236 (p-rpS6 S235/236) was able to serve as a predictive biomarker of HCC unresponsiveness to sorafenib (5,7).

### Proteomic analysis of ligamentum flavum from patients with lumbar spinal stenosis

Lumbar spinal stenosis (LSS) is a syndromic degenerative spinal disease and is characterized by spinal canal narrowing with subsequent neural compression causing gait disturbances. Although LSS is a major age-related musculoskeletal disease that causes large decreases in the daily living activities of the elderly, its molecular pathology has not been investigated using proteomics. We used 2-dimensional image converted analysis of LC/MS (2DICAL) to compare LF obtained from individuals with LSS to that obtained from individuals with disc herniation (non-degenerative control). We detected 64,781 MS peaks and identified 1675 differentially expressed peptides derived from 286 proteins. We verified four differentially expressed proteins (fibronectin, serine protease HTRA1, tenascin, and asporin) by quantitative proteomics using SRM/MRM. The present proteomic study is the first to identify proteins from degenerated and hypertrophied LF in LSS, which will help in studying LSS.

### Hippo pathway gene mutations in malignant mesothelioma

Malignant mesothelioma (MM) is often unresectable and rarely responds to conventional cytotoxic drugs. It is therefore necessary to develop new therapeutics specifically targeting molecules essential for the development and/or progression of MM. In this study we first adopted an unbiased approach to examining the MM genome using whole-exon (exome) and RNA (transcriptome) sequencing. We found a novel gene fusion between the large tumor suppressor-1 and presenilin-1 genes (LATS1-PSEN1) (Fig. 1). The fusion gene product lacked the kinase activity of LATS1, and the LATS1 locus was inactivated by a two-hit genetic event. This initial discovery prompted us to sequence all exons of the 40 known Hippo pathway genes in 23 patients with MM. We found that the NF2, LATS2, RASSF1, and SAV1 genes were mutated with a frequency of 35% (8/23).

### Prognostic and predictive significance of ACTN4 in locally advanced pancreatic cancer

Several clinical trials have compared

chemotherapy alone and chemoradiotherapy (CRT) for locally advanced pancreatic cancer (LAPC) treatment. However predictive biomarkers for optimal therapy of LAPC remain to be identified. We retrospectively estimated amplification of the ACTN4 gene to determine its usefulness as a predictive biomarker for LAPC. The copy number of ACTN4 in 91 biopsy specimens of LAPC before treatment was evaluated using fluorescence in situ hybridisation (FISH). There were no statistically significant differences in overall survival (OS) or progression free survival (PFS) of LAPC between patients treated with chemotherapy alone or with CRT. In a subgroup analysis of patients treated with CRT, patients with a copy number increase (CNI) of ACTN4 had a worse prognosis of OS than those with a normal copy number (NCN) of ACTN4 ($P$ = 0.0005 log-rank test). However, OS in the subgroup treated with chemotherapy alone was not significantly different between patients with a CNI and a NCN of ACTN4. In the patients with a NCN of ACTN4, the median survival time (MST) of PFS in CRT-treated patients was longer than that of patients treated with chemotherapy alone ($P$ = 0.049) (Fig. 2). The copy number of ACTN4 is a predictive biomarker for CRT of LAPC.

**Research of PARP and PARG inhibitors for cancer treatment**

Poly(ADP-ribose) polymerase (PARP) inhibitors are now in clinical trials and act by blocking DNA repair. On the other hand, PARP inhibitor olaparib was demonstrated to affect epigenetic regulation in cancer cells through DNA methyltransferase 3b downregulation. PARP inhibitor can target various PARP family proteins for epigenetic regulation. A collaborative study further showed the involvement of PARP7 as well as PARP1 in the maintenance of epigenetic regulation in ES cell models (11). Inhibition of poly(ADP-ribose) glycohydrolase (PARG) leads to block of DNA repair and causes cell death through poly(ADP-ribose) accumulation. Therefore, PARG inhibitors have been recently considered as a potential anti-cancer target (13). To develop specific and potent PARG inhibitors, a collaborative study with other institutions was initiated and novel PARG inhibitors have been identified and their structures are being optimized. Phenolic hydrazide hydrazines are one group of these compounds that show inhibition of PARG catalytic activity (12). Through genome-wide analysis, the genes that affect lethality by PARG inhibition have been identified and validated using cancer cell lines.

**Studies for biological radiosensitization**

To achieve biological radiosensitization in tumor radiation therapy, a comprehensive screening of the genes, which cause radiosensitization were performed. Besides known radiosensitizing genes when knocked down, including *PARP1*, *PARP-2* and *Rad51* genes, genes of various functions, such as DNA repair and chromatin regulation were picked up as candidate genes. The generation of gene clusters based on the networks of functional interactions was found to be a useful method for identifying 'radiosensitizing gene clusters'. A mechanistic study of a focused candidate gene that could effectively radiosensitize the particular cancer cells has been carried out.

**Basic studies on boron neutron-captured therapy**

The project of developing accelerator-based BNCT (boron neutron-capture therapy) system in NCC is ongoing. To support the biological evaluation of the accelerator-based BNCT, a collaborative study of BNCT with other institutes has been undertaken from 2012. The experimental systems to evaluate the radiation protection, safety and effectiveness of BNCT have been established using mouse models. The basic studies to optimize therapeutic effects of BNCT and search for the biomarkers for tumor cell death are also ongoing (14). Using tumor graft models, dynamics of DNA damage response markers after BNCT irradiation were studied. The early upregulation of HMGB1 and later augmentation pattern of poly(ADP-ribose) and γH2AX were found as the characteristic changes after BNCT (3). Comprehensive analysis of protein and gene expression was also performed after BNCT condition.

## Future Prospects

With the increase of the cancer patients of advanced age, noninvasive cancer treatments with lower side-effects are currently being required. Through the further accumulation of the knowledge of cancer therapeutic targets and cancer heterogeniety, cancer treatment strategies including chemotherapy and radiation therapy are expected to become patient-friendly and effectively optimized for individual patients.


**Figure 1. The novel gene fusion between the large tumor suppressor-1 and presenilin-1 genes (LATS1-PSEN1)**

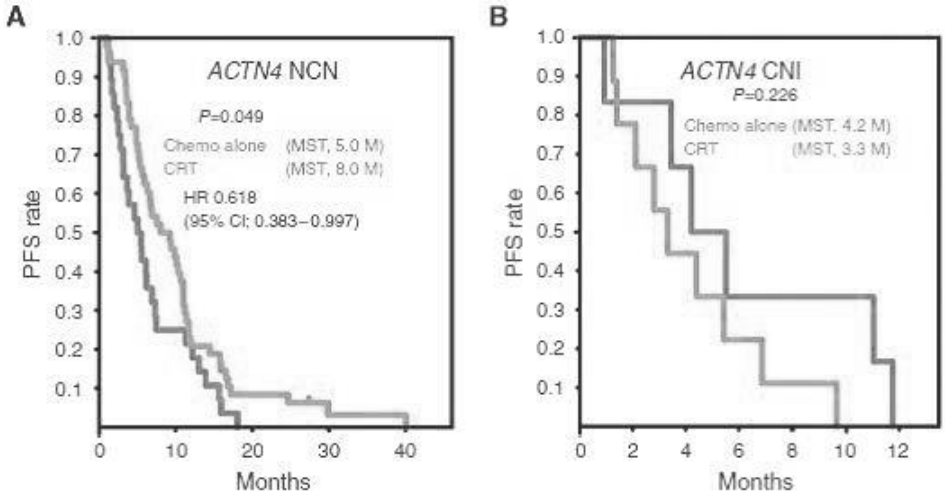


**Figure 2. Progression-free survival of LAPC patients with NCN (A) and CNI (B) of ACTN4**

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# Division of Cancer Pathophysiology

**Yasuhito Uezono, Seiji Shiraishi, Masami Suzuki, Kanako Miyano, Junko Ezuka, Yukiko Araki, Kiyoshi Terawaki, Katsuya Ohbuchi, Chika Miyagi, Koichiro Minami, Tohru Yokoyama, Satoshi Murakami, Hideya Kokubun, Akinobu Yokoyama, Hitomi Nishimura, Megumi Kawaida, Shiori Sato, Etsuko Nemoto, Takamichi Arima, Hirotsugu Kuwata, Chihiro Kojima, Yusuke Hamada**

## 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) prevention and development of novel treatments for cancer cachexia symptoms. Based on the 2nd Basic Plan to Promote Cancer Control Programs established in Japan in 2012, basic to clinical, and also clinical to basic translational collaborative research with the clinical laboratory groups comprises our main research protocols and has been ongoing.

## Routine activities

A weekly conference/research seminar is held with all members including students at the Division of Cancer Pathophysiology.

## Research activities

**Translational research to innovate new strategies to improve pain analgesia in cancer patients**

The aim of our studies is to develop new therapies for chemotherapy-induced peripheral neuropathy, and refractory cancer pain, both of which make the quality of life of cancer patients even worse. One of the targets is oral stomatitis induced by chemotherapy and/or radiotherapy.

The cancer patients who undergo chemotherapy, radiotherapy and terminal palliative care often have a wide range of stomatitis, which induces severe pain and limits the fundamental basics of life such as eating, drinking and talking. In clinical sides, lidocaine is normally used for cancer patients with stomatitis to relieve oral pain. However, lidocaine removes not only the pain but also the ability to discriminate taste and texture, since it nonselectively suppresses the activation of all neurons by blocking the voltage-gated $Na^+$ channels. Therefore, a novel analgesic drug, which selectively blocks the pain-related neuron alone, is required to allow patients to eat without losing or changing the taste and texture. We have focused on a "compound X" as the novel analgesic drug for stomatitis, and established the method to evaluate the intensity of oral pain using stomatitis model animals. With the model, lidocaine not only inhibited pain but also caused numbness in normal oral mucosa. On the contrary, the compound X suppressed the pain in the ulcer, but had no effects on normal tissues. Further, the analgesic effect of the compound X was longer than that of lidocaine, indicating that the compound X is expected to be a more superior analgesic drug than lidocaine. Further, we have been elucidating the pharmacological actions of the compound X (e.g., how does it block only the pain-related neurons?) with cultured cell models. By connecting such a basic study to a clinical study, we want to develop "the new pain-killer compound X, which can remove the oral pain without changing the texture and taste of food" for cancer patients with severe painful stomatitis. This research project now has been intellectually and financially supported as "an innovative seed" by the Drug Discovery Support Network, which was newly established at the National Institute of Biomedical Innovation.

Second target is severe pain such as one with bone-metastasized patients. We previously showed that a platelet-activating factor (PAF) antagonist produced profound and long lasting anti-allodynia effects in several different neuropathic pain models in mice including a partial sciatic nerve ligation

injury model. Also we have found that the PAF antagonist showed extremely excellent analgesic effects on both the bone-metastasized cancer pain model mice and the chemotherapy-induced peripheral neuropathy model mice. In addition, we discovered that knocking out PAF synthase by siRNA technology in mouse model with severe pain by nerve ligation injury model, significantly reduced pain, demonstrating that existence of PAF seems to produce pain. We currently are developing both novel PAF receptor and PAF synthase antagonists. The pain-relieving action of PAF-signal antagonists are found to be effective for the treatment of pain.

**Prevention, and decrease the cachexic symptoms or chemotherapy-induced side effects by Japanese traditional KAMPO medicines and opioid-related compounds**

We established novel cancer cachexia animal models and then undertook molecular and cellular analyses to identify the mechanisms of action of the expected compounds to improve the quality of life of patients suffering from cancer cachexia with biological, biochemical and electrophysiological approaches. We found that a Japanese Kampo (traditional Oriental) medicine "rikkunshito" usually administered for the prevention of gastritis, nausea and vomiting since the 17th century in Japan, improved the symptoms of cancer cachexia. In addition to rikkunshito, we summarize the mechanisms of action of other traditional Japanese Kampo medicines to improve chemotherapy-induced side effects, and their potential use for improvement of the symptoms of cancer cachexic patients and the side effects in cancer patients who take anticancer agents.

In addition, the dormancy of tumor cells is a major problem in chemotherapy, since it limits the therapeutic efficacy of anti-tumor drugs that only target dividing cells. One potential way to overcome chemo-resistance is to “wake up” these dormant cells. Here we show that the opioid antagonist methylnaltrexone (MNTX) enhances the effect of docetaxel (Doc) by blocking a cell growth-suppressive pathway. We found that PENK, which encodes opioid growth factor (OGF) and suppresses cell growth, is predominantly expressed in diffuse-type gastric cancers (GCs). Blockade of OGF signaling by MNTX released cancer cells from their arrest and enhanced the effect of Doc. The combined use of Doc and MNTX significantly prolongs survival, alleviates abdominal pain, and diminishes Doc-resistant spheroids on the peritoneal membrane in model mice in comparison with the use of Doc alone. We showed that blockade of these pathways by MNTX may enhance the effects of anti-tumor drugs.

## Education

We have two graduate students and 6 students.

## List of papers published in 2014

## Journal


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# Division of Molecular and Cellular Medicine

**Kazunori Aoki, Kenta Narumi, Yoko Kobayashi, Tsukasa Shinohara, Ryousuke Ueda, Hisayoshi Hashimoto, Yosei Rin, Masaki Nagasato, Yuki Yamamoto**

## Introduction

Research programs in the Division of Molecular and Cellular Medicine (Aoki group) 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. The specific activities in 2014 were as follows: 1) Investigation of molecular basis of immune microenvironment in pancreatic and colon cancer; 2) Development of cancer-targeting vectors using the peptide-display adenovirus library.

## Research activities

### Investigation of molecular basis of immune microenvironment in pancreatic and colon cancer

We investigated the immunological function of inflammaoty protein S100A8/A9 and immunostimulatory cytokine type I interferon (IFN) in tumor microenvironment.

1) Whether the expression of S100A8/A9 in tumors predicts a good or poor prognosis is controversial in the clinical setting. To clarify the in vivo role of S100A8/A9 in the tumor microenvironment, we subcutaneously inoculated Pan02 (pancreatic cancer cell line) stably expressing S100A8 and S100A9 proteins (Pan02-S100A8/A9) in syngeneic mice. Unexpectedly, after small tumor nodules were once established, they rapidly disappeared. Flow-cytometry showed that the number of NK cells in the tumors was increased, and a depletion of NK cells promoted the growth of Pan02-S100A8/A9 subcutaneous tumors. Although the S100A8/A9 proteins alone did not change the IFN-γ expression of NK cells in vitro, a co-culture with Pan02 cells, which express Rae-1, induced IFN-γ production, and Pan02-S100A8/A9 cells further increased the number of IFN-$\gamma^+$ NK cells, suggesting that S100A8/A9 enhanced the NKG2D ligand-mediated intracellular activation pathway in NK cells. We then examined whether NK cell activation by S100A8/A9 was via their binding to RAGE by using the inhibitors. RAGE antagonistic peptide and anti-RAGE antibody inhibited the IFN-γ production of NK cells induced by S100A8/A9 proteins. Since S100A8/A9 strongly enhances the activity of NK cells, the S100A8/A9-NK cells axis may be useful for cancer immunotherapy.
2) IFN-α can effectively induce an antitumor immunity by the activation of tumor-specific T cells and maturation of dendritic cells. Unknown, however, is how the type I IFN alters the immunotolerant microenvironment in the tumors. Here, we found that intratumoral IFN-α gene transfer significantly decreased the frequency of regulatory T cells (Tregs) per $CD4^+$ T cells in tumors. The concentration of a Treg-inhibitory cytokine, IL-6, was correlated with the IFN-α expression level in tumors, and intratumoral $CD11c^+$ cells produced IL-6 in response to IFN-α stimulation. To confirm the role of IL-6 in the suppression of Tregs in tumors, an anti-IL-6 receptor antibody was administered in IFN-α-treated mice. The antibody increased the frequency of Tregs in the tumors, and attenuated systemic tumor-specific immunity induced by IFN-α. Furthermore, the IFN-α-mediated IL-6 production increased the frequency of Th17 cells in the tumors, which may be one of the mechanisms for the reduction of Tregs. The study demonstrated that IFN-α creates an environment strongly supporting the enhancement of antitumor immunity through the suppression of Tregs.

**Development of cancer-targeting vectors using the peptide-display adenovirus library**

The addition of a targeting strategy is necessary to enhance oncolysis and secure safety of a conditionally replicative adenovirus (CRAd). We have constructed an adenovirus library displaying random peptides on the fiber, and have successfully identified a pancreatic cancer-targeting ligand (SYENFSA). The usefulness of cancer-targeted CRAd for pancreatic cancer was examined as a preclinical study. First, we constructed a survivin promoter-regulated CRAd expressing enhanced green fluorescent protein gene (EGFP), which displayed the identified targeting ligand (AdSur-SYE). The AdSur-SYE resulted in higher gene transduction efficiency and oncolytic potency than the untargeted CRAd (AdSur) in several pancreatic cancer cell lines. An intratumoral injection of AdSur-SYE significantly suppressed the growth of subcutaneous tumors, in which AdSur-SYE effectively proliferated and spread. An ectopic infection in adjacent tissues and organs of intratumorally injected AdSur-SYE was decreased compared with AdSur. Then, to examine whether the targeting ligand actually enhanced the infectivity of CRAd in human pancreatic cancer tissues, tumor cells prepared from surgical specimens were infected with viruses. The AdSur-SYE increased gene transduction efficiency 6.4-fold higher than did AdSur in single cells derived from human pancreatic cancer, whereas the infectivity of both vectors was almost the same in the pancreas and other cancers. AdSur-SYE resulted in a stronger oncolysis in the primary pancreatic cancer cells co-cultured with mouse embryonic fibroblasts than AdSur did. We showed the usefulness of enhanced tumor targetability in oncolytic therapy.

## Education

2 graduate students (doctoral course) linking with Keio University, 1 graduate student (master course) and 1 student linking with Tokyo Medical Dental University, studied about cancer immunology and virus therapy in our laboratory.

## Future prospects

We are investigating the relationship between cancer gene expression profile and immune micoenvironment in pancreatic and colon cancer, which may open a novel perspective on immune therapy for cancer. In addition, CRAd in combination with a tumor-targeting ligand is promising as a next-generation of oncolytic virotherapy for pancreatic cancer.

## List of papers published in 2014

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# Division of Molecular and Cellular Medicine

**Takahiro Ochiya, Fumitaka Takeshita, Ryou-u Takahashi, Takeshi Katsuda, Yusuke Yoshioka, Yu Fujita, Hiroaki Miyazaki, Yutaka Nezu, Akira Yokoi, Ayako Inoue, Maki Abe, Mizuyo Arashi, Satoko Takizawa, Makiko Ichikawa, Kana Kurosaki, Mayuko Yamamura, Satomi Fukuda, Kazumi Nagao, Luc Gailhouste, Kurataka Ootsuka, Hayato Kurata, Rie Tamai, Hiroshi Naito, Nao Nishida, Keitaro Hagiwara, Naoomi Tominaga, Ken Yasukawa, Liew Lee Chuen**

## Introduction

The focus of the Division of Molecular and Cellular Medicine lies in the development of novel diagnosis and treatments for cancer patients. The specific activities were as follows: 1) Studies on microRNA (miRNA) regulation in cancer cells and development of RNA interference (RNAi) -based therapeutics; 2) Exosomes as a novel diagnosis and therapeutic tool against cancer; 3) Study of stem cells and its therapeutic applications.

## Research activities

1) Studies on miRNA regulation in cancer cells and development of RNAi-based therapeutics.

RNAi-based therapeutics is promising approach as novel and potentially more effective treatments for cancer and miRNAs are identified as important modulators of tumor-related genes (4,5,17, 27,30).

We identified miRNAs which show abnormal expression in a highly malignant osteosarcoma (1,21-23). Silencing of miR-133a with locked nucleic acid (LNA) reduced cell invasion and systemic administration of LNA along with chemotherapy suppressed lung metastasis and prolonged the survival of osteosarcoma-bearing mice. Furthermore, in a clinical study, high expression levels of CD133 and miR-133a were significantly correlated with poor prognosis, whereas high expression levels of the four miR-133a target genes were correlated with good prognosis. We previously demonstrated that silencing of ribophorin II (RPN2) efficiently induced apoptosis and reduced resistance to docetaxel in human breast cancer cells (9,24). Recently, we also reported the clinical relevance of RPN2 expression in osteosarcoma (3). Higher RPN2 expression was significantly correlated with poor prognosis. The RNAi-induced RPN2 knockdown showed reduced tumor growth and lung metastasis in mice model of osteosarcoma. Now we proceed with the preparation of clinical trials of RPN2-siRNA treatment for drug-resistant breast cancer. This will be the first clinical trial of siRNA on human performed in Japan.

2) Exosomes as a novel diagnosis and therapeutic tool against cancer

The circulating exosomes could be found in variety of body fluids including serum, plasma, urine, saliva, and breast milk (18). The existence of circulating exosomes in the blood of cancer patients has raised the possibility that exosomes may serve as a novel diagnostic marker (7,13,16,19,20,26). For this reason, a new high sensitive method of circulating exosomes has been developed (2). Moreover, we found that CD147 and CD9 double-positive exosomes were significantly higher in serum from colorectal cancer patients than in serum from healthy donors (2). Cell-cell communication of cancer cells and surrounding noncancerous cells are critical for the acquisition of malignancy in human cancer. We discovered that the effects of bone marrow mesenchymal stem cells (BM-MSCs) on breast CSCs were attributable to the transfer of miRNAs from BM-MSCs to breast CSCs through exosomes. We revealed that exosomal miR-23b promoted dormancy and decreased CD44 surface abundance in breast cancer cells (28). These findings prompted us into applying exosomes in diagnosis and therapy against cancer development (11,12,14).

3) Study of stem cells and its therapeutic

applications

While cancer stem cell (CSC) properties such as tumorigenicity and drug resistance are a major focus in current cancer research, the molecular mechanisms for the regulation of CSC properties are not fully understood. MiRNA is also identified as the target involved in the regulation of CSC properties (10, 15). We found that some specific miRNAs played an important role in the acquisition of CSC properties (10, 15). We also investigated the functions of these miRNAs in vivo using animal model and found that modulation of miRNAs efficiently suppressed the tumor seeding ability and drug resistance of CSCs (29). Therefore, these results suggest that conventional cancer therapy with modulating the expression of miRNA improves the treatment of cancer patients.

4) Mesenchymal Stem Cell (MSC) Therapy

We are interested in the therapeutic potential of MSCs. Especially, our main focus is on the realization of the clinical application of adipose tissue derived-mesenchymal stem cells (ADSC) in liver diseases (8,25). Recently, MSCs attract much attention not only for their own potential as cells, but also for their secretory capacity of extracellular vesicles (EVs) that can have therapeutic benefits (6).

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## Journal

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# Division of Rare Cancer Research

**Tadashi Kondo, Rieko Ohki, Bunsho Shiotani, Xiaoqing Pan, Parlayan Cuneyd, Yukiko Nakamura, Yohko Yamaguchi, Yoko Takai, Yukiko Araki, Fusako Kito, Marimu Sakumoto, Aska Matsuo, Naofumi Asano, Kosuke Hirota, Takashi Tajima, Kazutaka Kikuta, Yuki Tani, Junko Otsuka, Yoshinori Asano, Issei Ezawa, Yu Chen, Miku Shimizu, Shiori Suzuki, Yuhei Takano, Raira Saigawa, Shu Matsushita, Maiko Minegishi**

## Introduction

The Division of Rare Cancer Research aims the innovative seeds for novel therapy for rare cancers. The rare cancer research has unique difficulty due to small number of patients and clinical samples. We challenge the fundamental problems in rare cancer research, discover innovative seeds for novel therapy, and establish unique approach to cancers with low incidence.

