Annual Report 2013

National Cancer Center

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

CONTENTS

Exploratory Oncology Research & Clinical Trial Center

Research Center for Cancer Prevention and Screening

Center for Cancer Control and Information Services

Greeting from the President

"Not to get cancer, not to be defeated by cancer, live with cancer"

My second term of the National Cancer Center (NCC) presidency has begun. I would like to extend my warmest greetings to everyone.

The NCC has been providing for cancer patients and their families for over 50 years, as one of the leading national cancer treatment facilities since its foundation in 1962. The NCC delivers the latest and best treatment to patients not only locally, but also nationally. At the same time the NCC has been conducting cutting-edge research to develop treatment, and playing a central role to train specialized doctors, nurses, and other medical professionals as a place where they can get practice in cancer medicine based on the foundation developed by proper clinical trials. In April 2010, the NCC has changed its status to what we call an "Independent Administrative Institute" from operating directly under the Japanese Ministry of Health, Labour and Welfare. This year is the final year of the mid-term plan for Independent Administrative Institutes. Approved by the Cabinet last December, the NCC's objective was set to maximize the outcome of research and development, and the NCC was placed as an organization that should work on tasks which are difficult for universities or private companies to work on.

In the meantime, we have witnessed major changes. First, the "Basic plan to promote cancer control" was reviewed in 2012 and one new goal, "creating a society where cancer patients feel secure," has been made, adding to the two major goals already-set; "reducing the cancer mortality rate" and "reducing the pain of both patients and their families, and improving their quality of life." That widely focusses on the social point of view. Secondly, the cancer registration law was passed in 2013, which welcomes an era that enables us to conduct and rate cancer control based on the national data. The responsibility for the national registry is going to go to the NCC. Lastly, a new "ten year strategy for cancer control" has begun, setting the slogan as "Clear up, prevent, and live together with cancer" subtitled, "Research in collaboration with patients, and society." This forms an essential strategic plan of the Japan Cancer Research Project under the body of Japan Medical Research Development, or the Japanese version of the US National Institutes of Health (NIH).

The NCC works hard to increase the patients' quality of life not only through providing highly advanced, and pioneering medical care, but also by working with designated cancer care hospitals, promoting clinical research networking, practicing palliative care, developing a model for counseling and support, and providing information. To aim at the final goal of conquering cancer, the NCC keeps developing effective methods of cancer prevention, diagnosis, and treatment at each life stage for each patient. In addition, the NCC is promoting translational research projects that connect basic research to practice. We are aware of the public expectations that we should serve a main role in the fields of medical treatment and research. "Not to get cancer, not to be defeated by cancer, live with cancer", that's what the NCC aims at as a national center, and every NCC worker brings out all the professional skills that they possess, and disseminate the outcomes widely to the world.

We highly appreciate your warm support, and any advice you can give us is always welcome.

Thank you and best regards,

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

Organization of National Cancer Center

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Tomomitsu Hotta

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- Auditors
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    - Chief: Takeharu Yamanaka
  - Office for Advanced Medical Care Evaluation
    - Chief: Yasuhiro Fujiwara

Sections Directed by President

Office of Policy, Strategic Planning Bureau

Yasuhiro Fujiwara, Yasuhiro Fujii, Chikara Tsukamoto, Teruhiko Yoshida, Toshikazu Ushijima, Tatsuhiro Shibata, Takashi Kono, Kenkichi Masutomi, Hisao Asamura, Minoru Esaki, Akira Kawai, Hidehito Horinouchi, Kenji Tamura, Miyuki Sone, Ken Ohashi, Ken Shimizu, Fumiko Mori, Yoshinori Makino, Nobuko Ushirozawa, Atsushi Ohtsu, Toshihiko Doi, Tetsuo Akimoto, Takayuki Yoshino, Akimasa Ito, Atsushi Ochiai, Takeharu Yamanaka, Katsuya Tsuchihara, Miho Kurhihara, Yasuhiko Ichida, Fumihiko Wakao, Takahiro Higashi, Tatsuhiro Shibata, Hiroshi Kajino, Yasuhiro Kuroda, Yasunori Kikuchi, Kota Tagawa, Shoko Koike, Kiyotaka Watanabe, Miyako Horikoshi, Chie Shirai, Tomoe Yoneyama, Yuki Hatano, Seiichiro Yamamoto, Sakiko Suzuki, Maria Imada

The underlining delineates members of the Office of Policy.

Introduction

The Strategic Planning Bureau of the National Cancer Center (NCC) was established as a think tank to serve the President of the NCC. The Bureau works on: 1) Identifying the tasks faced by the NCC and the nation-wide challenges associated with controlling cancer in Japan; 2) Disseminating their findings to the Japanese industry, academia, and government; 3) Providing data that contribute to the nation's policy planning; and 4) Proposing policy, in cooperation with the Division of Health Services Research at the Center for Cancer Control and Information Services and the Department of Public Health Policy at the Research Center for Cancer Prevention and Screening.

In 2013, the Bureau completed three major tasks. First, we prepared a proposal to be submitted to the Panel of Experts on the Future of Cancer Research, which was chaired by our President. Second, we discussed the future directions of the NCC and compiled these into a report. Third, we established and documented an opinion on the role that the National Center should play among the Centers for Creating Innovative Medical Technologies, to be submitted to the Special Advisor Meeting on the Health and Medical Strategy for which our President serves as a special advisor.

The future direction of cancer research

In the Panel of Experts on the Future of Cancer Research, which was chaired by the President, Dr. Hotta, and held from April 15 to August 9, 2013, we reported the results of our evaluation and analysis of the whole Research Program at the 3rd-term Comprehensive Strategy for Cancer Control. This was conducted under the 3rd-term Comprehensive 10-year Strategy for Cancer Control, at about the 8.5 year mark. An interim report, the "Future Direction of Cancer Research", was awarded the Health and Labour Sciences Research Grant and was conducted as a designated program in the 3rd-term Comprehensive Strategy for Cancer Control. The Principal Investigator on the interim report was Tomomitsu Hotta. We also contributed to preparing a report issued by a panel of experts on the future of cancer research: "The Future Direction of Cancer Research—Radical Cures, Prevention, and Coexistence—Cancer Research Working in Partnership with Society" (August 2013, the Panel of Experts on the Future of Cancer Research) http://www.mhlw.go.jp/stf/shingi/0000014994.html.

The future direction of the NCC

Since the end of 2012, the NCC has been discussing the future mission and role of our Center with respect to cancer control in Japan, considering the government's policy on cancer control as a whole, in order to make policy proposals to the President.

We have held 24 meetings of core members to discuss the NCC's current state and challenges, as well as future directions and required countermeasures for each issue. Also, we held five symposiums asking for honest opinions from outside experts on how NCC could improve.

Based on the above, we compiled a "Report on the Future Direction of the NCC" (Strategic Planning Bureau, October 25, 2013) and submitted it to the President.

Although we think that the role of the NCC may vary over time, considering the development of cancer control measures and scientific technologies in the world, we hope that the report will contribute to the President's current decisions on the NCC's direction. For some issues, we have only proposed alternative countermeasures.

We also feel that it is important that we continue to work as patient advocates, and that we advance this mission by having opportunities to regularly meet with and solicit feedback from patients and citizens receiving NCC's services.

<Archive of the Core Member Meeting of Strategic Planning Bureau (review meeting)>

1st	October 22, 2012 (Mon)
2nd	November 26, 2012 (Mon)
3rd	December 12, 2012 (Wed)
4th	January 11, 2013 (Wed)
5th	January 31, 2013 (Thu)
6th	February 25, 2013 (Mon)
7th	March 11, 2013 (Mon)
8th	April 1, 2013 (Tue)
9th	April 8, 2013 (Tue)
10th	April 22, 2013 (Mon)
11th	May 13, 2013 (Mon)
12nd	May 27, 2013 (Mon)
13th	June 10, 2013 (Mon)
14th	June 26, 2013 (Wed)
15th	July 9, 2013 (Tue)
16th	July 22, 2013 (Mon)
17th	August 5, 2013 (Mon)
18th	August 19, 2013 (Mon)
19th	August 26, 2013 (Mon)
20th	September 2, 2013 (Mon)
21th	September 12, 2013 (Thu)
22nd	September 17, 2013 (Tue)
23th	September 19, 2013 (Thu)
24th	October 1, 2013 (Tue)

< Archive of the Symposium "How should NCC be performing in the future?" >
- The 2nd symposium
April 15, 2013 (Mon)
Theme: The role of NCC in medical treatment and cultivating human resources
Symposiasts (honorific titles omitted):
Manabu Muto (Professor of the Department of Therapeutic Oncology, Kyoto University Graduate School of Medicine)
Kagami Yoshikazu (Professor of the Department of Radiology, School of Medicine, Showa University)
Hideo Kunito (Director of the Department of Respiratory Medicine of Mitsui Memorial Hospital)
Takeshi Sano (Director of the Department of Gastroenterological Surgery, the Cancer Institute Hospital of JFCR)

- The 3rd symposium
June 24, 2013 (Mon)
Theme: What can we expect from the NCC research projects?
Symposiasts (honorific titles omitted):
Kohei Miyazono (Dean and Professor, Graduate School of Medicine, The University of Tokyo)
Hiroyuki Mano (Professor, the Department of Cellular Signaling, Graduate School of Medicine, the University of Tokyo)
Keitaro Matsuo (Director of the Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute)
Tomotaka Sobue (Professor of the Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University)

- The 4th symposium
July 26, 2013 (Fri) Theme: The role to be played by and expectations for the NCC internationally
Symposiasts:
Dr. Jin Soo Lee (President of the National Cancer Center, Korea
Dr. Ann Chao (Cancer research program director, Beijing Office of the National Cancer Institute, United States)
Dr. Patrick Johnston (Dean of the Medical School, Queen's University Belfast, United Kingdom)
Dr. Bruce A. Chabner (Clinical Research Director, Cancer Center of Massachusetts General Hospital, United States

- The 5th symposium
September 24, 2013 (Tue)
Theme: Expectations for Nursing in the NCC
Symposiasts (honorific titles omitted):
Kazue Aoki (Vice President, Shizuoka Cancer Center)
Masako Akiyama (Director of Hakuju-ji Home Visit Nursing Station)
Noriko Morishita (Director of the National Hospital Organization Osaka Medical Center Clinical Research Center)
Hiroko Komatsu (Professor, Faculty of Nursing and Medical Care)

Preparation of the opinion to be submitted to the Special Advisor Meeting on Health and Medical Strategy

We prepared an opinion on the significance of the NCC as a part of the Center for Creating Innovative Medical Technologies to be submitted by President Hotta, a member of the Special Advisor Meeting, to the Special Advisor Meeting on Health and Medical Strategy (http://www.kantei.go.jp/jp/singi/kenkouiryou/sanyokaigou/kaisai.html), which studies and discusses the growth strategy for the health and medical sectors and important issues associated with medical research.

Office of Public Relations, Strategic Planning Bureau

Kiyotaka Watanabe, Shinichiro Takahashi, Rika Kojima, Miyako Horikoshi, Chie Shirai, Kajitsu Ogawa, Yuki Hatano

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. Our task is management of the NCC homepage (http://www.ncc.go.jp/), publication of reports, coverage and delivery of press conferences and preparing press releases. By sharing the mission and vision between staff 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 Strategic Planning Bureau, we performed prompt decision making regarding the public relations policy; organized a PR committee and received information on the publicity work from each department; and drafted out the publication plan. Also, through distribution of intramural information for staff members, we shared vital messages via e-mail and/or bulletin boards to facilitate communication between the staff and the executive. We distributed information promptly by publishing and sharing press releases, press conference and seminars about novel treatment, research activities and notable accomplishments within NCC and elsewhere.

- Renewal of homepage (September): PR activities, event information, booklet, etc.
- Public information magazine "hibiho" (November): for patients in NCC Hospital and NCC Hospital East
- Revision of NCC pamphlet (June)
- Crisis control PR seminar for executive and staff (December)
- Support of events, seminars and distribution of public information
  (idea exhibition for daily life 2013, Black-Jack seminar 2013, the seventh NCC Hospital East campus day, etc.)
- Media support at press conferences, press releases and media coverage

Office of International Affairs, Strategic Planning Bureau

Seiichiro Yamamoto, Sakiko Suzuki, Maria Imada

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

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

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

Human resource development

The Office is preparing several MOUs (Memorandam Of Understanding) with cancer centers world-wide and will sign them next year. Along with the MOUs, we are planning to exchange staff and conduct collaborative research projects. This plan aims to develop human resources not only for medical doctors and researchers but also for staff in every department. As the first step, the office supported the dispatch of a medical oncologist to the US National Cancer Institute and is in preparation to send nurses to Massachusetts General Hospital next year.

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.

Medical contributions

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 2013, the NCC has had 95 visiting fellows, 146 a-couple-of-days observers at both the Tsukiji (Tokyo) and Kashiwa (Pref. of Chiba) campuses. They came mostly from Asian countries. The Office has begun an alumni organization of fellows this year to allow us all to keep in contact.

As an another important topic, NCC supports several activities planned and conducted by the Japanese government such as the Ministry of Health, Labour, and Welfare and the Ministry of Economy, Trade and Industry for inbound and outbound expansion of Japanese medicine and cutting-edge medical technology.

Multi-institutional Clinical Trial Support Center

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

Introduction

The Multi-institutional Clinical Trial Support Center is a direct sector reporting directly to the President of the National Cancer Center. The Center supports multi-institutional clinical trials conducted by the Japan Clinical Oncology Group (JCOG) aiming to improve the standard treatment for cancer patients. The JCOG is a nationwide, multi-institutional, multi-disease, multi-modality cooperative study group supported by the National Cancer Center Research and Development Fund and the Health Sciences Research Grants from the Ministry of Health, Labour and Welfare. The JCOG has 16 disease-oriented or modality-oriented subgroups covering most cancer types except leukemia and pediatric cancer, and approximately 4,000 physicians from 200 hospitals participate in the JCOG.

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

Routine activities

At the end of 2013, the Center had supported 36 open trials, 30 trials on follow-up, 14 trials in preparation, and the yearly patient accrual was 2,827. As for safety management, 70 adverse event reports for serious and/or unexpected adverse events were submitted to and reviewed by the Data and Safety Monitoring Committee (DSMC). The DSMC also reviewed 3 interim analysis reports, and 68 protocol amendments/revisions. The Audit Committee made site visits for 56 sites in 18 hospitals, and a total of 166 cases were audited. A central pathology review is on-going in 5 trials (2 on lymphomas, 1 on osteosarcomas, 1 on lung cancer, and 1 on pancreatic cancer). The quality control program for radiotherapy continued in 13 trials. A web-based 24-hour online patient registration system is available in 31 trials among 36 open trials.

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

Research activities

The Center is conducting intramural studies related to clinical trial methodology including statistical methods and data management, such as a timing analysis for streamlining clinical trial protocol development, a validity analysis of clinical tumor response and pathological tumor response by chemotherapy, an outcome analysis of institutional difference, a propensity score analysis comparing stereotactic body radiotherapy and lobectomy for operable clinical stage IA lung cancer, and a validity analysis of surrogate time-to-event endpoints.

List of papers published in 2013
Journal

1. Kurokawa Y, Shibata T, Ando N, Seki S, Mukaida H, Fukuda H. Which is the optimal response criteria for evaluating preoperative treatment in esophageal cancer: RECIST or histology? Ann Surg Oncol, 20:3009-3014, 2013
2. Shirao K, Boku N, Yamada Y, Yamaguchi K, Doi T, Goto M, Nasu J, Denda T, Hamamoto Y, Takashima A, Fukuda H, Ohtsu A. Randomized Phase III study of 5-fluorouracil continuous infusion vs. sequential methotrexate and 5-fluorouracil therapy in far advanced gastric cancer with peritoneal metastasis (JCOG0106). Jpn J Clin Oncol, 43:972-980, 2013
3. Iwasaki Y, Sasako M, Yamamoto S, Nakamura K, Sano T, Katai H, Tsujinaka T, Nashimoto A, Fukushima N, Tsuburaya A. Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancers (JCOG0210). J Surg Oncol, 107:741-745, 2013
4. Nakamura K, Katai H, Mizusawa J, Yoshikawa T, Ando M, Terashima M, Ito S, Takagi M, Takagane A, Ninomiya M, Fukushima N, Sasako M. A phase III study of laparoscopy-assisted versus open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric Cancer (JCOG0912). Jpn J Clin Oncol, 43:324-327, 2013
5. Takizawa K, Takashima A, Kimura A, Mizusawa J, Hasuike N, Ono H, Terashima M, Muto M, Boku N, Sasako M, Fukuda H. A phase II clinical trial of endoscopic submucosal dissection for early gastric cancer of undifferentiated type: Japan Clinical Oncology Group study JCOG1009/1010. Jpn J Clin Oncol, 43:87-91, 2013
6. Mukai H, Watanabe T, Mitsumori M, Tsuda H, Nakamura S, Masuda N, Yamamoto N, Shibata T, Sato A, Iwata H, Aogi K. Final results of a safety and efficacy trial of preoperative sequential chemoradiation therapy for the nonsurgical treatment of early breast cancer: Japan Clinical Oncology Group Study JCOG0306. Oncology, 85:336-341, 2013
7. Ogura M, Itoh K, Ishizawa K, Kobayashi Y, Tobinai K, Kinoshita T, Hirano M, Ueda R, Shibata T, Nakamura S, Tsukasaki K, Hotta T, Shimoyama M, Morishima Y. Phase II study of ABV (doxorubicin with increased dose, bleomycin and vinblastine) therapy in newly diagnosed advanced-stage Hodgkin lymphoma: Japan Clinical Oncology Group study (JCOG9705). Leuk Lymphoma, 54:46-52, 2013
8. Shibui S, Narita Y, Mizusawa J, Beppu T, Ogasawara K, Sawamura Y, Kobayashi H, Nishikawa R, Mishima K, Muragaki Y, Maruyama T, Kuratsu J, Nakamura H, Kochi M, Minamida Y, Yamaki T, Kumabe T, Tominaga T, Kayama T, Sakurada K, Nagane M, Kobayashi K, Nakamura H, Ito T, Yazaki T, Sasaki H, Tanaka K, Takahashi H, Asai A, Todo T, Wakabayashi T, Takahashi J, Takano S, Fujimaki T, Sumi M, Miyakita Y, Nakazato Y, Sato A, Fukuda H, Nomura K. Randomized trial of chemoradiotherapy and adjuvant chemotherapy with nimustine (ACNU) versus nimustine plus procarbazine for newly diagnosed anaplastic astrocytoma and glioblastoma (JCOG0305). Cancer Chemother Pharmacol, 71:511-521, 2013
9. Morizane C, Okusaka T, Mizusawa J, Takashima A, Ueno M, Ikeda M, Hamamoto Y, Ishii H, Boku N, Furuse J. Randomized phase II study of gemcitabine plus S-1 versus S-1 in advanced biliary tract cancer: a Japan Clinical Oncology Group trial (JCOG 0805). Cancer Sci, 104:1211-1216, 2013
10. Yamada Y, Boku N, Nishina T, Yamaguchi K, Denda T, Tsuji A, Hamamoto Y, Konishi K, Tsuji Y, Amagai K, Ohkawa S, Fujita Y, Nishisaki H, Kawai H, Takashima A, Mizusawa J, Nakamura K, Ohtsu A. Impact of excision repair cross-complementing gene 1 (ERCC1) on the outcomes of patients with advanced gastric cancer: correlative study in Japan Clinical Oncology Group Trial JCOG9912. Ann Oncol, 24:2560-2565, 2013

Department of Biostatistics

Takeharu Yamanaka, Aya Kuchiba, Shogo Nomura, Seiichiro Yamamoto, Taro Shibata

Introduction

The Department of Biostatistics was newly launched in July 2013. One of our major activities is to provide essential collaboration with medical researchers, from devising efficiently-designed research projects, driving studies, drawing up analytical plans, and implementing statistical analyses, to publishing the results. We target all types of medical research carried out in the National Cancer Center (NCC). As an interdisciplinary department shared by the entire NCC that covers both the Tsukiji and Kashiwa Campuses, our Department aims at providing cross-sectional and essential contributions.

Routine activities

Biostatistics is a major field of statistics that focuses on medical and public hygiene research tasks, and studies how to collect data (design) and how best to draw information from the data (analysis). At the Department of Biostatistics, staff members take part in actual medical research projects, and provide the standard or the latest statistical methodologies, and, at the same time, use such experiences to identify on-site problems and develop new statistical methods using mathematical techniques. These two-way activities may be likened to the wheels of a car; indeed, our mission is to contribute to enhancing the quality and quantity of research carried out at the NCC through the two activities. As of December 31, 2013, the Department of Biostatistics is an organization comprising five expert biostatisticians, an impressive lineup that makes the Center one of the top research institutions in Japan and thus enables us to continue releasing high-quality research results.

Research activities

Through joint research, we work to identify statistical problems that arise from various fields of application, and develop new research frameworks and mathematical models to solve those problems. After next year, we plan to successively publish our research results for statistical methodology. Our researchers tackle a broad range of themes, from clinical study methodologies to genomic analyses, and molecular epidemiology research, to name just a few. Besides, with the goal of training outstanding personnel who contribute to promoting clinical research and activating the center's clinical studies, we carry out diverse lectures and seminars on the methodology and practice of biostatistics and clinical research. Part of the content is already being distributed nationwide via the web (http://www.icrweb.jp/).

Office for Advanced Medical Care Evaluation

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

Introduction

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

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

Intellectual Property and Research Alliance Division

Shizuo Ao, Genta Ohno, Yuji Shinoda, Yasuo Murata, Reiko Takizaki, Shizuka Makino, Aki Okano, Hiroshi Sato

The National Cancer Center (NCC) promotes the development of cancer diagnosis and treatment, and the improvement of quality of life of cancer patients through its research results which are then made available to society. The Intellectual Property and Research Alliance (IPRA) promotes the practical use of diagnostic agents, therapeutic agents, and medical devices through translation of research results jointly with private companies and academia partners under collaborative research agreements with them.

Activities

IPRA mainly performs activities such as acting as the administrative office for both the NCC Collaborative Research Review Committee and for the NCC Invention Review Committee. This includes the following:

1. Agreement administration including collaborative agreements, licensing agreements, material transfer agreements and confidential disclosure agreements, and so on.
2. Research results administration including inventions such as patent applications and their maintenance associated with acquisition of intellectual property rights and licensing.
3. Coordinating industry-academia partnerships.

The number of NCC's collaborative research agreements and related research fees have been increasing significantly in recent years as shown in Figure 1: (1) The number of agreements Year 2011 (155), Year 2012 (188), (2) The total research fees Year 2011 (¥183 M), Year 2012 (¥248 M).

NCC has a number of patent applications with companies and academia research institutes. In order to focus on promising patents, NCC cuts its cost for the maintenance of patents or/patent applications from a practical perspective. As shown in Figure 2, The number of patent applications in 2012 was 36, the number of abandoned patent applications was 53 and the number of maintained patents and/or patent applications was 218. Compared to 2011 (235) the number of maintained patents and/or patent applications in Year 2012 dropped by 17.

Patent applications

NCC's research results are globally significant and fulfill novel and inventive steps required for patentability.

Recent years have seen a large drop in the worth of patents concerning potential drug targets and screening methods which are not directly linked to the commercialization of products. NCC needs to promote translational research and to make a joint effort with pharmaceutical companies or academic research organizations to achieve commercially available products. Considering the

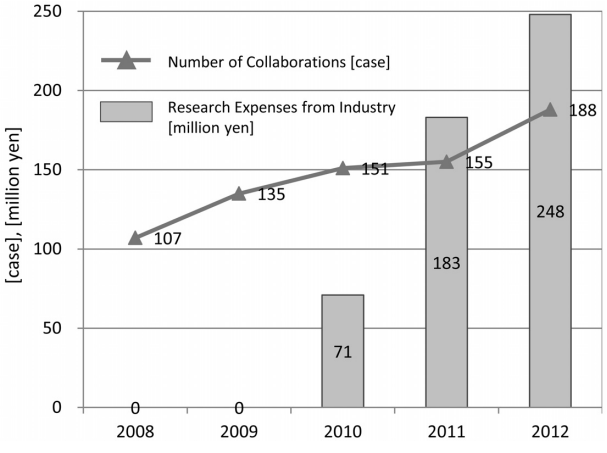

Figure 1. Collaborative Research with Industry

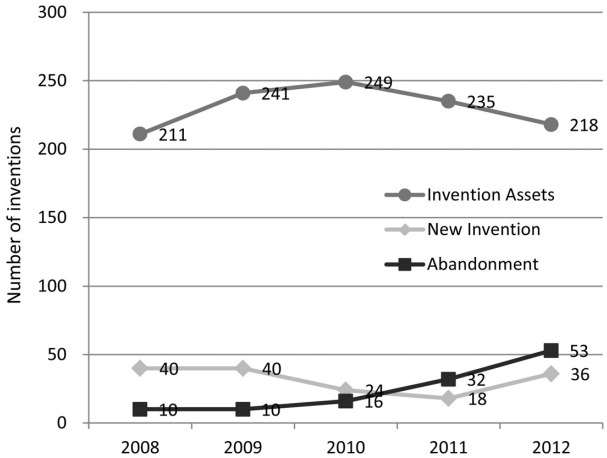

Figure 2. Invention Management

obstacle mentioned above, capability of assessment from the viewpoint of marketability is required in the implementation of a patent application. IPRA performs its duties at a high level, with four staff members having experience in research development, licensing and patents with pharmaceutical companies or medical device companies, and 3 staff members educated to doctoral level in related fields.

Open innovation

In recent years independent companies have found it difficult to develop the technology related to diagnostic drugs and drug discovery on their own. Many companies used to have research and development strategies to complete research and development independently using their own internal resources. Companies now tend towards collaboration with external organizations such as NCC as a research partner.

The cases mentioned below are examples of the tendency of pharmaceutical companies toward collaboration with academia research institutes such as NCC as a research partner.

Daiichi Sankyo has started to fund to universities and academia research institutes to enter into drug discovery collaborative research (TaNeDS) with researchers at universities and academia research institutes in Japan. Asteras has A-cube, and Shionogi runs FINDS to provide grants to academia institutes to enter into collaboration research.

After NCC's transformation into an independent administrative institution, it is important that NCC acquires external funds from industry besides its subsidized operating expenses and other competitive funds.

Organizational academia-industry collaboration

IPRA is developing a system of organizational collaborative research with a partner company or academic institute to promote collaboration under its trend of openness on innovation.

IPRA supports more organizational and more effective collaborative research performance tailored to NCC's research capability and to partner company's or academic institutes' needs.

IPRA foresees the possibility of developing comprehensive collaborative research, and to further the research being performed by both industry researchers and NCC researchers. IPRA performs its activities with the aim of fulfilling such comprehensive research activities so that IPRA promotes collaboration with companies and academia research institutes such as Daiichi Sankyo, RIKEN for drug discovery research, Sysmex for diagnostic products development, Shimadzu for medical devices and AstraZeneca, Merck Serono for clinical trials and translational research.

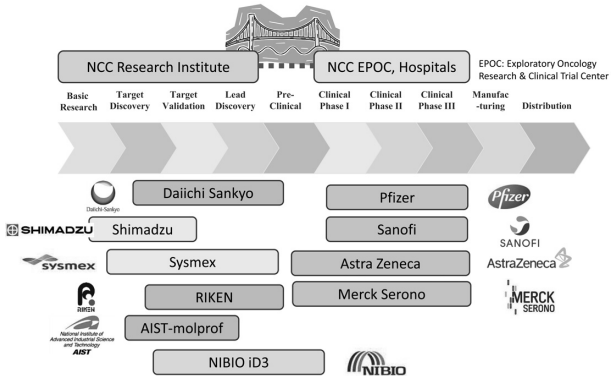

Figure 3. Strategic Alliance with industry

Commercialized products by our research

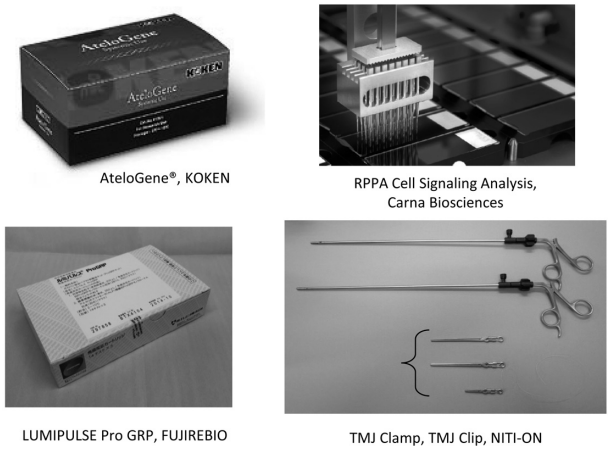

Figure 4. Commercialized products

Press release in relation to academia-industry collaboration

2013/11/07 Sanofi and NCC signed a partnership agreement for clinical trials.

2013/10/28 Sysmex and NCC signed a partnership agreement for the diagnostic drug development of cancer.

2013/09/24 Merck Serono and NCC signed a partnership agreement for clinical trials and translational research.

2013/07/04 Molecular Profiling Research Center for Drug Discovery of Advanced Industrial Science and Technology (AIST) and NCC signed a drug discovery research collaboration agreement.

2012/05/22 Daiichi Sankyo and NCC signed a comprehensive research alliance agreement in drug discovery.

2011/07/19 AstraZeneca and NCC signed a master clinical study agreement.

2011/06/05 Shimadzu and NCC signed a comprehensive collaborative research agreement.

2011/05/25 Pfizer Japan and NCC signed a partnership agreement for clinical trials.

Hospital

Preface

The National Cancer Center Hospital (NCCH) serves the highest level of standard of care with the missions of overall research and development for cancer, striving for novel diagnostic and treatment approaches, palliative care, and patient support.

Followed by the major reorganization in 2012 consisting of 13 common departments and 30 clinical departments, the Orphan Cancer Center was newly set up in collaboration with the National Cancer Center East Hospital (NCCHE) this year. Patients with orphan cancer have been taken care of the appropriate clinical department, however, it is more beneficial, not only in terms of efficient service for patients but also the overall approach to treatment and research to establish a cross-sectional organization consisting of several clinical departments in both the NCCH and NCCHE, Research Institute, and Exploratory Oncology Research & Clinical Trial Center. In addition, it works very closely with the Center for Information Service, which provides information related to orphan cancer.

The construction of the new Medical Examination Building was completed in December. The Department of Radiation Oncology is located in this building and plans to start boron-neutron capture therapy (BNCT) as the first hospital-based BNCT center in the world. On the first basement level, screening is planned to start in May 2014 in the medical examination unit of the Research Center for Cancer Prevention and Screening. Some medical equipment has been moved for use in the examination from the NCCH, so that we expect more effective work and better overall service in the Tsukiji campus. There are chief offices of each clinical department on the second and third floor, and on the fourth and fifth levels, we have placed the Endoscopy Center, which is the largest and well known in Japan. The Center for Information Service and the research units of the Research Center for Cancer Prevention and Screening are placed on the sixth, seventh and eighth levels. We plan to renovate the endoscopy rooms as an ambulant treatment center in the hospital building and to prepare offices for head physicians and attending staff members.

In January, the electronic health record system was renewed, and renamed as MISSION.

In March, we integrated several departments and sections supporting patients, such as the Departments of Palliative Care and Psycho-oncology, Patient Counseling Center and Appearance Supportive Center into the Patient Supportive Care Center (tentative). This center will start full-scale operation in the fiscal year 2014.

At the end of the fiscal year 2013, as a part of the personnel system, the position of the chief in each of twenty-five clinical departments was filled through open recruitment.

We have almost completed the reformation of the NCCH into a regenerated National Cancer Center this year with major changes in the organization and personnel affairs.

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

Organization

President:
Tomomitsu Hotta

Director:
Yasuaki Arai

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

Office of Safety Management
Chief: Hirokazu Chuuman

Office of Infection Control and Prevention
Chief: Minoru Esaki

Clinical Departments — Departments
Chiefs

Common Departments

Outpatient Treatment Center
Chief: Kenji Tamura

Endoscopy Center
Chief: Yutaka Saito

Consultation, Counseling and Support Service Center
Chief: Masashi Kato

Appearance Support Center
Chief: Keiko Nozawa

Rare Cancer Center
Chief: Akira Kawai

Radiation
Chief Technologist: Tomohiko Aso
Chief Technologist: Yoshihisa Abe

Clinical Laboratories
Chief Technologist: Satoshi Nakajima

Surgical Center
Chief: Hitoshi Katai

Physician Referral Service Office
Chief: Hidehito Horinouchi

Clinical Trial Coordination (& Support) Office
Chief: Noboru Yamamoto

Nutrition Management Office
Chief: Mayumi Miyauchi

Health Information Management Office
Chief: Hiroshi Nishimoto

Department of Pharmacy
Chief: Yoshikazu Hayashi

Department of Nursing
Chief: Kazuko Nasu

Clinical Departments

Director:
Yasuaki Arai

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

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

Activities of the Departments

Department of Neurosurgery and Neuro-Oncology

Soichiro Shibui, Yoshitaka Narita, Yasuji Miyakita, Makoto Ohno, Hideyuki Arita

Introduction

Patients with primary and metastatic brain tumors are treated by four neurosurgeons and one senior resident in the Department of Neurosurgery and Neuro-Oncology. Three hundred thirty-four patients were admitted and 106 craniotomies for tumor removal were carried out in 2013 including 39 gliomas, 40 metastatic brain tumors, 7 primary CNS lymphomas, and 12 meningiomas (Table 1). Fifteen ventriculo-peritoneal shunts and 1 neuroendoscopic surgical procedure were also carried out for patients with hydrocephalus. Every craniotomy was performed with the aid of a surgical navigation system (Stealth station). The site of the craniotomy and the extent of tumor removal were visualized on the CRT of this system in real time, contributing to safer and more precise surgery. Intraoperative monitoring with motor- and sensory evoked potential (MEP and SEP) recording as well as preoperative functional MRI and MR tractography were also used to preserve patient neurological function. Twelve awake surgeries were also performed, particularly for removal of gliomas near the speech center. We started work with our intraoperative MRI system in February 2012 and this system was used for most craniotomies. Patients with malignant brain tumors are 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 is held with doctors of the Department of Radiation Oncology on the diagnosis and treatment of patients with brain tumors. Usually 20 patients are hospitalized and two or three of them undergo surgical treatment every week. The Stealth navigation system is used for surgical planning during every craniotomy. The patients with malignant brain tumors receive postoperative radiotherapy and chemotherapy. Statistical analysis revealed that surgical removal of as much of the tumor as possible yielded better survival rates even for the most malignant glioblastomas, which usually recur soon after the surgery without radiotherapy. Concomitant use of chemotherapy is considered to enhance the anti-tumor effect of radiotherapy. Temozolomide has been given to all malignant glioma patients during radiotherapy and repeated every month for 2 years. The 5-year survival rates of the patients with anaplastic astrocytomas and glioblastomas were 66.1% and 10.1%, respectively, which were better than those recorded in the Brain Tumor Registry of Japan. (Table 2). High dose methotrexate is administered to the patients with primary CNS lymphoma before radiotherapy.

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

Research activities

Patients with brain tumors have been registered in the Brain Tumor Registry of Japan (BTRJ) since 1969. More than 100,000 patients have been registered and followed up. The Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, contributes as a managing office of the BTRJ and established on-line registration using the University Hospital Medical Information Network (UMIN) system in 2009. Clinical data during 2001 and 2004 were collected and the report will be published in 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 Cancer Genomics, the National Cancer Center Research Institute. Tumor samples of malignant gliomas were collected and were analyzed with a DNA microarray. FISH analysis using 1p/19q/EGFR/PTEN probes, the determination of the methylation status of O^6-methylguanine-DNA methyltransferase (MGMT) and the mutation of IDH1/2 are also carried out to predict the prognosis of the patients with malignant gliomas.

Clinical trials

The Japan Clinical Oncology Group (JCOG)-Brain Tumor Study Group was organized in 2002 and a multi-institutional randomized controlled trial entitled "A randomized controlled phase II/III study of chemoradiotherapy using ACNU versus procarbazine and ACNU for astrocytoma grade 3 and 4" was conducted. The overall survival of both arms was longer than that of a Temozolomide (TMZ) study conducted by EORTC, however, adverse events such as granulocytopenia and thrombocytopenia were observed more frequently. The enrollment of patients for another randomized study entitled "A multicenter randomized phase II trial of Interferon-beta and Temozolomide combination chemoradiotherapy for newly diagnosed glioblastomas (JCOG 0911)" was finished in January 2012 and the result will be published soon. A clinical trial for metastatic brain tumors is also still ongoing: "A Randomized phase III trial of postoperative whole brain radiation therapy compared with salvage stereotactic radiosurgery in patients with one to four brain metastasis (JCOG 0504)". The efficacy of the gamma knife will be compared to that of whole brain irradiation. A new clinical trial for primary CNS lymphoma and grade III gliomas will start in 2014. These studies, under the surveillance of JCOG, aim to set a standard protocol for treating malignant brain tumor patients. Moreover, a proper methodology for performing randomized studies will be established in the field of neuro-oncology.

Table 1. Number of surgeries by year, 2011-2013

	2013	2012	2011
Glioma	43	47	35
Metastatic brain tumor	41	33	39
Meningioma	12	7	5
Primary CNS lymphoma	7	4	6
Other brain tumor	8	5	7
Others	27	36	31
Total	140	132	123

Table 2. Type of procedure

Craniotomy	106
V-P shunt	15
Placement of Ommaya's reservoir	4
Others	15

Table 3. Survival rates

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

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

List of papers published in 2013
Journal

1. Shibui S, Narita Y, Mizusawa J, Beppu T, Ogasawara K, Sawamura Y, Kobayashi H, Nishikawa R, Mishima K, Muragaki Y, Maruyama T, Kuratsu J, Nakamura H, Kochi M, Minamida Y, Yamaki T, Kumabe T, Tominaga T, Kayama T, Sakurada K, Nagane M, Kobayashi K, Nakamura H, Ito T, Yazaki T, Sasaki H, Tanaka K, Takahashi H, Asai A, Todo T, Wakabayashi T, Takahashi J, Takano S, Fujimaki T, Sumi M, Miyakita Y, Nakazato Y, Sato A, Fukuda H, Nomura K. Randomized trial of chemoradiotherapy and adjuvant chemotherapy with nimustine (ACNU) versus nimustine plus procarbazine for newly diagnosed anaplastic astrocytoma and glioblastoma (JCOG0305). Cancer Chemother Pharmacol, 71:511-521, 2013
2. Arita H, Narita Y, Ohno M, Miyakita Y, Okita Y, Ide T, Shibui S. Management of glioblastoma in an NF1 patient with moyamoya syndrome: a case report. Childs Nerv Syst, 29:341-345, 2013
3. Arita H, Narita Y, Fukushima S, Tateishi K, Matsushita Y, Yoshida A, Miyakita Y, Ohno M, Collins VP, Kawahara N, Shibui S, Ichimura K. Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. Acta Neuropathol, 126:267-276, 2013
4. Okita Y, Narita Y, Suzuki T, Arita H, Yonemori K, Kinoshita T, Fujiwara Y, Tsuda H, Komoike Y, Nakagawa H, Tamaki Y, Tomita Y, Shibui S, Maruno M. Extended trastuzumab therapy improves the survival of HER2-positive breast cancer patients following surgery and radiotherapy for brain metastases. Mol Clin Oncol, 1:995-1001, 2013
5. Ohno M, Narita Y, Miyakita Y, Matsushita Y, Yoshida A, Fukushima S, Ichimura K, Shibui S. Secondary glioblastomas with IDH1/2 mutations have longer glioma history from preceding lower-grade gliomas. Brain Tumor Pathol, 30:224-232, 2013
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7. Momota H, Narita Y, Miyakita Y, Shibui S. Secondary hematological malignancies associated with temozolomide in patients with glioma. Neuro Oncol, 15:1445-1450, 2013
8. Fukushima S, Narita Y, Miyakita Y, Ohno M, Takizawa T, Takusagawa Y, Mori M, Ichimura K, Tsuda H, Shibui S. A case of more than 20 years survival with glioblastoma, and development of cavernous angioma as a delayed complication of radiotherapy. Neuropathology, 33:576-581, 2013
9. Sato A, Okada M, Shibuya K, Watanabe E, Seino S, Suzuki K, Narita Y, Shibui S, Kayama T, Kitanaka C. Resveratrol promotes proteasome-dependent degradation of Nanog via p53 activation and induces differentiation of glioma stem cells. Stem Cell Res, 11:601-610, 2013
10. Arita H, Narita Y, Takami H, Fukushima S, Matsushita Y, Yoshida A, Miyakita Y, Ohno M, Shibui S, Ichimura K. TERT promoter mutations rather than methylation are the main mechanism for TERT upregulation in adult gliomas. Acta Neuropathol, 126:939-941, 2013

Department of Ophthalmic Oncology

Shigenobu Suzuki, Yukiko Aihara

Introduction

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

Routine activities

Our outpatient service is open for three 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) Retinoblastomas

Unless the patient's family has anxiety about preserving the affected eye, if the eye has already suffered from complications such as secondary glaucoma or severe hemorrhage, or if extraocular extension of the retinoblastoma is strongly suspected, we can offer the family eye-preserving treatment. Initial systemic chemotherapy and additional local procedures, 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 in the Western literature 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. A 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, rhabdomyosarcomas are a malignant tumor that require systemic chemotherapy and radiation after biopsy. The most common orbital tumors in adults include cavernous hemangiomas, lacrimal gland tumors, lymphomas, metastatic tumors, and orbital inflammatory diseases. Patients with a biopsy-confirmed orbital lymphoma are referred to the Department of Hematology, and Hematopoietic Stem Cell Transplantation. Total resection with 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 carcinomas, sebaceous carcinomas, and squamous cell carcinomas. 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 retinoblastomas via selective ophthalmic artery infusion using a balloon catheter. This procedure was first introduced in our hospital in 1987, and has been modified and performed after 2009 in more than 20 countries. We are planning a clinical trial on selective ophthalmic

artery injection therapy for an initial treatment method.