## Research activities

Our research activities focus on three subjects. [Establishment of fundamental research system of rare cancers] Patient Derived Xenograft models and primary cell lines were established from surgical specimens of sarcoma patients. Omics database was constructed by integrating our original data and publically available data. [Study on rare cancers] <Biomarker developement> Omics study for biomarker discovery was performed using the clinical samples (tumor tissues and blood samples) of sarcoma patients. Evaluation and validation studies were done for biomarker candidates. Study for assay system development was done for predictive diagnosis. <Discovery of therapeutic target> By comparative proteomic study, tyrosine kinases (TKs) with aberrant auto-phosphorylation were identified, and the effects of TK inhibitors were examined using *in vitro* cells. <Molecular backgrounds of rare cancers> Associations of ATR and clinical and pathological features of sarcomas were examined at molecular level. Aberrant regulation of novel p53 target gene, PHLDA3, was discovered in pancreatic neuroendocrine tumor. Its significances in clinical features and carcinogenesis were examined at molecular level. {Reverse innovation] <Systematic survey of effects of cancer drugs> To identify cancer drugs applicable for sarcomas, the inhibitor library was screened in the sarcoma cell line panel. Molecular backgrounds of sensitivity and resistance were examined by multi-OMICS study. <Development of novel methods for scare amount samples> Novel proteomics application based on unique separation modes was developed for scare amount samples.

## Education

Young doctors, PhD students, and students joined our Division from Keio University, Kyorin University, Chiba University, Waseda University, and Tokyo College of Biotechnology.

## Future prospects

Fundamental research system to approach to the essential problem in rare cancer research, such as “small number of cases and samples for research” will be established. Novel innovative seeds for rare cancer therapies will be discovered and applied to clinical applications. Methods for cancers with small number of cases and samples will be established, and applied to cancer research in future.

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## Journal


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# Division of Refractory and Advanced Cancer

**Ryuichi Sakai, Hideki Yamaguchi, Masato Enari, Takuya Shirakihara, Katsuhiko Nakashima, Yumi Hasegawa, Emi Saito, Yuko Hibiya**

## Introduction

The malignant characteristics of cancers causing the invasion into surrounding tissue, metastasis to distant organs, and acquirement of resistance to therapeutics 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, invasion and drug resistance. One of the goals of our research is to establish models of the novel therapy to overcome these malignant characteristics of progressed cancers by targeting critical proteins and signals involved in these procedures.

## Research activities

*Regulation of Anaplastic Lymphoma Kinase (ALK) activity and drug resistance in cancers*

Although the ALK-fusion gene is detected in approximate 5% of pulmonary cancer and the ALK inhibitor is used as therapeutic drug for this type of lung cancer, the problem of recurrence elicited by tiny fraction of cancer cells resistant to the ALK inhibitor remains unresolved. We recently found that ALK-fusion protein inhibited the p53 pathway via the unique mechanism and that activation of the p53 pathway reduced the drug resistance to the ALK inhibitor. We are now pushing forward further conclusive evidence using clinical specimens.

Activation of ALK either by mutation or overexpression, has been indicated as a significant oncogenic factor in neuroblastoma. Flotillin-1 (FLOT1), a plasma membrane protein known to be involved in endocytosis, was found among 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. RNAi-mediated attenuation of FLOT1 expression in neuroblastoma cells caused ALK dissociation from endosomes along with membrane accumulation of ALK, thereby triggering activation of ALK and downstream effector signals. These features enhanced the malignant properties of neuroblastoma cells in vitro and in vivo. Our findings suggest that the loss of FLOT1-mediated regulation of ALK contributes to malignancy of clinical neuroblastoma cases and those cases might be sensitive to ALK inhibitors even without the genetic alteration of ALK.

*Interaction between Cancers and Stromal Cells*

Scirrhous gastric carcinoma (SGC) shows rapid expansion through progressive invasion, peritoneal dissemination and frequent metastasis to lymph nodes. We investigated the role of stromal fibroblasts (SFs) in invasion and extracellular matrix (ECM) remodeling by SGC cells. When SGC cells were cocultured with SFs on three-dimensional (3D) Matrigel, they were attracted together to form large cellular aggregates that invaded into the Matrigel. By utilizing this assay system for inhibitor library screening, we have identified several inhibitors that potently suppress the cooperation between SGC cells and SFs to form the invasive structures. Among them, a Src inhibitor dasatinib impaired the interaction between SGC cells and SFs both in vitro and in vivo and effectively blocked peritoneal dissemination of SGC cells. These results indicate that SFs mediate mechanical remodeling of the ECM by SGC cells, thereby promoting invasion and peritoneal dissemination of SGC.

It was revealed that cancer cells transact the surrounding fibroblasts to cause decreased expression of p53, which results in CAF-like transition of these cells and enhanced expression of a four transmembrane-spanning protein, TSPAN12. The fibroblasts expressing TSPAN12 could trigger the invasiveness of the cancer cell through direct attachment between these cells.

*Molecules regulating Metastasis and Invasion of Cancers*

We have demonstrated that a membrane protein CDCP1 is the critical regulator of anoikis resistance, distant metastasis, and peritoneal dissemination of cancer cells. It was shown that CDCP1 is 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 Ras pathway. Therapeutic antibodies and chemicals which block the CDCP1-mediated signaling are being screened.

TSPAN2, another four transmembrane-spanning protein, was found among the proteins induced by p53-inactivation. It was demonstrated that TSPAN2 interacts with CD44 and enhances invasion and metastasis of lung adenocarcinoma cells through efficient removal of reactive oxygen species (ROS) in cancer cells.

## Future prospects

In patients with advanced stages of cancers, the control of metastasis, invasion and drug resistance is crucial for maintaining the quality of life (QOL) in addition to the prolonged survival. Our approach to elucidate the underling mechanism to these malignant characteristics of cancers will give way to develop novel therapeutic strategies for advanced cancers.

## List of papers published in 2014

### Journal


1. Nakaoku T, Tsuta K, Ichikawa H, Shiraishi K, Sakamoto H, Enari M, Furuta K, Shimada Y, Ogiwara H, Watanabe S, Nokihara H, Yasuda K, Hiramoto M, Nammo T, Ishigame T, Schetter AJ, Okayama H, Harris CC, Kim YH, Mishima M, Yokota J, Yoshida T, Kohno T. Druggable oncogene fusions in invasive mucinous lung adenocarcinoma. Clin Cancer Res, 20:3087-3093, 2014
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# Research Support Division

**Teruhiko Yoshida, Tesshi Yamada, Toshio Imai, Issay Kitabayashi, Tatsuhiro Shibata, Hiromi Sakamoto, Fumie Hosoda, Yae Kanai, Hitoshi Ichikawa, Hiroki Sasaki, Yasuhito Arai, Masaya Ono, Tadashi Kondo, Mami Takahashi, Yoshinori Ikarashi, Takuo Katsumoto, Koji Okamoto, Tetsuya Ishikawa (including collaborating staff).**

## Introduction

The concept of the Research Core Facility (CF) has originated from the 1st lecture given by Dr. Hitoshi Nakagama on May 9, 2011 after his appointment as the Director of the National Cancer Center (NCC) Research Institute (RI). Along with the biobank, the CF has been positioned between the NCCRI and the NCC hospital to establish a bidirectional translational bridge (Fig. 1). The combination of the rich collection of high quality clinical samples and advanced, reliable analytical power should be a crucial asset of our Institute. However, the latest genome and other omics technologies demand heavy and stable investments both in hardware and its maintenance and human expertise, especially in the field of bioinformatics, which are increasingly difficult if not impossible to afford for individual laboratories, such as those led by young PIs and physician scientists. As a consequence, the CF has become an essential component integrated in many leading biomedical research institutes in the world. Characteristically, our CF is a virtual organization based on the mutual help among the research scientists and laboratories, each engaging in their own competitive research.

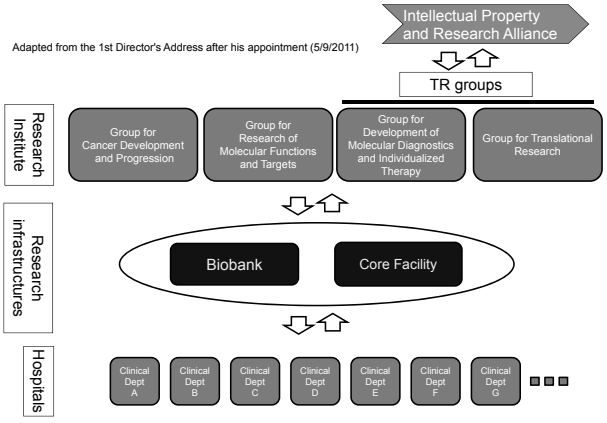


**Figure1. Concept of CF: Director's Initiative**

Figure 2 shows the original CF system officially started on September 5, 2011 with 4 major arms: Genome & Epigenome, Proteome, Biology, and Common Equipment for self-service use of shared resource-demanding machines in terms of cost, space and other installation specifications. The Research Support Division corresponds to the Genome & Epigenome CF and Proteome CF. The Biology CF function is being offered by the Central Animal Division and reported in its pages.

In August 2014, the Fundamental Innovative Oncology Core (FIOC) has been established, and the Research Support Division now belongs to the new FIOC system.

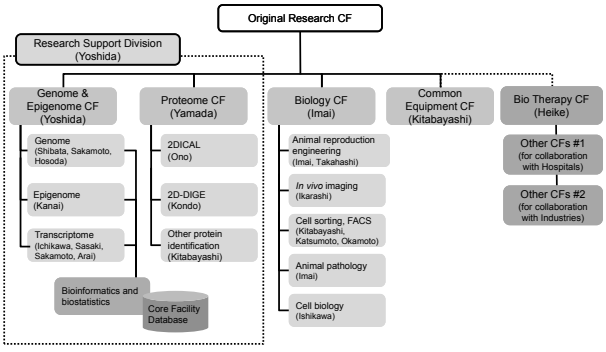


**Figure 2. CF Organization**

## Research activities

The mission of the CF is not limited to the mutual support and collaboration inside the NCCRI, but extends to other sectors of NCC as a whole. For instance, the CF offers genotyping service for population-based cohort studies in the Research Center for Cancer Prevention and Screening (RCCPS), and helping observation studies in the framework of clinical trials in the hospital. The CF is also supporting a transitional

zone between research and clinical practice, such as genetic diagnosis of hereditary cancer syndromes (Fig. 3).

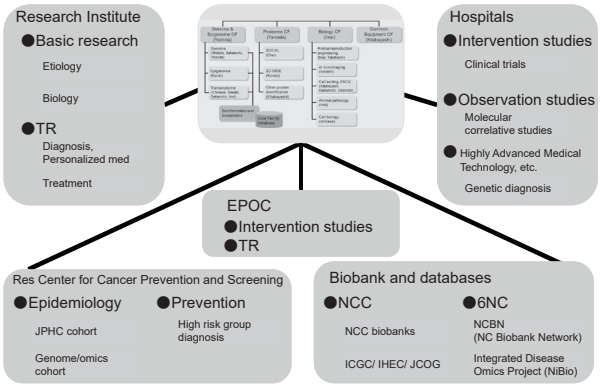


**Figure 3. CF Interactions and Participations**

Because the CF covers such diverse activities, its performance is difficult to quantify, but just as a simplified example, the numbers of the individual research projects and samples submitted to the CF are summarized in Figure 4.

## Education

Although not always apparent, one of the most important contributions of the CF may be the discussion and consultation BEFORE offering the actual CF service.

## Future prospects

CF should keep exploring the latest needs among the NCC researchers and revising its service menu accordingly. It is also crucial to evaluate the effort offered by the CF staff in an appropriate way and develop sound and effective incentive for an active commitment to the CF service. At least a part of the CF financial fundamentals need to be supported by the NCC in-house budget, such as machine maintenance and basic human resource cost.

As a member of the newly established FIOC, the Research Support Division will contribute to its mission in line with the grand strategy and directives of FIOC.

| CF Area | Applications | # projects | | | | # samples | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | FY 2011 | FY 2012 | FY2013 | FY2014 | FY 2011 | FY 2012 | FY2013 | FY2014 |
| Genome | Next Generation Sequencer | 11 | 8 | 5 | 18 | 248 | 180 | 160 | 1,203 |
| | SNP array/TagMan assay | 10 | 9 | 8 | 8 | 1,993 | 1,574 | 1,762 | 529 |
| | Agilent array and others | 5 | 9 | 4 | 0 | 366 | 652 | 123 | 0 |
| Epigenome | NGS | 2 | 2 | 1 | 1 | 102 | 14 | 8 | 30 |
| | Infinium array | 7 | 6 | 9 | 11 | 1,646 | 569 | 801 | 705 |
| Transcriptome | NGS | 3 | 8 | 0 | 7 | 44 | 157 | 0 | 243 |
| | Affymetrix GeneChip | 5 | 4 | 2 | 2 | 97 | 76 | 110 | 208 |
| | Agilent array | 5 | 3 | 4 | 2 | 58 | 56 | 68 | 24 |
| Proteome | 2DICAL | 7 | 2 | 2 | 3 | 524 | 112 | 54 | 126 |
| | 2D-DIGE | 0 | 7 | 4 | 1 | 0 | 308 | 83 | 199 |
| | Protein identification | 0 | 1 | 2 | 6 | 0 | 483 | 612 | 1,573 |
| Animal reproduction engineering | Embryo/ sperm freezing stock | 2 | 5 | 5 | 4 | 9 | 36 | 17 | 6 |
| | Microbiological cleaning | 1 | 1 | 5 | 1 | - | 1 | 5 | 1 |
| In vivo imaging | IVIS/ OV110 | 12 | 4 | 4 | 5 | - | - | - | - |
| Animal histopathology | FFPE, frozen sections | 12 | 12 | 11 | 14 | 1,743 | 2,974 | 1,778 | 1,721 |
| | Examination and diagnosis | 4 | 4 | 6 | 14 | - | - | - | - |
| Cell biology | Cell line/xenograft establishment | 1 | 1 | 0 | 3 | 5 | 2 | 0 | 56 |
| Total | | 87 | 86 | 72 | 100 | 6,835 | 7,194 | 5,581 | 6,624 |

**Figure 4. CF Activities in FY 2011-2014 (excluding the self-service type)**

# Central Animal Division

**Toshio Imai, Mami Takahashi, Tetsuya Ishikawa, Yoshinori Ikarashi, Teruo Komatsu, Kotomi Otsubo, Naoaki Uchiya, Masashi Yasuda, Manabu Tsuchida, Ayami Kawashima, Satoshi Ikeda, Junichi Zukeyama, Shiho Ozawa, Yudai Seki, Takuya Matsuyama, Junya Asahira, Shumpei Ohnami, Hitoshi Nakagama, Mitsuko Masutani, Gen Fujii**

## Introduction

A pivotal role of the Central Animal Division is supportive actions for basic/clinical/public health researchers on the basis of biological resources in 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. Some researchers and technical staff act also for several support services, which are provided based on their biological skills, such as reproductive technologies for animal cleaning/embryo-sperm preservation, histopathological techniques for animal tissues and establishment of expandable cells/xenograft transplantable models from clinical cancer tissues (PDX models).

## Research activities

Research activities of the Central Animal Division have focused on studies of chemical carcinogenesis using laboratory animals, genetically modified cancer developing animal models and occasionally clinical samples.

1) Association of pancreatic fatty infiltration (FI) with pancreatic ductal adenocarcinoma

Epidemiologically, obesity and diabetes are risk factors for pancreatic cancer, but the underlying mechanisms are not clearly understood. Obesity and diabetes are also associated with degree of FI in the pancreas. We reported that the degree of FI in non-cancerous part of pancreatic sections was significantly higher in pancreatic cancer patient cases than in the controls and positively associated with pancreatic cancer development. Severe pancreatic FI could be a risk factor of pancreatic cancer. The role of obesity and pancreatic fatty infiltration (FI) in pancreatic carcinogenesis is being investigated in animal models.

2) Mechanisms of promotion of mammary carcinogenesis associated with a high-fat diet

The effects of a high-fat diet (HFD) during prepubertal and pubertal stages were investigated in 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in female F344 rats. The results obtained indicated that HFD promoted carcinogenesis. Molecular mechanisms of the promotion as assessed with DNA microarray analysis for the non-cancerous mammary tissues were suggested to be associated with altered expression of cell cycle/differentiation-related genes, which were at least partly affected by DNA methylation.

3) Mechanistic analysis of inflammation in tumorigenesis with an intestinal orgnoid 3D culture approach

Mechanisms of tumorigenesis by inflammation are not clearly understood. An inflammatory response *in vivo* is very complicated because it involves many kinds of cytokines and immune cells. In this approach, we focused on a pro-inflammatory cytokine interleukin-22 (IL-22) and analyze its roles with an intestinal organoid 3D cultural method. IL-22 was found to disrupt

intestinal barrier functions, and it was suggested that unregulated IL-22 signaling could enhance tumorigenic inflammatory responses.

4) Human induced hepatic lineage-oriented stem cells (hiHSCs); autonomous specification of human iPS cells toward hepatocyte-like cells without any exogenous differentiation factors

Self-renewing hiHSCs mixed with Matrigel were subcutaneously injected into immune-deficient mice and serum biochemical analysis revealed elevated human albumin levels to 0.6–1.6 μg/mL. In this study, a differentiation potential of hiHSCs, which were histopatholgically developed to teratomas *in vivo*, to hepatocytes was at least partly confirmed.

## Future prospects

Research approaches using immune-deficient/severely immune-deficient mice have become increasingly important these several years, and microbiological controls of the animal experimentation facility should become more strictly controlled. For development of research fields to conquer rare cancers/refractory cancers, establishment of their PDX models should be systematically organized.

## List of papers published in 2014

### Journal


1. Hori M, Takahashi M, Hiraoka N, Yamaji T, Mutoh M, Ishigamori R, Furuta K, Okusaka T, Shimada K, Kosuge T, Kanai Y, Nakagama H. Association of pancreatic Fatty infiltration with pancreatic ductal adenocarcinoma. Clin Transl Gastroenterol, 5:e53, 2014
2. Yamada I, Matsuyama M, Ozaka M, Inoue D, Muramatsu Y, Ishii H, Junko U, Ueno M, Egawa N, Nakao H, Mori M, Matsuo K, Nishiyama T, Ohkawa S, Hosono S, Wakai K, Nakamura K, Tamakoshi A, Kuruma S, Nojima M, Takahashi M, Shimada K, Yagyu K, Kikuchi S, Lin Y. Lack of associations between genetic polymorphisms in GSTM1, GSTT1 and GSTP1 and pancreatic cancer risk: a multiinstitutional case-control study in Japan. Asian Pac J Cancer Prev, 15:391-395, 2014
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# Department of Biobank and Tissue resources

**Yae Kanai, Izumi Kobayashi, Teiko Yamane, Masumi Tanaka**

## Activities of the National Cancer Center Biobank

The National Cancer Center Biobank was conducted under the supervision by the National Cancer Center Biobank Administration Committee (Figure 1).

In 2014, 8,738 vials of tissue specimens obtained from surgically resected materials of 1,657 patients were newly deposited into the National Cancer Center Biobank and 2,316 vials of tissue specimens obtained from surgically resected materials of 1,344 patients were provided to researches approved by the National Cancer Center Ethics Committee. The ratio of the number of the patients of whom samples were provided to researches to that of whom samples were newly deposited into the Biobank was about 81%. At the end of 2014, we reposited 72,510 vials of tissue specimens of 17,577 patients.

In 2014, 27,133 vials of plasma samples drawn from 6,837 patients were newly deposited into the National Cancer Center Biobank and 1,688 vials of plasma samples drawn from 1,053 patients were provided to researches approved by the National Cancer Center Ethics Committee. At the end of 2014, we reposited 110,214 vials of blood samples of 27,743 patients who consented to blood sampling for research purposes.

We have built up the catalog database, named the HosCanR Biobank Edition, by extracting appropriate information from the Interview Sheet Database in the common form among six National Centers in Japan and HosCanR, an application specialized for the National program of Cancer Registry. Researchers, biobank users, can find out samples which are suitable for their own research plans using search commands of this catalog database. In 2014, we made it able to automatically extract appropriate information, which should be provided to the central database of the National Center Biobank Network (NCBN), from the

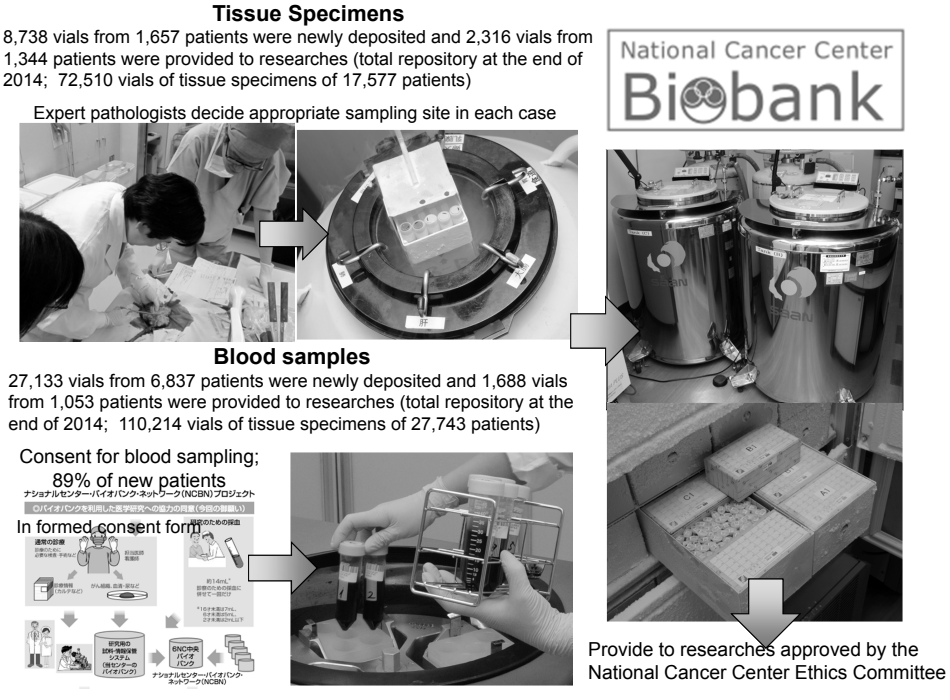


**Figure 1. National Cancer Center Biobank**

HosCanR Biobank Edition. In addition, we now able to confirm the informed consent status in the HosCanR Biobank Edition which has been connected to computerized medical records system.

Researchers who received samples from the Biobank have published 279 scientific papers (total impact factor; 1435.574, total citation index; 3,586). 63% of the published papers were based on collaborative researches between researchers of National Cancer Center and other institutes or universities.