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

The National Registry of Retinoblastomas 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 provides epidemiological data.

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

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

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

Table 1. Number of patients

Retinoblastoma	54
Choroidal melanoma	27
Other intraocular tumors	27
Eyelid tumor	21
Conjunctival tumor	11
Orbital tumor	16
Ocular adnexal lymphoma	14
Other	24
Total	194

Table 2. Type of procedure

Retinoblastoma	
Selective ophthalmic arterial injection	122
Laser and/or vitreous injection	138
Ruthenium brachytherapy	11
Enucleation	18
Examination under general anesthesia	6
Choroidal melanoma	
Ruthenium brachytherapy	6
Enucleation	2
Resection of ciliary body tumor	2
Resection of eyelid tumor	13
Resection of conjunctival tumor	8
Resection of orbital tumor	5
Others	17
Total	349

List of papers published in 2013
Journal

1. Inaba K, Ito Y, Suzuki S, Sekii S, Takahashi K, Kuroda Y, Murakami N, Morota M, Mayahara H, Sumi M, Uno T, Itami J. Results of radical radiotherapy for squamous cell carcinoma of the eyelid. J Radiat Res, 54:1131-1137, 2013
2. Honda K, Yamamoto N, Nokihara H, Tamura Y, Asahina H, Yamada Y, Suzuki S, Yamazaki N, Ogita Y, Tamura T. Phase I and pharmacokinetic/pharmacodynamic study of RO5126766, a first-in-class dual Raf/MEK inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 72:577-584, 2013

Department of Head and Neck Oncology

Seiichi Yoshimoto, Fumihiko Matsumoto, Tsutomu Nomura, Daisuke Maki, Sadahiro Kishishita

Introduction

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

Our Department has developed and performed the original surgical procedures 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 the National Cancer Center Hospital (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 2013, 303 patients with head and neck tumors underwent surgery under local or general anesthesia; 95 and 208, respectively, including 46 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. Table 3 shows the rate of postoperative complications.

Research activities

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

Clinical trials

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

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

Tongue	40
Oral Cavity (without tongue)	35
Nasal and paranasal cavity	22
Nasopharynx	3
Oropharynx	26
Hypopharynx	63
Cervical esophagus	10
Larynx	15
Salivary Gland	11
Thyroid	20
Parathyroid	1
Neck	52
Others	5
Total	303

Table 2. Type of procedure

Skull base (+reconstruction)	1(1)
Maxillectomy (+reconstruction)	21(2)
Glossectomy (+reconstruction)	33(6)
Resection of Oral Cavity (+reconstruction)	33(11)
Nasopharyngectomy	3
Oropharyngectomy (+reconstruction)	16(4)
Endoscopic resection of hypopharynx	35
Partial pharyngectomy (+reconstruction)	11(7)
Total laryngopharyngectomy (+recon.)	10(10)
Partial laryngectomy	3
Total laryngectomy (+reconstruction)	5(2)
Thyroidectomy	20
Parathyroidectomy	1
Parotidectomy	10
Neck dissection (+reconstruction)	24(1)
Resection of parapharyngeal tumor	3
Voice prosthesis	7
Lymphadenectomy	49
Others (+reconstruction)	18(2)
Total	303(46)

Table 3. Operative morbidity and mortality

Major surgical complications	7 cases	(3.4%)
Postoperative death within 30 days	0 case	
Postoperative hospital death	0 case	

List of papers published in 2013
Journal

1. Ohtomo R, Mori T, Shibata S, Tsuta K, Maeshima AM, Akazawa C, Watabe Y, Honda K, Yamada T, Yoshimoto S, Asai M, Okano H, Kanai Y, Tsuda H. SOX10 is a novel marker of acinus and intercalated duct differentiation in salivary gland tumors: a clue to the histogenesis for tumor diagnosis. Mod Pathol, 26:1041-1050, 2013
2. Yamazaki H, Mori T, Yazawa M, Maeshima AM, Matsumoto F, Yoshimoto S, Ota Y, Kaneko A, Tsuda H, Kanai Y. Stem cell self-renewal factors Bmi1 and HMGA2 in head and neck squamous cell carcinoma: clues for diagnosis. Lab Invest, 93:1331-1338, 2013

Department of Plastic and Reconstructive Surgery

Shimpei Miyamoto, Shuji Kayano, Masanobu Sakisaka, Masaki Arikawa

Introduction

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

Routine activities

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

Research activities

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

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

With the objective of addressing these four aspects, establishing a standard of reconstructive surgery and developing new techniques of reconstructive surgery are the most important aims of our studies.

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

Other developments in reconstructive procedures in cooperation with other Divisions such as Orthopedic Surgery, Breast Surgery, and so on, are proceeding, as shown in Table 1.

Table 1. Cooperative efforts with other divisions

Head and Neck	48
Orthopedic Surgery	67
Breast Surgery	81
HB&P Surgery	4
Esophageal Surgery	2
Dermatology	2
Others	5

Table 2. Operative Procedures

Free flap	106
Other microsurgery	12
Pedicled flap	36
Others	138

List of papers published in 2013
Journal

1. Miyamoto S, Kayano S, Umezawa H, Fujiki M, Sakuraba M. Vastus lateralis muscle flaps for monitoring buried anterolateral thigh flaps. J Craniofac Surg, 24:1739-1740, 2013
2. Miyamoto S, Kayano S, Umezawa H, Fujiki M, Sakuraba M. Flow-through fibula flap using soleus branch as distal runoff: a case report. Microsurgery, 33:60-62, 2013
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Department of Breast Surgery

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

Introduction

The Breast Surgery Division deals with the treatment of breast cancer, as well as the diagnosis of breast diseases and assessment of lymph nodes in the axillary and clavicular regions which are suspected of harboring metastases. Although breast-conserving therapy (BCT) has accounted for 51.8% of the cases, BCT was not indicated in more than 40% of the cases even when the cancer was at an early stage. In 2010, immediate breast reconstruction became one of the choices for these patients in whom breast preservation was impossible, and a total of 65 immediate breast reconstructions were performed in 2013, comprising more than 12% of all the cases. The number of cases of immediate breast reconstruction has gradually increased year by year to match the increased needs of patients. Sentinel lymph node (SLN) biopsies (SLNB) were performed in 74.2% of the cases. Following SLNB, the axillary lymph node dissection (ALND) could be avoided when the SLNB was negative. In conjunction with the one-step nucleic acid amplification (OSNA) assay, more positive nodes including micrometastases have been detected, compared to traditional diagnosis by frozen section alone and 20.6% of the cases after SLNB needed additional ALN dissection.

Routine activities

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

BCT usually consists of local excision of the tumor followed by postoperative irradiation of the remaining breast, and is usually indicated for a tumor smaller than 3 cm. Patients with multi-focal lesions or extensive micro-calcifications detected with mammography are not eligible for BCT. Neo-adjuvant chemotherapy (NAC) and neo-adjuvant endocrine therapy (NAET) for operable advanced breast cancer are performed to avoid a mastectomy and to test the tumor sensitivity to therapeutic agents. Patients receive adjuvant chemo-endocrine therapy depending upon their prognostic and predictive factors, which include the number of lymph nodes involved, the histological grade of the tumor and secondary prognostic markers (HER2/neu, ER, PgR, and so on). Widely accepted factors that predict a response to a specific therapy are estrogen and progesterone receptors for hormone therapy and HER2 for trastuzumab. Since hormone-receptor positive patients tend to receive less chemotherapy nowadays, NAC has been decreasing and only 7.0% of all patients received neoadjuvant therapy in 2013.

Research activities

Sentinel node biopsy after Neo-adjuvant chemotherapy

As indications for NAC become more widespread, the question arises if SLNB is appropriate for axillary staging in patients after NAC. The accuracy and feasibility of SLNB after NAC have been evaluated (Kinoshita et al.).

MR guided-surgery and Real-time Virtual Sonography

A feasibility study to establish the standard surgery for breast tumors using diagnostic images during surgery in an MRX operating room is ongoing (Hojo et al.). A study to evaluate the utility of the impact of supine MRI on surgical decision making was conducted. Supine MRI had more accuracy in the measurement of invasive ductal carcinoma compared to prone MRI, suggesting the usefulness

of supine MRI before breast conserving surgery (Kinoshita et al.). A feasibility study using Real-time Virtual Sonography (RVS) is also being planned for breast conserving surgery. RVS can synchronize the US images and the MRI or CT images using a position tracking system with a magnetic sensor. It is thought to be useful for making an accurate excision line when US cannot detect suspicious daughter lesions or intraductal spread revealed with MRI or CT.

Radiofrequency Ablation (RFA)

With the widespread application of screening mammography and novel imaging techniques such as MRI, the mean size of the breast tumors detected has continued to decrease.

RFA, which is thought to be a less invasive surgical maneuver, has been introduced in the field of breast cancer therapy. We previously validated the safety and efficacy of RFA of small breast cancers (less than 1.0 cm) using saline-cooled electrodes (Phase I/II study; Kinoshita et al.). Our secondary goals are to determine the size, configuration and pathological features of acute RFA treatment of breast cancers, and clinical studies have been conducted to evaluate the oncologic safety of RFA in terms of local recurrence.

Sentinel lymph node biopsy with One-Step Nucleic acid Amplification (OSNA)

The OSNA assay that quantitatively measures CK19 mRNA detects sentinel lymph node metastases even at the molecular level. To evaluate the clinical significance of intraoperative SLN metastases detected by OSNA, we compare the OSNA results with that from conventional histological diagnosis. Furthermore, we examine the possibility of omitting axillary lymph node dissection in limited subsets of patients by using both methods.

Clinical trials

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

   A trial of image-guided radiofrequency ablation (non-surgical therapy) has been accomplished for early-stage breast carcinomas of less than 1.0 cm in diameter. After the trial period of some years, the indication has just been expanded up to 1.5 cm in diameter and this technique is certified as an advanced medical treatment by the Ministry of Health, Labour and Welfare.

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

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

3) Denosumab adjuvant treatment (D-CARE)

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

4) Scalp-cooling device during chemotherapy

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

5) Sentinel lymph node (SLN) biopsy

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

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

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

7) Registration Data-base System of breast cancer patients who underwent lymph node metastasis diagnosis with the OSNA® method (LynoLog Data-base)

   The aim of this study is to accumulate the administrative data of cases with OSNA method in a common database, LynoLog, and to construct various new treatment guidelines based on the data.

Table 1. Number of patients

		2012	2013
Primary breast cancer		494	555
	cStage 0	76	99
	I	199	215
	II	194	203
	III	17	33
	IV	8	5
	unknown	2	0
Other malignant breast disease		3	4
Total		497	559

16 case were bilateral breast cancer.

Table 2. Type of procedure

	2010		2011		2012		2013	
Total number of operations	482		576		581		613	
Total numbers of primary breast cancer	482		525		494		555	
Mastectomy (%)	213	(44)	250	(48)	234	(45)	263	(47)
Breast-conserving surgery (%)	269	(56)	269	(51)	275	(53)	283	(51)
Radiofrequency ablation (%)			6	(1)	6	(1)	9	(2)
Axillary lymph node dissection (ALND) (%)	136	(28)	205	(42)	188	(38)	93	(18)
Sentinel lymph node biopsy (SLNB) (%)	316	(66)	402	(81)	409	(83)	347	(66)
ALND after SLNB (%)			113	(23)	103	(21)	83	(16)
Immediate breast reconstruction (%)	13	(3)	74	(14)	62	(13)	65	(12)
Neoadjuvant therapy	72	(15)	57	(11)	45	(8)	38	(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

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Journal

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Department of Breast and Medical Oncology

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

Introduction

The Breast and Medical Oncology Division is engaged in the clinical management of and research into adult malignancies including breast cancer, gynecologic cancer, soft-tissue sarcoma, tumors of unknown primary sites and other rare types of solid tumors. We envision becoming a premier oncology department which leads cancer care in Japan and in the world. Our mission is to provide patient-centered, state-of-the-art medical care to cancer patients, to pursue the development of new effective cancer treatment through clinical and translational research, and to nurture specialists in breast and medical oncology. An evidence-based, research-oriented and multi-disciplinary approach is the core value of our practice.

Clinical activities

1. Setup

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

2. Performance

There were a total of 782 first visits of new patients in 2013 (Table 1). Approximately two thirds of the new patients were referred from other division of NCCH. About half of the new patients are breast cancer patients, but it is noteworthy that there were 111 and 87 patients with primary unknown cancers and adult sarcomas, respectively. The number of outpatient chemotherapy procedures delivered by our division was 7777, which accounts for 30% of the total number and ranks first among the number of treatments delivered at the Outpatient Treatment Center.

We have approximately 26 (range 22-35) inpatients daily. Terminally-ill patients are transferred to palliative care units or in-home care clinics outside the National Cancer Center Hospital (NCCH), and 29 patients from our Division died in NCCH in 2013. An autopsy was undertaken in five patients.

3. Conference

The Briefing Conference is held every morning to discuss the evidenced-based care for individual patients. The research conference is held on Thursdays, and the Journal Club on Fridays. Multidisciplinary Case Conferences with diagnostic radiologists, surgeons, and pathologists are held once a week for breast and gynecologic cancer patients. We also participate in the Exploratory Oncology Research and Clinical Trial Center Conference on Monday as an active member.

A monthly Breast Cancer Conference is held with the participation of multidisciplinary specialists to discuss recent topics in breast oncology and to update institutional treatment guidelines. The treatment guidelines for breast cancer, both primary and metastatic, were updated in January, 2013.

4. Coordination of care

Three board-certified Breast Cancer Specialist Nurses help the smooth running of the Department through providing seamless and comprehensive care to breast cancer patients. Group-assigned pharmacists support patients in the ward and in the clinic. We encourage patients who receive chemotherapy to participate in the "Cosmetic Program" which is run by the Appearance Care Center.

Most patients are supported by the Consultation, Counseling and Support Service Center for coordination of care. Post-operative breast cancer patients without disease recurrence are referred to local breast cancer specialists participating in the Tokyo Breast Consortium network (http://breastcons.com/).

Research activities

Our research interests extend across a wide range of topics related to treatment and clinical program development. Many of our studies are secured by public and consignment research grants. In 2013, we conducted ten research programs as the primary investigator and also participated in an additional nine programs as the co-investigator in research programs secured by competitive research funds.

In 2013, we actively enrolled patients in phase I studies as well as national and international studies

(Table 2). Of note we launched a pharmacokinetic and dose-finding study on eriburin/oraparib in anthracycline- and taxane-pretreated triple negative breast cancer as our fourth investigator-initiated clinical trial. A new molecular imaging study has been launched in cooperation with the Research Institute.

We value cancer survivorship as our research theme in order to develop a patient-centered comprehensive care program. In 2013 we took leadership in developing a guideline for young breast cancer patients who wish to preserve their fertility after treatment in cooperation with gynecologist and reproductive specialists. The study is planned to be published this year (2014).

Education

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

Future prospects

We continue in proposing a near-future model of the clinical management of adult solid tumors. Based in particular on our rich clinical experience in rare adult tumors, we aim to build a comprehensive program which includes a tumor registry, translational research, clinical trials and patient care. We would also like to improve the efficiency and efficacy of drug development by coordinating basic and translational studies in early-phase clinical trials.

List of papers published in 2013
Journal

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10. Nagatsuma AK, Shimizu C, Takahashi F, Tsuda H, Saji S, Hojo T, Sugano K, Takeuchi M, Fujii H, Fujiwara Y. Impact of recent parity on histopathological tumor features and breast cancer outcome in premenopausal Japanese women. Breast Cancer Res Treat, 138:941-950, 2013
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Table 1. Demographics of Patients at their first Visit to the Clinic of the Breast and Medical Oncology Division (Jan - Dec, 2013)

No of 1st Visits	n	%	
Total	782		
Breast	372	47.5	
GYN	131	16.8	
Cancer of primary unknown origin	111	14.1	
Sarcoma	87	11.1	
Others	81	10.3	
Purpose of consultation			
2nd opinion	34	4.3	
Treatment at NCCH	67	8.5	
Referrals from other hospitals	219	28.0	
Referrals from other divisions in NCCH	503	64.3	(100)
Breast surgery	320		(63.6)
GYN	82		(16.3)
Urology	21		(4.2)
Orthopedics	16		(3.1)
Others	64		(12.7)
Others	1	0.1	

Table 2. Active Clinical Trials (Jan. 2013-Dec. 2013)

Disease	Clinical setting	Phase	Protocol	Regimen	status
Breast	Adjuvant	III	BEATRICE	CTx vs CTx + bevacizumab	Active, not recruiting
		III	ALTTO	lapatinib vs HCN vs lapa/HCN	Active, not recruiting
		III	CREATE-X(JBCRG04)	capecitabine vs none post-NAC	Active, not recruiting
		III	D-CARE	Denosumab vs placebo	Active, not recruiting
		III	APHINITY	CTx+HCN/placebo vs CTx/HCN/ pertuzumab	Active
		III	POTENT	HTx+S1 vs HTx alone	Active
	Metastatic	III	JCOG1017	Surgery vs no surgery for primary Stage IV BC	Active
		III	MARIANNE	RO5304020+/- RO4368451 vs HCN/ PTX	Active
		III	NK105	NK105 vs paclitaxel	Active
		III	PALOMA-2	Letrozole +/- PD0332991	Active
		III	ELTOP (WJOG)	lapa/capecitabine vs HCN/capecitabine	Active
		II	CAPTURE	Paclitaxel/bevacizumab vs maintenance endocrine therapy	Active
		II	TARGET	Tamoxifen vs high-dose tamoxifen	Active
		II	lapaHER	lapatinib/HCN	Active
		II	CBDCA/S1 for TNBC	CBDCA/S1	Active
		I/II	CAPIRI	capecitabine/CPT-11	Active
		I/II	S1/docetaxel	S1/docetaxel	Active
		I/II	Lapatinib/eriburin	Lapatinib/eriburin	Active
		I/II	EO	Eriburin/AZD2281	Active
		PK	Eriburin PK	eriburin	Active
Ovary	Adjuvant	III	AZD2281	Chemotherapy+/-AZD2281	
	Advanced	III	JCOG0602	primary surgery vs NAC	Active
		III	JGOG3017	TC vs. CDDP/CPT-11	Active
		III	GOG213	TC +/- bavacizumab	Active
		III	GOG218 (RDT)	TC +/- bevacizumab	Active
		III	AMG386	PTX+/-AMG386	Active, not recruiting
		III	AZD2281	Chemo +/- AZD2281	Active
		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	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 tumors		I	AZD1208	AZD1208	Active
		I	AZD5363	AZD5363	Active
		I	PD0332991	PD0332991	Active
Soft tissue sarcomas		II	ET-743	ET-743	Active
CIPN SNPs		translational	Paclitaxel induced peripheral neuropathy	Paclitaxel	Active
Molecular Imaging		0	Molecular imaging JST/MEXT-	nano-dose, radio-labeled trastuzumab	Active

Department of Thoracic Surgery

Hisao Asamura, Shun-ichi Watanabe, Hiroyuki Sakurai, Kazuo Nakagawa, Tsugumasa Kamata, Kyohei Masai, Yukio Watanabe

Introduction

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

Routine activities

The division has four attending surgeons. Three subteams with attending surgeons and residents perform all of the inpatient care, operations, examinations, and outpatient care. In 2013, we performed a total of 669 operations; for lung cancer in 451 patients, metastatic tumors in 96, mediastinal tumors in 29, and others in 93.