Sixty-six founders and/or contact persons of 11 bioresource repositories of other universities and hospitals and two television crews visited the National Cancer Center Biobank to study knowhow of management of biobank in 2014. We have been consulted by contact persons of 15 bioresource repositories of other universities about storage system of specimens.

Staffs of the National Cancer Center Biobank participate in the General Ethics Support Sector, the Sample Utilization Review Working Group, the Sample Handling System Review Working Group and the Medical Information System Review Working Group of the NCBN. In 2014, the Central Database Management Sector of the NCBN collected individual data sheets of samples of each National Center. Ethical, legal and social issues about wide distribution of samples which are not based on collaborative researches have been discussed in the NCBN.

## Future prospects

Consecutive collection of samples for various research needs and management of biobank including quality clinicopathological information database are considered as national mission. The National Cancer Center Biobank should be continued and become a more robust and permanent research base. The National Cancer Center Biobank should continuously support the NCBN and connect intention of voluntary donors to next generation personalized medicine.

# Department of Patient-Derived Cell Line and Xenograft

**Tohru Kiyono**

## Introduction

There are mainly two approaches to amplify cancer cells from patients, in vitro cell culture and patient-derived xenograft (PDX). Since HeLa cell line, the first human cancer cell line, has been established, human cancer cell lines have been essential for cancer research. Patient-derived xenografts (PDXs) generated from fresh tumor specimens generally reflect histopathology, tumor behavior, and the metastatic properties of the original tumor. Both PDX models and cell line-derived xenograft (CDX) models are considered to be important preclinical tools in recent years. However, the success rate to establish new cell lines or PDX lines is not satisfactory.

## Routine activities

This Department was founded in 2014 for establishment of new cancer cell lines and PDX lines. We are preparing for the system that stores valuable cancer specimens so that cancer tissues or cancer cells can be transplanted into immune-deficient mice or cultivated in vitro.

## Research activities

This year, a series of metastatic liver cancer specimens of colorectal carcinomas were selected for initial test for the storage since large amount of specimens can be generally obtained from each patient. Once the freezing condition has been fixed, other cancer specimens will be added for the storage.

## Future prospects

The in vitro carcinogenesis model with reversible control of oncogene expression enabled de novo development of PDAC from quasi-normal human tissues pre-formed subcutaneously in mice and might be applicable to carcinogenesis models in many organ sites. These models will be useful for preclinical assessment of new cancer therapies.

# Department of Molecular imaging & Pharmacokinetics

**Akinobu Hamada, Shuichi Shimma, Makiko Yamashita, Hiroaki Aikawa, Shoraku Ryu**

## Introduction

Development of Pharmacokinetic analysis for a new anticancer agent using LC-MS/MS and MALDI imaging Mass Spectrometry.

## Research activities

Drug exposure and distribution in tumor tissues impact pharmacology and efficacy in drug development. However, a conventional PK analysis, using HPLC and LC-MS/MS, has limitations in providing a comprehensive assessment of real tissue distribution. Now investigators in PK lab demonstrated a drug visualizing system using MALDI (matrix-assisted laser desorption ionization) Imaging Mass Spectrometry that provides the possibility to evaluate the concentration and spatial distribution in target tumor tissue.

## List of papers published in 2014

### Journal


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4. Tsuchiya K, Hayashida T, Hamada A, Kato S, Oka S, Gatanaga H. Low raltegravir concentration in cerebrospinal fluid in patients with ABCG2 genetic variants. J Acquir Immune Defic Syndr, 66:484-486, 2014
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8. Anan T, Shimma S, Toma Y, Hashidoko Y, Hatano R, Toyoda M. Real time monitoring of gases emitted from soils using a multi-turn time-of-flight mass spectrometer "MULTUM-S II". Environ Sci Process Impacts, 16:2752-2757, 2014
9. Fujii K, Fujiki T, Koiso A, Hirakawa K, Yamashita M, Matsumoto T, Hasegawa T, Morimatsu F, Katakura Y. Identification of anti-allergic lactic acid bacteria that suppress Ca2+ influx and histamine release in human basophilic cells. J Funct Foods, 10:370-376, 2014
10. Yamashita M, Nonaka T, Hirai S, Miwa A, Okado H, Arai T, Hosokawa M, Akiyama H, Hasegawa M. Distinct pathways leading to TDP-43-induced cellular dysfunctions. Hum Mol Genet, 23:4345-4356, 2014
11. Yatsuga C, Toyohisa D, Fuj i sawa TX, Nishitani S, Shinohara K, Matsuura N, Ikeda S, Muramatsu M, Hamada A, Tomoda A. No association between catechol-Omethyltransferase (COMT) genotype and attention deficit hyperactivity disorder (ADHD) in Japanese children. Brain Dev, 36:620-625, 2014

# Department of Innovative Seeds Evaluation

**Tadashi Kondo, Tsutomu Ohta**

## Introduction

The Department of Innovative Seeds Evaluation aims at the establishment of efficient methods to evaluate novel seeds, and evaluate research outcome for innovative therapies. Taking advantages of National Cancer Center such as easy access to clinical materials with high quality, we challenge the two following subjects. [In vitro evaluation system for novel innovative seeds] In vitro assay system is essential for preclinical study. Establishment of Patient Derived Xenograft (PDX) and primary cultured cell lines, and experiment system for evaluation of novel drug candidates is the first step for our goal. [Screening system of cancer drugs] Establishment of effective evaluation system using cell line panels is undertaken in our Department. Omics data are linked to the response to drug treatments, and integrated in the database to characterize the molecular backgrounds of response, and predict the effects of novel drugs.

## Research activities

[In vitro evaluation system for novel innovative seeds] Protocol to establish PDX and primary cultured cell lines from surgical specimens were established, and applied to sarcomas. [Screening system of cancer drugs] Protocol to screen the effects of approximately 400 inhibitors in the cell line panel was established. Development of novel algorithm to examine and integrate the transcriptome data, which were obtained before and after the treatments with cancer drugs, was launched.

## Future prospects

To facilitate the clinical applications of research outcome, methods to evaluate innovative seeds for novel therapy will be established, and applied to our findings.

## List of papers published in 2014

## Journal


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2. Nakadate Y, Kodera Y, Kitamura Y, Shirasawa S, Tachibana T, Tamura T, Koizumi F. KRAS mutation confers resistance to antibodydependent cellular cytotoxicity of cetuximab against human colorectal cancer cells. Int J Cancer, 134:2146-2155, 2014
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4. Fujiwara T, Katsuda T, Hagiwara K, Kosaka N, Yoshioka Y, Takahashi RU, Takeshita F, Kubota D, Kondo T, Ichikawa H, Yoshida A, Kobayashi E, Kawai A, Ozaki T, Ochiya T. Clinical relevance and therapeutic significance of microRNA-133a expression profiles and functions in malignant osteosarcoma-initiating cells. Stem Cells, 32:959-973, 2014
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7. Motoyama N, Morita K, Shiraishi S, Kitayama T, Kanematsu T, Uezono Y, Dohi T. Relief of cancer pain by glycine transporter inhibitors. Anesth Analg, 119:988-995, 2014
8. Hosoya N, Sakumoto M, Tomita Y, Kondo T. Approach to spot overlapping problem in 2D-PAGE revealed clinical and functional significance of RKIP and MnSOD in renal cell carcinoma. EuPA Open Proteomics, 4:129-139, 2014
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12. Ichikawa H, Kanda T, Kosugi S, Kawachi Y, Wakai T, Kondo T. Proteomic and metatranscriptomic study on lymph node metastasis in gastric cancer. EuPA Open Proteomics, 3:183?194, 2014
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19. Murakami A, Takahashi F, Nurwidya F, Kobayashi I, Minakata K, Hashimoto M, Nara T, Kato M, Tajima K, Shimada N, Iwakami SI, Moriyama M, Moriyama H, Koizumi F, Takahashi K. Hypoxia increases gefitinibresistant lung cancer stem cells through the activation of insulin-like growth factor 1 receptor. PLoS One, 9:e86459, 2014

# Department of Clinical Genomics

**Hitoshi Ichikawa, Fumie Hosoda, Sachiyo Mitani, Shizuka Shinohara, Erika Arakawa**

## Introduction

The aim of our Department is to realize molecular profile-based personalized medicine for cancer patients by supporting genome and transcriptome analyses of clinical tumor samples. For personalized cancer medicine, next generation sequencer-based clinical sequencing is a promising molecular profiling method to efficiently detect genetic alterations from tumor tissues. We are developing and improving an original target sequencing system for clinical sequencing, and are providing sequencing services with small-scale next generation sequencers, Illumina MiSeq and Ion Proton.

## Research activities

Development of a target sequencing system for FFPE tumor samples

We developed an original target sequencing system for clinical sequencing, which can identify gene amplifications and fusions as well as mutations from FFPE tumor tissue samples. In the present version of this system, 90 potentially targetable or actionable genes were selected as an in-house cancer panel (NCC oncopanel v2), and all exons of these 90 genes and introns of 10 genes among them are captured and sequenced for detection of mutations/gene amplifications and gene fusions, respectively. To ensure a stable operation on FFPE samples, we also developed a method to qualify FFPE tissue-derived DNA using the content of PCR-amplifiable DNA as a quality value. By changing the DNA quantity used for sequencing depending on their quality values, we were able to successfully analyze approximately 90% of the archived FFPE samples. For detection of genetic alterations, we adopted a novel algorithm which was developed by researchers of the Department of Bioinformatics. By the use of this algorithm, we achieved highly accurate mutation detection with more than 99% accuracy for base substitution mutations and more than 90% accuracy for insertion/deletion mutations.

Use for clinical sequencing

As a collaborative work with the Division of Translational Research and the Department of Experimental Therapeutics of EPOC, we designed and performed a feasibility study to use our target sequencing system for patient entry into early phase clinical trials of molecular target drugs, which was named TOPICS-1 (Trial of Onco-Panel for Introduction into Clinical Study-Phase 1). Totally 131 patients with many types of cancers were subjected to the sequencing analysis in this study. The results showed the feasibility of our system in a clinical setting. On average, 1.9 mutations and 0.3 amplifications were found in each patient, and nearly half of the patients had at least 1 actionable alteration, which is informative for entry into some clinical trials.

Other target sequencing services

We provided target sequencing services using our original target sequencing system and commercially available cancer panel systems, upon requests from researchers in Research Institute and Hospital. This year, more than 500 samples of various types of cancers were analyzed.

## List of papers published in 2014

## Journal


1. Nakaoku T, Tsuta K, Ichikawa H, Shiraishi K, Sakamoto H, Enari M, Furuta K, Shimada Y, Ogiwara H, Watanabe S, Nokihara H, Yasuda K, Hiramoto M, Nammo T, Ishigame T, Schetter AJ, Okayama H, Harris CC, Kim YH, Mishima M, Yokota J, Yoshida T, Kohno T. Druggable oncogene fusions in invasive mucinous lung adenocarcinoma. Clin Cancer Res, 20:3087-3093, 2014
2. Totoki Y, Tatsuno K, Covington KR, Ueda H, Creighton CJ, Kato M, Tsuji S, Donehower LA, Slagle BL, Nakamura H, Yamamoto S, Shinbrot E, Hama N, Lehmkuhl M, Hosoda F, Arai Y, Walker K, Dahdouli M, Gotoh K, Nagae G, Gingras M-C, Muzny DM, Ojima H, Shimada K, Midorikawa Y, Goss JA, Cotton R, Hayashi A, Shibahara J, Ishikawa S, Guiteau J, Tanaka M, Urushidate T, Ohashi S, Okada N, Doddapaneni H, Wang M, Zhu Y, Dinh H, Okusaka T, Kokudo N, Kosuge T, Takayama T, Fukayama M, Gibbs RA, Wheeler DA, Aburatani H, Shibata T. Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. Nat Genet, 46:1267-1273, 2014
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4. Arai E, Sakamoto H, Ichikawa H, Totsuka H, Chiku S, Gotoh M, Mori T, Nakatani T, Ohnami S, Nakagawa T, Fujimoto H, Wang L, Aburatani H, Yoshida T, Kanai Y. Multilayeromics analysis of renal cell carcinoma, including the whole exome, methylome and transcriptome. Int J Cancer, 135:1330-1342, 2014
5. Fujiwara T, Katsuda T, Hagiwara K, Kosaka N, Yoshioka Y, Takahashi RU, Takeshita F, Kubota D, Kondo T, Ichikawa H, Yoshida A, Kobayashi E, Kawai A, Ozaki T, Ochiya T. Clinical relevance and therapeutic significance of microRNA-133a expression profiles and functions in malignant osteosarcoma-initiating cells. Stem Cells, 32:959-973, 2014
6. Mizukami T, Shiraishi K, Shimada Y, Ogiwara H, Tsuta K, Ichikawa H, Sakamoto H, Kato M, Shibata T, Nakano T, Kohno T. Molecular mechanisms underlying oncogenic RET fusion in lung adenocarcinoma. J Thorac Oncol, 9:622- 630, 2014
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8. Gotoh M, Ichikawa H, Arai E, Chiku S, Sakamoto H, Fujimoto H, Hiramoto M, Nammo T, Yasuda K, Yoshida T, Kanai Y. Comprehensive exploration of novel chimeric transcripts in clear cell renal cell carcinomas using whole transcriptome analysis. Genes Chromosomes Cancer, 53:1018-1032, 2014
9. Otsubo C, Otomo R, Miyazaki M, Matsushima- Hibiya Y, Kohno T, Iwakawa R, Takeshita F, Okayama H, Ichikawa H, Saya H, Kiyono T, Ochiya T, Tashiro F, Nakagama H, Yokota J, Enari M. TSPAN2 is involved in cell invasion and motility during lung cancer progression. Cell Rep, 7:527-538, 2014
10. Kobayashi K, Mitsui K, Ichikawa H, Nakabayashi K, Matsuoka M, Kojima Y, Takahashi H, Iijima K, Ootsubo K, Oboki K, Okita H, Yasuda K, Sakamoto H, Hata K, Yoshida T, Matsumoto K, Kiyokawa N, Ohara A. ATF7IP as a novel PDGFRB fusion partner in acute lymphoblastic leukaemia in children. Br J Haematol, 165:836-841, 2014
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12. Masuzawa A, Kiyotani C, Osumi T, Shioda Y, Iijima K, Tomita O, Nakabayashi K, Oboki K, Yasuda K, Sakamoto H, Ichikawa H, Hata K, Yoshida T, Matsumoto K, Kiyokawa N, Mori T. Poor responses to tyrosine kinase inhibitors in a child with precursor B-cell acute lymphoblastic leukemia with SNX2-ABL1 chimeric transcript. Eur J Haematol, 92:263-267, 2014

# Department of Translational Oncology

**Hiroki Sasaki, Kazuhiko Aoyagi, Masashi Tamaoki, Masayuki Komatsu, Rie Komatsuzaki, Fumiko Chiwaki, Akio Ashida, Kanako Nakamura, Risa Ichinohe**

## Introduction

In 2014, the three major research areas of the Department of Translational Oncology were 1) preclinical studies using newly established gastric cancer cell lines for derivation of industrial and academia seeds/drugs to EPOC, and 2) development of personalized cancer diagnosis and treatment.

Preclinical Studies Using Newly Established Gastric Cancer Cell Lines

Genome-wide genetic information in 963 cancer cell lines is available on COSMIC DB (Sanger Center, UK); however, among them, only 21 cell lines are derived from gastric cancer (GC). Almost all of the 21 GC cell lines have been established many years ago. Only insufficient clinical and pathological information is attached. Establishment of new GC cell lines, especially from metastatic sites after therapy, has been awaited. Peritoneal metastasis is most frequent in GCs, especially diffuse-type GCs. Furthermore, since driver gene mutation frequency in a certain cancer is often less than 5%, establishment of cell lines from each patient to be analyzed is desired for functional selection of driver gene mutations. In collaboration with Division of Genetics, we have newly established 44 diffuse-type GC derived cell lines (NSC-1~37 series) from the cancer ascites of 24 patients. Now we possess 77 GC cell lines including 65 diffuse-type (new 44 and existing 21) and 12 intestinal-type. We are conducting omics analyses for gene expression and copy number variation, and hot spot- and genome wide-gene alteration in these cell lines. Moreover, to establish the peritoneal metastasis model, their tumorigenicity and histopathological characteristics of PDXs, such as fibroblast rich-, hypovascular-, and dormant-state, were evaluated. By collaboration with three pharmaceutical industries, *in vitro* and *in vivo* preclinical studies were conducted to derivate them to the Exploratory Oncology Research & Clinical Trial Center (EPOC).

Development of Personalized Diagnosis and Treatment for Cancer

Two major research projects are underway. First, we developed mini DNA chips containing 6 marker and 3 control genes for predicting gastric cancer recurrence from peritoneal washings. Peritoneal cytology (CY) offers important prognostic information for gastric cancer after surgery; however, CY provides only a limited sensitivity and the task requires great skill. Our goal is to develop a sensitive tool that could be used in a clinical laboratory agency as a substitute for skilled cytology. Our collaborating company continues to prepare many supporting data for submitting the mini DNA chip to Pharmaceuticals and Medical Devices Agency (PMDA) for marketing approval as an in vitro diagnostic (IVD). Second, we successfully identified 5 intrinsic subtypes of esophageal squamous cell carcinomas by hundreds' gene expression profile-based unsupervised clustering of 274 biopsy samples obtained before treatment. The 274 profiles were divided into a test set (107 cases containing 35 and 72 cases received CRT or surgery) and a validation set (167 cases containing 90 and 77 cases, respectively). Five intrinsic subtypes (1a/F3/M1, 2a/I, 3b, 5/D/M2, 7/B/E) including 2 new subtypes (2a/I, 3b) were identified in the test set, and these were reproducibly found in the validation set. For the cases treated with CRT, the 5-y survival rate was 24% in subtype M2, whereas it was 74% in subtype E. Furthermore, we found transcriptional pathways activated characteristically in each subtype; the subtype E showed a differentiation phenotype, while the non-E subtypes including M1 and M2 showed an epithelial-mesenchymal transition phenotype. Our findings may contribute not only to the elucidation of CRT responsiveness but also for the future therapeutic development. To develop

an IVD, we successfully selected each 50 genes for predicting these two CRT-sensitive and –insensitive subtypes.

## List of papers published in 2014

### Journal


1. Oue N, Naito Y, Hayashi T, Takigahira M, Kawano-Nagatsuma A, Sentani K, Sakamoto N, Zarni Oo H, Uraoka N, Yanagihara K, Ochiai A, Sasaki H, Yasui W. Signal peptidase complex 18, encoded by SEC11A, contributes to progression via TGF-α secretion in gastric cancer. Oncogene, 33:3918-3926, 2014
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3. Maeda R, Ishii G, Neri S, Aoyagi K, Haga H, Sasaki H, Nagai K, Ochiai A. Circulating CD14+CD204+ cells predict postoperative recurrence in non-small-cell lung cancer patients. J Thorac Oncol, 9:179-188, 2014
4. Oue N, Anami K, Schetter AJ, Moehler M, Okayama H, Khan MA, Bowman ED, Mueller A, Schad A, Shimomura M, Hinoi T, Aoyagi K, Sasaki H, Okajima M, Ohdan H, Galle PR, Yasui W, Harris CC. High miR-21 expression from FFPE tissues is associated with poor survival and response to adjuvant chemotherapy in colon cancer. Int J Cancer, 134:1926-1934, 2014
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# Department of Analytical Pathology

**Nobuyoshi Hiraoka, Yoshinori Ino-Ishikawa**

## Introduction

In the Analytical Pathology Department the pathobiological and clinicopathological characteristics of the target molecules are analyzed for evaluating their potential significance in applying diagnostic or treatment use in future. Expression of the molecules or genes in human tissues is assessed by morphological techniques, immunohistochemistry, RT-PCR, i*n situ hybridization*, etc., and the results are compared to clinicopathological information. We also try to develop new, more reliable, or more effective analytical methods and tools.

## Research activities

In 2014 two staff members made preparations for the Department start and studied tumor immune microenvironment clinicopathologically and pathobiologically.

## Education

Teaching the analytical techniques to technicians and researchers in several departments of National Cancer Center was performed.

## Future prospects

We will answer the requests from the selected project in various types of study containing basic, preclinical, and clinical studies, and assess the clinicopathological or pathobiological significance of the target molecules. We will develop methods of quantitative analysis to evaluate morphological findings that are currently analyzed qualitatively.

## List of papers published in 2014

## Journal


1. Furukawa D, Chijiwa T, Matsuyama M, Mukai M, Matsuo E, Nishimura O, Kawai K, Suemizu H, Hiraoka N, Nakagohri T, Yasuda S, Nakamura M. Zinc finger protein 185 is a liver metastasis-associated factor in colon cancer patients. Mol Clin Oncol, 2:709-713, 2014
2. Hayashi T, Horiuchi A, Sano K, Hiraoka N, Ichimura T, Sudo T, Ishiko O, Yaegashi N, Aburatani H, Konishi I. Potential diagnostic biomarkers: differential expression of LMP2/ β 1i and cyclin B1 in human uterine leiomyosarcoma. Tumori, 100:99e-106e, 2014
3. Hori M, Takahashi M, Hiraoka N, Yamaji T, Mutoh M, Ishigamori R, Furuta K, Okusaka T, Shimada K, Kosuge T, Kanai Y, Nakagama H. Association of pancreatic Fatty infiltration with pancreatic ductal adenocarcinoma. Clin Transl Gastroenterol, 5:e53, 2014
4. Inagawa Y, Yamada K, Yugawa T, Ohno S, Hiraoka N, Esaki M, Shibata T, Aoki K, Saya H, Kiyono T. A human cancer xenograft model utilizing normal pancreatic duct epithelial cells conditionally transformed with defined oncogenes. Carcinogenesis, 35:1840-1846, 2014
5. Kishi Y, Shimada K, Nara S, Esaki M, Hiraoka N, Kosuge T. Basing treatment strategy for non-functional pancreatic neuroendocrine tumors on tumor size. Ann Surg Oncol, 21:2882-2888, 2014
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8. Qiu Y, Jiang H, Shimada K, Hiraoka N, Maeshiro K, Ching WK, Aoki-Kinoshita KF, Furuta K. Towards prediction of pancreatic cancer using SVM study model. JSM Clin Oncol Res, 2:1031, 2014
9. Qiu Y, Shimada K, Hiraoka N, Maeshiro K, Ching W-K, Aoki-Kinoshita KF, Furuta K. Knowledge discovery for pancreatic cancer using inductive logic programming. IET Syst Biol, 8:162-168, 2014
10. Sato Y, Ojima H, Onaya H, Mori T, Hiraoka N, Kishi Y, Nara S, Esaki M, Shimada K, Kosuge T, Sugihara K, Kanai Y. Histopathological characteristics of hypervascular cholangiocellular carcinoma as an early stage of cholangiocellular carcinoma. Hepatol Res, 44:1119-1129, 2014
11. Shoji H, Morizane C, Hiraoka N, Kondo S, Ueno H, Ohno I, Shimizu S, Mitsunaga S, Ikeda M, Okusaka T. Twenty-six cases of advanced ampullary adenocarcinoma treated with systemic chemotherapy. Jpn J Clin Oncol, 44:324-330, 2014
12. Yamamoto Y, Hiraoka N, Goto N, Rin Y, Miura K, Narumi K, Uchida H, Tagawa M, Aoki K. A targeting ligand enhances infectivity and cytotoxicity of an oncolytic adenovirus in human pancreatic cancer tissues. J Control Release, 192:284-293, 2014
13. Yamazaki K, Masugi Y, Effendi K, Tsujikawa H, Hiraoka N, Kitago M, Shinoda M, Itano O, Tanabe M, Kitagawa Y, Sakamoto M. Upregulated SMAD3 promotes epithelialmesenchymal transition and predicts poor prognosis in pancreatic ductal adenocarcinoma. Lab Invest, 94:683-691, 2014

# Department of Functional Analysis

**Fumitaka Takeshita**

## Introduction

The Department of Functional Analysis carries out functional analysis to development of scientific basis diagnosis and pre-clinical studies in corporation with other department in Core Center.

Recently, optical imaging technologies for clinical use have been sized down to make them available for non-invasive in vivo imaging for small animals. The development of molecular imaging using luminescence or fluorescence in vitro have facilitated in vivo imaging to detect the molecular events in tumor cells on living animals. "In vivo imaging" and "In vivo molecular imaging" are now being established as a new field of research. Promptness and handiness of the in vivo imaging are rapidly changing the design of the animal experiments not only in cancer research but in the whole of biology.

## Research activities

In our laboratory, evaluation of treatments with cancer model studies and imaging for the gene medicine molecule such as microRNA are done by making good use of this imaging device that detects luminescence and fluorescence from the living animals (Fujita, Biomed Res Int., Seino, J Food Sci., Ono, Sci Signal., Fujiwara, Stem Cells).

## Clinical trials

The preparation of clinical trial of RPN2-siRNA treatment for chemo-resistant breast cancer has been preceded collaborated with the Division of Molecular and Cellular Medicine and the Department of Breast and Medical Oncology in the NCC Hospital.

# Department of Animal Experimentation

**Toshio Imai, Masako Ochiai, Yoshitaka Hippo, Tetsuya Matsuura, Takashi Nishizawa**

## Introduction

A pivotal role of this Department is establishment of cancer animal models (human cancer tissue/cell-transplanted immune-deficient mice). In experiments using immune-deficient/severely immune-deficient mice, microbiological environment of the animal experimentation facility should be strictly controlled and technical staffs take great care.

## Routine activities

Establishment of xenograft transplantable models from clinical cancer tissues (patient-derived xenograft-PDX models) or cultured cancer cells (ectopic or orthotopic cancer cell implantation models) and evaluation of drug efficacy using PDX or cancel cell implantation models are performed.

## Research activities

Research activities of the Department of Animal Experimentation are focused on studies of recapitulation of multi-step adenocarcinogenesis for diverse organs through an *in vitro* approach. Whereas both genetic and environmental factors cooperate for tumorigenesis *in vivo*, we demonstrated that the lentivirus-mediated introduction of genetic alterations in murine primary epithelial cells could lead to development of adenocarcinoma in the dorsal skin of immune-deficient mice. Notably, tumor initiation and subsequent step-wise progression from normal cells via pre-cancerous lesions to carcinoma could be accurately recapitulated for various vital organs in a cell-autonomous manner. By taking this approach, genetic and/or environmental interactions toward tumorigenesis could be conveniently investigated *in vitro*, which would likely accelerate elucidation of the molecular mechanisms underlying carcinogenesis.

## List of papers published in 2014

### Journal

1. Ochiai M, Hippo Y, Izumiya M, Watanabe M, Nakagama H. Newly defined aberrant crypt foci as a marker for dysplasia in the rat colon. Cancer Sci, 105:943-950, 2014

2. Igarashi M, Hippo Y, Ochiai M, Fukuda H, Nakagama H. AKT is critically involved in cooperation between obesity and the dietary carcinogen amino-1-methyl-6-phenylimidazo [4,5-b] (PhIP) toward colon carcinogenesis in rats. Biochem Biophys Res Commun, 443:852-857, 2014

# Department of Cell Culture Technology

**Tohru Kiyono**

## Introduction

Human cells in culture have limited life span and undergo non-dividing state named senescence. The replicative senescence is caused by telomere shortening since most human somatic cells do not express telomerase to the level sufficient for maintenance of telomere length. Human epithelial cells also undergo non-dividing state much earlier not because of telomere shortening but because of accumulation of $p16^{INK4A}$ and activation of pRB. Stem or progenitor cells of human epithelia often express higher levels of TERT so that telomere shortening is delayed. In a certain culture condition which induces higher levels of TERT expression and inhibits $p16^{INK4A}$ induction, they could proliferate infinitely without any transgenes.

## Routine activities

This Department was founded in 2014 for developing better methods to cultivate normal human cells as well as cancer cells derived from clinical specimens obtained by operation, biopsy and therapy.

## Research activities

Recently a culture condition with feeder layer cells and the ROCK inhibitor, Y-27632, has been developed for infinite proliferation of several epithelial cell types. Based on the improved method developed by the Division of Carcinogenesis and Cancer Prevention, we now can cultivate so far difficult-to-cultivate primary human cells, such as hepatocytes, pancreatic duct cells, gastric epithelial cells and colon epithelial cells without feeder cells. These cell types have been immortalized by transduction of CDK4, cyclin D1 and TERT so as to be cultivated in more general culture conditions. On the other hand, some cell types are still difficult to passage and quickly amplify in vitro without transgenes. Our goal is to establish the cell culture method that can easily amplify every cell type including normal, pre-neoplastic and cancer cells. These include organoid culture as well as conventional two-dimensional culture.

## Future prospects

Once cells-of-origin of every cancer could be easily amplified in vitro, they can be used for normal control cells for each cancer. Causal relationship of a gene mutation found in cancer and a certain phenotype such as drug resistance could be directly evaluated by transducing the mutant gene into them. They might also be applied to development of cell transplantation therapy.

# Department of Bioinformatics

**Isao Kurosaka, Eisaku Furukawa, Joe Miyamoto**

## Introduction

Missions of our department are 1) bioinformatics analysis support for experimental groups in the Fundamental Innovative Oncology Core, 2) bioinformatics analysis support for other groups in NCC, and 3) to develop new bioinformatics and data-analysis methods necessary for emerging genomics technologies.

## Research activities

- We took charge of the bioinformatics part in the clinical sequencing project in NCC. The bioinformatics part consists of 1) development of DNA-alteration calling program and 2) development of medical information system for clinical sequencing.
  1). We developed a new software system optimized for FFPE samples used in clinical sequencing. This system detects SNV, indels, gene fusions, and copy number alterations from a large amount of data produced by the next generation sequencer (NGS). We compared our program with other well-known programs (, which were originally developed for cell-line or frozen samples for research purposes). We confirmed that our program greatly outperformed the other programs.
  2) We developed the first version of a medical information system that integrates DNA alterations detected in clinical sequencing with clinical information taken from electronic medical records. By this system, medical doctors can view, search, and edit results of expert panel. This system can automatically calculate the statistics and can be used as a database.
- We developed a pipeline program to help discover new cancer subtypes, using trans-omics data in lung adenocarcinoma as a part of the Medical Big Data project.
- We provided bioinformatics support for studies on liver cancer and bile duct cancer as a part of ICGC, and on multi-regional liver cancer and on pancreas cancer in the Division of Cancer Genomics; for studies on DNA adductome, gene expression of cancer stem cells, miRNAs in the Division of Cancer Development System; and for a study on germinoma in the Division of Brain Tumor Translational Research.
- We conducted an experiment of a new technology – single-cell sequencing – to reveal intra-tumor heterogeneity and cancer-cell evolution, collaborating with the Division of Caner Genomics and the Division of Cancer Development System. We performed single-cell exome and transcriptome sequencing and informatics analysis, confirming the feasibility of this newly emerging technology.

## Education

We educated two new technical staff members through on-the-job training, and advised bioinformatics technical staff in the Division of Cancer Genomics.

## Future prospects

We will advance development and management of information system for clinical sequencing ultimately aiming at personalized medicine. We will also develop algorithms to find novel tumor molecular markers and cancer subtypes, using medical big data that will be accelerated by clinical sequencing. We will keep continue to provide bioinformatics support for other groups in the Center. We will develop new bioinformatics methodologies and theories for the

emerging technology, single-cell sequencing, to reveal tumor heterogeneity.

## List of papers published in 2014

### Journal


1. Fukushima S, Otsuka A, Suzuki T, Yanagisawa T, Mishima K, Mukasa A, Saito N, Kumabe T, Kanamori M, Tominaga T, Narita Y, Shibui S, Kato M, Shibata T, Matsutani M, Nishikawa R, Ichimura K. Mutually exclusive mutations of KIT and RAS are associated with KIT mRNA expression and chromosomal instability in primary intracranial pure germinomas. Acta Neuropathol, 127:911-925, 2014
2. Totoki Y, Tatsuno K, Covington KR, Ueda H, Creighton CJ, Kato M, Tsuji S, Donehower LA, Slagle BL, Nakamura H, Yamamoto S, Shinbrot E, Hama N, Lehmkuhl M, Hosoda F, Arai Y, Walker K, Dahdouli M, Gotoh K, Nagae G, Gingras M-C, Muzny DM, Ojima H, Shimada K, Midorikawa Y, Goss JA, Cotton R, Hayashi A, Shibahara J, Ishikawa S, Guiteau J, Tanaka M, Urushidate T, Ohashi S, Okada N, Doddapaneni H, Wang M, Zhu Y, Dinh H, Okusaka T, Kokudo N, Kosuge T, Takayama T, Fukayama M, Gibbs RA, Wheeler DA, Aburatani H, Shibata T. Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. Nat Genet, 46:1267-1273, 2014
3. Mizukami T, Shiraishi K, Shimada Y, Ogiwara H, Tsuta K, Ichikawa H, Sakamoto H, Kato M, Shibata T, Nakano T, Kohno T. Molecular mechanisms underlying oncogenic RET fusion in lung adenocarcinoma. J Thorac Oncol, 9:622-630, 2014
4. Suenaga Y, Islam SMR, Alagu J, Kaneko Y, Kato M, Tanaka Y, Kawana H, Hossain S, Matsumoto D, Yamamoto M, Shoji W, Itami M, Shibata T, Nakamura Y, Ohira M, Haraguchi S, Takatori A, Nakagawara A. NCYM, a Cisantisense gene of MYCN, encodes a de novo evolved protein that inhibits GSK3 β resulting in the stabilization of MYCN in human neuroblastomas. PLoS Genet, 10:e1003996, 2014

# Department of Omics Network

**Masaru Katoh**

## Introduction

The Department of Omics Network, established in August 2014, is derived from Masaru Katoh's laboratory, which is also known as the Katoh's Unit (from 2009 to 2014) and the Genetics and Cell Biology Section (from 1998 to 2009). The Department has been researching the WNT (PMID: 17634527), FGF (PMID: 23696246), Notch (PMID: 17143535) and Hedgehog (PMID: 19860666) signaling cascades and the Forkhead-box (FOX) family of transcription factors (PMID: 23022474). The goal of the Department is the establishment of Knowledgebase focused on the regulatory signaling network for the development of novel diagnostics and therapeutics.

### Fundamental and constitutive projects

WNT, FGF, Notch, Hedgehog and FOX are fundamental and constitutive projects of the Department. The fundamental theme in 2014 was therapeutics targeted to the FGF receptors (FGFRs).

FGFs are involved in a variety of cellular processes, such as stemness, proliferation, anti-apoptosis, drug resistance and angiogenesis. Gene amplification of *FGFR1* occurs in lung cancer and estrogen receptor (ER)-positive breast cancer, and that of *FGFR2* in diffuse-type gastric cancer and triple-negative breast cancer. Chromosomal translocation of *FGFR1* occurs in the 8p11 myeloproliferative syndrome and alveolar rhabdomyosarcoma, as with *FGFR3* in multiple myeloma and peripheral T-cell lymphoma. *FGFR1* and *FGFR3* genes are fused to neighboring *TACC1* and *TACC3* genes, respectively, due to interstitial deletions in glioblastoma multiforme. Missense mutations of *FGFR2* are found in endometrial uterine cancer and melanoma, and similar *FGFR3* mutations in invasive bladder tumors, and *FGFR4* mutations in rhabdomyosarcoma. Dovitinib, Ki23057, ponatinib and AZD4547 are orally bioavailable FGFR inhibitors, which have demonstrated striking effects in preclinical model experiments. Because there are multiple mechanisms of actions for FGFR inhibitors to overcome drug resistance, FGFR-targeted therapy is a promising strategy for the treatment of refractory cancer (Figure 1).

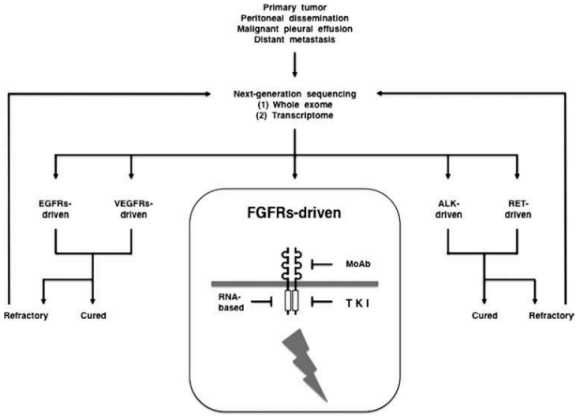


**Figure 1. Perspectives on FGFR-targeted therapeutics**

Whole-exome sequencing combined with transcriptome sequencing will be applied in clinical laboratory test to determine driver mutations in tumor samples. Primary and refractory tumors driven by aberrantly activated FGFRs will be treated with FGFR-targeted therapeutics, such as small-molecule FGFR inhibitor (TKI), human/humanized anti-FGFR monoclonal antibody (MoAb), and RNA-based drug.

### Cutting-edge and mobile projects

Cellular adhesion, epigenetics and microRNA (miRNA) are cutting-edge and mobile projects of the Department. The cutting-edge theme in 2014 was miRNA-based diagnostics.

Cardiovascular diseases and cancers are the leading causes of morbidity and mortality in the world. miR-24, miR-125b, miR-195 and miR-214 were selected as representative cardio-miRs that are upregulated in human heart failure. ACVR1B, BCL2, BIM, eNOS, FGFR3, JPH2, MEN1, MYC,

p16, and ST7L are miR-24 targets that have been experimentally validated in human cells. ARID3B, BAK1, BCL2, BMPR1B, ERBB2, FGFR2, IL6R, MUC1, SITR7, Smoothened, STAT3, TET2, and TP53 are representative miR-125b targets. ACVR2A, BCL2, CCND1, E2F3, GLUT3, MYB, RAF1, VEGF, WEE1, and WNT7A are representative miR-195 targets. BCL2L2, ß-catenin, BIM, CADM1, EZH2, FGFR1, NRAS, PTEN, TP53, and TWIST1 are representative miR-214 targets. miR-125b is a good cardio-miR that protects cardiomyocytes; miR-195 is a bad cardio-miR that elicits cardiomyopathy and heart failure; miR-24 and miR-214 are bi-functional cardio-miRs. By contrast, miR-24, miR-125b, miR-195, and miR-214 function as oncogenic or tumor suppressor miRNAs in a cancer (sub) type-dependent manner. Circulating miR-24 is elevated in diabetes, breast cancer and lung cancer. Circulating miR-195 is elevated in acute myocardial infarction, breast cancer, prostate cancer and colorectal adenoma. Circulating miR-125b and miR-214 are elevated in some cancers. Cardio-miRs and onco-miRs bear some similarities in functions and circulation profiles. Because circulating miRNA profiles are modulated by genetic and environmental factors and are dysregulated by genetic and epigenetic alterations in somatic cells (Figure 2), circulating miRNA association studies (CMASs) within several thousands of cases each for common non-cancerous diseases and major cancers are necessary for miRNA-based diagnostics.

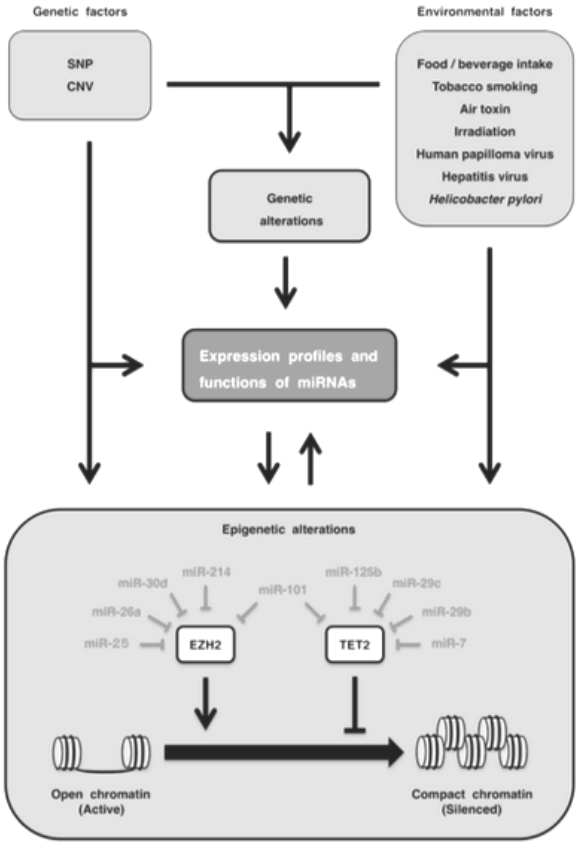


**Figure 2. Regulation of circulating miRNAs**

Genetic factors and environmental factors are involved in the regulation of expression profiles and functions of miRNAs (upper part). miRNA expression is downregulated by epigenetic silencing, while epigenetic regulators are repressed by multiple miRNAs. miRNAs and epigenetics are in the relationship of mutual regulation (lower part). Genetic and environmental factors regulate circulating miRNA profiles directly as well as indirectly through genetic and epigenetic alterations.

**Contribution to the global scientific community**

Masaru Katoh has been contributing to the global scientific community based on manuscript publication, reviewer activity and editor activity. Katoh carried out peer review of grant proposals or journal manuscripts written in English 69 times in 2014. Katoh is an Academic Editor of *PLoS ONE*, and has carried out editorial decision 177 times in 2014. Masaru Katoh is the Chief Editor of *Frontiers in Molecular Medicine* that aims to address the gap between cell and developmental biology and clinical medicine, together with 92 editorial board members.

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 641 times by others in 2014.

## List of papers published in 2014

### Journal

1. Katoh M, Nakagama H. FGF receptors: cancer biology and therapeutics. Med Res Rev, 34:280-300, 2014
2. Katoh M. Cardio-miRNAs and onco-miRNAs: circulating miRNA-based diagnostics for noncancerous and cancerous diseases. Front Cell Dev Biol, 2:61, 2014

### Book

1. Katoh M. WNT signaling in neoplasia. In: Gelmann EP, Sawyers CL, Rauscher FJ III (eds), Molecular Oncology, U.K., Cambridge University Press, pp 243-257, 2014

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 in 2012, which focus on early/exploratory clinical trial and translational research (TR). The NCC-EPOC has been actually activated in April 2013 consisting of a phase I unit in each campus, central/data center function unit for clinical trials, and a translational research (TR) unit. The TR unit additionally included the immunotherapy division in July 2013. For innovative oncology drug developments from Japan, three missions are hung up in the NCC-EPOC: to conduct first-in-human (FIH) trials, investigator-initiated trials (IIT) with unapproved agents, and TRs during early clinical studies. The activity in each unit in 2013 is described as below.

1) Phase I unit: The Experimental Therapeutics Department consisting of several medical oncologists with backgrounds from each organ department was newly organized in both hospitals in order to conduct all comer type FIH/phase I studies. Regular weekly teleconference is held to collaborate the two groups in each hospital. In 2013, 6 sponsor-initiated FIH trials have already been conducted in total at both hospitals. The number of the phase I studies in the NCC is ranked as the largest academic center in Asia. There were several international phase I studies including FIH study.

2) IIT support unit: The central support/data center for IIT has been established with a total of 37 members including project manager, monitor, data manager, biostatistician, medical writer, and auditors. Since launched in 2012, the NCC-EPOC has initiated 14 registrational IITs in accordance with ICH-GCP (so-called "ishi-syudo chiken") with an unapproved agent. Eight of the 18 studies has already completed its accrual in collaboration with several major cancer centers. These IITs are categorized into three group: 4 developmental studies with new academia seeds, 7 exploratory studies unapproved agents developed by industry, and 4 studies as expanded access program for unapproved agents. As for the academic seeds development, 11 seeds are being designated for clinical implications including three seeds already under clinical trials. Alliance contract between the NCC and the National Institute of Biomedical Innovation has been formally achieved for establishing a nation-wide oncology seeds collection network. Intellectual property in the NCC is being integrated for efficient new seeds/drugs development.

3) TR unit: New procedure of companion diagnosis for RET fusion gene, which was originally discovered in the NCC-Research Institute, was established and transferred to a laboratory company, which became a basis of the nation-wide genome screening network (LC-SCRUM). Several pharmaceutical companies, who conducted similar new agent development studies for tiny population with driver gene alterations, joined this network under contract with NCC. A similar screening system for some driver gene has also started in colorectal cancers using original developed screening panel, followed by an organization of nation-wide genome screening academia-industry consortium (SCRUM-JAPAN) using a cutting-edge pan-cancer NGS panel. A total of 13 pharmaceutical companies are collaborating with the consortium for 4,500 patients with lung and gastrointestinal cancer genome screening in association with new agent studies. This study will contribute to make a public data base of genome profiling and a distribution of precision medicine in Japan. In the immunotherapy division, an IIT with an originally developed cancer vaccine has already been studied and a new immune-modulating agent is being developed in collaboration with investigators in the University of Tokyo. Another project of new immune cell therapy with FITC-CART is also under preclinical investigations. A biotech company focusing on the development of new CAR-T therapy was launched in February 2015, which is the first venture company in NCC.

The goal of the NCC-EPOC is to establish a top innovative academic research organization 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

President:
Tomomitsu Hotta

Director:
Atsushi Ohtsu

### Phase I Group

#### Department of Experimental Therapeutics

Chief (Kashiwa): Toshihiko Doi
Chief (Tsukiji): Noboru Yamamoto

##### Clinical Trial Management Office

Chief (Kashiwa): Koichi Goto
Chief (Tsukiji): Noboru Yamamoto

### Translational Research Group

#### Division of Translational Research

Chief (Kashiwa): Katsuya Tsuchihara
Chief (Tsukiji): Takashi Kohno

#### Division of Cancer Immunotherapy

Chief (Kashiwa): Tetsuya Nakatsura
Chief (Tsukiji): Kiyoshi Yoshimura

# Activities of the Divisions

# Department of Experimental Therapeutics

**[Kashiwa] Toshihiko Doi, Yoichi Naito, Kohei Shitara, Hideaki Takahashi, Kiyotaka Yoh, Tomoko Yamazaki Takahiro Kogawa**
**[Tsukiji] Noboru Yamamoto, Kenji Tamura, Yutaka Fujiwara, Shunsuke Kondo, Satoru Iwasa, Shigehisa Kitano, Yuko Tanabe, Akihiko Shimomura**

## Introduction

The NCC-EPOC Phase I Group has been organized to promote the early drug development especially the first in human (FIH) trial in 2012. The Phase I group consisted of two sub-units (NCCE-Kashiwa & NCC-Tsukiji) which are organized by each hospital. The goal of the NCC-EPOC Phase I Group is to perform initial clinical evaluation of promising new anti-cancer compounds emerging from the laboratory. Our Phase 1 unit is the largest program in Japan, indeed in Asia, and we contribute to the development of new cancer drugs through early phase trials.