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

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

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

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

Research activities

We started a new modality, radiofrequency ablation (RFA), for malignant tumors of the lung in 2007. This modality should be effective for patients in whom it would be difficult to perform surgical resection, radiotherapy, or chemotherapy because of their poor risk. We 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 was closed in 2013.

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

Minimally invasive surgery with the thoracoscope for thoracic malignancies is also an important challenge in our division. In particular, the indications and surgical techniques of video-assisted surgery for early lung cancer are of special

interest because of the increased incidence of such minute tumors due to improvements in CT devices and CT screening.

Clinical trials

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

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

Table 1. Number of patients in 2013

Primary lung cancer	451
Metastatic lung tumor	96
Mediastinal tumor	29
Pleural disease	27
Chest wall tumor	8
Benign lung nodule	28
Others	30
Total	669

Table 2. Type of procedure in 2013

Lung resection	578
Lobectomy	349
Pneumonectomy	18
Segmentectomy	78
Wedge resection	133
Tracheal resection	0
Surgery for mediastinal tumors	30
Surgery for pleural tumors	19
Surgery for chest wall tumors	6
Others	36
Total	669

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

Pathological stage (TNM-7)	No. of pts	5-yr survival (%)
IA	1902	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
Total	3,551	

Operation period: 2003.1-2011.12

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Department of Thoracic Oncology

Tomohide Tamura, Noboru Yamamoto, Hiroshi Nokihara, Yutaka Fujiwara, Hidehito Horinouchi, Shintaro Kanda, Shinji Nakamichi, Satoru Kitazono, Hidenori Mizugaki, Kuniko Sunami, Shigehiro Yagishita, Yuichiro Koga, Takahiro Tsuji

Introduction

Lung cancer is the leading cause of cancer death in Japan and worldwide. The majority of lung cancer patients are diagnosed at an advanced stage, and the prognosis of these patients is poor. The standard treatments for non-small cell lung cancer (NSCLC) are chemoradiotherapy for locally advanced disease and platinum doublet chemotherapy for metastatic disease. Recently, several driver gene alterations such as EGFR mutation and ALK, Ros 1, or RET fusion gene, have been identified in NSCLC. Inhibitors for these molecules show excellent response against tumors with these driver gene alterations. Optimal treatment selection based on tumor molecular analysis and biomarker analysis is a major research issue in this field. The standard treatments for small cell lung cancer (SCLC) are chemoradiotherapy with etoposide plus cisplatin (EP) and accelerated hyperfractionated thoracic radiotherapy (AH-TRT) for limited disease and irinotecan plus cisplatin (IP) for extensive disease.

The Department of Thoracic Oncology provides the most effective treatment available for each patient and also works on the establishment of new effective treatments against lung cancer and other thoracic malignancies.

Routine activities

The Department of Thoracic Oncology includes 6 staff physicians. A total of 5 chief residents, 9 residents and 4 short-term residents joined the Department during 2013. The staff physicians attend outpatient services for thoracic diseases, and the division has 55-60 beds in the hospital. Inpatient care is carried out by five teams. Each team consists of one staff physician and one or two chief residents and residents. Case conferences are scheduled every Monday afternoon and Thursday evening. Protocol conference and a journal club are scheduled every Monday morning and Thursday morning, respectively. The chest conference, a tumor board, is held on Thursday afternoons to discuss cases with thoracic surgeons, pathologists, radiologists and radiation oncologists.

A total of 299 new patients were admitted in 2013 (328 and 305 patients in 2012 and 2011, respectively). The diagnoses for these patients and initial treatments for 270 lung cancer patients are listed in Tables 1 and 2, respectively. The survival outcomes of lung cancer patients treated in the Department are shown in Table 3.

Research activities

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

Clinical trials

The Department carried out more than 40 clinical trials in 2013. Some studies were based on the JCOG Lung Cancer Study Group research program, and some were carried out under contract with pharmaceutical companies or as an in-house protocol. In the JCOG 0509 study, amrubicin pus cisplatin failed to show non-inferiority to the standard IP for extensive-stage SCLC (J Clin Oncol, in press). In the JCOG0202 study, IP was not superior to EP after chemoradiotherapy with 1 cycle of EP and AH-TRT in limited-stage SCLC (Lancet Oncol). Alectinib, a new ALK inhibitor, showed an excellent response rate and progression-free survival with minimum toxicity for ALK-fusion positive NSCLC in a phase I/II study (Lancet Oncol). The translational study to investigate circulating endotherial cells (CEC) as a biomarker for response to anti-angiogenic agents, and PK/PD studies of erlotinib and crizotinib are ongoing.

Table 1. Number of New Inpatients in 2013

Non-small cell lung cancer	234
Adenocarcinoma	180
Squamous cell carcinoma	38
Others	16
Small cell lung cancer	36
Mesothelioma	3
Thymic cancer	8
Thymoma	1
Others	17
Total	299

Table 2. Initial Treatments for New Inpatients with Lung Cancer in 2013

Chemotherapy	167
Chemoradiotherapy	40
Adjuvant chemotherapy following surgery	40
Preoperative chemoradiotherapy	1
Thoracic radiotherapy	1
Supportive care alone (including palliative radiotherapy)	21
Total	270

Table 3. Survival Outcomes

Non-small cell lung cancer			
Unresectable stage III	204 patients treated with concurrent chemoradiotherapy in 1994-2005	Median	24.0 mo
		1-Year	75.5 %
		3-Year	34.7 %
		5-Year	22.8 %
Stage IV	480 patients treated with initial chemotherapy in 2000-2006	Median	13.2 mo
		1-Year	52.7 %
		3-Year	14.8 %
		5-Year	4.8 %
Small cell lung cancer			
limited disease	50 patients treated with concurrent chemoradiotherapy in 2001-2004	Median	28.8 mo
		2-Year	60.0 %
		5-Year	31.7 %
Extensive disease	108 patients treated with initial chemotherapy in 2001-2004	Median	12.1 mo
		2-Year	15.7 %
		3-Year	5.6 %

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Journal

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Department of Esophageal Surgery

Yuji Tachimori, Hiroyasu Igaki, Nobukazu Hokamura, Takayoshi Kishino, Hidetsugu Nakazato

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. 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. In Japan, squamous cell carcinomas still constitute the largest proportion of esophageal tumors, and the proportion of adenocarcinomas was 7% in our hospital in 2013.

Routine activities

The Department of Esophageal Surgery consists of three staff surgeons, one chief resident and 2-3 rotating senior residents. A multidisciplinary conference is held weekly in which surgeons, medical oncologists, radiation oncologists, endoscopists, radiologists, and pathologists who are involved in the treatment of esophageal diseases meet and discuss the diagnosis, staging, and treatment plans for patients with esophageal tumors.

Every week, 2-3 patients with esophageal cancer undergo surgery. Ninety one patients underwent esophagectomy including 2 patients with cervical esophageal cancer and 12 with adenocarcinoma in the esophagogastric junction, and also including four with carcinosarcoma and two with malignant melanoma. Of the 91 patients who underwent esophagectomy, a curative resection was completed for 90%. No hospital death occurred due to an operative complication. Preoperative chemotherapy was recommended for 48 patients and preoperative chemoradiotherapy was recommended for 11 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 54 patients as our standard procedure. Video-assisted thoracic surgery was introduced for esophagectomy as minimally invasive surgery in 23 patients.

In a paradigm shift toward organ-sparing procedures, the number of patients who receive definitive chemoradiotherapy as their primary treatment for resectable tumor, especially squamous cell carcinoma, is increasing. Of 33 patients with stage I squamous cell carcinoma, only 5 patients underwent esophagectomy. Persistent or recurrent loco-regional disease is not infrequent after chemoradiotherapy. Ten patients underwent salvage esophagectomy after the failure of definitive chemoradiotherapy in 2013. A three-field dissection is avoided for salvage esophagectomy.

Research activities

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

Clinical trials

The results of a multi-institutional randomized controlled trial (JCOG9907) confirmed preoperative chemotherapy with cisplatin and 5FU before esophagectomy as standard therapy for resectable Stage II-III esophageal cancer. A new multi-institutional randomized controlled trial comparing standard preoperative chemotherapy (5FU and cisplatin), an intensive one (5FU and cisplatin plus docetaxel), and preoperative chemoradiotherapy (5FU and cisplatin plus 41.4 Gy irradiation) for Stage II-III esophageal cancer (JCOG1109) started on December, 2012 and is ongoing. A Phase II trial for definitive chemoradiotherapy with or without salvage esophagectomy (JCOG0909) is continuing 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. For a Stage I lesion, a multi-institutional randomized controlled comparison between surgery and definitive chemoradiotherapy (JCOG0502) has finished registration.

Table 1. Number of patients who underwent surgery

Cervical esophageal squamous cell carcinoma	2
Thoracic esophageal squamous cell carcinoma	85
Adenocarcinoma	12
Carcinosarcoma	4
Malignant melanoma	2
GIST	1
Gastric tube cancer	1
Total	106

Table 2. Type of surgical procedure

Esophagectomy with reconstruction	58
Salvage esophagectomy with reconstruction	8
Video-assisted esophagectomy with reconstruction	21
Video-assisted salvage esophagectomy with reconstruction	2
Esophagectomy without reconstruction	2
Staged reconstruction	5
Enucleation of esophageal submucosal tumor	1
Gastric tube resection with reconstruction	1
Salvage lymph node dissection	8
Exploration	1
Total	108

Table 3. Table 3 Survival after esophagectomy (2004-2008)

pStage (UICC TNM 6th)	Number	5-year survival (%)
pStage I	114	91.0
pStage IIA	76	64.5
pStage IIB	103	62.6
pStage III	193	34.7
pStage IVA	27	37.0
pStage IVB	84	26.6

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Department of Gastric Surgery

Hitoshi Katai, Takeo Fukagawa, Shinji Morita, Masaki Ohashi, Hiroshi Katayama, Masahiro Maeda, Nao Yoshizawa

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 Gastrointestinal Medical Oncology Division, so that specialists from both divisions can treat patients with gastric cancer. Patients with stage I disease are followed-up without adjuvant chemotherapy. Adjuvant S-1 chemotherapy is used for patients with stage II and III disease. Neoadjuvant chemotherapy is frequently used for patients with locally advanced tumors.

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

We consider the education of foreign surgeons to be an important function. In 2013, more than 20 surgeons from various countries visited this Department for 2 weeks to 6 months to learn about the management of gastric cancer patients, especially surgical techniques for lymph node dissection and postoperative care. All staff surgeons have sufficient experience in teaching in English.

Research activities

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

Clinical trials

Our Division has been playing a central role in conducting multi-institutional clinical trials. H. Katai is a representative of the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG). Patients with gastric cancer are, when eligible, invited to participate in one of the ongoing clinical trials mentioned below. Randomized controlled trials are currently underway in a multi-institutional setting. The JCOG 0501 phase III trial to evaluate the effect of neo-adjuvant (S-1 and CDDP) and adjuvant chemotherapy (S-1) for large type III and type IV tumors has been completed for accrual. JCOG0705 is a trial to evaluate the significance of reduction surgery. JCOG 1001 is designed to evaluate the significance of bursectomy for advanced cancer. This trial includes the evaluation of long-term survival, postoperative morbidity, and mortality. The JCOG 0912 phase III trial is a study to prove the non-inferiority of laparoscopic gastrectomy over its open counterpart for patients with clinical stage IA and IB gastric cancer. The JCOG1002, phase II study of systemic chemotherapy with Docetaxel, CDDP, and S-1 followed by surgery in advanced cancer with extensive lymph node metastasis has been completed for accrual. JCOG1302-A is a study to evaluate accuracy of pre-operative staging for advanced tumor. A phase II study to check feasibility of Oxaliplatin, and S-1 neoadjuvant chemotherapy for stage III disease has been carried out.

Table 1. Number of Patients

Adenocarcinoma	443
GIST	12
Others	20
Total	475

Table 2. Operative morbidity and mortality after gastrectomy

	Number of patients	%
Major complications	41	12.0
Minor complications	96	28.0
Postoperative hospital deaths	0	0
Total	342	

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	167
Total gastrectomy	71
Completion gastrectomy	11
Pylorus-preserving gastrectomy	46
Proximal gastrectomy	18
Wedge resection	15
Pancreaticoduodenectomy	1
Laparoscopic distal gastrectomy	14
Laparoscopic pylorus preserving gastrectomy	14
Other (bypass, exploration, etc.)	118
Total	475

Table 4. Survival Rates

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

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

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Journal

1. Kawabata H, Oda I, Suzuki H, Nonaka S, Yoshinaga S, Katai H, Taniguchi H, Kushima R, Saito Y. Bone metastasis from early gastric cancer following non-curative endoscopic submucosal dissection. World J Gastroenterol, 19:5016-5020, 2013
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Department of Colorectal Surgery

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Introduction

The Colorectal Surgery Division deals with colorectal cancer and allied malignancies in the colon and rectum. Liver metastasis from colorectal cancer is treated in cooperation with the Hepatobiliary and Pancreatic Surgery Division. Lung metastasis from colorectal cancer is also treated in cooperation with the Thoracic Surgery Division. 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 Gastrointestinal Oncology Division, Endoscopy Division, Radiology Division and Pathology Division every week, and decide treatment strategy with a multi-disciplinary team (MDT) before treatment is started.

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 8B and 15A, B. An MDT meeting is held for cancer patients as a form of institutionalized communication every Tuesday morning (7:15-8:00), and a conference is held for the diagnosis of colorectal cancer: colorectal surgeons, endoscopists, and radiologists discuss the diagnosis for preoperative patients every Tuesday evening (18:30-19:30). Every Wednesday morning (7:00-7:30), a conference is held for the treatment of colorectal cancer: colorectal surgeons discuss treatments for preoperative and postoperative patients. Ten to twelve operations are performed a week in our division. Thus, we operate upon 450 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 (JCOG1007, iPACS) is ongoing. Patients with resectable liver metastasis are treated in cooperation with the Hepatobiliary and Pancreatic Surgery Division and adjuvant chemotherapy regimens are being evaluated in a clinical trial (JCOG0603 study).

Research activities

As described in "Routine Activities", clinical trials are integrated into our routine work. Twelve clinical trials are underway, and the details are described in "Clinical Trials". We are evaluating new surgical procedures, including intersphincteric resection (ISR) for very low rectal cancer, laparoscopic surgery, and surgery for pelvic recurrence of rectal cancer. We also carry out basic research in cooperation with scientists at the National Cancer Center Research Institute and the identification of a suitable treatment based on such a prediction is one of our important goals. In 2013, we published papers, and the results of our research in 2013 are summarized as follows.

Clinical trials

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

1. JCOG0205: A randomized study that compares adjuvant oral UFT + LV to intravenous 5-FU +l-LV for pathological stage III colorectal cancer. One thousand, one hundred and ten eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
2. JCOG0212: A randomized study that compares mesorectal excision (ME) to ME with pelvic lateral lymph node dissection for clinical stage II or stage III lower rectal cancer patients. Seven hundred and one eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
3. JCOG0404: A randomized study that compares laparoscopic to open colectomy for clinical stage II or stage III colon cancer located at the cecum, ascending colon, sigmoid colon or rectosigmoid cancer. One thousand and fifty-seven eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
4. JCOG0603: A randomized study that compares adjuvant modified FOLFOX (5-FU + 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.
5. JCOG0903: A phase I/II trial of chemoradiotherapy concurrent with S-1 plus mitomycin C in patients with clinical stage II/III squamous cell carcinoma of the anal canal is on-going.
6. JCOG0910: A randomized study that compares adjuvant Capecitabine to TS-1 for pathological stage III colorectal cancer. One thousand five hundred and five patients have been enrolled and recruitment is complete. Follow-up is on-going.
7. 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.
8. JCOG1007: A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer is ongoing.
9. 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.
10. 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	108	122
High anterior resection	12	8
Low anterior resection	60	38
Abdominoperineal resection	18	1
Hartmann's operation	5	
Intersphincteric resection	10	3
Total extirpation of large intestine	1	1
Total pelvic exenteration	2	
Total pelvic exenteration with sacrectomy	0	
Bypass	5	
Colostomy or ileostomy	52	
Local excision	1	
Other	55	

List of papers published in 2013
Journal

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Department of Gastrointestinal Medical Oncology

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Introduction

The Gastrointestinal Medical Oncology Division is focused on the development of new drugs and standard chemotherapy regimens combined with or without surgery and radiation for advanced colorectal, gastric and esophageal cancer, gastrointestinal stromal tumors and other gastrointestinal (GI) malignancies. Over recent years, a new generation of therapeutic agents has been developed. The highlights include the development of a molecular-targeted antibody directed against vascular endothelial growth factor (bevacizumab [BV]), and the finding that it causes changes in the microenvironment of the tumor by inhibiting angiogenesis. Another two molecular target-based drugs are the anti-epidermal growth factor receptor antibodies, cetuximab and panitumumab, which were approved in 2008 and 2010 for metastatic colorectal cancer. A multi-kinase inhibitor, regorafenib, was approved for colorectal cancer in 2013. For gastric cancer, an anti-HER2 monoclonal antibody, named trastuzumab, was also approved in 2011. In the near future we expect to identify other novel agents for the treatment of metastatic GI cancers that inhibit intracellular signal transduction or cellular interactions. However, many unusual adverse effects and a marked increase in medical cost have led to extensive discussion on more accurate targeting of the population using biomarkers. Although the response rates of these molecular-targeted drugs up to now have not been high (about 10 to 20%) when used broadly in a large population of patients, there are a few new candidate biomarkers that may be useful for identifying patients for whom these molecular-targeted drugs will be effective. For example, *K-ras* mutation in tumor tissue is one of negative predictive factors for the response to cetuximab. Accordingly, the identification of molecular markers that can be used to monitor tumor shrinkage or assist prognosis will be critical for the identification of possible new targets and for tailored treatments based on patient genotype or marker expression.

Routine activities

The staff of the GI Medical Oncology Division consists of 8 medical oncologists, 1 senior resident, and 3 or 4 residents. We hold a daily case conference together at 8 am before the morning rounds. Inter-group meetings with each surgical division (the Colorectal, Gastric, and Esophageal Surgery Divisions) and the Radiation Oncology Division are held weekly to decide upon treatment strategies for each individual case or to discuss future treatment strategies for the disease. Palliative care that considers the physical and psychological aspects of each case is another important issue discussed in staff meetings. The Palliative Care team and psycho-oncologists advise us on how to minimize patient discomfort and anxiety throughout end-of-life care. In 2013, we treated 2,210 hospitalized patients (635 of whom were newly diagnosed). Of these patients, 162 were entered in protocol studies.

Research activities

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

We also measured the gene mutations of possible predictive biomarkers in paraffin-embedded GI cancer specimens obtained from surgical resection or endoscopic biopsy, and investigated the correlation between enzymes related to anti-cancer drug metabolism and clinical outcomes with a RT-PCR assay. Some of these results on the correlation between gene mutation profile and cancer outcomes

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

Clinical trials

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

1. Colorectal Cancer

We investigated establishing combination chemotherapy regimens based on the oral fluoropyrimidine, S-1 (S-1/oxaliplatin/BV [SOXB], S-1/irinotecan/BV [SIRB]), for metastatic disease. Combination treatment with oral fluoropyrimidines is an important candidate to improve patient QOL, medical cost and medical staff burden. From the result of a randomized phase III trial to compare SOXB with FOLFOX plus BV at first-line chemotherapy for metastatic colorectal cancer (SOFT), non-inferiority of SOXB to FOLFOX plus BV has been demonstrated (Yamada Y et al. Lancet Oncol. 2013). We are also investigating whether SIRB is non-inferior to XELOX plus BV at first-line chemotherapy for metastatic colorectal cancer in a multicenter phase III trial (TRICOLORE).