In April 2013, the Department of Experimental Therapeutics has been launched to strongly promote the EPOC missions as previously described. The members of the Department of Experimental Therapeutics consisted of the specialists of their oncology fields (shown as a staff list).

## Routine activities

The Department plays an important role of the new anti-cancer drug development in our center as well as in Japan. The top priority is to conduct the FIH trials, and we also perform the Phase I trials for solid tumors (i.e., all comers). Recently, we join the global Phase I trial to accelerate the new drug development in Japan. Web- or tel.-conferences are held with the EU and US sites, and we are discussing about the patient enrollment as well as the further developmental strategy. Routine web-conference are also held between Kashiwa and Tsukiji campus every Friday morning, and we are sharing information about adverse event, patient enrollment and are referring the candidate each other to accelerate enrollment.

## Research activities

The elucidation of the proof of concept is essential in the new anti-cancer drug development especially in early phase, we conduct several translational researches in collaboration with the research institute adjoins. In each campus, the comprehensive genomic analyses, those are named as ABC-study and TOP-GEAR-study in Kashiwa and Tsukiji, respectively, are ongoing to facilitate the patient enrollment for the new molecular targeted drugs under investigation.

## Clinical trials

In 2014, 39 Phase I trials have been conducted in both campus (Table 1).

**Table 1. Phase I trials in the Dept. of Experimental Therapeutics in 2014**

| No. | Site | Target | FIH | Target | Enrollment in 2013 | Status |
|---|---|---|---|---|---|---|
| 1 | Kashiwa+Tsukiji | CDDP micelles | | Solid tumors | 5 | Closed |
| 2 | Kashiwa+Tsukiji | CDK4/6 | | Solid tumors | 5 | Closed |
| 3 | Kashiwa+Tsukiji | PD-L1 | | Solid tumors | 16 | Closed |
| 4 | Kashiwa+Tsukiji | FGFR | ○ | Solid tumors | 12 | Closed |
| 5 | Kashiwa+Tsukiji | FGFR | ○ | Solid tumors | 10 | Ongoing |
| 6 | Kashiwa+Tsukiji | PD-1 | | Solid tumors | 23 | Ongoing |
| 7 | Tsukiji | PIM | ○ | Solid tumors | 2 | Closed |
| 8 | Tsukiji | PI3K | | Solid tumors | 2 | Closed |
| 9 | Tsukiji | PARP | | Solid tumors | 3 | Closed |
| 10 | Tsukiji | PI3K | | Solid tumors | 9 | Closed |
| 11 | Tsukiji | CDK4/6 | | Solid tumors | 11 | Closed |
| 12 | Tsukiji | Hedgehog | | Solid tumors | 7 | Closed |
| 13 | Tsukiji | tubulin | | Solid tumors | 3 | Closed |
| 14 | Tsukiji | B7-H3 | ○ | Solid tumors | 3 | Ongoing |
| 15 | Tsukiji | FGFR | ○ | Solid tumors | 2 | Ongoing |
| 16 | Tsukiji | PD-L1 | | Solid tumors | 10 | Ongoing |
| 17 | Tsukiji | HSP90 | ○ | Solid tumors | 9 | Ongoing |
| 18 | Tsukiji | CTLA-4 | | Solid tumors | 6 | Ongoing |
| 19 | Kashiwa | c-Met | | Solid tumors | 0 | Closed |
| 20 | Kashiwa | targeting hypoxia | | Solid tumors | 5 | Closed |
| 21 | Kashiwa | anti-cancer-stem cell | | Solid tumors | 7 | Ongoing |
| 22 | Kashiwa | PTK2 | | Solid tumors | 4 | Ongoing |
| 23 | Kashiwa | FGFR | | Solid tumors | 4 | Ongoing |
| 24 | Kashiwa | epirubicin micelles | | Solid tumors | 9 | Ongoing |
| 25 | Kashiwa | EGFR | | Solid tumors | 13 | Ongoing |
| 26 | Kashiwa | c-Met | | Solid tumors | 17 | Ongoing |
| 27 | Kashiwa | ***** | | Solid tumors | 17 | Ongoing |
| 28 | Kashiwa | TEM-1 | | Solid tumors | 6 | Ongoing |
| 29 | Kashiwa | PI3K | | Solid tumors | 1 | Ongoing |
| 30 | Kashiwa | MEK | | Solid tumors | 2 | Ongoing |
| 31 | Kashiwa | c-Met | | Solid tumors | 5 | Ongoing |
| 32 | Kashiwa | c-Met | | Solid tumors | 3 | Ongoing |
| 33 | Kashiwa | MEK | | Solid tumors | 2 | Closed |
| 34 | Kashiwa | EGFL7 | | Solid tumors | - | Withdrawal |
| 35 | Kashiwa | **** | | Solid tumors | 7 | Ongoing |
| 36 | Kashiwa | FGFR | ○ | Solid tumors | 4 | Ongoing |
| 37 | Kashiwa | IGFIR | | Solid tumors | 5 | Ongoing |
| 38 | Kashiwa | **** | | Solid tumors | 0 | Ongoing |
| 39 | Kashiwa | **** | | Solid tumors | 0 | Ongoing |

FIH: first in human trial

## List of papers published in 2014

## Journal

## Phase I Group (Tsukiji)


1. Kobayashi T, Masutomi K, Tamura K, Moriya T, Yamasaki T, Fujiwara Y, Takahashi S, Yamamoto J, Tsuda H. Nucleostemin expression in invasive breast cancer. BMC Cancer, 14:215, 2014
2. Ono M, Kosaka N, Tominaga N, Yoshioka Y, Takeshita F, Takahashi RU, Yoshida M, Tsuda H, Tamura K, Ochiya T. Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells. Sci Signal, 7:ra63, 2014
3. Hashimoto K, Tsuda H, Koizumi F, Shimizu C, Yonemori K, Ando M, Kodaira M, Yunokawa M, Fujiwara Y, Tamura K. Activated PI3K/ AKT and MAPK pathways are potential good prognostic markers in node-positive, triplenegative breast cancer. Ann Oncol, 25:1973-1979, 2014
4. Takiguchi Y, Sekine I, Iwasawa S, Kurimoto R, Sakaida E, Tamura K. Current status of medical oncology in Japan--reality gleaned from a questionnaire sent to designated cancer care hospitals. Jpn J Clin Oncol, 44:632-640, 2014
5. Hirakawa A, Yonemori K, Kuwatsuka Y, Kodaira M, Yamamoto H, Yunokawa M, Hamada A, Shimizu C, Tamura K, Gemma A, Fujiwara Y. A descriptive analysis of postchemotherapy development of interstitial lung disease using spontaneous reporting data in Japan. Curr Drug Saf, 9:220-226, 2014
6. Katsui Taniyama T, Hashimoto K, Katsumata N, Hirakawa A, Yonemori K, Yunokawa M, Shimizu C, Tamura K, Ando M, Fujiwara Y. Can oncologists predict survival for patients with progressive disease after standard chemotherapies? Curr Oncol, 21:84-90, 2014
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# Division of Translational Research (Kashiwa)

**Katsuya Tsuchihara, Sachiyo Mimaki, Hideki Makinoshima, Shingo Matsumoto, Wataru Okamoto, Atsushi Yagishita, Akiko Nagatsuma, Takayuki Yoshino, Atsushi Watanabe, Kazuyoshi Yanagihara, Yuka Nakamura, Atsushi Ochiai, Takeshi Kuwata, Yasuhiro Matsumura**

## Introduction

Basic and translational researchers at the National Cancer Center (NCC) Kashiwa Campus are involved in this division, the aim of which is to develop novel anti-cancer therapeutics as well as to prove their concepts. The Division also closely collaborates with intramural and extramural clinical research teams to develop a precision medicine of cancer treatment.

## Routine activities

Weekly conferences for the whole division and individual research groups are held. A monthly tele-conference is held with the Division of Translational Research at Tsukiji Campus.

## Research activities

1. Implication of genome biomarkers for cancer therapy
   ABC study, a pilot study in which feasibility and effectiveness of trans-organ multiplex genomic biomarker testing were investigated, has done. More than 250 cases with various solid tumors were analyzed and comprehensive clinical reports were returned to the physicians. Following the success of the study, we plan a nation-wide multi-center genome screening program for advanced lung and gastro-intestinal cancers. We named the program, "SCRUM-Japan" and it will be launched in 2015.
2. Genome-wide identification of the driver gene alterations of small cell lung cancer (SCLC) has done. About 40% of the patients harbored activating alterations of PI3K/AKT pathway molecules and these alterations could be targets for PI3K/MTOR inhibitors. An investigator-initiated trial to prove the efficacy of a PI3K/MTOR inhibitor for SCLC patients with alterations of PI3K/AKT pathway molecules is planned.
3. Comprehensive genome, epigenome and transcriptome analyses of lung adenocarcinoma cell lines performed by next-generation sequencing were finished. This dataset is consisted with multi-omics data of 26 cell lines, and 13 of 26 cell lines were established from Japanese patients' samples which have not been well characterized. All the data are compiled into a database which is open for public (http://dbtss/hgc/jp/) and it is expected to be used for exploring new therapeutic targets and biomarkers.
4. EGFR inhibition for EGFR-mutated lung adenocarcinoma is one the most successful molecular targeted therapies. We identified that EGFR inhibitors suppress lung adenocarcinoma cell-specific activation of aerobic glycolysis via the inhibition of kinase activities of EGFR. These findings highlight the importance of metabolic regulation of cancer cells to achieve therapeutic efficacy in molecular-targeted therapies.

## Clinical trials

1. Analyses of Biopsy Samples for Cancer Genomics (ABC Study): Study representative and secretariat
2. Biomarker Research for Anti-EGFR Monoclonal Antibodies by Comprehensive Cancer Genomics (BREAC Study): Secretariat

## Education

This division accepted and trained the following trainees;

Graduate students from the University of Tokyo (4), Tokyo Medical and Dental University (1), Keio University (1) and Juntendo University (1), Staff physician (2), senior resident (1), junior resident (3), Visiting scientists (6)

## Future prospects

We aim to establish cancer precision medicine using cutting-edge technologies identifying useful molecular biomarkers. As well as exploring and implicating biological findings which stratify each cancer patient, it is important to provide infrastructures to securely and robustly use biomarkers for daily clinical use.

## List of papers published in 2014

### Journal


1. Umemura S, Mimaki S, Makinoshima H, Tada S, Ishii G, Ohmatsu H, Niho S, Yoh K, Matsumoto S, Takahashi A, Morise M, Nakamura Y, Ochiai A, Nagai K, Iwakawa R, Kohno T, Yokota J, Ohe Y, Esumi H, Tsuchihara K, Goto K. Therapeutic priority of the PI3K/AKT/mTOR pathway in small cell lung cancers as revealed by a comprehensive genomic analysis. J Thorac Oncol, 9:1324-1331, 2014
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3. Suzuki A, Makinoshima H, Wakaguri H, Esumi H, Sugano S, Kohno T, Tsuchihara K, Suzuki Y. Aberrant transcriptional regulations in cancers: genome, transcriptome and epigenome analysis of lung adenocarcinoma cell lines. Nucleic Acids Res, 42:13557-13572, 2014
4. Nasuno T, Mimaki S, Okamoto M, Esumi H, Tsuchihara K. Effect of a poly(ADP-ribose) polymerase-1 inhibitor against esophageal squamous cell carcinoma cell lines. Cancer Sci, 105:202-210, 2014

# Division of Translational Research (Tsukiji)

**Takashi Kohno, Hitoshi Ichikawa, Akinobu Hamada, Shuichi Shinma, Natsuko Hama, Yuka Kitamura, Yusuke Yoshioka, Tatsuhiro Shibata, Hiroki Sasaki**

## Introduction

This division facilitates early phase clinical trials by conducting translational research (TR) focusing on the development of therapeutic and companion diagnostic seeds and the discovery of biomarkers.

## Research activities

Clinical sequencing for early phase clinical trials

A next generation sequencer-based clinical sequencing, which enables us to identify genetic alterations, including gene fusions in 90 cancer-related genes, were applied to analyze 130 cases of advanced cancers in the TOPICS-1 (Trial of Onco-Panel for Introduction into Clinical Study-Phase 1) study (Figure 1). The actionable gene aberrations were defined in Expert Panel meetings to subject patients to phase I clinical trials to address "proof-of-concept" of the relationship between gene aberrations and therapeutic effects. Gene aberrations with therapeutic implications were found in about a half of cases, and <10% of patients were enrolled into phase I clinical trials according to "match" between genetic alterations and drug targets.

Novel Pharmacodynamic analysis for the development of new anticancer agents

Drug exposure and distribution in several tissues impact pharmacology, toxicology, and efficacy in drug development. MALDI (matrix-assisted laser desorption ionization) Mass Imaging system enables us to evaluate concentrations and spatial distributions of anticancer agents and metabolites within target tumor tissues. Procedures of processing of tumor tissues, analysis, and data processing have been set for the analysis of patient samples.

Preclinical Studies Using Newly Established Gastric Cancer Cell Lines

Tens of cell lines of gastric cancer of Japanese patients were obtained by culturing tumor samples, since such cell lines had not been available up to the present. Omics analysis, such as expression profiling and NGS-based mutation screening, were conducted to obtain basic information on these cell lines. In vitro and in vivo preclinical studies of molecular-targeted drugs are being conducted by collaborative studies with pharmaceutical industries to deriver new therapeutic agents to early phase clinical trial projects in EPOC.

## Education

Graduate students, post-doctoral fellows, and chief residents in NCC were educated through the "on the job training" in several translational research projects.

## Future prospects

Feasibility of clinical sequencing in academic institutions has been shown by our study. The next step is to establish quality assurance and accuracy to apply to cancer clinic in NCC. Early phase clinical trials will further progress through utilization of Mass Imaging as well as original cancer cell lines.

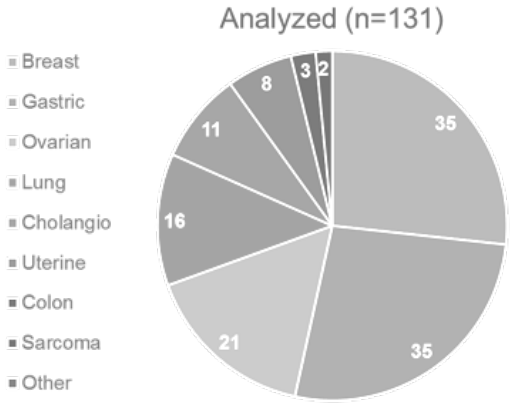


**Figure 1. Subjects enrolled into the TOPICS-1 study**

## List of papers published in 2014

## Journal


1. Hirakawa A, Yonemori K, Kuwatsuka Y, Kodaira M, Yamamoto H, Yunokawa M, Hamada A, Shimizu C, Tamura K, Gemma A, Fujiwara Y. A descriptive analysis of postchemotherapy development of interstitial lung disease using spontaneous reporting data in Japan. Curr Drug Saf, 9:220-226, 2014
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# Division of Cancer Immunotherapy

**Tetsuya Nakatsura, Yasushi Uemura, Toshiaki Yoshikawa, Keigo Saito, Manami Shimomura, Shoichi Mizuno, Yumi Tokumitsu, Kayoko Shoda, Yukiko Kozaki, Yoshitaka Tada, Tatsuaki Iwama, Norihiro Fujinami, Shiori Sugai, Nobuhiro Tsuchiya, Kaori Kobayashi, Megumi Ozaki**

## Introduction

Our Division aims to investigate evidenced-based cancer immunotherapy, repeating basic research and translational research. The Division is focused on developing not only more effective immunotherapies but also immunological method for suppression of recurrence or for cancer prevention.

## Research activities

Specific cellular immunotherapy for cancer requires efficient generation and expansion of cytotoxic T lymphocytes (CTLs) that recognize tumor-associated antigens. However, it is difficult to isolate and expand functionally active T-cells *ex vivo*. We investigated the efficacy of a new method to induce expansion of antigen-specific CTLs for adoptive immunotherapy. We used tumor-associated antigen glypican-3 (GPC3)-derived peptide and cytomegalovirus (CMV)-derived peptide as antigens. Treatment of human peripheral blood mononuclear cells (PBMCs) with zoledronate is a method that enables large-scale γδ T-cell expansion. To induce expansion of γδ T cells and antigen-specific CTLs, the PBMCs of healthy volunteers or patients vaccinated with GPC3 peptide were cultured with both peptide and zoledronate for 14 days. The expansion of γδ T cells and peptide-specific CTLs from a few PBMCs using zoledronate yields cell numbers sufficient for adoptive transfer. The rate of increase of GPC3 specific CTLs was approximately 24- to 170,000-fold. This study indicates that simultaneous expansion of γδ T cells and peptide-specific CTLs using zoledronate is useful for adoptive immunotherapy (1).

Lung cancer is the leading cause of cancer related deaths worldwide. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib, have demonstrated marked clinical activity against non-small cell lung cancer (NSCLC) harboring activating epidermal growth factor receptor (EGFR) mutations. However, in most cases, patients develop acquired resistance to EGFR TKI therapy. The threonine to methionine change at codon 790 of EGFR (EGFR T790M) mutation is the most common acquired resistance mutation, and is present in ~50% cases of TKI resistance. New treatment strategies for NSCLC patients harboring the EGFR T790M mutation are required. We evaluated the immunogenicity of an antigen derived from EGFR with the T790M mutation. Using BIMAS we selected several EGFR T790M derived peptides bound to human leukocyte antigen (HLA)-A*02:01. T790M-A peptide (789-797) (IMQLMPFGC)-specific CTLs were induced from PBMCs of HLA-A2+ healthy donors. An established T790M-A-specific CTL line showed reactivity against the NCSLC cell line, H1975-A2 (HLA-A2+, T790M+), but not H1975 (HLA-A2-, T790M+), and the corresponding wild-type peptide (ITQLMPFGC)-pulsed T2 cells using an interferon-γ (IFN-γ) enzyme-linked immuno spot (ELISPOT) assay. This CTL line also demonstrated peptide-specific cytotoxicity against H1975-A2 cells. This finding suggests that the EGFR T790M mutation-derived antigen could be a new target for cancer immunotherapy (2).

We previously reported that heat shock protein 105 (HSP105) is overexpressed in a variety of human cancers, including colorectal, pancreatic and esophageal cancer and has proven to be a novel biomarker for the immunohistochemical detection of these cancers. We used HLA-transgenic mice (Tgm) and the PBMCs of colorectal cancer patients to identify HLA-A2 and HLA-A24-restricted HSP105 epitopes, as a means of expanding the application of HSP105-based immunotherapy to HLA-A2- or HLA-A24-positive cancer patients. In addition, we investigated by *ex vivo* IFN-γ ELISPOT assay whether the HSP105-derived peptide of cytotoxic T cells (CTLs) exists in PBMCs of pre-surgical colorectal cancer

patients. We found that four peptides, HSP105 A2-7 (RLMNDMTAV), HSP105 A2-12 (KLMSSNSTDL), HSP105 A24-1 (NYGIYKQDL) and HSP105 A24-7 (EYVYEFRDKL), are potential HLA-A2 or HLA-A24-restricted CTL HSP105-derived epitopes (3).

GPC3 is expressed by>40% of ovarian clear cell carcinoma (CCC) and is a promising immunotherapeutic target. Therefore, we conducted a phase II trial to evaluate the clinical outcome of ovarian CCC patients treated with a GPC3-derived peptide vaccine. The GPC3 peptide was administered at a dose of 3 mg per body. Patients received an intradermal injection of the GPC3 peptide emulsified with incomplete Freund's adjuvant. Vaccinations were performed biweekly from the first until the 6th injection and were then repeated at 6-week intervals after the 7th injection. Treatment continued until disease progression. We herein present two patients with chemotherapy-refractory ovarian CCC who achieved a significant clinical response in an ongoing trial of a GPC3 peptide vaccine. Case 1, a 42-year-old patient with advanced recurrent ovarian CCC with liver and retroperitoneal lymph node metastases, received the HLA-A24-restricted GPC3 peptide vaccine. Contrast-enhanced CT at week 10 revealed a partial response (PR) using RECIST criteria. Case 2 was a 67-year-old female with multiple lymph node metastases. She was injected with the HLA-A2-restricted GPC3 peptide vaccine. According to RECIST, PR was achieved at week 37 (4).

## Clinical trials

We completed Phase II study of GPC3 peptide vaccine as adjuvant treatment for HCC after surgical resection or RFA and Phase I study of peptide cocktail vaccine for patients with refractory pediatric sarcoma. We are performing 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 2014

### Journal


1. Yoshikawa T, Takahara M, Tomiyama M, Nieda M, Maekawa R, Nakatsura T. Large-scale expansion of γ δ T cells and peptide-specific cytotoxic T cells using zoledronate for adoptive immunotherapy. Int J Oncol, 45:1847-1856, 2014
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# Research Center for Cancer Prevention and Screening

# Preface

The Research Center for Cancer Prevention and Screening (RCCPS) was established in February 2004 to research effective cancer prevention and screening methods, and create a scientific basis for the efficient dissemination of these methods to the public. As of 2013, the organization consisted of the following: the Epidemiology and Prevention Group (Division of Prevention and Division of Epidemiology), the Screening Research Group (Division of Screening Assessment and Management and Division of Screening Technology and System Development), the Common Research Group (Division of Public Health Policy), and the Division of Cancer Screening which is responsible for carrying out cancer screenings. Our mission is to advance cancer prevention and screening research in order to provide correct information and the most appropriate methods for preventing cancer cases and fatalities to the greatest degree possible.

The Epidemiology and Prevention Group consists of the Division of Epidemiology which mainly conducts evidence-building that contributes to the investigation of cancer causes and the clarification of pathologic conditions and the Division of Prevention which conducts the development of evidence-based prevention methods; both Divisions mutually cooperates to fulfill the group's mission. In 2014, the Division of Epidemiology pursued continuous, long-term epidemiological studies of various sizes such as the Japan Public Health Center-based Prospective Study (JPHC Study) and the JPHC Study for the Next Generation (JPHC-NEXT), and published analyses of the accumulated data sets. In addition, utilizing the know-how gained from managing large-scale, long-term cohort studies, the Division completed the drafting of standardized protocols for new molecular epidemiology cohort studies as well as a highly-acclaimed project that will form the basis for unifying the existing cohort data. On the other hand, the Division of Prevention played a central role in systematically collecting research results especially at the national level and evaluating anti-cancer effects and carcinogens, ultimately recommending (updating) prevention guidelines for the Japanese public. In addition, based on the results of the cohort studies, the Division developed and released the "Cancer Risk Check," a series of diagnostic tools available online that determine cancer risks. The Group also participated in international projects that contribute to cancer prevention worldwide.