For second-line chemotherapy, we are investigating the additive effect and feasibility of Aflibercept, a human recombinant fusion protein with antiangiogenic effects that functions as a decoy receptor to bind VGEF-A and B and placental growth factor, combined with FOLFIRI (5-FU/l-LV/Irinotecan) for colorectal cancer patients who failed to respond to first line treatment with FOLFOX or XELOX plus BV.

An adjuvant trial, JCOG0910, comparing S-1 with one of the standard regimens, capecitabine alone, started in March 2010 and finished patient recruitment (more than 1500 patients had been accrued from JCOG hospitals) in August 2013 on schedule. The phase III part of JCOG0603, a randomized study of adjuvant chemotherapy with mFOLFOX6 after complete resection of liver metastasis from colorectal cancer, is ongoing. The phase II part of JCOG0903, a phase I/II trial of chemoradiation with S-1/MMC for anal canal squamous cell carcinoma, continues to enroll patients.

2. Gastric cancer

A phase III study comparing three regimens (5-FU vs CPT-11/CDDP vs S-1) (JCOG9912) was already published in 2009. This was a pivotal study that established a new standard care protocol for advanced gastric cancer and cited the "New Japanese guidelines for diagnosis and treatment of carcinoma of the stomach", 2010 edition. A new pivotal phase III trial comparing S-1/CDDP (CS) to S-1/CDDP/Docetaxel (DCS) was started from April, 2012, and is progressing as expected. A phase I/II study of 5-FU/l-LV/paclitaxel (FLTAX) combination therapy as first-line therapy against this population has finished. A phase II/III study, comparing FLTAX with 5FU alone for patients who are inappropriate for CDDP usage due to severe peritoneal dissemination, started from April 2013. From the result of a randomized phase III trial to compare SOX with CS as first-line chemotherapy for metastatic gastric cancer (G-SOX), the non-inferiority of SOX to CS has been shown on PFS in the ASCO-GI meeting 2013.

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 additive effect of Nimotuzumab, an anti-epidermal growth factor receptor antibody, combined with irinotecan in second-line chemotherapy (ENRICH) has started as targeted on patients with high expression of EGFR. We also started a phase III trial which evaluates the additive effect of Olaparib, an inhibitor of poly ADP ribose polymerase (PARP), combined with paclitaxel in second-line treatment for the population against ENRICH trial.

For HER2 positive gastric cancer, we evaluated the second-line activity of trastuzumab with weekly paclitaxel in a multicenter phase II trial, and the feasibility and efficacy were shown in the 2013 ASCO meeting. We started a phase III trial which is evaluating the additive effect of Pertuzumab with capecitabine and cisplatin plus trastuzumab in the first-line treatment of metastatic HER2 positive gastric cancer. In second-line treatment of HER2 positive gastric cancer, a phase II/III trial comparing TDM-1 (ado-trastuzumab emtansine) with paclitaxel also started.

3. Esophageal Cancer

The results of our phase III study of preoperative versus postoperative 5-FU/CDDP (FP) (JCOG9907) were reported in 2007. Preoperative

FP was proven to be significantly superior to postoperative FP with regard to overall survival. Based on the results of this trial, the standard care for stage II/III esophageal cancer has been changed to preoperative FP followed by surgery. The large pivotal trial JCOG1109 which compared standard preoperative FP to DCF regimen (FP+Docetaxel) or FP +radiation regimen started from December 2012, and is progressing on schedule. A phase II study (JCOG0909) on the FP/RT (50.4 Gy) regimen plus salvage surgery with endoscopic resection in stage IB, II or III esophageal cancer is ongoing. A phase I/II study (JCOG0807) of a triplet regimen (5-FU+CDDP+Docetaxel) has finished the final analysis and has shown the feasibility of bi-weekly DCF regimen and a better tumor response compared with historical data at the 2013 ASCO meeting. A phase III trial comparing biweekly DCF with the standard FP regimen for metastatic esophageal cancer is under preparation in JCOG. Nimotuzumab is one of the anti-EGFR antibodies, which has shown activity for head and neck, gastric, and lung cancer. A phase I study of 5-FU+CDDP+Radiation with Nimotuzumab has finished and showed feasibility for stage IB/II/III/IVA esophageal cancer patients. A phase II study of BKM120, a PIK3CA inhibitor, in salvage line treatment is ongoing.

4. Other

An international phase III trial, RADIANT-4, which compared RAD001 to best supportive care in neuroendocrine tumor (NET) patients, has finished. For metastatic neuroendocrine carcinoma (NEC) in the GI-tract and hepato-billiary-pancreatic field, a phase III trial comparing irinotecan plus CDDP with etoposide plus CDDP as first-line treatment is under preparation in JCOG. We are participating in a phase II trial on neoadjuvant imatinib treatment for large gastric GIST, proceeding in Asian countries. Several phase I studies have been conducted as in the Table.

Table 1. Number of Patients Treated

	Total no. of hospitalized pts.	No. of newly diagnosed pts.	No. of pts. enrolled protocol
1) Esophageal cancer	770	188	
BKM120 (phase II)			7
Stage IB/II/III CRT+Salvage JCOG0909 (phase II)			8
Stage IB/II/III neoadjuvant CF vs DCF vs CF-RT JCOG1109 (phase III, NExT study)			24
2) Gastric cancer	767	191	
Bevacizumab/capecitabine/cisplatin (AVAGAST)			1
CS vs DCS JCOG1013 (phase III)			37
FL vs FLTAX JCOG1108 (phase II/III)			1
wPTX±Olaparib (phase III)			4
CPT-11±DE766 (phase III)			9
XP+Tmab±Pertuzumab (phase III)			1
T-DM1 vs wPTX (phase II/III)			6
3) Colorectal cancer	540	208	
Adjuvant Capecitabine vs S-1 JCOG0910 (phase III)			23
OCV*C02 (vaccine, phase I)			5
FOLFIRI+aflibercept (phase II)			3
Observation vs adjuvant FOLFOX for colorectal cancer after hepatic metastatectomy JCOG0603 (phase II/III)			3
Stage II/III S-1/MMC for anal canal cancer JCOG0903 (phase I/II)			3
FOLFIRI±IMC-1121B (ramucirumab/placebo) (phase III)			3
CapeOX+bevacizumab vs TS-1/irinotecan+bevacizumab (TRICOLORE, phase III)			19
mFOLFOX7 or CAPOX+Bevacizumab vs 5-Fluorouracil/Leucovorin or Capecitabine+Bevacizumab JCOG1018 (phase III)			12
4) Others	133	48	
NC6004 (phase I)			1
MSB0010718C (PDL-1, phase I)			2
LEE001 (phase I)			6
AMN107 vs imatinib (GIST, phase III			1
RAD001 vs BSC (NET, phase III)			3
BYL719 (phase I)			3
Total	2210	635	185

List of papers published in 2013
Journal

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Department of Endoscopy, Gastrointestinal Endoscopy Divison

Yutaka Saito, Takahisa Matsuda, Ichiro Oda, Yasuo Kakugawa, Takeshi Nakajima, Shigetaka Yoshinaga, Yosuke Otake, Haruhisa Suzuki, Satoru Nonaka, Taku Sakamoto, Seichiro Abe and Minori Matsumoto, Shinji Sasada, Takaaki Tsuchida, Takehiro Izumo

Introduction

Our Endoscopy Division moved to a 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 has been increased to 16 and two endoscopy engineers are working with us.

The Gastrointestinal Endoscopy Division has 12 staff physicians in the National Cancer Center Hospital (NCCH) and in the Screening Technology and Development Division, four chief residents, 11 residents, three trainees and several rotating residents.

The Bronchoscopy Division has three staff and resident doctors and the total number of bronchoscopies and therapeutic procedures has dramatically increased.

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

Routine activities in GI Endoscopy

Various diagnostic techniques including chromoendoscopy, magnifying endoscopy and endoscopic ultrasonography (EUS) are used to detect and evaluate early malignant lesions. Capsule endoscopy also has been accepted as being far less invasive. In our facility, small intestine capsule endoscopy has been performed since 2005. In order to obtain more accurate endoscopic diagnosis of gastrointestinal disease, we routinely use the recently developed narrow-band imaging (NBI) system. A total of 11,314, 3,367, 477, 85, 45, 140 and 29 screening and/or diagnostic procedures were performed in 2013 with gastroscopy, colonoscopy, EUS, EUS-fine needle aspiration (EUS-FNA), endoscopic retrograde cholangiopancreatography (ERCP), capsule endoscopy and double balloon endoscopies, respectively.

Due to the increasing number of patients with superficial gastrointestinal neoplasms, the number of therapeutic endoscopy procedures is also increasing in this field. In 2013, 2,146 endoscopic resections were carried out (pharynx 34, esophagus 189, stomach 375 and colon 1,582). Among these, ESD, which was developed for large en-bloc resections with a low-risk of local recurrence, was performed for 92 superficial esophageal cancers, 375early gastric cancers and 184 superficial colorectal neoplasms. For colorectal ESDs and some esophageal ESDs, the newly developed B-knife and IT-knife nano were used together with CO_2 insufflation. These procedures and devices were originally developed by our colleagues.

ESD achieves a higher en-bloc resection rate compared to the standard EMR technique and is less invasive than a surgical operation while EUS-FNA provides a less invasive procedure to improve diagnosis for patients with pancreatic tumors,

Table 1. Endoscopy Center

Year	2007	2008	2009	2010	2011	2012	2013
Upper GI Endoscopy	10,910	10,909	10,174	10,644	10,810	11,193	11,314
Colonoscopy	3,569	3,161	2,670	2,756	2,924	3,232	3,367
EUS	373	375	402	395	372	393	477
EUS-FNA				48	59	69	85
Therapeutic Endoscopy	1,854	1,848	1,849	1,756	1,984		
Gastric EMR/ESD	24/410	19/397	36/375	23/334	23/343	361	375
Esophageal EMR/ESD	89/25	94/25	95/43	102/45	132/61	115/66	97/92
Colorectal EMR/ESD	1,212/97	1,216/97	1,177/123	1,132/120	1,210/125	1,402/133	1,398/184

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 a 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 multicenter prospective study on endoscopic treatment of large early colorectal neoplasia conducted by the Colorectal Endoscopic Resection Standardization Implementation Working Group of the Japanese Society for Cancer of the Colon and Rectum and the Japan Gastroenterological Endoscopy Society.

In a recent translational study, it was shown that *Helicobacter pylori* (*H. pylori*) infection induces methylation of CpG islands in non-cancerous mucosae and the methylation level in *H. pylori*-negative patients is closely associated with the risk of gastric cancer. Metachronous gastric cancer after EMR/ESD is now an issue of concern so we need to identify an appropriate biomarker. Based on our recent results, we started a multicenter prospective observational study in 2008 to confirm the usefulness of the methylation level as a risk marker for metachronous gastric cancer after EMR/ESD. The recommended sample size is 1,000 and over 600 patients have already been enrolled in this particular study.

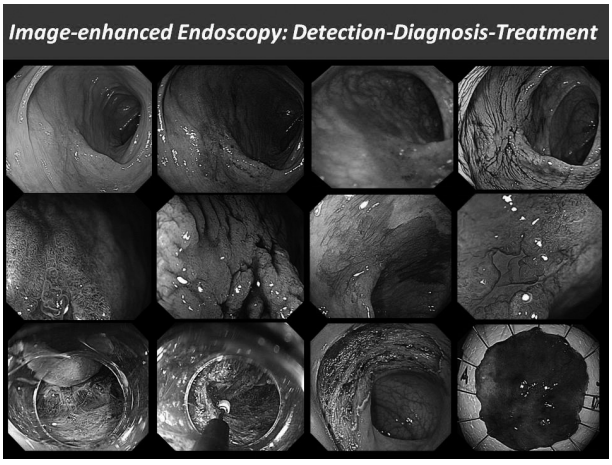

Figure 1. Endoscopic diagnosis using image-enhanced endoscopy (high-resolution endoscopy, narrow-band imaging and autofluorescence imaging) and endoscopic submucosal dissection (ESD) procedure for treating early colon cancer

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 chemoradiotherapy for clinical stage I esophageal carcinoma (JCOG 0508).

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

RCTs concerning colorectal neoplasms are ongoing as well. The Japan Polyp Study (JPS) was started in February 2003. The JPS is a multicenter RCT designed to evaluate colorectal cancer surveillance strategies in patients who have undergone complete colonoscopies on two occasions using a high-resolution colonoscope with the removal of all detected neoplasia including flat and depressed lesions.. Finally, about 4,000 patients were enrolled in this study. This multicenter RCT has been 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 the long-term outcomes of patients treated for submucosal colon and rectal cancer. We collected data from 549 patients with submucosal colon cancer and 209 with submucosal rectal cancer who underwent endoscopic or surgical resection at 6 institutions, over a median follow-up period of 60.5 months. We assessed recurrence rates, 5-year disease free survival, and 5-year overall survival. As a result, of patients treated with only endoscopic resection, the risk for local recurrence was significantly higher in high-risk patients with submucosal rectal cancer than patients with submucosal colon cancer. The addition of surgery is therefore recommended for patients with submucosal rectal cancer with pathology features indicating a high risk of tumor progression (Gastroenterology 2012). Considering this study result, we are now planning a prospective cohort study for the possibility of chemoradiotherapy for high-risk rectal submucosal cancer after endoscopic resections.

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Department of Endoscopy, Respiratory Endoscopy Division

Shinji Sasada, Takaaki Tsuchida, Takehiro Izumo

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 on CT imaging, which can lead to earlier surgical treatment and less-invasive treatments including bronchoscopic procedures. This is facilitated by a multi-purpose bronchoscopy system consisting of a flat-panel fluoroscope in combination 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 is held. Furthermore, we attend 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 five 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 (9 cases), photodynamic therapy and endobronchial electrocautery ablation (11 cases). Medical thoracoscopy under local anesthesia in the operation suite was performed in 20 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

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

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

Clinical trials

We have started a clinical trial on detection of biomarker profiling using small specimens obtained with bronchoscopy or thoracoscopy in patients with lung cancer. We are additionally planning a prospective study for evaluation of the use of the IT knife for medical thoracoscopy.

Table 1. Type of procedure

Diagnostic bronchoscopy under X-ray fluoroscopy	554
Diagnostic bronchoscopy without X-ray fluoroscopy	211
Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA)	175
Medical thoracoscopy	20
Airway stent placement	9
Photodynamic therapy (PDT), Electrocautery ablation	11
Bronchial occlusion (EWS)	6
Total	986

List of papers published in 2013
Journal

1. Izumo T, Sasada S, Chavez C, Nagai Y, Kitagawa M, Torii J, Iwase T, Aso T, Nakamura Y, Mizumori Y, Deng C, Xu W, Tsuchida T, Moriyama N. The value of chest tomosynthesis in locating a ground glass nodule (GGN) during endobronchial ultrasonography with a guide sheath: a case report. J Thorac Dis, 5:E75-77, 2013
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Department of Hepatobiliary and Pancreatic Surgery

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

Introduction

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

Routine Activities

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

Operation and perioperative care

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

Conferences

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

Surgical strategies for HBP malignancies

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

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

Biliary cancer – cholangiocarcinoma & gall bladder cancer: Based on careful imaging evaluations of the extent of the cancer, a wide variety of surgical resections can be applied to biliary cancer. Pancreatoduodenectomy is conducted for middle to distal bile duct cancer. Extended hemihepatectomy with extrahepatic bile duct resection is considered as the first-line procedure for hilar cholangiocarcinoma.

Research Activities and Clinical trials

Dr. Kosuge et al. reported on 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 the "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 devices in HBP surgery; 1) "Safety of stapler vs. non-stapler closure of the pancreatic remnant after distal pancreatectomy: a multicenter randomized controlled trial (SNS-RCT)," 2)"The impact of use

of an energy-based device during parenchyma transection of the liver: a multicenter randomized controlled trial (EPL-RCT)," and 3) "Effect of stapled vs. hand-sewn duodenal reconstruction on delayed gastric emptying during pancreaticoduodenectomy: a dual-center randomized controlled trial (SH-RCT)." In all these studies, patients' recruitment and registration have finished and data are being analyzed. Dr. Nara et al. are now proceeding with a study to evaluate the feasibility of laparoscopic hepatectomy in this hospital. These studies are supported by Grants-in-Aid for scientific research from the Ministry of Health, Labour and Welfare of Japan.

Table 1. Number of patients

	n
Invasive pancreatic cancer	81
Other pancreatic neoplasms	36
Hepatocellular carcinoma	32
Hepatic metastases	69
Intrahepatic cholangiocarcinoma	4
Bile duct cancer	23
Gallbladder cancer	10
Ampullary cancer	8
Duodenal cancer	3
Others	46
Total	312

Table 2. Type of procedures

	n
Hepatectomy without biliary resection	105
Hepatectomy with biliary resection	16
Left hemihepatectomy and pancreaticoduodenectomy (HPD)	2
Classical Whipple (CW)	25
Pylorus-preserving pancreaticoduodenectomy (PPPD)	45
Distal pancreatectomy	35
Appleby operation	1
Medial pancreatectomy	4
Total pancreatectomy	6
Extended cholecystectomy	10
Other resections	33
No resection	30
Total	312

Table 3. Survival rates

Invasive ductal carcinoma (2001-2010)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	12	57	57
II	7	67	50
III	88	54	42
IVa	254	40	27
IVb	126	25	15
Total	487	40	28

Hepatocellular carcinoma (2001-2010)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	37	86	71
II	156	88	80
III	216	72	59
IV	77	58	41
Total	486	76	64

List of papers published in 2013
Journal

1. Otsuka T, Morizane C, Nara S, Ueno H, Kondo S, Shimada K, Kosuge T, Ikeda M, Hiraoka N, Okusaka T. Gemcitabine in patients with intraductal papillary mucinous neoplasm with an associated invasive carcinoma of the pancreas. Pancreas, 42:889-892, 2013
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Department of Hepatobiliary and Pancreatic Oncology

Takuji Okusaka, Hideki Ueno, Chigusa Morizane, Shunsuke Kondo, Yasunari Sakamoto, Hideyuki Hayashi, Satoshi Shiba

Introduction

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

Routine activities

The Division consists of five staff oncologists and three to four residents. In 1990, the Division began using percutaneous ethanol injection (PEI) to treat patients with small HCCs. In 1999, radiofrequency ablation therapy (RFA) was introduced clinically as an alternative to PEI. Based on long-term observations of PEI-treated patients, we have used percutaneous ablation therapy as a valuable alternative to surgery for most patients with 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 division are made by all staff oncologists and residents every morning and evening.

Research activities

A phase III study was designed to investigate the noninferiority of S-1 alone and superiority of gemcitabine plus S-1 compared with gemcitabine alone with respect to overall survival (Ueno et.al). The participants were chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer. In the total of 834 enrolled patients, the median overall survival was 8.8 months in the gemcitabine group, 9.7 months in the S-1 group, and 10.1 months in the gemcitabine plus S-1 group. The noninferiority of S-1 to gemcitabine was demonstrated (hazard ratio, 0.96; 97.5% CI, 0.78 to 1.18; $P < .001$ for noninferiority), whereas the superiority of gemcitabine plus S-1 was not (hazard ratio, 0.88; 97.5% CI, 0.71 to 1.08; $P = .15$). All treatments were generally well tolerated, although hematologic and GI toxicities were more severe in the gemcitabine plus S-1 group than in the gemcitabine group. Monotherapy with S-1 demonstrated noninferiority to gemcitabine in overall survival with good tolerability and presents a convenient oral alternative for locally advanced and metastatic pancreatic cancer.

A randomized phase II trial was designed to evaluate the safety and efficacy of two regimens: gemcitabine plus S-1 (GS) and S-1 (Morizane et al). The regimen with a higher 1-year survival would be selected for a subsequent phase III trial. For the GS (n = 51) and S-1 (n = 50) arms, the 1-year survival was 52.9% (95% confidence interval, 38.5-65.5) and 40.0% (95% confidence interval, 26.5-53.1), and the median survival times were 12.5 and 9.0 months, respectively. Grade 3/4 hematological toxicities were more frequent in the GS arm than in the S-1 arm. In conclusion, GS was considered to be more promising and was selected as the test regimen for a subsequent phase III trial comparing GS with gemcitabine plus cisplatin combination therapy.

Using pancreatic carcinoma cell lines and gene transfectant, we measured the long pentraxin (PTX3) level in culture solution and carried out a cellular migration assay *in vitro* (Kondo et al). Elevated PTX3 production was observed in several cell lines, and a direct relationship between migratory activity and the PTX3 level was identified *in vitro*. A high PTX3 level (117 days) was significantly less than that of patients with a low PTX3 level (357 days,

P<0.001). A multivariate analysis of the pancreatic carcinoma revealed a strong correlation between pentraxin family member expression and prognosis of pancreatic carcinoma. Pentraxin family members, especially PTX3, may be used as promising biomarkers in the prognosis of pancreatic carcinoma patients.

Clinical trials

Thirty-two clinical trials are ongoing, including seven phase III trials, such as adjuvant chemotherapy versus placebo in HCC patients who had undergone hepatic resection or local ablation therapy, and chemotherapy with a new regimen versus standard chemotherapy in biliary cancer patients. Two studies are collaboration trials with the Department of Diagnostic Radiology, and one with the Department of Radiation Oncology. Three trials are being conducted to evaluate cancer immunotherapy. Our studies are supported by the National Cancer Center Research and Development Fund (Grant No. 23-A-22, No. 23-B-5), Health and Labour Sciences Research Grants (Grant No. H23-ganrinsho-ippan-006, No. H25-sanjigan-shitei-006, No. H25-kanen-ippan-014) from the Ministry of Health, Labour, and Welfare of Japan.

Table 1. Number of patients

	No. of pts.
Pancreatic cancer	
Invasive ductal	126
Neuroendocrine	6
Others	12
Biliary tract cancer	
Extrahepatic bile duct	7
Gallbladder	10
Papilla of Vater	2
Liver cancer	
Hepatocellular	208
Intrahepatic cholangiocarcinoma	6

Table 2. Type of procedure

	No. of pts.
Pancreatic cancer	
Systemic chemotherapy	128
Chemoradiotherapy	14
Biliary tract cancer and Intrahepatic cholangiocarcinoma	
Systemic chemotherapy	25
Hepatocellular carcinoma	
Ethanol injection	11
Radiofrequency ablation	46
Transcatheter arterial (chemo)embolization	111
Intra-arterial chemotherapy	18
Systemic chemotherapy	32
Radiotherapy	9

Table 3. Survival rates

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

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Department of Urology

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

Introduction

In the Urology Division, 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 five staff physicians and two residents. In addition, with the participation of a radiation oncologist, multi-disciplinary treatments for advanced disease including renal cancer, urothelial cancer, hormone-refractory prostate cancer and metastatic germ cell tumors, are performed. Every morning clinical rounds are started at 7:30 a.m., and a weekly conference to discuss inpatient management is held on Monday evenings. A clinicopathological conference is scheduled on alternating Wednesdays.

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

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

Research activities

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

1. Urothelial cancer: The effectiveness of a phase III study to confirm the efficacy of BCG instillation for high grade T1 bladder cancer (JCOG1019) is ongoing. For metastatic disease, a weekly CBDCA + PTX regimen has been indicated.
2. Prostate cancer: A phase II study to evaluate the efficacy of robotic assisted laparoscopic radical prostatectomy for low and intermediate risk prostate cancer is ongoing. A new operative method to achieve a complete surgical margin (extended radical prostatectomy) has been developed, and its efficacy in patients with specimen-confined disease has been evaluated without neoadjuvant endocrine therapy. To provide a more precise preoperative diagnosis, a new imaging strategy using 3.0 Tesla MRI has been developed. To identify the most effective treatment for the recurrence of PSA failure after radical prostatectomy, a phase III study to evaluate the efficacy of salvage irradiation vs hormone ablation for postoperative PSA failure in T1c-T2 prostate cancer (JCOG0401) is under review. In local advanced disease, a phase III study to evaluate the survival benefit of continuous endocrine therapy after 3D conformal radiotherapy is still underway. For hormone-refractory prostate cancer, a study on a new hormonal regime with TAK700 has completed enrollment.
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: TAK700 for hormone-refractory prostate cancer
5. A phase II study: IKT1 for chemo-refractory prostate cancer

Table 1. Patient statistics: Major treatment

	2008	2009	2010	2011	2012	2013
Radical/partial nephrectomy	28	43	35	30	46	39
Nephroureterectomy	11	16	15	12	17	8
Total cystectomy	22	26	31	24	25	24
TURBT	161	163	130	140	130	117
M-VAC	31	42	62	50	62	45
GC	-	50	71	84	83	70
Radical prostatectomy	105	111	98	111	87 (RALP 2)	84 (RALP32)
Prostatic biopsy	186	247	168	175	151	128
High orchiectomy	7	6	12	8	6	6
Retroperitoneal lymphadenectomy	10	7	8	13	6	5
Chemotherapy for testicular cancer	10	9	14	30	35	7
Retroperitoneal tumor resection	9	9	15	10	18	13

List of papers published in 2013
Journal

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Department of Gynecology

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

Introduction

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

Routine activities

1. The staff members of the Department of Gynecology comprise five gynecologic oncologists. In addition, our division includes 2 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 high-grade dysplasia, carcinoma in situ, or Ia1 cervical cancer. Patients with stages Ia2 to IIIa 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. 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. In our practice, positive peritoneal cytology is not a poor prognostic factor for patients with a well-differentiated tumor confined to the uterus, whereas postoperative adjuvant chemotherapy is performed for patients with extra-uterine disease.
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 several courses of chemotherapy, an interval debulking surgery (IDS) is usually performed for these patients. Surgery alone can offer the chance of cure for patients with recurrence, but only when the disease is completely resectable. The type of surgical procedure, patient number, and survival rates are shown in Tables 1, 2, and 3.

Research activities

A phase III study of dose dense TC chemotherapy (JCOG PC1311) for patients with advanced or recurrent cervical cancer is now being projected. 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 is also being planned. A multicenter retrospective study on rare tumors of . gynecologic malignancy is in progress.

Clinical trials

A phase III study to compare treatment starting with neoadjuvant chemotherapy and primary cytoreductive surgery followed by postsurgical chemotherapy (JCOG 0602) for advanced ovarian cancer is ongoing as planned. A nonrandomized confirmatory trial of modified radical hysterectomy for patients with FIGO stage Ib1 (< 2 cm) uterine cervical cancer (JCOG1101) has been started. A phase I/II study on Heavy Ion Radiotherapy with concurrent chemotherapy for locally advanced cervical adenocarcinoma using the Heavy Ion Medical Accelerator is ongoing in Chiba (HIMAC, National Institute of Radiological Sciences).

Table 2. Type of procedure

Radical hysterectomy	27
Simple hysterectomy	165
±Salpingo-oophorectomy	
± Lymphadenectomy	
± Omentectomy	
± Lymphadenectomy	
Conization	10
Vulvectomy	1
Others	17
Total	220

Table 1. Number of patients

	Stage	2007	2008	2009	2010	2011	2012
Cervical cancer	IA	6	8	7	5	4	7
	IB	29	32	33	40	33	23
	II	18	13	13	5	4	15
	III	18	12	7	13	12	10
	IV	2	4	8	2	5	10
	Total	73	69	68	65	58	65
Endometrial cancer	I	40	42	42	41	39	49
	II	7	5	6	4	8	5
	III	14	20	15	9	22	10
	IV	3	1	9	4	2	2
	Total	64	68	72	58	71	66
Ovarian cancer	I	15	15	13	16	9	13
	II	9	3	4	3	4	3
	III	8	11	18	13	11	17
	IV	7	2	5	3	2	1
	NAC[a]	8	9	5	8	9	13
	Total	47	40	45	43	39	47

[a] Neo adjuvant chemotherapy

List of papers published in 2013
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Department of Musculoskeletal Oncology and Rehabilitation

Hirokazu Chuuman, Akira Kawai, Fumihiko Nakatani, Yoshikazu Tanzawa, Eisuke Kobayashi, Koichi Ogura, Daisuke Kubota, Nokitaka Setsu, Tomohiro Fujiwara

Introduction

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

Routine activities

The Musculoskeletal Oncology division of the NCCH consists of 5 staff doctors (Drs. Hirokazu Chuman, Akira Kawai, Fumihiko Nakatani, Yoshikazu Tanzawa and Eisuke Kobayashi), 4 residents and 2 physiotherapists, 1 occupational therapist and 1 speech therapist. Occasionally, several fellows from Japan and overseas join our group. Outpatient consults are held every weekday. A consistent number of about 34 patients are hospitalized to undergo an operation, chemotherapy or radiation therapy. Five or six major operations are routinely performed every week. In 2013, 272 operations were performed under general anesthesia, including palliative operations for pathological fractures or spinal cord compression from metastatic bone and soft tissue tumors. Sarcomas in the trunk, including the thoracic wall, retroperitoneal space and head and neck lesions, were excised in cooperation with thoracic, general or head-neck surgeons, respectively. A total of 54 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 Research Institute of the NCC to develop novel molecular target therapies or tailor-made treatments for sarcoma patients. With a genome-wide microarray system or a protein-wide two dimensional fluorescence difference gel electrophoresis (2D-DIGE) system, we have been analyzing the complete expression levels of mRNA and protein in the tumor samples from patients with Ewing's family tumors, osteosarcomas and sarcomas of soft tissues.. Combined with each patient's clinical information, we have been establishing novel biomarkers for prediction of 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 sarcomas and osteosarcomas with the aim of developing novel molecular targeted therapies

Clinical trials

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

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 3 clinical trial of multidrug adjuvant chemotherapy for osteosarcomas (JCOG 0905) ongoing since 2010.
2. A multi-institutional phase 3 study of trabectedin for advanced soft tissue sarcoma active since 2012.
3. A multi-institutional phase 2 study of Eribulin (an inhibitor of microtubule dynamics) for advanced soft tissue sarcoma which started in 2011.
4. A multi-institutional phase 3 clinical trial of multidrug adjuvant chemotherapy for high grade soft part sarcoma (JCOG 1309) has started in February 2014.

Table 1. New patients (2013)

1	Soft tissue sarcomas	101
2	Bone sarcomas	32
3	Benign bone and soft tissue tumors	74
4	Spine or bone metastasis	11
Total		217

Table 2. Type of procedure

1	Soft tissue sarcomas	105
2	Bone sarcomas	29
3	Benign bone and soft tissue tumors	99
4	Spine or bone metastasis	31
	Plastic surgery combined	54
	Reconstruction with prosthesis	15
	Spine surgery	3
Total		290

List of papers published in 2013
Journal

1. Takahashi H, Nakayama R, Hayashi S, Nemoto T, Murase Y, Nomura K, Takahashi T, Kubo K, Marui S, Yasuhara K, Nakamura T, Sueo T, Takahashi A, Tsutsumiuchi K, Ohta T, Kawai A, Sugita S, Yamamoto S, Kobayashi T, Honda H, Yoshida T, Hasegawa T. Macrophage migration inhibitory factor and stearoyl-CoA desaturase 1: potential prognostic markers for soft tissue sarcomas based on bioinformatics analyses. PLoS One, 8:e78250, 2013
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Department of Dermatologic Oncology

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Introduction

The Department of Dermatologic Oncology has consistently served as the core hospital for the establishment of treatment strategies for malignant skin tumors since the National Cancer Center opened in 1962, and over 1800 cases of malignant melanoma have been accumulated thus far; an impressive number for a hospital or research institution in Japan. Today, patients are referred from throughout Japan. Of particular note, the number of patients with malignant melanoma was 191, which was approximately twice - the number 3 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 four staff dermatologic oncologists and three residents. We are also engaged in routine outpatient activities on Wednesdays and Thursdays in the National Cancer Center East.

In 2013, a total of 327 patients were examined for the first time in the Dermatology Department for a malignant skin tumor. The numbers of patients with malignant melanoma (191) and extramammary Paget's disease (16) were particularly large, and were approximately 4 times and 2 times, respectively, the numbers 15 years ago. There were also 10 cases of the rare cancer, angiosarcoma.

About 20 patients are hospitalized to undergo surgery, chemotherapy, or radiation therapy. In 2013, 254 operations were performed including 106 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 melanoma

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

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

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

We planned a phase 2 clinical study of an original nivolumab administration method: 2 mg/m^3, every 3 weeks. Enrolment of the 35 patients was started all over Japan in December 2011 and was completed in 4 months. That was quite a surprise, because it was very quick. At the same time it was once again very clear that there are many melanoma patients, and not only was it clear that melanoma patients exist, but that both patients and physicians are troubled by the lack of drugs for treatment and have been hoping for the development of new drugs. The results of the phase 2 study of nivolumab showed a response rate of 22.9%. The most dangerous adverse effect, interstitial pneumonia, developed in only one patient.

Extramammary Paget's disease

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

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

Clinical trials

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

(1) Sentinel lymph node detection in malignant melanoma patients using real-time fluorescence navigation with indocyanine green.
(2) Postoperative natural interferon beta therapy in stage II, III cutaneous malignant melanoma.
(3) A phase I dose-escalation, safety/tolerability and preliminary efficacy study of intratumoral administration of GEN0101 in patients with advanced melanoma.

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

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

Table 1. Number of New Patients

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

Table 2. Operative Procedures (total number)

Wide local excision	150
Local excision	74
Sentinel node biopsy	42
Lymph node biopsy	9
Lymph node dissection	25
(neck)	6
(axilla)	7
(inguinal)	4
(groin)	8
(popliteal)	0
(epitrochlear)	0
Skin graft	23
Local flap	6
Free flap	1
Amputation	8
others	2

Table 3. New Agent Studies in 2013

Agent	Eligible Cancer Type	Trial Phase
ONO-4538	Melanoma	II
ONO-4538	Solid Tumors	I
MAGE-A3	Melanoma	III
BCX1777	T/NK-Cell Lymphoma	I
E7777	Peripheral/Cutaneous T Cell Lymphoma	I/II
Lenalidomide	ATL, Peripheral T Cell Lymphoma	I
PDX	Peripheral T Cell Lymphoma	I/II
Romidepsin	Peripheral/Cutaneous T Cell Lymphoma	I/II
Vemurafenib	Melanoma	I/II
Ipilimumab	Melanoma	II
SCH54031	Melanoma	I
Dabrafenib	Solid Tumors	I
BYL719	Solid Tumors	I
RO4987655	Solid Tumors	I
WT4869	Solid Tumors	I
AZD8931	Gastric Cancer	II
PF-00299804	Lung Cancer	III
Lenalidomide	ATL	II
Dabrafenib/Trametinib	Melanoma	I/II
LGX818	Solid Tumors	I
MEK162	Melanoma	III

List of papers published in 2013
Journal

1. Namikawa K, Yamazaki N. A case of scalp angiosarcoma with lung metastases presenting as multiple thin-walled cysts. Jpn J Clin Oncol, 43:101, 2013
2. Kiyohara Y, Yamazaki N, Kishi A. Erlotinib-related skin toxicities: treatment strategies in patients with metastatic non-small cell lung cancer. J Am Acad Dermatol, 69:463-472, 2013
3. Honda K, Yamamoto N, Nokihara H, Tamura Y, Asahina H, Yamada Y, Suzuki S, Yamazaki N, Ogita Y, Tamura T. Phase I and pharmacokinetic/pharmacodynamic study of RO5126766, a first-in-class dual Raf/MEK inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 72:577-584, 2013

Department of Hematology

Kensei Tobinai, Yukio Kobayashi, Dai Maruyama, Tatsuya Suzuki, Wataru Munakata, Suguru Fukuhara, Kenichi Miyamoto, Hideaki Kitahara

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 Department 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 four rotating residents are involved in these activities.

Research activities

In addition to immunophenotypic analyses, molecular diagnosis is routinely performed, using the 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, etc. Our recent research has focused on indolent B-cell non-Hodgkin lymphoma (B-NHL). Clinical as well as molecular and cytogenetic analyses of ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma cases led to the discovery of a new tumor suppressor gene deleted at 6q23; we identified the A20 gene as a tumor suppressor gene in various B-cell malignancies (Nature 2009;459:712-6). The gene is involved in NFkappaB signaling and its status could be a biomarker for BCR inhibitors.

This year, we authored or coauthored 23 original articles related to hematological malignancies. We have constructed a tumor sample banking system, collecting the rest of samples taken as routine diagnostic procedures. The DNA and RNAs are extracted from the samples and reserved for future use.

Clinical trials

In 2013, we conducted 27 new-agent studies, including 8 international studies, and 7 cooperative group studies in Japan (Tables 2 and 3). The numbers are still increasing including the domestic studies. 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, Labour and Welfare (MHLW).

Various phase I and II trials are ongoing on T-cell malignancies. The agents include mogamulizumab, lenalidomide, romidepsin, forodesine, and denileukin diftitox. Some of the agents are being evaluated in global studies. For indolent ATL, we started to evaluate anti-viral agents of interferon-alfa and AZT, as a phase III study (JCOG 1111).

A phase I study of oligopeptide vaccine OCV-501 against WT1 protein in AML cells to keep patients in complete remission, was completed and moved on to a randomized phase II trial. The agent was developed in Japan, and this is the first study against hematological malignancies aiming at approval by the MHLW.