With the aim of reducing cancer mortality rates, the Screening Research Group (Division of Screening Assessment and Management) promotes cancer screening assessments, cancer screening implementation management, and screening as a countermeasure to cancer. While the Division has been conducting continuous researches like randomized controlled trials on cancer screening and investigations into the effectiveness of various cancer screenings, in this fiscal year, the Division also achieved the publication of updated gastric cancer screening guidelines. Using checklists, the Division conducted investigations into municipal public screenings, evaluations and training workshops for the standardization of cancer screening accuracy control, and the standardization of improvements to Quality Assurance (QA) and Quality Assurance (QA) accuracy control. The Division also updated its website contents for relevant government personnel. Moreover, as a measure for increasing cancer screening consultation rates and as an investigation into cancer screening provision systems, the Division conducted a comparative study of cancer screening provision systems in Asia and Oceania.

The Common Research Group (Division of Public Health Policy Research) conducts research for the dissemination of scientific evidence concerning the public health field (cancer prevention, screening, and survival). To establish a research infrastructure, the Division also conducts methodological researches on behavioral science, epidemiology, and statistics, supports and accumulates know-how from large-scale interventional studies, and teaches medical research methodologies. The Division supports municipalities, and develops and provides tools for further cancer screening and consultation awareness. Starting in this fiscal year, it implemented model programs in five prefectures that achieved definite results.

Furthermore, in this fiscal year, the Division released its children's cancer education comics as e-books to promote their use, and conducted two evaluation studies.

In addition, the Division also registered 4,100 patients (cumulative total) in a breast cancer cohort study. Regarding human resources development, it created 45 units of new content for distribution on an e-learning site for clinical research education and developed an iPhone application.

The Division of Screening Practice conducts cancer screenings with the primary goal of research based on the comprehensive consent of screening participants. In the fiscal year 2013, malignant tumors were detected in 37 people out of 489 new participants and1,467 repeat participants (8 people among new participants and 29 people among repeat participants) who underwent RCCPS screenings. Detection rates were 1.64% and 1.98%, respectively. As part of its research, the Division is continuously conducting evaluations of pulmonary nodules in lung cancer CT screenings. In addition, it has introduced tomosynthesis mammography cameras and ultrasound automated breast volume scanners in breast cancer screenings and begun evaluating their clinical utility.

Research results are returned to the public through paper publications, conference presentations, lectures, information on Cancer Information Service by the Center for Cancer Control and Information Services, and other websites, leaflets and pamphlets, etc. To achieve our mission, all members of the RCCPS share a strong will to keep moving forward steadily and diligently.

Shoichiro Tsugane, M.D., D.M.Sc.
Director, Research Center for Cancer Prevention and Screening

## Organization

President:
Tomomitsu Hotta

Director:
Shoichiro Tsugane

- Epidemiology and Prevention Research Group
  - Chief: Shoichiro Tsugane
    - Division of Epidemiology
      Chief: Motoki Iwasaki
    - Division of Prevention
      Chief: Shizuka Sasazuki
- Screening Assessment and Management Group
  - Chief: Hiroshi Saito
    - Division of Screening Assessment and Management
      Chief: Hiroshi Saito
    - Division of Screening Technology and System Development
      Chief: Hiroshi Saito
- Research Infrastructure Group
  - Chief: Shoichiro Tsugane
    - Division of Public Health Policy Research
      Chief: Seiichiro Yamamoto
- Deputy Director:
  Yasuaki Arai
  - Division of Screening Practice
    Chief: Yukio Muramatsu

# Activities of the Divisions

# Division of Epidemiology

**Motoki Iwasaki, Norie Sawada, Taiki Yamaji, Izumi Mishiro, Sanjeev Budhathoki, Thomas Svensson, Kayo Ohashi, Yuri Ishii, Tomomi Mukai, Jun Umesawa, Hiroko Ogata, Yurie Shinozawa, Izumi Matsumoto**

## Introduction

Research is conducted aimed at constructing evidence connected to the development of cancer prevention by clarifying the causes of cancer in humans by using a study base of large-scale cohort study and others of local residents.

## Research activities

1. Japan Public Health Center-based Prospective Study (JPHC study) / JPHC Study for the NEXT Generation (JPHC-NEXT)

Follow-up surveys and data analysis of the Japan Public Health Center-based Prospective Study (JPHC study) with 140,000 local residents as subjects have been conducted continuously since 1990. This year, we reported results such that we observed no evidence of a protective association between soy food or isoflavone intake and endometrial cancer risk; and that dietary fiber is inversely associated with advanced prostate cancer.

Structuring of the cohort for the JPHC Study for the NEXT Generation (JPHC-NEXT) is proceeding according to schedule with the recruitment of participants currently underway by obtaining questionnaire information from about 76,000 participants, and by obtaining biological samples and information from about 38,000 participants (Table).

2. The Program to Improve Preventive Medicine by Analysis of Cohort Data Linked to Medical Records

We clarified issues and problems for the purpose of promoting a large-scale molecular epidemiologic cohort study in Japan, and at the same time, we proposed an implementation system necessary for the realization and implementation of a consortium formation based on large scale molecular epidemiologic cohort studies. We also obtained a comprehensive evaluation of "S" in post-project evaluation.

3. Molecular epidemiologic studies to investigate the cause of cancer through means such as omics data analysis

We identified new susceptibility loci in Asians through genome-wide association studies of breast cancer and colon cancer conducted through international collaborative research.

4. Research by the Research Center for Cancer Prevention and Screening (RCCPS) on examinees who have undergone cancer screening

Through a case-control study of colorectal adenoma in colonoscopy examinees, we reported an association between coffee consumption and reduced risk of adenoma and an association between the intake of processed meats and heterocyclic amine and an increased risk of adenoma in women.

5. Epidemiologic studies of immigrants of Japanese descent

Comparison of plasma levels of nutrient-related biomarkers among Japanese populations in Tokyo, Japan, São Paulo, Brazil, and Hawaii, USA, was conducted and we reported that the highest level of blood carotenoid concentration was found in the Japanese population in Sao Paulo.

## Education

- Supervised the research of two research resident fellowships and one graduate student. Supervised the education of one medical student of short-term trainee.
- Dispatched Dr. Norie Sawada, Section Head, to Imperial College London in England to carry out The European Prospective Investigation into Cancer and Nutrition (EPIC) from September 2, 2014 to March 6, 2015.

## Future Prospects

While focusing on the cohort structure of the JPHC Study for the Next Generation (JPHC-NEXT) that becomes the study base, we hope to contribute to the development of cancer prevention through the analysis of information and samples of existing epidemiologic studies by identifying new risk factors and the continued evaluation of risks in Japanese people.

**Table 1. Progress of the JPHC for the NEXT generation (JPHC-NEXT)**

| Area | Total number of questionnaire | Total number of questionnaire and biospecimen | Status of data collection |
|---|---|---|---|
| Akita, Yokote | 26,752 | 11,077 | Ongoing |
| Nagano, Saku | 31,395 | 13,333 | Completed |
| Ibaraki, Chikusei | 9,172 | 7,124 | Ongoing |
| Kochi, Konan | 3,840 | 1,594 | Completed |
| Kochi, Aki | 1,799 | 1,799 | Ongoing |
| Nagasaki (2014~) | 1,031 | 1,031 | Ongoing |
| Ehime, Ohzu (2014~) | 2,382 | 2,382 | Ongoing |
| Total | 76,317 | 38,340 | |

## List of papers published in 2014

## Journal


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# Division of Prevention

**Shizuka Sasazuki, Taichi Shimazu, Michihiro Mutoh, Charvat Hadrien, Akihisa Hidaka, Yoshitaka Tsubono, Masayuki Tatemichi, Junko Ishihara, Minatsu Kobayashi, Ribeka Takachi, Azusa Hara, Manami Inoue, Yingyan Gong, Eiko Saito, Issei Ezawa, Ruri Nakanishi, Rikako Ishigamori, Masami Sakano, Ayaka Miura, Ayako Toyama, Yasuko Iba, Michiko Okajima, Yuko Kato**

## Introduction

The Epidemiology and Prevention Division has conducted research activities as one division until May, 2013 and was then recognized as two divisions. Prevention Division focuses on prevention researches to investigate and develop prevention methods (lifestyle, chemoprevention, molecular marker etc.), risk prediction, risk stratification models, and evidence-based cancer prevention guideline.

## Research activities

Evaluation of cancer prevention strategies in Japan and cancer prevention guideline

To develop an evidence-based cancer prevention strategy in Japan, a systematic review of epidemiological research was conducted. The strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report, in which evidence was classified as 'convincing','probable', 'possible' and 'insufficient' . Through this method, diabetes was evaluated to have a "probable" effect on increasing the risk of liver cancer. Red meat was evaluated to have a "probable" effect on increasing the risk of colorectal cancer. A decrease in risk for breast cancer with consumption of soy products was "possible."

An evidence based, currently recommended cancer prevention guideline, 'Cancer prevention guideline for Japanese' was updated to meet the latest evaluation of evidence.

Pooled analysis of Japanese Cohort Studies and Asia Cohort Consortium

To obtain summary estimates of the relationship between factors and cancer, pooled analysis of Japanese cohort studies were conducted. As of 2014 November, 10 cohort studies namely, the Japan Public Health Center-based Prospective Study, Cohort I (JPHC-I) and Cohort II (JPHC-II); the Japan Collaborative Cohort Study; the Miyagi Cohort Study; the Three-Prefecture Miyagi; the Ohsaki National Health Insurance Cohort Study; the Three-Prefecture Aichi; the Takayama Study; the Three-Prefecture Osaka; and the Life Span Study (being processed) were participated in this pooling project. Based on pooled analysis of eight cohort studies, an increased risk of postmenopausal breast cancer among women with higher BMIs was confirmed among Japanese. In addition, we reported a significant positive association between BMI and premenopausal breast cancer, suggesting that body mass in Asian women might have different effects on breast cancer compared with Western women. Based on another pooled analysis of four cohort studies, we reported that vegetable intake reduce gastric cancer risk, especially the risk of distal gastric cancer among men.

The Asia Cohort Consortium (ACC) is a collaborative effort seeking to understand the relationship between genetics, environmental exposures, and the etiology of disease through the establishment of a cohort of at least one million healthy people around the Asian countries. The ACC Coordinating Center has been established at the Fred Hutchinson Cancer Research Center and moved to the Prevention Division in 2014. The data analysis system on site and via remote access is now under construction. Burden of total and cause-specific mortality related to tobacco smoking among adults aged 45+ years in Asia was estimated. Among men, approximately 11.4%, 30.5%, and 19.8% of deaths due to cardiovascular diseases, cancer, and respiratory diseases, respectively, were shown to be attributable to tobacco smoking.

Development of prevention measures based on interventional research

We reported that aspirin suppresses the occurrence of new adenomas in patients with a history of multiple colorectal adenomas through a double-blind, randomized clinical trial. Now, we are trying to evaluate whether interval colonoscopy with polypectomy allows a safe strategy different from surgery to prevent development of colorectal cancer in familial adenomatous polyposis patients who decline surgery. Another clinical research aimed to develop colorectal cancer chemopreventive drugs is in progress.

Population-based Prospective Study (the JPHC study and the JPHC-NEXT Study) (primarily the development of preventive measures such as risk prediction; searching for chemoprevention candidates and the establishment of an integrated methodology for data harmonization)

Based on a nested case-control study of the JPHC Study, it was shown that plasma insulin is positively associated with two- fold increased risk of gastric cancer. In men, C-peptide and higher HOMA-IR were also positively associated with a significant risk, which suggested that Japanese population with higher insulin and C-peptide levels derived from insulin resistance have an elevated risk of gastric cancer. Based on another nested case-control study of the JPHC Study, considering gene-environmental interaction, ADH1C G allele carriers who drink ≥150g/week of ethanol had a 2.5-fold increased risk of gastric cancer relative to AA genotype carriers who drink 0 to <150g/week (P for interaction = 0.02). ALDH2 A allele carriers who drink ≥150g/week also had an increased risk relative to GG genotype carriers who drink 0 to <150g/week (P for interaction = 0.08).

In addition, we started research on collecting stomach cancer tissue in order to consider subtypes of tumors by molecular biomarkers which can be derived through mutational analysis of oncogenes or tumor suppressor genes in tumor tissues and the analysis of epigenetic abnormalities such as CpG island methylator phenotype (CIMP).

A standard protocol for a genomic epidemiological cohort study in Japan is projected to be developed based on the JPHC-NEXT protocol. The method for calibration of data derived from different questionnaires and the results of analysis were reported.

## Education

Instructed data analysis, scientific paper-writing, and conference presentation for a research resident and led to submission of two scientific papers (results are mentioned in the eariler section: the JPHC Study). The presentation of one of his works was registered as 'Selected Paper Workshop' in the 25th Annual Scientific Meeting of the Japan Epidemiological Association. Provided data analysis guidance to a Central Hospital resident.

## Future prospects

We will focus on research for the development of effective cancer prevention strategies. In addition to current established evidence, new perspectives such as biomarkers from blood and tumor tissues will be incorporated. This approach may lead to more accurate cancer prevention strategy by risk stratification. Also, we continuously expand human resource development in the relating field.

## List of papers published in 2014

## Journal


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# Division of Screening Assessment and Management

**Hiroshi Saito, Chisato Hamashima, Kumiko Saika, Chikako Yamaki, Ryoko Machii, Koichi Nagata, Ayako Aoki, Yoshiki Ishikawa, Sayuri Amanuma, Junko Asai, Kanoko Matsushima, Kazuko Matsuda, Noriaki Takahashi, Akiko Totake , Keiko Kawarabata**

## 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 2007 and revised in 2012. Thus, the Screening Assessment and Management Division has developed and updated screening guidelines (Cancer Screening Assessment) and constructed quality assurance systems for the screening programs (Cancer Screening Management).

## Routine activities

- Development of cancer screening guidelines

Guidelines on screening for gastric cancer have been developed and will be published in 2015.

- Quality Assurance (QA) in cancer screening at municipalities

The Division collected the information related to implementation of cancer screening and its management situation using Checklists (CLs) as a structure indicator in QA 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 goodness so that each city compares its indicator with those of other cities. CLs score in 2014 collected this year were improved by 5-8% for 5 cancer screening programs as compared to those in 2009. An additional survey on prevalence of a call-recall system, which is essential for high screening participation rate, revealed only less than 5% of municipalities have been fully equipped with the system. The data is used for interim evaluation of progress status of the Basic Cancer Control Plan.

The Division set up the website which allows support toward municipalities such as provision of their QA data archives and information relevant to cancer screening. In this year, the manual of QA for staffs at each municipality was placed on the website. CLs data were collected from municipalities and evaluation results were fed back on the website. 1414 municipalities (81%) utilized the website by registering as members of the site.

- Workshop on cancer screening management

The Division held one-day educational workshops for the members of prefectural committees of cancer screening management, aiming at activating QA activities in each of 47 prefectures. The themes this year were stomach and colorectum. The main contents of the workshops were the methods of quality assurance of the screening programs within each prefecture. Other basic issues required to conduct organized cancer screening programs such as those issues of screening assessment were also included in the contents. As of this year, the Division added a similar workshop targeting the new members of cancer control section at each prefectural government.

There were 63 participants in the workshops from 34 prefectures, who consisted of administrative officers (51%) and members of the committee (49%). This activity was performed as the project of the Center for Cancer Control and Information Services and will be continued on an annual basis.

According to the survey on the activity of the prefectural committees, 36 to 38 prefectures

held the meeting to discuss on cancer screening management and 25 to 27 ( 9 to 22 in the previous year) released the evaluation results of municipalities using CLs for each of 5 cancers. These figures have been increasing after starting the workshop suggesting the effect of the previously held workshop on the activity of the committees.

## Research activities

- A randomized controlled trial (RCT) of colonoscopic screening and other RCTs

A randomized controlled trial evaluating one-time colonoscopic screening for colorectal cancer was started in 2009. The division has been responsible for designing and managing the study as the head office of the study. The cumulative number of subjects who gave informed consent, and who were thus enrolled in the study, was 7,680 at December 2014, corresponding to 77% of the planned number. Data monitoring results showed randomization has been performed successfully. No serious adverse effect was reported on screening colonoscopy. The Division has participated also in other RCTs (breast cancer and lung cancer screening) as a member of headquarters of the research and supported those studies.

- Evaluation and accuracy studies on gastric cancer screening

A community-based, cohort study was conducted to evaluate the effectiveness of endoscopic screening in Niigata city. The 57% mortality reduction from gastric cancer was suggested by endoscopic screening for gastric cancer.

## List of papers published in 2014

### Journal


1. Ishida T, Suzuki A, Kawai M, Narikawa Y, Saito H, Yamamoto S, Tohno E, Sobue T, Fukuda M, Ohuchi N. A randomized controlled trial to verify the efficacy of the use of ultrasonography in breast cancer screening aged 40-49 (J-START): 76 196 women registered. Jpn J Clin Oncol, 44:134-140, 2014
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# Division of Public Health Policy Research

**Seiichiro Yamamoto, Yuri Mizota, Michiyo Tada, Takako Osato, Hiromi Koitabashi, Yoko Takahashi, Kumiko Toshima, Rika Nakamura**

## Introduction

The Division of Public Health Policy Research was established in June 2013. The Division investigates the methods of distribution and dissemination of scientific evidence concerning cancer prevention, screening, and survivorship. The aim of the research is to fill the gap between the scientific evidence and the behavior of people for cancer prevention and screening by supporting local government and directly approaching to the public. In addition, because of the lack of evidence, we try to establish scientific evidence for cancer survivorship.

As for the activity for establishing research infrastructure, we conduct methodological research and education concerning behavior science, epidemiology and biostatistics and support large scale interventional studies.

## Research concerning promotion of cancer prevention and screening using social marketing method

The examples of the achievement of this year for promoting cancer screening participation are as follows: development of materials for client reminder such as the leaflets for stomach and lung cancer, the post cards for colorectal, breast, and cervical cancer, and the envelops (Figure 1), support of the local municipalities by conducting workshops 9 times and disseminate information from the website. In addition, we evaluated the participation rates of cancer screening for 5 model municipalities which we supported in 2013 and obtained increased participation rates for almost all the cities and towns. To promote cancer education for kids, we developed an e-book version of "Gan no Himitsu (Secret of Cancer)" which we had developed last year as a comic style education material. It is available from the website (http://kids.gakken.co.jp/index.html) and also by downloading its application for smartphone for free of charge. We promoted the book strategically using newspaper, radio, magazine, and website. We are also planning to conduct research for the promotion of participation for the HCV testing in collaboration with local municipalities in order to prevent liver cancer.

## Research for cancer survivorship

A large cohort is being established for breast cancer patients, to investigate the effect of lifestyle and psychosocial factors on their QOL and prognosis. The cohort consists of several sub-cohorts including collaborative cohorts of clinical trials, a cohort in the National Cancer Center, and a collaborative cohort with Setouchi cancer registry. As of February 2015, we recruited more than 700 breast cancer patients this year and 4,100 patients in total. The cohort became one of the largest patient cohorts in the world. We are planning to extend the cohorts for other cancer such as colon and rectum.

## Education of staffs involved in clinical research

We develop an e-learning website for the education of staffs involved in clinical research such as researchers, data managers, clinical research coordinators, and members in institutional review boards. ICRweb (http://icrweb.jp) provides more than 120 contents. As of February 2015, more than 8,000 new users were registered this year and more than 35,000 users were registered in total. We conducted 11 seminars and provided 45 new contents from the website. In order to improve convenience of the users, we developed iPhone applications as well.


**Figure 1. Leaflets for client reminder for stomach and lung cancer screening**


**Figure 2. Postcards for client reminder for breast, colorectal, and cervical cancer screening**


**Figure 3. Envelops for client reminder for lung cancer screening**

## List of papers published in 2014

### Journal

1. Ishida T, Suzuki A, Kawai M, Narikawa Y, Saito H, Yamamoto S, Tohno E, Sobue T, Fukuda M, Ohuchi N. A randomized controlled trial to verify the efficacy of the use of ultrasonography in breast cancer screening aged 40-49 (J-START): 76 196 women registered. Jpn J Clin Oncol, 44:134-140, 2014

# Division of Screening Practice

**Yukio Muramatsu, Ryutaro Kakinuma*, Takashi Terauchi*, Gen Iinuma*, Nachiko Uchiyama*, Yasuo Kakugawa*, Minoru Machida*, Seiko Kuroki*, Yosuke Otake*, Takehiro Izumo*, Minori Matsumoto, Tomoyasu Kato*, Mitsuya Ishikawa*, Syunichi Ikeda*, Yasuaki Arai* (*NCCH)**

## Introduction

The Division of Screening Practice moved in the first floor of the Sinryoto in April, 2014. But, CT, PET, gynecological examination, barium enema and endoscopy were carried out at the National Cancer Center Hospital except for ultrasonography, mammography and blood and urinary sampling. 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. 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, 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 before 2013 has been planned for applicants 40 years or older who give written informed consent for the screening, including blood samples for genetic analysis, and who take the questionnaire survey concerning lifestyles. These study protocols have been approved by the Institutional Review Board (IRB). Applicants who have been diagnosed as having cancer, and/or have a history of cancer treatment, such as surgery or endoscopic mucosal resection or chemotherapy within the previous one year, are excluded. On the other hand, there is not condition setting to receive cancer screening programs about the new participants after May, 2014. But an inclusion agreement about the study is optionally demanded.

3. Cancer screening methods

In the multiphasic cancer screening programs, CT for lung cancer, abdominal US for cancer of the liver, gall bladder, pancreas, and kidney, gynecological examinations with Pap-smear and HPV test for uterus cancer, and MMG and US for breast cancer are performed on the first day. On the following day, gastroscopy for cancer of the esophagus and stomach, and total colonoscopy for cancer of the colon and rectum are conducted. If a barium enema is chosen, the examination is carried out on the third day. Moreover, from the beginning of December 2010, CT-colonography (CTC) has been provided as an optional method for cancer screening. FDG-PET is offered on the first day as an option, if the participants wish to undergo the examination. In addition, the one day cancer screening programs with the combination of gastrointestinal endoscopic examinations and other methods except PET or the combination of PET and other methods except for total colonoscopy were newly started in May, 2014.

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 2014 patients. We have therefore presented confirmed data from the previous year. 1,956 participants underwent multi-phasic programs (new, 489; repeater, 1467) in the research data. Malignant tumors were detected in 8 out of

489 new participants and in 29 out of 1467 repeaters who underwent multi-phasic clinical programs in 2013(Tables 1 and 2). Detection rates were 1.64% and 1.98%, respectively.

## Research activities

1. The first breast tomosynthesis system in Japan was installed at the 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. From May, 2014 in breast cancer screening, the examination that combined tomosynthesis with automated breast volume scanner (ABVS) began. The sensitivity and specificity of tomosynthesis in comparison with ABVS and pathological findings are in the process of evaluation.
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. The follow-up system of pulmonary solitary solid nodules for evaluation of growth is being developed with CANON.

## Future prospects

Based on cancer screening data such as an examination result, medical institution findings, follow-up findings, the questionnaire survey concerning lifestyles for 10 years, the effective evaluation of chest CT, endoscope and PET-CT are enabled.