For treatment of B-cell malignancies, a phase III trial for newly diagnosed, diffuse large B-cell lymphoma (JCOG 0601) is ongoing. In this trial, a dose-intense schedule of rituximab is being

compared with that of a standard 3-weekly regimen. We completed a phase II study of a rituximab-incorporating dose-intensified chemotherapy for untreated mantle cell lymphoma (JCOG 0406), using high-dose chemotherapy with autologous stem cell transplantation. For symptomatic multiple myeloma patients ineligible for transplantation, we initiated 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
Acute myelocytic leukemia (AML)	9	10	6	10	8	13	12	7
Acute lymphocytic leukemia (ALL)	4	9	8	2	2	1	1	6
Chronic myelocytic leukemia (CML)	10	11	3	3	2	2	2	2
Myelodysplastic syndrome (MDS)	3	9	8	20	9	3	3	6
Hodgkin lymphoma (HL)	21	11	12	7	11	16	15	13
Non-Hodgkin lymphoma (NHL)	265	210	208	151	185	243	172	193
Adult T-cell leukemia-lymphoma (ATL)	6	4	5	5	3	6	6	4
Chronic lymphocytic leukemia (CLL)	4	5	6	4	2	1	4	1
Multiple myeloma (MM)	9	8	10	12	9	10	7	8
Waldenström macroglobulinemia (WM)	0	2	3	1	2	2	1	0
Total	331	279	269	215	233	297	223	240

Table 2. Clinical trials for new agents

Disease	Agents	Phase	Enrolment in 2013	Total
CML	Nilotinib	III	0	1
	Bosutinib	I/II	0	3
	Ponatinib	I	2	3
MDS	Panobinostat + Azacitidine	Ib	4	4
	Rigosertib	I	1	1
AML	WT1 vaccine	I	1	4
	WT1 (maintenance)	I	2	4
	Volasertib	I	5	6
ALL	Inotuzumab ozogamicin	I	1	1
MM	Carfilzomib	I	1	1
	Carfilzomib	I/II	5	8
	Anti-BAFF antibody	I	2	2
	Pomalidomide	I	2	2
ATL	Lenalidomide	II	0	1
PTCL	Forodesine	I/II	3	3
	Romidepsin	I/II	0	6
FL	Ofatumumab vs. Rituximab	III	6	31
	Ofatumumab + Bendamustine	III	2	4
	Obinutuzumab	III	4	16
MCL	R-B +/- Ibrutinib	III	1	1
DLBCL	Ofatumumab	III	2	3
	Inotuzumab ozogamicin	III	0	7
	Obinutuzumab	III	2	2
	Alisertib (MLN8237)	I	2	5
HL	SGN-35	III	2	2
B-NHL	Ibrutinib	I	4	7
AML, ML, MM	OPB-51602	I	1	2

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 97	III	(98-01)	15	79%	47% (5-yr)
JALSG-AML 201	III	(02-06)	13	78%	57% (5-yr)
JALSG-APL 97	III	(98-02)	2	95%	86% (4-yr)
JALSG-APL 204	III	(04-11)	2	94.5%	89% (5-yr)
JALSG-AML209	IV	(11-)	11	NA	NA
Therapy-related leukemia	II	(96-99)	16	75%	40% (3-yr)
ALL/Lymphoblastic lymphoma					
JCOG 9004	II	(91-94)	14	83%	31% (7-yr)
JCOG 9402	II	(94-99)	10	81%	29% (5-yr)
JALSG-ALL 97	II	(98-01)	8	74%	32% (5-yr)
JALSG-ALL 202	II	(03-10)	9	NA	NA
CML					
JALSG-CML 207	III	(08-10)	1	NA	NA
Hodgkin lymphoma					
JCOG 9305	II	(93-97)	7	79%	89% (5-yr)
JCOG 9705	II	(98-00)	6	70%	81% (5-yr)
Aggressive NHL					
JCOG 9505	II(c)	(95-98)	2	56%	42% (4-yr)
JCOG 9506	II	(95-97)	6	50%	49% (5-yr)
JCOG 9508	II	(96-99)	19	80%	68% (5-yr)
JCOG 9809	III	(99-02)	55	62%	56% (8-yr)
JCOG 0601	III	(08-)	49	NA	NA
JCOG 0406	III	(08-)	5	NA	NA
JCOG 0908	III	(08-)	16	NA	NA
Indolent B-cell lymphoma					
JCOG 0203	II/III	(02-07)	52	77%	88% (6-yr)
Adult T-cell leukemia-lymphoma					
JCOG 9303	II	(94-97)	6	36%	31% (2-yr)
JCOG 9801	III	(98-03)	6	33%	19% (3-yr)
JCOG 1111	III	(13-)	1	NA	NA
Nasal NK/T-lymphoma					
JCOG 0211-DI	I/II	(03-07)	8	77%	78% (2-yr)
Multiple myeloma					
JCOG 9301	III	(93-98)	10	50% (d)	50% (4-yr)
JCOG 0112	III	(02-05)	9	46% (d)	63% (2-yr)
JCOG 0904	II	(09-)	7	NA	NA
JCOG 1105	III	(13-)	1	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

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Journal

1. Tamura S, Maruyama D, Miyagi Maeshima A, Taniguchi H, Kakugawa Y, Mori M, Azuma T, Kim SW, Watanabe T, Kobayashi Y, Tobinai K. Epstein-Barr virus-associated enteropathy as a complication of infectious mononucleosis mimicking peripheral T-cell lymphoma. Intern Med, 52:1971-1975, 2013
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Department of Hematopoietic Stem Cell Transplantation

Takahiro Fukuda, Takuya Yamashita, Sung-Won Kim, Saiko Kurosawa, Shigeo Fuji, Yoshiki Hayashi, Ayumu Ito, Yoshitaka Inoue, Reiko Ito

Introduction

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

Routine activities

Five staff physicians (Drs. Yamashita, Kim, Kurosawa, Fuji, and Fukuda) and 4 chief residents (Drs. Hayashi, Ito A, Inoue and Ito R) participate in the transplant program. Children who have undergone HSCT are managed in collaboration with Dr. Ogawa, the medical staff of the Pediatric Oncology Division, and the transplant team. In 2013, a total of 110 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 2013 are shown in Tables 1 and 2, respectively. At the weekly conference on Monday afternoons, in collaboration with doctors of the Hematology Divisions, about 30 hospitalized HSCT patients and those who have been referred for HSCT, are reviewed for clinical management and a decision regarding their eligibility for HSCT. The transplant unit is staffed by 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 2013, 416 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 (mini-transplant) for elderly patients. One clinical trial of gene therapy using the HSV-TK suicide gene for T-cell add-back following haploidentical HSCT is ongoing. A clinical trial of post-transplant consolidation with the WT1 vaccine is also ongoing.

We have been working on expansion of the indication of drugs used for the treatment of GVHD and infections. In the Division, 18 clinical trials are ongoing, and 5 trials have completed patient accrual. A nationwide large survey of quality of life (QOL) was conducted for 576 patients with acute leukemia who received chemotherapy or HSCT. In 2013, we have published 26 articles in peer-reviewed international journals and 6 manuscripts have been accepted for E-pub before print or are in press for publication.

Table 1. Number of each type of HSCT

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

Table 2. Number of patients who underwent HSCT between 2008 and 2013

Diagnosis	Allogeneic	Autologous
Acute myeloid leukemia	197	1
Myelodysplastic syndrome	39	0
Acute lymphocytic leukemia	73	0
Malignant lymphoma (including ATL)	173	67
Multiple myeloma	0	25
Solid tumors	2	25
Others	11	0
Total	495	118

List of papers published in 2013
Journal

1. Kurosawa S, Miyawaki S, Yamaguchi T, Kanamori H, Sakura T, Moriuchi Y, Sano F, Kobayashi T, Yasumoto A, Hatanaka K, Yanada M, Nawa Y, Takeuchi J, Nakamura Y, Fujisawa S, Shibayama H, Miura I, Fukuda T. Prognosis of patients with core binding factor acute myeloid leukemia after first relapse. Haematologica, 98:1525-1531, 2013
2. Kurosawa S, Yakushijin K, Yamaguchi T, Atsuta Y, Nagamura-Inoue T, Akiyama H, Taniguchi S, Miyamura K, Takahashi S, Eto T, Ogawa H, Kurokawa M, Tanaka J, Kawa K, Kato K, Suzuki R, Morishima Y, Sakamaki H, Fukuda T. Recent decrease in non-relapse mortality due to GVHD and infection after allogeneic hematopoietic cell transplantation in non-remission acute leukemia. Bone Marrow Transplant, 48:1198-1204, 2013
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6. Tada K, Kurosawa S, Hiramoto N, Okinaka K, Ueno N, Asakura Y, Kim SW, Yamashita T, Mori SI, Heike Y, Maeshima AM, Tanosaki R, Tobinai K, Fukuda T. Stenotrophomonas maltophilia infection in hematopoietic SCT recipients: high mortality due to pulmonary hemorrhage. Bone Marrow Transplant, 48:74-79, 2013
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16. Murata M, Nakasone H, Kanda J, Nakane T, Furukawa T, Fukuda T, Mori T, Taniguchi S, Eto T, Ohashi K, Hino M, Inoue M, Ogawa H, Atsuta Y, Nagamura-Inoue T, Yabe H, Morishima Y, Sakamaki H, Suzuki R. Clinical factors predicting the response of acute graft-versus-host disease to corticosteroid therapy: an analysis from the GVHD Working Group of the Japan Society for Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant, 19:1183-1189, 2013

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20. Kanda Y, Kanda J, Atsuta Y, Maeda Y, Ichinohe T, Ohashi K, Fukuda T, Miyamura K, Iida H, Mori T, Iwato K, Eto T, Kawa K, Morita S, Morishima Y. Impact of a single human leucocyte antigen (HLA) allele mismatch on the outcome of unrelated bone marrow transplantation over two time periods. A retrospective analysis of 3003 patients from the HLA Working Group of the Japan Society for Blood and Marrow Transplantation. Br J Haematol, 161:566-577, 2013

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Department of Blood Transfusion and Cellular Therapy

Ryuji Tanosaki

Introduction

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

Routine activities

Currently, our staff members consist of 1 JSTMCT-accredited medical doctor and 4 specifically-engaged medical technologists (including 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 this Department and the Clinical Departments of Surgery and Internal Medicine, chief of the Department of Pharmacy, vice-chief of the Nursing Division, and a secretary. An administrative meeting is also held weekly, the attendees consisting of two chief doctors and three head doctors of this Department and the Department of Pathology and Clinical Laboratories, and the head and vice-head medical technologists. An all-staff meeting is held once a month.

As an in-hospital transfusion service section, we purchase blood products, which are required and ordered by clinicians, from the Red Cross, and examine and confirm the ABO blood type, and provide them for clinical use without any delay. Last year, the total units of red cell concentrates (RCC), platelet concentrates (PC) and fresh frozen plasma (FFP), which were consumed in our hospital, were 9545, 38835 and 4746, respectively. In 2013, the wastage of total blood products was 0.3%; RCC 1.2%, PC 0.03%, FFP 1.1%. Thanks to the Tokyo Red Cross and the convenient location of our hospital, blood products are available within 1 hour almost every time when they are needed in an emergency.

We employ the Type & Screen and computer cross-match system, but special attention is paid to blood typing, because about 100 cases of hematopoietic stem cell transplantation (SCT) are performed in our hospital every year including many ABO-mismatched donor-recipient pairs. To avoid any mistake of transfusions going to the incorrect recipients, we have established a very solid 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 electric medical record system is planned to be renewed in January 2014, the safety system for blood transfusion has also been strengthened.

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 a PC pack is performed in patients who have experienced repetitive or severe transfusion-associated reactions. Severe adverse events must be reported to the Red Cross and to the Ministry of Health, 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, all of which have been cryopreserved in liquid nitrogen. Each graft is registered and allotted its unique code number, which is recognized as its bar code. We believe that this bio-vigilant system is important for improving the practical aspects of cell therapy because the incidence of adverse reactions associated with graft infusion is significantly high.

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 and clinical trials

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

The chief doctor also contributes to transplantation activities, especially for adult T-cell leukemia-lymphoma in collaboration with the Department of Hematopoietic Stem Cell Transplantation and members of the hematology/oncology group at the Institute of Medical Science, Tokyo University.

List of papers published in 2013

Journal

1. Tamai Y, Hasegawa A, Takamori A, Sasada A, Tanosaki R, Choi I, Utsunomiya A, Maeda Y, Yamano Y, Eto T, Koh K-R, Nakamae H, Suehiro Y, Kato K, Takemoto S, Okamura J, Uike N, Kannagi M. Potential contribution of a novel Tax epitope-specific CD4+ T cells to graft-versus-Tax effect in adult T cell leukemia patients after allogeneic hematopoietic stem cell transplantation. J Immunol, 190:4382-4392, 2013
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Department of Pediatric Oncology

Chitose Ogawa, Hiroshi Kawamoto, Naoko Yasui, Chika Kohno, Ako Hosono, Yuko Araki, Hide Kaneda

Introduction

Pediatric oncology includes a wide variety of malignancies in children and adolescents such as acute leukemia and malignant lymphomas, as well as solid tumors including osteosarcomas, soft tissue sarcomas, neuroblastomas, Wilms' tumors and retinoblastomas. 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 four pediatric oncologists and two pediatric surgeons. 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 8 teachers work daily.

Routine activities

The pediatric outpatient clinic is open from Monday through Friday to manage new patients 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 stem cell transplantation (SCT), as indicated.

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

We provide personnel training and education for the global standard skills of diagnosis/treatment for hematological malignancies and solid tumors, which we regard as an important role of this center.

Research activities

1. For newly diagnosed patients, we participate in several multicenter studies, including those by the Japan Ewing Sarcoma Study Group (JESS) and the Rhabdomyosarcoma Study Group (JRSG). 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 veno-occlusive disease which is one of the fatal complications in SCT, a phase I registration trial for the standard drug in EU and USA has been finished.
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

The two trials (3 and 6 below) are investigator-initiated 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 neuroblastomas.
(5) A phase Ib study of VPA and 13-cis-RA (isotretinoin) combination therapy for advanced and recurrent neuroblastomas.
(6) A feasibility trial of ch14.18 combined with IL-2 and various colony-stimulating factors for recurrent neuroblastomas.
(7) A phase I trial of immunotherapy using HLA-A2- and A24-restricted glypican-3 peptide vaccine for pediatric tumors.

Table 1. Number of patients

Acute lymphoblastic leukemia	3
Acute myeloid leukemia	1
Non-Hodgkin lymphoma	0
Hodgkin lymphoma	1
Other hematologic malignancies	0
Neuroblastoma	7
Retinoblastoma*	9
Osteosarcoma	10
Ewing sarcoma family	9
Rhabdomyosarcoma	7
Other soft tissue tumors	10
Germ cell tumor	2
Other solid tumors	3
Total	62

*; advanced case only

Table 2. Type of procedure

Tumor resection	
retroperitoneum	3
pelvic	1
abdominal wall(Lap)	1
ovary	3
Tumor biopsy(Lap)	2
Lung wedge resection(Lap assist)	4
Surgery for mediastinal tumor(Lap assist)	2
Surgery for pleural tumor(Lap assist)	1
Pylorus-preserving pancreaticoduodenectomy(PPPD)	1
Lymph node dissection	5
Lymph node biopsy	4
Central venous(CV) port / catheter	
placement	31
cutdown	1
remove	9
Total	68

List of papers published in 2013
Journal

1. Yasui N, Koh K, Kato M, Park MJ, Tomizawa D, Oshima K, Uchisaka N, Gocho Y, Arakawa A, Seki M, Oguma E, Kishimoto H, Watanabe S, Kikuchi A, Hanada R. Kasabach-Merritt phenomenon: a report of 11 cases from a single institution. J Pediatr Hematol Oncol, 35:554-558, 2013
2. Kato M, Yasui N, Seki M, Kishimoto H, Sato-Otsubo A, Hasegawa D, Kiyokawa N, Hanada R, Ogawa S, Manabe A, Takita J, Koh K. Aggressive transformation of juvenile myelomonocytic leukemia associated with duplication of oncogenic KRAS due to acquired uniparental disomy. J Pediatr, 162:1285-1288, 1288.e1, 2013

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

Routine activities

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

Cardiology:

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

Diabetology:

We have provided more than 500 diabetes consultations in 2013, which include perioperative management of diabetes, treatment of steroid-induced hyperglycemia during chemotherapy, and so on. In many cases, initiation of insulin is the treatment of choice. We also offer close follow-up on an outpatient basis for those who have diabetes during their cancer treatment at NCCH.

Infectious diseases:

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

Nephrology:

To deal with the consultations from NCCH cancer specialists is the main work (332 consultations per year in 2013). The details of the consultations are as follows: assessment and treatment of acute kidney injury (AKI), management of chronic kidney disease (CKD) (including assessment of the optimal drug dose for CKD patients), treatment of electrolyte imbalance (hyponatremia, hypernatremia, hyperkalemia, hypokalemia, hypercalcemia, hypocalcemia, hypomagnesemia), assessment of polyuria (diabetes insipidus, salt wasting syndrome (SWS), diabetes mellitus and so on), assessment of edema, management of hypertension (including refractory hypertension, like renovascular hypertension), assessment and treatment of the nephrotic syndrome especially after hematopoietic stem cell transplantation, and so on. In case of the necessity for further evaluation of a patient, this is done in cooperation with the Department of Internal Medicine, Keio University Hospital.

An apparatus for hemodialysis was installed in October, 2012. Therefore, hemodialysis patients have been able to receive cancer treatment at NCCH.

Research activities

An article with the title "Complete remission of repeated recurrent membranous nephropathy after non-myeloablative allogeneic peripheral blood stem cell transplantation" was published in The Japanese Journal of Nephrology.

List of papers published in 2013

Journal

1. Kasuga M, Ueki K, Tajima N, Noda M, Ohashi K, Noto H, Goto A, Ogawa W, Sakai R, Tsugane S, Hamajima N, Nakagama H, Tajima K, Miyazono K, Imai K. Report of the Japan Diabetes Society/Japanese Cancer Association Joint Committee on Diabetes and Cancer. Cancer Sci, 104:965-976, 2013
2. Kasuga M, Ueki K, Tajima N, Noda M, Ohashi K, Noto H, Goto A, Ogawa W, Sakai R, Tsugane S, Hamajima N, Nakagama H, Tajima K, Miyazono K, Imai K. Report of the JDS/JCA Joint Committee on Diabetes and Cancer. Diabetol Int, 4:81-96, 2013
3. Takase S, Osuga J, Fujita H, Hara K, Sekiya M, Igarashi M, Takanashi M, Takeuchi Y, Izumida Y, Ohta K, Kumagai M, Nishi M, Kubota M, Masuda Y, Taira Y, Okazaki S, Iizuka Y, Yahagi N, Ohashi K, Yoshida H, Yanai H, Tada N, Gotoda T, Ishibashi S, Kadowaki T, Okazaki H. Apolipoprotein C-II deficiency with no rare variant in the APOC2 gene. J Atheroscler Thromb, 20:481-493, 2013

Department of Dentistry

Takao Ueno

Introduction

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

Routine activities

1) Management of oral complications of high-dose chemotherapy and/or stem cell transplant before treatment begins
2) Prevention and treatment of oral complications during chemotherapy and/or radiation therapy
3) Perioperative dental management for the prevention of postoperative pneumonia with oral, pharyngeal and esophageal surgery
4) Making prostheses for restoration of postoperative facial defects
5) Prevention and treatment of bisphosphonate-associated osteonecrosis
6) Cooperation enterprises with departments of medicine and dentistry in the Kanto area to seek optimum solutions to dental problems associated with the cancer patient)

Research activities

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

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

Table 1. Number of new patients

oral care before operation (head and neck, esophagus) and radiation therapy to the head and neck	158
Introduction to the cooperation dental clinic (oral health care before operation)	338
oral care and treatment of mucositis , oral infection during chemotherapy	312
dental check up and oral care before chemotherapy	165
dental check up and oral care before using bone modifying agents	142
Total	1023

Department of Genetic Counseling

Teruhiko Yoshida, Kokichi Sugano, Takeshi Nakajima

Introduction

Approximately 5% of all cancer cases are considered to have a highly penetrant monogenic mutation. Most of the causative genes for major hereditary cancer syndromes were identified in the 1990s, and genetic diagnosis has been introduced as the standard medical care for some tumors. However, cancer medical genetics still has a number of issues to be addressed (Figure 1).

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 research and clinical practice.

Routine activities

The National Cancer Center Hospital (NCCH) launched the Outpatient Genetic Counseling Clinic in 1998 as a part of collaboration with the Research Institute, and since then, total 1,124 clients from 744 families have visited the Clinic as of December 2013. Based on the present, past and detailed family histories, risks of the most likely hereditary cancer syndrome, if any, will be explained followed by the discussion about the prevention scheme for clients and relatives. If appropriate, genetic tests may be offered, too.

Regular conferences of the Genetic Counseling Clinic were held from June 1998 to December 2005. In December 10, 2013, hereditary cancer syndromes were selected as the theme of the 7th Research Conference, and the avid discussion by a large audience from various sectors of the NCC resulted in the new series of the Genetic Counseling Clinic conferences which resumed from February 2014.

Research activities

In general, sensitivity of the current standard genetic tests has remained approximately 70-80% even for the cases well-matched to the clinical criteria for hereditary cancer syndromes. To exploit the latest genome technology for the undiagnosed patients, a variant call pipeline based on the whole-exome sequencing by the next generation sequencer and genome-wide SNP array has been established in the Division of Genetics and Genome Core Facility of the NCC Research Institute, which have been in charge of the area of in-house genetic tests at the Genetic Counseling Clinic. However, the technology alone cannot solve the problem, and the importance of family study, ascertaining genome samples and clinical information from relatives with or without the disease, has been confirmed.

Clinical trials

The Genetic Counseling Clinic has participated in a prospective clinical study to optimize BRCA1/2 genetic tests and a clinical trial of PARP inhibitor for patients with ovarian cancer both directed by the Department of Breast and Medical Oncology.