**Table 1. Cancerous detection rate in new participants (2013.4.1-2014.3.31)**

| | No. of cancerous cases | No. of new participants | Detection rate (%) |
|---|---|---|---|
| prostate | 2 | 313 | 0.64 |
| colo-rectum | 2 | 489 | 0.41 |
| esophagus | 1 | 489 | 0.20 |
| stomach | 1 | 489 | 0.20 |
| lung | 1 | 489 | 0.20 |
| pharynx | 1 | 489 | 0.20 |
| Total | 8 | 489 | 1.64 |

**Table 2. Cancerous detection rate in repeat participants (2013.4.1-2014.3.31)**

| | No. of cancerous cases | No. of new participants | Detection rate (%) |
|---|---|---|---|
| breast | 7 | 496 | 1.41 |
| prostsate | 6 | 971 | 0.62 |
| stomach | 7 | 1467 | 0.48 |
| colo-rectum | 5 | 1467 | 0.34 |
| liver | 1 | 1467 | 0.07 |
| kidney | 1 | 1467 | 0.07 |
| urinary bladder | 1 | 1467 | 0.07 |
| others | 1 | 1467 | 0.07 |

## List of papers published in 2014

### Journal

1. Sakamoto T, Sato C, Makazu M, Sekiguchi M, Mori G, Yamada M, Kinjo Y, Turuki E, Abe S, Otake Y, Nakajima T, Matsuda T, Saito Y. Short-term outcomes of colorectal endoscopic submucosal dissection performed by trainees. Digestion, 89:37-42, 2014
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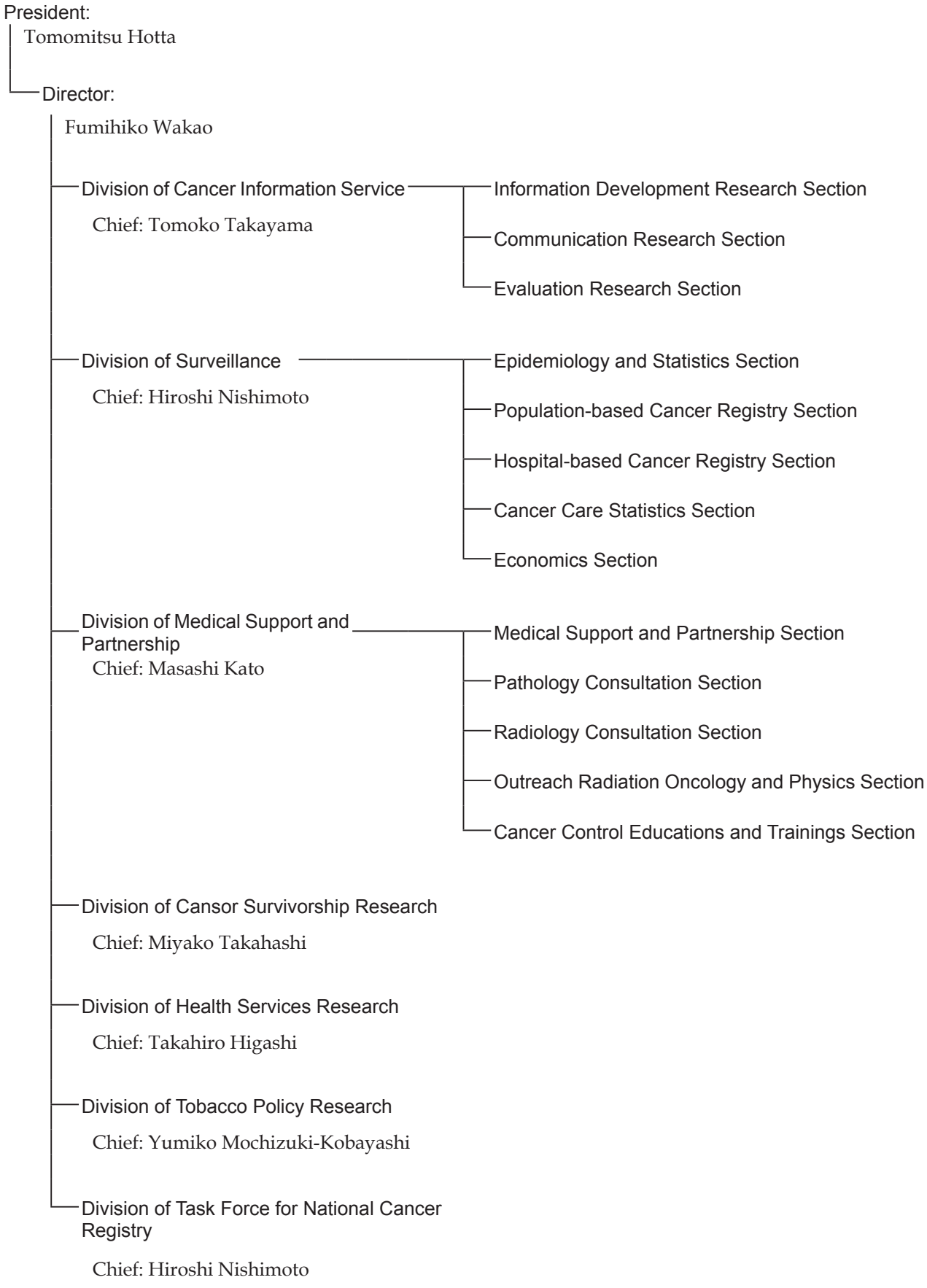
8. Minamimoto R, Senda M, Jinnouchi S, Terauchi T, Yoshida T, Inoue T. Performance profile of a FDG-PET cancer screening program for detecting gastric cancer: results from a nationwide Japanese survey. Jpn J Radiol, 32:253-259, 2014
9. Yoneyama T, Tateishi U, Terauchi T, Inoue T. Correlation of metabolic tumor volume and 11C-choline uptake with the pathology of prostate cancer: evaluation by use of simultaneously recorded MR and PET images. Jpn J Radiol, 32:155-163, 2014
10. Minamimoto R, Senda M, Jinnouchi S, Terauchi T, Yoshida T, Uno K, Iinuma T, Murano T, Nakashima R, Inoue T. Detection of lung cancer by FDG-PET cancer screening program: a nationwide Japanese survey. Anticancer Res, 34:183-189, 2014

### Book

1. Uchiyama N, Kinoshita T, Hojo T, Asaga S, Machida M, Tani H, Kikuchi M, Arai Y, Otsuka K. Usefulness of a Combination DBT (Digital Breast Tomosynthesis) and Automated Volume Analysis of Dynamic Contrast-Enhanced Breast (DCEB) MRI in Evaluation of Response to Neoadjuvant Chemotherapy (NAC). In: Fujita H, Hara T, Muramatsu C (eds), Breast Imaging: 12th International Workshop, IWDM 2014, Gifu City, Japan, June 29 - July 2, 2014. Proceedings, Switzerland, Springer International Publishing, pp 312-319, 2014
2. Uchiyama N, Machida M, Tani H, Kikuchi M, Arai Y, Otsuka K, Fieselmann A, Jerebko A, Mertelmeier T. Clinical Efficacy of Novel Image Processing Techniques in the Framework of Filtered Back Projection (FBP) with Digital Breast Tomosynthesis (DBT). In: Fujita H, Hara T, Muramatsu C (eds), Breast Imaging: 12th International Workshop, IWDM 2014, Gifu City, Japan, June 29 - July 2, 2014. Proceedings, Switzerland, Springer International Publishing, pp 320-326, 2014
3. Tani H, Uchiyama N, Machida M, Kikuchi M, Arai Y, Otsuka K, Jerebko A, Fieselmann A, Mertelmeier T. Assessing Radiologist Performance and Microcalcifications Visualization Using Combined 3D Rotating Mammogram (RM) and Digital Breast Tomosynthesis (DBT). In: Fujita H, Hara T, Muramatsu C (eds), Breast Imaging: 12th International Workshop, IWDM 2014, Gifu City, Japan, June 29 - July 2, 2014. Proceedings, Switzerland, Springer International Publishing, pp 142-149, 2014

Center for Cancer Control
and Information Services

## Organization



# Activities of the Divisions

# Division of Cancer Information Service

**Tomoko Takayama, Haruto Ikeyama, Chikako Yamaki, Ayako Ishikawa, Akiko Urakubo, Satoko Matsumoto, Yoshimi Ishibashi, Tomoko Ono, Masayo Sakurai, Eimi Sawai, Tamaki Kumagai, Yuko Ogo, Tomoko Matsuzawa Yukako Urata, Sachiko Kawaguchi, Ayumi Kishimoto, Sanae Nemoto, Hitomi Yamashita, Kaori Shioda, Jun Nakamachi**

## Introduction

The mission of the Cancer Information Services (CIS) is to provide credible information about cancer. In the National Cancer Information Network, the CIS plays an important role in disseminating cancer-related information directly to a wide range of audience, including patients, caregivers, health professionals, policy makers, researchers, advocates, the news media and other stakeholders. The information we disseminate, are made available over the internet, distributed in brochure formats, and through a range of both public and closed forums and symposiums throughout Japan. Our dissemination channels also include the 409 designated cancer care hospitals and their respective cancer information and support teams. One of our key mandates is to provide all patients and their loved ones, with the means to access comprehensive cancer-related information at the point of need, and with appropriate context. Over the past year, our key delivery channel "ganjoho.jp" has undergone its third major make-over, with the intent to allow users to reach the information they require more quickly via enhanced contextual navigation aids. For those who are unable to navigate the net, we have also compiled a more comprehensive all-in-one handbook for cancer patients and their families: "Guidebook for Cancer Patients", and a sister publication for working patients "Working With Cancer – a comprehensive FAQ" – in our never ending effort to ensure widest reach for essential information requested by patients over the years. In the last few years, we have also greatly expanded existing partnering agreements with the health insurers and pharmaceutical companies, which have committed to providing additional venues for the dissemination of our many publications intended for the public at large.

## Line of service

### Information Development Research Section

The Information Development Research 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. As part of continually providing reliable information in an easily understood format, cancer information contents are developed by translating based on the latest treatment guidelines, and evaluated by domain experts (for accuracy) and by editorial review teams (professional writers as well as patients for clarity and usability). Information is disseminated through various media formats, including the website "Cancer Information Service http://ganjoho.jp/", a wide range of patient education brochures, flyers and handbooks that contain comprehensive cancer information to help empower patients and families throughout the continuum of cancer survivorship. To make the brochures more widely available, we have introduced a publication ordering system, to cater to increasing demand from hospitals, clinics and even regional governments. More than 0.9 million brochures were ordered from 490 organizations in FY2014. The Section also helps direct health care providers by providing access to an extensive library of articles on cancer treatment and supportive information that have undergone the CIS peer reviews, as well as other cancer information sources that are of interest to health care professionals.

**Communication Research Section**

The Communication Research Section is in charge of supporting the smooth operation of cancer information services among the Cancer Information & Support Centers (CISCs) in designated cancer hospitals (409 locations around the nation). The Section handles developing training materials and provides basic and advanced level trainings for the CISCs staffs. To provide quality education program, the Section operates the "CISC-expert panel" which consists of 11 supporters with variety of professionals and regional backgrounds, and they check if the program is effective throughout the year.

**Evaluation Research Section**

In order to disseminate reliable cancer information to the public, the Evaluation 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 support groups, and prefectural government units responsible for planning and managing their respective regional cancer programs. The Section helps to manage the regional trainings and networking forums for the CISCs staffs, in addition to seminars for the public and local health care workers. The Section also prepares and manages the collaborative work with the "Patient-civil panel" which consists of 100 supporters with a variety of experiences with cancer and different regional backgrounds from throughout Japan, and provides mutual educational forums for media professionals. The Section also operates the hotline "Cancer Information Support Center" which helps to provide cancer information to the public and professionals through telephone.

## Research activities

In our division, three sections jointly conduct research activities.

To ensure timely dissemination of accurate and pertinent information on cancer, and to more effectively support decision-making by patients, their families and the general public, 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 need to be part of the delivery/dissemination network. Increasingly, we are also involving with regional community stakeholders, (patients, caregivers, health practitioners, and municipal governments), to help to compile more regionally pertinent set of information, in the effort to improve our community outreach efforts.

To overcome disparities of cancer related information all over Japan and to contribute to build better cancer information and support systems, our division 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. In 2014, we started to examine the barriers of health professionals' usage of information for people with visual impairments.

## List of papers published in 2014

### Journal


1. Nakanotani T, Akechi T, Takayama T, Karato A, Kikuuchi Y, Okamoto N, Katayama K, Yokoo M, Ogawa A. Characteristics of elderly cancer patients' concerns and their quality of life in Japan: a Web-based survey. Jpn J Clin Oncol, 44:448-455, 2014
2. Yokoo M, Akechi T, Takayama T, Karato A, Kikuuchi Y, Okamoto N, Katayama K, Nakanotani T, Ogawa A. Comprehensive assessment of cancer patients' concerns and the association with quality of life. Jpn J Clin Oncol, 44:670-676, 2014

# Division of Surveillance

**Hiroshi Nishimoto, Koichi B. Ishikawa, Akiko Shibata, Kota Katanoda, Tomohiro Matsuda, Kumiko Saika, Megumi Hori, Yoshiko Emori, Kaori Nakano, Mariko Niino, Masako Sato**

## Introduction

The Division of Surveillance is in charge of providing credible cancer statistics to patients and their families, the public, healthcare professionals, policy makers and researchers. The Division also collects accurate and useful information on cancer statistics at the national level. We promote the standardization of hospital-based cancer registries in designated cancer care hospitals and population-based cancer registries in prefectures. The data are collected from both hospital-based and population-based cancer registries, analyzed to calculate accurate cancer statistics and disseminated throughout Japan. Newly incorporated economics section will augment epidemiologic data with economic information crucial for formulation of future policy.

## Routine activities

Population-based Cancer Registries

The Division has continuously exerted efforts to develop a reliable cancer surveillance system in Japan, which is stated as a key element in the Cancer Control Act. The Division supports all these 47 registries, by disseminating up-to-date information through websites and mailing lists; by setting up a Q&A service; by holding 2-day educational workshops for cancer registrars and administrative officers in charge of cancer control newly assigned to their post in May, with a total of 72 participants; and organizing 2-day advanced educational workshops with a total of 118 participants in December. The Division also provided site visiting as part of training for the Standard Database System (SDS), for promoting the protection of personal information, and for cancer registry start-up preparation. This activity supported a total of 17 prefectures this year. 41 registries had introduced the SDS as of January 2015. Introduction is in progress in one registry. The self-check software on security control in cancer registration, and security educational materials for new workers were updated and provided by the Division. In accordance with the Act on Promotion of Cancer Registry enacted in 2013, the Division participated in preparations for establishment of the National Cancer Registry Data Center. Specifically, the preparation activities included advice for the Ministry of Health, Labour and Welfare, forming the materials and data for discussion, development of the National Cancer Registry System, checking the data of the current regional cancer registries, and visiting prefectures for explanation of the act.

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 other 300 hospitals in 2013. In collaboration with other relevant parties, the Division develops data standards for HCR, modifies datasets, and distributes the standardized software "Hos-CanR PLUS" which is used in about 800 hospitals. In 2014, individual records for 313,377 cancer cases diagnosed in 2012 were collected from 397 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 12 cities in which about 1,500 registrars participated. Furthermore, the

Division performed site visits to 33 DCCHs in 2013.

Cancer Statistics

The Division is in charge of providing information on cancer statistics. The updated data of cancer mortality, incidence, survival, and prevalence, the secular trends of cancer mortality and incidence, and the framework of cancer control in Japan have been published both on the web site and in the book titled "Cancer Statistics in Japan."

## Research activities

Population-based Cancer Registries

The national cancer incidences in 2008 and 2009 were estimated based on the data from 37 and 31 cancer registries, respectively. The number of prefectures that have met the data quality standards 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 are presented at conferences both in Japan and abroad.

Cancer Statistics

International comparisons of cancer burden and survival rate were conducted based on the WHO mortality, GLOBOCAN, and cancer registry database. Updated trend analysis of cancer incidence and mortality in Japan was conducted. Descriptive analysis was also conducted for myelodysplastic syndrome in Japan. Tobacco control situations were analyzed in three East Asian countries, Japan, China and the Republic of Korea, and the association between environmental tobacco smoke and stroke was examined.

Economic studies on cancer care

A nation-wide database of inpatient and outpatient clinical practice is constructed with DPC-survey compliant data from over 1,000 hospitals. Using this data, we published a data book on the use of pharmaceuticals related to chemotherapy. Findings from this database and other information related to utilization of services are linked with population estimates to form future forecasts of supply and demand in cancer care.

**Table 1. Population-based Cancer Registries from Prefectural Registries**

| Year of Diagnosis | Prefectures | Number of New Cancer Cases |
|---|---|---|
| 2011 | 40 (14 for estimation and 39 for inter-regional comparison) | 851,537 |

**Table 2. Population-based Cancer Registries from Prefectural Registries**

| Year of Diagnosis | Applied Hospitals | Number of New Cancer Cases |
|---|---|---|
| 2010 | 387 | 548,979 |
| 2011 | 395 | 584,120 |
| 2012 | 397 | 613,377 |

## List of papers published in 2014

## Journal


1. Katanoda K, Kamo K, Saika K, Matsuda T, Shibata A, Matsuda A, Nishino Y, Hattori M, Soda M, Ioka A, Sobue T, Nishimoto H. Shortterm projection of cancer incidence in Japan using an age-period interaction model with spline smoothing. Jpn J Clin Oncol, 44:36-41, 2014
2. Higashi T, Nakamura F, Shibata A, Emori Y, Nishimoto H. The national database of hospital-based cancer registries: a nationwide infrastructure to support evidence-based cancer care and cancer control policy in Japan. Jpn J Clin Oncol, 44:2-8, 2014
3. Iwanaga M, Chiang C-J, Soda M, Lai M-S, Yang Y-W, Miyazaki Y, Matsuo K, Matsuda T, Sobue T. Incidence of lymphoplasmacytic lymphoma/ Waldenstrom's macroglobulinaemia in Japan and Taiwan population-based cancer registries, 1996-2003. Int J Cancer, 134:174-180, 2014
4. Katanoda K, Kamo K, Hori M, Tsugane S. Estimated prevalence of thyroid cancer in Fukushima prior to the Fukushima Daiichi nuclear disaster. BMJ[Internet], 2014
5. Matsuda A, Yamaoka K, Tango T, Matsuda T, Nishimoto H. Effectiveness of psychoeducational support on quality of life in early-stage breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. Qual Life Res, 23:21-30, 2014
6. Matsuda A, Katanoda K. Five-year relative survival rate of ovarian cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 44:196, 2014
7. Katanoda K, Matsuda T. Five-year relative survival rate of liver cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 44:302-303, 2014
8. Matsuda T, Matsuda A. Five-year relative survival rate of pancreas cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 44:398-399, 2014
9. Chihara D, Ito H, Matsuda T, Shibata A, Katsumi A, Nakamura S, Tomotaka S, Morton LM, Weisenburger DD, Matsuo K. Differences in incidence and trends of haematological malignancies in Japan and the United States. Br J Haematol, 164:536-545, 2014
10. Matsuda A, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H. Cancer incidence and incidence rates in Japan in 2008: a study of 25 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol, 44:388-396, 2014
11. Katanoda K, Jiang Y, Park S, Lim MK, Qiao Y-L, Inoue M. Tobacco control challenges in East Asia: proposals for change in the world's largest epidemic region. Tob Control, 23:359-368, 2014
12. Tamaki T, Dong Y, Ohno Y, Sobue T, Nishimoto H, Shibata A. The burden of rare cancer in Japan: application of the RARECARE definition. Cancer Epidemiol, 38:490-495, 2014
13. Chihara D, Ito H, Katanoda K, Shibata A, Matsuda T, Sobue T, Matsuo K. Incidence of myelodysplastic syndrome in Japan. J Epidemiol, 24:469-473, 2014
14. Katanoda K, Matsuda T. Five-year relative survival rate of breast cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 44:611, 2014
15. Katanoda K. The dynamics of cancer burden in Asia. Ann Transl Med, 2:67, 2014
16. Matsuda T, Hori M. Five-year relative survival rate of bladder cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 44:776, 2014
17. Hori M, Katanoda K. Five-year relative survival rate of skin cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 44:881, 2014
18. Nishino Y, Tsuji I, Tanaka H, Nakayama T, Nakatsuka H, Ito H, Suzuki T, Katanoda K, Sobue T, Tominaga S. Stroke mortality associated with environmental tobacco smoke among never-smoking Japanese women: a prospective cohort study. Prev Med, 67:41-45, 2014
19. Yako-Suketomo H, Katanoda K, Sobue T, Imai H. Practical use of cancer control promoters in municipalities in Japan. Asian Pac J Cancer Prev, 15:8239-8244, 2014
20. Saika K, Matsuda T, Sobue T. Incidence rate of thyroid cancer by histological type in Japan. Jpn J Clin Oncol, 44:1131-1132, 2014
21. Ito Y, Miyashiro I, Ito H, Hosono S, Chihara D, Nakata-Yamada K, Nakayama M, Matsuzaka M, Hattori M, Sugiyama H, Oze I, Tanaka R, Nomura E, Nishino Y, Matsuda T, Ioka A, Tsukuma H, Nakayama T. Long-term survival and conditional survival of cancer patients in Japan using population-based cancer registry data. Cancer Sci, 105:1480-1486, 2014
22. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang X-S, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo E Silva G, Chen W-Q, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25 676 887 patients from 279 populationbased registries in 67 countries (CONCORD-2). Lancet, 385:977-1010, 2014
23. Katanoda K, Matsuda T. Five-year relative survival rate of testis cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 44:1248, 2014

# Division of Medical Support and Partnership

**Masashi Kato, Yasuaki Arai, Jun Itami, Nobuyoshi Hiraoka, Yoshinori Makino, Miki Hosoya, Yoko Nakazawa, Kanako Kono, Saho Wada, Tadakazu Shimoda, Hiroaki Onaya, Toshiyuki Minemura, Takashi Hanada, Yuki Aono, Saran Yoshida, Naotoshi Atoda, Naoya Ikeno, Ryoji Kushima, Hiroko Suketomo, Megumi Fukuda, Ritsuko Chinda, Yuri Yamauchi, Hiromi Nakamura, Toshiko Sakaguchi, Shiho Hirai, Hiroyo Ohchi, Ito Chisako, Sasaki Erina**

## Introduction

The Division builds partnership with the Designated Cancer Care Hospitals to support all health-allied professionals concerned with for cancer control in Japan. The Medical Support and Partnership Section (MSPS) plays a unique role in supporting the Designated Cancer Care Hospitals in Japan. The Pathology Consultation Section (PCS) makes effort to perform human pathology research based on histology of tumor cells and tumor-stromal cells to improve diagnostic pathology of the tumors. The Radiology Consultation Section (RCS) provides a consultation service and a cancer image reference database (NCC-CIR). A radiology consultation service 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 Education and Training Section (CCET) plays a central role in the planning, management and evaluation of specialized and multidisciplinary training programs for physicians and other health professionals as trainers of each designated cancer care hospital, to promote a comprehensive and systematic cancer control program in Japan.

## Routine activities

### A. Networking among Designated Cancer Care Hospitals

The MSPS held the Designated Cancer Care Hospitals Liaison-council and the Palliative Care Committee (a subsidiary organization) to enhance partnership for cancer control in Japan. The designated cancer care hospitals are important partners with the NCC to promote comprehensive cancer control in Japan.

### B. Pathology consultation service

The PCS received 478 cases requested for specialist's second opinion regarding histopathological diagnosis in 2014. There are 82 consultants having been registered, many of them are highly recognized experts in specialty disciplines. One of them assigned as consultant examines the slides and rapidly sends back the report of opinion to each client. Most of the clients expressed satisfaction with the contents of the report and this consultation system. We also selected typical or educational cases from accumulated archives and constructed referential database.

### C. Radiology consultation service

74 consultation reports have been put together for requests mainly from the Kanto and Kyushu regions at the RCS. Hepato-biliary-pancreatic, musculoskeletal, and lung lesions were the common subjects. Consultation with a specialist was the most frequent reason 37.9% for consultation. The client radiologists have evaluated 314 (91.0%) of the 345 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 2013, about 100,000 per month. Cases with cancers who underwent musculoskeletal malignancies (n=4), head and neck cancers (n=2), urological malignancies (n=2), liver cancers (n=2), and other

cancers have been published, resulting in the total provision of 300 cases.

**E. Radiotherapy case service**

Mailed dosimetry and on-site dosimetry were performed in 129 institutions and 12 institutions, respectively at the ORPS. All data of the institutions were within the permissible limit.

## Research activities

**A. Evaluate changes in Palliative Care by Cancer Control Program**

To evaluate the changes of palliative care induced by the Basic Plan to Promote Cancer Control Program in Japan, an interview survey and a questionnaire survey are conducted at the MSPS.

**B. Develop a peer review method to implement a PDCA cycle in among the Designated Cancer Care Hospitals**

The MSPS developed a guide and a manual for carrying out peer review about palliative care.

**C. Support for clinical trials**

The RCS is currently trying to reconstruct the consultation system to make it more suitable for supporting central radiological review in clinical trials.

**D. Develop the IMRT quality control support program**

The ORPS were developing enforcement of the on-site dosimetry regarding the output dose of Intensity Modulated Radiotherapy (IMRT) in 2 institutions (designated regional cancer centers).

## Clinical trials

In Japan Clinical Oncology Group (JCOG1008, JCOG1208, JCOG1303) and Japanese Radiation Oncology Study Group (JROSG12-1), the ORPS performed the on-site dosimetry regarding the output dose of IMRT in 10 institutions.

## Education

The CCET provides and evaluates various oncology professional training programs about up-to-date information on early detection, diagnosis, treatment, nursing care, cancer research, clinical trials and cancer statistics for physicians, nurses, pharmacists, cancer information (CI) specialists, technologists and cancer registrars. The CCET also provides multidisciplinary training programs for Palliative Care Teams and Chemotherapy Teams. (Table 1)

## Future prospects

The MSPS conduct a needs assessment survey about the support for medical service of the Designated Cancer Care Hospitals, and search a support system to meet the need. All sections will continue to be involved in our routine activities and education.

**Table 1. Training programs conducted during April 2013 - March 2015**

| Category of Education and Training program | Titles of Education and Training program | Number of participants (April 2013 - March 2014) | Number of participants (April 2014 - March 2015) |
|---|---|---|---|
| Oncology nursing education | Continuing education and development of oncology nursing workshop for trainers | 44 | 74 |
| | Continuing education and development of oncology nursing workshop for trainers-Follow up | 11 | 60 |
| | Oncology nursing seminar for trainers | 362 | 505 |
| | Oncology nursing on the job training for trainers | 6 | - |
| | Oncology nursing on the job training for trainers-Follow up | 6 | - |
| | Certified Nurse Follow up Program | 38 | 51 |
| | End-of-life nursing education program for trainers | 76 | 84 |
| CI specialist education | CI Specialist Education Program -Basic course 1 | 680 | 624 |
| | CI Specialist Education Program -Basic course 2 | 658 | 633 |
| | CI Specialist Education Program -Basic course 3 | 339 | 338 |
| | CI Specialist Education Program -Upskill course | - | 92 |
| | CI Specialist Education Program for trainers | 52 | 188 |
| | CI Specialist Education Program for trainers-Follow up | 98 | 30 |
| Hospital-based cancer registrar training | Training program for instructors of hospital-based cancer registrars | 10 | 20 |
| | Continuous training program for instructors of hospital-based cancer registrars | 9 | 6 |
| | Supplementary training program for instructors of hospital-based cancer registrars | 93 | 96 |
| | Basic training program for hospital-based cancer registrars | 1,442 | 1,582 |
| | Supplementary training program for hospital-based cancer registrars of basic course completion | 770 | 1,079 |
| | Advanced training program for hospital-based cancer registrars | 155 | 155 |
| | Introduction program for implementation of hospital-based cancer registry | 70 | 72 |
| Training for population-based cancer registrars and administrative officers in charge of cancer control | Basic training programs on population-based cancer registry for population-based cancer registrars and administrative officers in charge of cancer control | 294 | 191 |
| Technologist education | Trainer training for oncologic radiology technologists | 15 | - |
| | Trainer training for oncologic laboratory medical technologists | 5 | - |
| Pharmacist education | Seminar for pharmacists of dispensing neoplastic agents to be trainers | 71 | 58 |
| | On the job training for pharmacists of dispensing neoplastic agents to be trainers | 19 | 24 |
| Palliative care physicians education | Palliative care education meeting for trainers | 53 | 62 |
| Psycho-oncologists education | Psycho-oncology education meeting for trainers | 53 | 27 |
| Palliative care team education | Palliative care team workshops for consultation-Basic course | 73 | 45 |
| | Palliative care team workshops for trainers | 34 | 38 |
| Chemotherapy team education | Chemotherapy team workshops to introduce a new drug safety | 64 | 32 |
| | Chemotherapy team workshops for regional trainers | - | 24 |
| Prefectual official education | Cancer control seminars and workshops | 110 | 77 |
| Total | | 5,710 | 6,267 |

## List of papers published in 2014

## Journal


1. Iwao Y, Ojima H, Onaya H, Sakamoto Y, Kishi Y, Nara S, Esaki M, Mizuguchi Y, Ushigome M, Asahina D, Hiraoka N, Shimada K, Kosuge T, Kanai Y. Early venous return in hepatic angiomyolipoma due to an intratumoral structure resembling an arteriovenous fistula. Hepatol Res, 44:700-706, 2014
2. Sato Y, Ojima H, Onaya H, Mori T, Hiraoka N, Kishi Y, Nara S, Esaki M, Shimada K, Kosuge T, Sugihara K, Kanai Y. Histopathological characteristics of hypervascular cholangiocellular carcinoma as an early stage of cholangiocellular carcinoma. Hepatol Res, 44:1119-1129, 2014
3. Imura C, Morita T, Kato M, Akizuki N, Kinoshita H, Shirahige Y, Suzuki S, Takebayashi T, Yoshihara R, Eguchi K. How and why did a regional palliative care program lead to changes in a region? A qualitative analysis of the Japan OPTIM study. J Pain Symptom Manage, 47:849-859, 2014
4. Kuno H, Onaya H, Fujii S, Ojiri H, Otani K, Satake M. Primary staging of laryngeal and hypopharyngeal cancer: CT, MR imaging and dual-energy CT. Eur J Radiol, 83:e23-35, 2014
5. Kuno H, Onaya H. A case of oropharyngeal squamous cell carcinoma with nasopharyngeal extension via the levator veli palatini muscle. Jpn J Clin Oncol, 44:195, 2014
6. Nakazawa Y, Kizawa Y, Hashizume T, Morita T, Sasahara T, Miyashita M. One-year followup of an educational intervention for palliative care consultation teams. Jpn J Clin Oncol, 44:172-179, 2014
7. Hirooka K, Miyashita M, Morita T, Ichikawa T, Yoshida S, Akizuki N, Akiyama M, Shirahige Y, Eguchi K. Regional medical professionals' confidence in providing palliative care, associated difficulties and availability of specialized palliative care services in Japan. Jpn J Clin Oncol, 44:249-256, 2014
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9. Kono K, Tamashiro DAA, Alarcon VB. Inhibition of RHO-ROCK signaling enhances ICM and suppresses TE characteristics through activation of Hippo signaling in the mouse blastocyst. Dev Biol, 394:142-155, 2014
10. Yoshida S, Amano K, Ohta H, Kusuki S, Morita T, Ogata A, Hirai K. A comprehensive study of the distressing experiences and support needs of parents of children with intractable cancer. Jpn J Clin Oncol, 44:1181-1188, 2014

# Division of Cancer Survivorship Research

**Miyako Takahashi, Makiko Tomita, Makiko Tazaki, Kyoko Onozawa**

## Introduction

The Division of Cancer Survivorship was established in April 2013. Our mission is to enhance the quality of life of people with cancer and their caregivers, and to promote social awareness in Japan about cancer survivorship issues.

## Routine activities

As for academic research, we mainly deal with various psychosocial issues experienced by cancer survivors and their caregivers during and after treatments such as employment, interpersonal relationships, sexuality and fertility, prejudice against cancer, and life-style modifications. In particular, we examine the influence of the Japanese socio-cultural background on living with and through cancer, and try to propose countermeasures based on the research findings.

As for activities to promote social awareness toward cancer survivorship, we plan and implement educational programs for the general public as well as healthcare providers.

In addition to the above mentioned activities, Dr. Miyako Takahashi, Division Chief, served as a member of "Cancer and Work" council organized by the Ministry of Health, Labour and Welfare in 2014.

## Research activities

The research projects we conducted in 2014 include "cancer and work", "psychosocial impact of appearance change among male cancer survivors", "pediatric cancer survivors' sexual development", "father-child communication when mother has cancer", and so on. As for research on cancer and work, we published "Cancer and Work Q&A 2nd edition", which is now available on Cancer Information Service website.

This year, we conducted keynote lectures, symposium presentations, and oral presentations in 13 academic meetings. Also, we published 4 articles in English, 10 articles, 1 edited book, and 4 chapters in co-authored book in Japanese.

## Education

As for education for healthcare providers in 2014, we delivered lectures in 3 universities for medical and nursing students, 3 lectures for advanced nursing courses, 2 lectures for the Tokyo Metropolitan Medical Association, 6 lectures for prefectural governments, and 22 lectures for medical institutions nationwide.

As for promoting social awareness of cancer survivorship, we planned and implemented 2 lecture series, "Community Center Café" and "Gotochi (Local) Café", which were open to the public. These café programs were held in a relaxed atmosphere with a cup of tea, consist of a lecture that takes up various cancer survivorship topics followed by a small group discussion by participants. It provided participants an opportunity to learn about cancer survivorship issues as well as exchange views each other. In 2014, we held The Community Center Café 6 times with 300 participants in total in the Tsukishima Community Center in Chuo ward, where National Cancer Center is located. The Gotochi (Local) Café, the other café program, has the same structure as the Community Center Cafe, but was co-sponsored by our division and healthcare providers in prefectures outside of Tokyo, and focused on high priority survivorship issues within the local community. In 2014, we held the Gotochi Café 4 times in Okinawa, Miyagi, Hokkaido, and Nara, and 200 people participated.

## List of papers published in 2014

### Journal

1. Saito N, Takahashi M, Sairenchi T, Muto T. The impact of breast cancer on employment among Japanese women. J Occup Health, 56:49-55, 2014
2. Takahashi M. Psychosocial distress among young breast cancer survivors: implications for healthcare providers. Breast Cancer, 21:664-669, 2014

# Division of Health Services Research

**Takahiro Higashi, Momoko Iwamoto, Izumi Inoue, Ayako Okuyama, Fumiaki Nakamura, Yoichiro Tsukada, Naoki Sakakibara, Rei Goto, Takehiro Sugiyama, Kaoru Konno**

## Introduction

In order to establish an evaluation system for health systems and health policy performance in cancer care in Japan, the Division of Health Services Research primarily focused on the following research projects in 2014.

## Routine activities

### i. Establishing a clinical database by linking hospital-based cancer registry and DPC / insurance claims data

As a first step in monitoring the quality of cancer care and ensuring equitable access to care in Japan, the division developed a large clinical database that linked hospital-based cancer registry data with DPC / insurance claims data obtained from designated cancer care hospitals throughout Japan. The Division distributed free encryption software designed to support different file formats used by various hospitals, which allowed multiple data sources to be synthesized smoothly into a single database. The database contains de-identified information on all procedures, tests, and prescriptions given to patients with major cancers who were diagnosed in 2011 from 182 hospitals across the country. We used the database to calculate 13 quality indicators (QIs) among 206 QIs that were previously developed by an expert panel led by Dr. Sobue Tomotaka, professor of Medicine at Osaka University, which ask if certain types of tests, procedures, or prescriptions were given to a specified set of patients, such as the proportion of stage III colorectal cancer patients that received adjuvant chemotherapy within 8 weeks of surgery. Results of the QI scores were fed back to participating hospitals through an interactive website that allows hospitals to compare its performance to other hospitals. We expect the hospitals to use the results for future quality improvements.

We also began collecting data of patients who were diagnosed with cancer in 2012 for all cancer types, and have finished creating a database containing DPC data of 232 hospitals. The data is currently being analyzed for QI measurement. We also plan to improve our quality metrics so that results are more relevant and meaningful for hospitals, and hope that the initiative will be sustainable.

### ii. Monitoring and Evaluation of National Cancer Control Programs

A clearly defined set of performance indicators to measure health policy performance in cancer care have never been developed in Japan. In order to develop such a system to monitor the performance of cancer control programs, the Division gathered a panel of experts including clinical specialists, patient representatives, biomedical and public health researchers, cancer information experts, and policy makers in early 2014. Using a modified Delphi method, we created a list of 91 performance indicators agreed upon by the expert panel and the Cancer Control Promotion Council to measure various outcomes and outputs of cancer control programs. We also conducted a series of group interviews by the panel and members of the Cancer Control Promotion Council to identify essential components of the three major goals of cancer control program.

1. Advancement of medicine
2. Provision to appropriate medical treatment
3. Disseminate cancer-related information to the public and provide help-desk for cancer patients
4. Addressing the economic burden of cancer and providing financial support
5. Mitigating the burden of family caregivers of cancer patients
6. Creating a society without discrimination and alienation against cancer patients

We broke these components into a series of questions to be asked to cancer patients and their families, and launched a patient experience survey to over 130 hospitals. The survey also included questions from the 91 performance measures. The Division is currently analyzing the results for reporting to the Cancer Control Promotion Council.

**iii. Evidence Generation for Rare Cancer Policy**

The Basic Plan to Promote Cancer Control Programs indicates the need for provision of better medical services and support for rare cancer patients, yet its definition of rare cancer has not been identified. Essential data on patterns of care of rare cancer patients are also lacking, making it impossible for policymakers to implement appropriate and impactful cancer programs. In order to support the activities of policymakers by providing them with evidence, we conducted a survey to physicians in oncology-related academic societies to develop a definition of rare cancer in Japan, using epidemiological data of rare cancer patients from registry data. We are also analyzing patterns of care of rare cancer patients using registry data and administrative data.

**iv. Search engine for finding cancer treatment hospitals**

Using hospital-based cancer registry data of 2,200,000 cancer patients who were registered between 2009 and 2012, we developed a search engine that could be used by counselors stationed at support centers in 46 Prefectural Designated Cancer Care Hospitals to provide information to cancer patients and their families in finding hospitals that have previous experience in treating a specified type of cancer patients. We hope to continue this system by updating the registry data on an annual basis.

## Research training and education

The Division has had a continuous flow of physicians and graduate students for research trainings throughout the year. We mentored two graduate students: one pursuing a clinical doctorate and another from nursing-related doctorate program. Additionally, the Division accepted four medical students from the University of Tokyo for a clerkship in Public Health.

## Future prospects

The Division supports evidence-based policymaking and strives to improve the care of cancer patients by monitoring the performance of cancer policy and quality of care among cancer treatment centers across the country. In addition to the current activities, the Division is working to provide an information exchange platform for specialists and various stakeholders, designed to foster smooth communication and active exchange of ideas for cancer policy planning at the local government level. The Divison will continue to endeavor towards making clinically relevant and evidence-based policy recommendations in order to help implement meaningful cancer control programs in Japan.

## List of papers published in 2014

## Journal


1. Higashi T, Nakamura F, Shibata A, Emori Y, Nishimoto H. The national database of hospital-based cancer registries: a nationwide infrastructure to support evidence-based cancer care and cancer control policy in Japan. Jpn J Clin Oncol, 44:2-8, 2014
2. Inohara T, Kohsaka S, Miyata H, Ueda I, Noma S, Suzuki M, Negishi K, Endo A, Nishi Y, Hayashida K, Maekawa Y, Kawamura A, Higashi T, Fukuda K. Appropriateness of coronary interventions in Japan by the US and Japanese standards. Am Heart J, 168:854-861 e811, 2014
3. Iwamoto M, Nakamura F, Higashi T. Estimated life expectancy and risk of death from cancer by quartiles in the older Japanese population: 2010 vital statistics. Cancer Epidemiol, 38:511-514, 2014
4. Inohara T, Kohsaka S, Miyata H, Ueda I, Ishikawa S, Ohki T, Nishi Y, Hayashida K, Maekawa Y, Kawamura A, Higashi T, Fukuda K. Appropriateness ratings of percutaneous coronary intervention in Japan and its association with the trend of noninvasive testing. JACC Cardiovasc Interv, 7:1000-1009, 2014
5. Ohura T, Higashi T, Ishizaki T, Nakayama T. Assessment of the validity and internal consistency of a performance evaluation tool based on the Japanese version of the modified barthel index for elderly people living at home. J Phys Ther Sci, 26:1971-1974, 2014
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7. Okuyama A, Nakamura F, Higashi T. Prescription trends of prophylactic antiemetics for chemotherapy-induced nausea and vomiting in Japan. Support Care Cancer, 22:1789-1795, 2014
8. Ishiguro M, Higashi T, Watanabe T, Sugihara K. Changes in colorectal cancer care in japan before and after guideline publication: a nationwide survey about D3 lymph node dissection and adjuvant chemotherapy. J Am Coll Surg, 218:969-977 e961, 2014

# Division of Tobacco Policy Research

**Yumiko Mochizuki-Kobayashi, Tomoyasu Hirano, Yuriko Nishikawa**

## Introduction

The death toll attributable to tobacco use is resulted from a manmade disaster worldwide, but many countries have successfully shown that it is avoidable with effective tobacco control regulations. Thus, to achieve the global standard level of tobacco policies, our missions are research activities and advocacies based on the following four pillars: 1. Monitoring and Evaluation, 2. Development and Research of Practical Programs, 3. Public Education and Information Services, and 4. Promoting Policy and Networking.

## Projects and Research activities

- Through the government commissioned projects, we gathered comprehensive information on the implementation of FCTC (Framework Convention on Tobacco Control) for Japan to be reported to the convention secretariat. In addition, we analysed and evaluated the methods and contents of the report in consultation with the FCTC Study Panel.

- As a cancer education program, we developed participatory workshop curriculums on tobacco prevention for elementary school children and carried out a test pilot case in Hokkaido in collaboration with a local consortium. Based on the results, we accomplished a project framework with essential program modules to promote this innovative educational project, "Tobacco Free Kids Japan," to generate a tobacco free generation.

- In order to facilitate the government effort to promote cessation services, we carried out a test trial of quitline services that was considered appropriate to Japan's situation by the Quitline Expert Panel. With the results of the trial, we reached to a semi-autonomous scheme building intended for the workplaces by private sectors which would act in a mutually complementary manner with the existing government model based on core cancer hospitals.

- To examine possible conflict of interests with respect to the evidence based tobacco policy developments among academic societies, we carried out a survey on the interactions of individual researchers with research institutions such as universities, scientific societies and the private companies (pharmaceutical, medical device and tobacco industry). As a result of the study, most researchers in the field of public health did not recognize the conflict of interests might exist in their interactions with tobacco companies. To increase their awareness of this issue, we delivered the survey results overview as well as the FCTC Article5.3 guidelines to all respondents in commemoration of the 10th anniversary of FCTC.

- To support the Tobacco Free Olympic Games Tokyo 2020, we carried out an internet survey for residents in Tokyo with a result that majority of the respondents supported an opinion seeking regulation of penalties. Based on the results, we urged the Governor of Tokyo Metropolitan Government to implement tobacco control policies reflecting public opinions.

- As a member of the Tobacco Free Committee of the Japan Science Council, we contributed to the Tokyo Metropolitan Government to drafting and issuance of urgent proposals for tobacco control policies to realize the Tobacco Free Olympic Games 2020. Also, as a member of the Tobacco Risk Assessment Committee of the Ministry of Health, Labor and Welfare, we demonstrated the introduction of regulatory science to tobacco control and global trends of E-cigarette use, with proposals to possible regulatory framework in Japan.

- We organized various public education events at the WHO World No Tobacco Days and Science Agora of Japan Science and Technology Agency (JST) to educate people on tobacco and cancer, and also contributed to governments, schools and NGO/NPOs to develop policies and programs.

In addition, through providing information and planning assistance to the various communities, non-governmental organizations and prefectural governments with good results in networking and capacity building.

# Division of Task force for National Cancer Registry

**Hiroshi Nishimoto, Naoyuki Sato, Tomohiro Matsuda, Akiko Shibata, Mariko Niino, Masako Sato (-March 2015), Rika Nabata (April 2015-), Yumi Nishikawa, Seiya Kondo**

## Introduction

The Project team was in charge of development of National Cancer Registry (NCR) in the National Cancer Center (NCC) which will be launched in January 2016, as provided for by the act on promoting cancer registry enacted in December 2013, on consignment from the Ministry of Health, Labour and Welfare (MHLW).

## Routine activities

1) Development of the National Cancer Registry database system (NCR-DBS) and the network linking the NCC and the 47 prefectures

In collaboration with Fujitsu Ltd., the team developed the NCR-DBS at the NCC. The 47 prefectures and the NCR-DBS server of the NCC were linked by the secured network (VPN), and the prefectures were equipped with the client PC. The electronic system for automated coding of causes of death (Iris) was introduced in the NCC as a sub-system of the NCR-DBS.

2) Development of the Prefectural cancer registry database system (Pref-DBS) and data migration from the Standard Database System (SDS)

In order to maintain consistency of the cancer statistics, the team developed the Pref-DBS replacing the SDS, and had a contract of use with the prefectures. 42 prefectures had introduced the Pref-DBS, and the data migration is in progress. Ahead of the data migration, the team verified the quality of cancer death data in 7 prefectures for an efficient procedure.

3) Development of the Electronic Cancer Reporting System (ECRS)

The team has developed the ECRS and released on the web site (ganjoho.jp) mainly for the clinics which do not conduct a hospital-based cancer registration, by using auto-encrypting PDF format.

4) Plan for the online data submission network

The team discussed about a future plan for the online data submission network with the MHLW and the online data submission by the hospital with the highest security.

5) Discussion on the government ordinance and the manuals

The team discussed about the settlement of the government ordinance on NCR. The team developed several manuals for cancer reporting, data security and data use. These manuals were uploaded on the website.

6) Provision Information on NCR

The team was in charge of development of the website and creation of a cancer registry PR movie, infographics, posters and pamphlet on cancer registration for the public. The team supports all the 47 registries by disseminating up-to-date information through websites and mailing lists as well as by setting up a Q&A service.

## Future Prospects

NCR in the NCC will be luanched in January 2016.

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