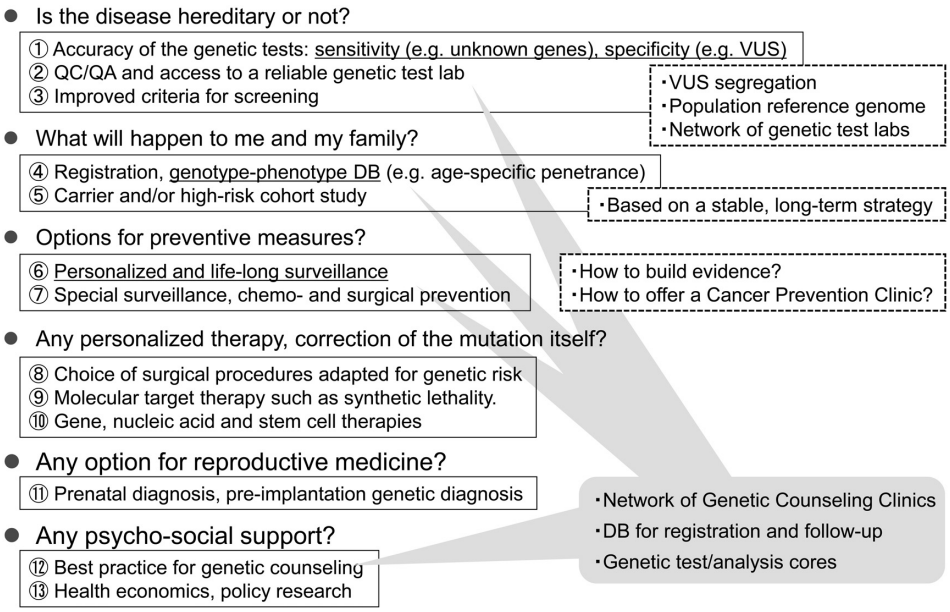

Figure 1. Major Questions by the Patients and Families with Hereditary Cancer Syndromes

Table 1. Number of patients by condition

	Proband	Relative	Total
Lynch syndrome (Hereditary Non-Polyposis Colon Cancer; HNPCC)	16	15	31
Familial Adenomatous Polyposis (FAP)	6	4	10
Retinoblastoma	10	2	12
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	56	8	64
MEN I (Multiple Endocrine Neoplasia Type I)	0	0	0
Other diseases	4	0	4
Counseling only	3	0	3
Total	95	29	124

List of papers published in 2013
Journal

1. Saeki N, Ono H, Sakamoto H, Yoshida T. Genetic factors related to gastric cancer susceptibility identified using a genome-wide association study. Cancer Sci, 104:1-8, 2013
2. Fujita T, Yanagihara K, Takeshita F, Aoyagi K, Nishimura T, Takigahira M, Chiwaki F, Fukagawa T, Katai H, Ochiya T, Sakamoto H, Konno H, Yoshida T, Sasaki H. Intraperitoneal delivery of a small interfering RNA targeting NEDD1 prolongs the survival of scirrhous gastric cancer model mice. Cancer Sci, 104:214-222, 2013
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4. Udagawa T, Narumi K, Suzuki K, Aida K, Miyakawa R, Ikarashi Y, Makimoto A, Chikaraishi T, Yoshida T, Aoki K. Vascular endothelial growth factor-D-mediated blockade of regulatory T cells within tumors is induced by hematopoietic stem cell transplantation. J Immunol, 191:3440-3452, 2013

Department of Anesthesia and Intensive Care

Tetsufumi Sato, Yoko Kinoshita, Minako Arai, Takashi Matuzaki, Nobuko Yokokawa, Rie Suzuki, Yousuke Kawaguchi, Kazumasa Hiroi, Takuma Hiraiwa, Sayo Iwasaki, Miyabi Takemura, Takuya Ohata, Kihoko Ichikawa

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 (ICU) has 8 beds and provides care for all specialties including general medical and general surgical cases. There are over 400 admissions annually and the ICU is also responsible for resuscitation services within the hospital.

Routine activities

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

Our ICU is certificated by the Japanese Society of Intensive Care Medicine. It provides care for all specialties including general medical, general surgical and neurosurgical cases. It is managed as a closed system, supported by two certificated intensivists and trainee. There are 8 operational ICU beds and 484 patient admissions annually. The ICU is also responsible for resuscitation services within the hospital.

A weekly conference is held with all anesthesiologist and intensivists to keep up-to-date with the current world standard of acute care medicine. A weekly lecture is also held for the education of intensive care nurses. Occasionally, a mortality and morbidity conference is held with doctors of other department.

Clinical trials

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

Table 1. Cases for anesthetic management

Thoracic surgery	643
Breast surgery	427
Colon surgery	458
Urologic surgery	257
Ophthalmologic surgery	319
Orthopedic surgery	264
Hepato-Biliary-Pancreatic surgery	281
Gynecologic surgery	197
Esophageal surgery	119
Head-neck surgery	168
Skin surgery	104
Other	351
Total	4193

Department of Palliative Care

Motohiro Matoba, Osamu Saito, Chio Shuto, Hironori Mawatari

Introduction

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

Routine activities

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

Education for residents

With regard to their clinical education and training, all the residents of the NCCH are required to train with our team for 1 month, within which a one-week home hospice course is mandatory. In total, 21 residents trained with our team during 2013. The course is whole-person-care oriented. The home hospice course offers an opportunity to understand the role of various occupations other than doctors, such as visiting nurses and care managers.

Research activities

In particular, establishment of a pain management monitoring system and a program for improving opioid consumption have been started at Aomori Prefectural Central Hospital.

Also, construction of a supporting system has been completed for children and their families whose father/mother are suffering and dying from advanced cancer.

Table 1. Number of patients

sarcoma	30
Lung cancer	19
Gastric cancer	13
Breast cancer	10
Colon cancer	9
Rectal cancer	9
Renal cancer	9
Pancreatic cancer	8
Primary unknown cancer	7
Malignant melanoma	6
Prostate cancer	5
Uterine cancer	5
Esophageal cancer	5
Leukemia	5
Malignant lymphoma	4
Others	37
Total	181

Table 2. Type of procedure

Adjustment of non-opioid analgesics	54
Commencement of opioid analgesics	21
Adjustment of opioid analgesics	77
Opioid rotation	30
Adjustment of adjuvant analgesics	33
Nerve block	5
Management of side effect of analgesics	39
Others	15

List of papers published in 2013

Journal

1. Oya H, Matoba M, Murakami S, Ohshiro T, Kishino T, Satoh Y, Tsukahara T, Hori S, Maeda M, Makino T, Maeda T. Mandatory palliative care education for surgical residents: initial focus on teaching pain management. Jpn J Clin Oncol, 43:170-175, 2013
2. Yamaguchi T, Shima Y, Morita T, Hosoya M, Matoba M. Clinical guideline for pharmacological management of cancer pain: the Japanese Society of Palliative Medicine recommendations. Jpn J Clin Oncol, 43:896-909, 2013

Department of Psycho-Oncology

Ken Shimizu, Rika Nakahara, Yoshio Oshima, Masashi Kato, Tomomi Takahashi

Introduction

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

Routine activities

The Psychiatry Division consists of two full time staff psychiatrists and one part time psychiatrist, and one chief resident. One staff psychotherapist and two part-time psychotherapists are available four days a week. The division provides two major services; a clinic for outpatients (four days a week) and consultation for referred inpatients. The purpose of the psychiatric consultation is to diagnose and treat the mental distress and cancer related psychological problems of patients who have been referred by their attending physicians. Since 1999, the division has played an active role as a member of the palliative care team.

A range of psychiatric diagnoses is based on the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) shown in the Table. In 2013, a total of 778 patients were referred for psychiatric consultation. The mean age was 50.9 years old and 13.2% of the referrals were outpatients. Three-hundred and eighty seven (49.7%) of the total number of referred patients were males. The most common psychiatric diagnosis was delirium (26.3%), followed by adjustment disorders (19.6%), and major depression (9.1%), while 19.6% of the referrals had no psychiatric diagnosis. The three common mental disorders; adjustment disorder, major depression and delirium, were responsible for half of the psychological problems. The most common cancer referrals were patients with sarcomas (16.4%), followed by hematological cancer (11.4%), breast cancer (9.5%), lung cancer (8.7%), stomach cancer (6.5%), colorectal cancer (6.5%), and esophageal cancer (6.4%).

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

Research activities

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

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

Table 1. Patient demographics

Patients	Total number	778	
	Age	50.9 years	
	Male	387	49.7%
	Inpatients	674	86.6%

Table 2. Number of cancers by site

Cancer site	Sarcoma	128	16.4%
	Hematological	89	11.4%
	Breast	74	9.5%
	Lung	57	8.7%
	Stomach	51	6.5%
	colorectal	51	6.5%
	Esophageal	50	6.4%

Table 3. Breakdown of diagnoses

Diagnosis	Delirium	205	26.3%
	Adjustment Disorders	153	19.6%
	Major Depression	71	9.1%
	No Diagnosis.	153	19.6%

List of papers published in 2013
Journal

1. Shimizu K. Effects of integrated psychosocial care for distress in cancer patients. Jpn J Clin Oncol, 43:451-457, 2013
2. Asai M, Akizuki N, Fujimori M, Shimizu K, Ogawa A, Matsui Y, Akechi T, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Impaired mental health among the bereaved spouses of cancer patients. Psychooncology, 22:995-1001, 2013

Department of Diagnostic Radiology

Yasuaki Arai, Masahiko Kusumoto, Ryutaro Kakinuma, Yasunori Mizuguchi, Gen Iinuma, Takashi Terauchi, Miyuki Sone, Hiroaki Onaya, Hiroaki Kurihara, Nachiko Uchiyama, Hirokazu Watanabe, Minoru Machida, Seiko Kuroki, Mari Kikuchi, Tomoko Manabe, Mototaka Miyake, Hiroaki Ishii, Syunsuke Sugawara, Hirotaka Tomimatu, Shinichi Morita, 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. 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	39,980
2	MRI	8,061
3	IVR	4,148
4	RI	4,356
5	Ultrasound	13,610
6	Radiograph	79,877
7	Gastrointestinal study	1,856

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 CO2 gas insufflation systems have been established in 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.

We evaluated the usefulness of additional ADc value in predicting extracapsular extension of prostate cancer using 3.0 T MR imaging.

Regarding the pulmonary subsolid nodules, a prospective multicenter study to clarify natural history of subsolid nodules on Chest CT is ongoing.

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 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.

A multi tracer consisting of [18F]FDG, [18F] FBPA, anti-[18F]FACBC, [11C]choline, [11C] methionine and [64Cu]-DOTA-antibody PET imaging has been studied for cancer patients to improve the sensitivity and specificity of detecting tumor sites or tumor characteristics. [18F]-FDG dynamic PET sampling with Patrak-plot analysis allows us to calculate the glucose metabolic rate of the tumor site. [18F]-FBPA PET/CT, known as an evaluator for boron neutron capture therapy (BNCT), has been conducted in 22 cancer patients in this year. Anti-[18F]-FACBC PET/CT has been also carried out in prostate cancer patients as a phase II clinical trial. [11C]-choline and [11C]-methionine PET/CT examinations have been scheduled routinely two day per week. As for [64Cu]-DOTA-antibody PET imaging, [64Cu]-DOTA-trastuzumab PET/CT has been conducted in HER-2 positive breast cancer patients. 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 19 thyroid cancer patients with use of radioactive iodine (I-131) chloride and 1 neuroblastoma patient with I-131 MIBG.

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) and a phase II study evaluating the efficacy of arterial infusion chemotherapy and radiotherapy for unresectable maxillary carcinoma (JIVROSG-0808).

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Journal

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Department of Radiation Oncology

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Introduction

The role of the Department is to provide state of art radiation therapy to all the relevant patients, to educate and develop the expertise of radiation oncologists, radiation technologists, and medical physicists, and to lead new developments in radiation oncology in Japan as well as worldwide. All Departmental Activities are dedicated to Cancer Patients. In this year, a new building for the hospital-based boron neutron capture therapy (BNCT) system using an accelerator was constructed and finished in Dec. 2013. The Department will be fully involved in the development of BNCT.

Routine Activities

The Department of Radiation Oncology of the National Cancer Center Hospital is one of the biggest radiation oncology departments in Japan. Four linear accelerators, one X-ray simulator, one XCT-simulator, and 7 treatment planning computers are working together under on-line networks to provide state-of-art precision external beam radiation therapy. In 2010, the X-ray simulator was updated to the newest machine, the Accusim from Varian. In addition to the conventional X-ray and electron therapies, stereotactic irradiations of brain and body tumors and intensity-modulated radiation therapy (IMRT) are employed to improve local control. Stereotactic brain irradiation was originally invented in this Department under the name of stereotactic multiarc radiation therapy (SMART) and has been employed in the treatment of metastatic as well as primary brain tumors. Stereotactic body tumor irradiation is performed in lung and liver tumors under respiratory gating. Three of the 4 linear accelerators have on-board kilovoltage CT imagers, which help to align patient and tumor coordinates precisely. These image guided radiation therapy (IGRT) facilities enable the precise delivery of IMRT in head and neck cancers, brain tumors, prostate cancers, and postoperative cervical cancers. From Dec. 2011, gold markers have been implanted to improve geometric precision of radiation field reproducibility. In the new building, the CyberKnife STI and True Beam Linac have already been installed and they will be clinically used from April 2014.

Brachytherapy is also performed very intensively to obtain local control and many patients are referred to us from all over Japan. For brachytherapy the following modalities are being employed, an Ir-192 high dose rate (HDR) afterloading system including a dedicated CT simulator and fluoroscopy, an I-125 seed implantation system, and other low dose rate (LDR) brachytherapy systems using Au grains, Ir-thin wires, and ruthenium eye plaques. The number of patients undergoing HDR brachytherapy continued to rise constantly in 2013 as in the past. This Department is the only one institution in Tokyo, where HDR interstitial as well as intracavitary irradiations can be performed. The HDR interstitial radiation is performed mainly in gynecological, genitourinary, and head and neck tumors. Additionally, there are 2 beds in the shielded ward in Floor 13B. Ruthenium mold therapy is performed by ophthalmologists to treat retinoblastomas and choroidal melanomas. LDR interstitial implants are carried out by radiation oncologists using Au-198 grains and Ir-192 thin wires for the management of head and neck tumors and gynecological malignancies.

Research Activities

Clinical research is an indispensable part of the daily activities of the Department. The primary interests of the research activities of the Department are 1) an optimal fractionation regimen for the pain palliation of bone metastasis; 2) the safety and feasibility of a shortened fractionation regimen for various malignancies, especially for breast cancer and vocal cord cancer; 3) HDR and LDR brachytherapy for genitourinary and gynecologic cancers; 4) hypofractionated stereotactic irradiation of brain and body tumors; 5) adaptive radiation therapy in accordance with the intratherapeutic tumor and normal tissue change; and 6) Development of an accelerator based BNCT system. These studies are financially supported by grants from the Ministry of Health, Labour and Welfare (MHLW), Japan.

Clinical Trials

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

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

Lung cancer: Stereotactic radiation therapy for histologically nonverified lung tumors.

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

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

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

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

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

Development of an Adaptive Radiation Therapy System

Table 1. Number of Radiation Treatment Plans

Primary Sites	No. of All Treatment Plans					
	2008	2009	2010	2011	2012	2013
Head & neck	115	95	128	166	158	257
Brain	117	99	113	97	77	83
Lung	397	431	429	348	430	425
Breast	549	452	487	503	485	582
Esophagus	220	213	265	237	268	248
Stomach	34	29	25	15	35	37
Colorectal	86	78	66	119	113	100
Pancreas and hepatobiliary	38	48	69	68	64	69
Gynecological	255	331	274	328	418	327
Genitourinary	128	159	192	169	172	191
Bone & soft tissue	75	69	103	92	86	90
Skin	16	26	58	71	58	54
Pediatric	22	32	25	66	49	24
Hematological	137	220	159	157	202	165
Other	47	52	19	14	39	25
Total	2236	2334	2412	2450	2654	2677

*: No. of Cases

Table 2. Purpose of Radiation Therapy

	No. of All Treated Patients					
	2008	2009	2010	2011	2012	2013
No. of Treatment Plans	2236	2334	2412	2450	2654	2677
Curative Intent	1535	1500	1587	1662	1858	1819
Palliative Treatment	701	834	825	788	796	858
Curative/Palliative	2.19	1.80	1.92	2.11	2.33	2.12
New Patients	1181	1210	1277	1288	1271	1861

Table 3. Special Radiation Therapy

	No. of Treated Patients			
	2010	2011	2012	2013
IORT	0	1	0	0
TBI	41	52	51	58
SRT-Brain	3	2	6	5
SRT-Body	33	45	37	55
IMRT-Brain	7	11	12	26
IMRT-H&N	34	45	62	108
IMRT-Thorax	1	3	6	2
IMRT-Gyne	6	14	23	13
IMRT-Prostate	46	55	56	69
IMRT-Others	11	9	13	24
Intracavitary RT 192Ir-HDR	50	49	40	48
Intracavitary RT 192Ir-LDR	0	0	0	0
Interstitial RT 192Ir-HDR	6	25	37	43
Interstitial RT 192Ir-LDR	0	0	1	0
Interstitial RT 198Au-LDR	6	4	7	7
Interstitial RT 125I-LDR	26	16	28	22
Interstitial RT 106Ru-LDR	10	13	17	20
Non-Sealed Radionuclide Therapy 89Sr	5	12	4	3
Non-Sealed Radionuclide Therapy 131I	14	21	24	16
Non-Sealed Radionuclide Therapy MIBG				1

IORT; intraoperative radiotherapy
TBI; total body irradiation

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Department of Pathology and Clinical Laboratories, Pathology Division

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Introduction

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

Routine activities

In 2013, a total of 14 board-certified pathologists, 8 residents and 11 medical technologists, including 11 cytotechnologists, cooperatively performed routine histological and cytopathological diagnosis of specimens obtained from patients at the National Cancer Center Hospital (NCCH) and the Research Center for Cancer Prevention and Screening, and education of the residents. Seven pathologists working exclusively in the NCCH also shared management of the Department. Another 7 pathologists are concurrently on the staff of NCC Research Institute (NCCRI).

1. Surgical pathology

A total of 20,205 histological diagnoses were provided consisting of 16,371 biopsy specimens including 1,886 intraoperative frozen sections and 3,834 surgically resected specimens. The intraoperative frozen sections comprised primary tumors, regional lymph nodes, and surgical margins of specimens. The one-step nucleic acid amplification (OSNA) assay was performed for 436 patients to examine metastasis intraoperatively.

2. Cytopathology

Cytopathological diagnoses were provided for a total of 12,188 patients including 357 for intraoperative diagnosis. The specimens comprised smears, sputa, body fluids, urine, and needle aspirates submitted from various departments. Intraoperative cytological examination of body fluids was utilized for disease staging and treatment decisions in the fields of gastric surgery and gynecology.

3. Autopsy

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

4. Outpatient clinic for pathology consultation (second opinion)

To 210 patients, we provided histopathological/cytopathological diagnosis as second opinion.

Research activities

1. Gastrointestinal pathology

Clinicopathological characteristics of adenocarcinoma at the esophago-gastric junction, and the GNAS and KRAS status of gastrointestinal neoplasia were studied in collaboration with clinical departments and research institute.

2. Hematopathology

Clinicopathological prognostic indicators of follicular lymphoma and transformed follicular lymphoma were studied. Long follow-up data of patients with B-cell lymphoma with a CD20-negative phenotypic change after rituximab-containing therapy were reported.

3. Pulmonary and mediastinal pathology

The clinical significance of *IGF-1R* gene copy number alterations, *ROS1* rearrangement, and IASLC

classification were studied in lung adenocarcinoma. Pitfalls of immunohistochemistry for ALK as well as squamous cell carcinoma and adenocarcinoma markers were studied.

4. Bone and soft tissue pathology

Anaplastic lymphoma kinase status was comprehensively assessed in >100 rhabdomyosarcomas using sensitive immunohistochemistry, FISH, and sequencing. A new fusion variant of PPFIBP1-ALK was discovered in an inflammatory myofibroblastic tumor.

5. Breast and gynecological pathology

The benefit of combination method for sentinel and nonsentinel lymph node assessment using one-step nucleic acid amplification and conventional histological examination was shown. The risk factors of early stage endometrial carcinoma were also assessed

Table 1. Numbers of Histopathological Specimens Diagnosed in the Pathology Section in 2013

Field	Number of specimens Total
Gastrointestinal tracts	8376
Breast	2501
Respiratory organs	2103
Hematology	1441
Gynecology	1241
Urology	830
Hepatobiliary and Pancreas	664
Head and Neck	657
Dermatology	564
Orthopedics	516
Others	947
Research Center for Cancer Prediction and Screening	365
Total	20205

Table 2. Numbers of Cytopathological Specimens Diagnosed in the Pathology Section in 2013

Field	Number of specimens Total
Gynecology	3949
Urology	2973
Respiratory organs	1876
Gastrointestinal tracts	778
Breast	458
Hepatobiliary and Pancreas	445
Hematology	290
Head and Neck	208
Radiation Oncology	178
Others	213
Research Center for Cancer Prediction and Screening	820
Total	12188

Table 3. Numbers of Autopsies Performed in the Pathology Section in 2013

Deaprtment/Division	Number
Hematology and Hematopoietic Stem Cell Transplantation	10
Gastrointestinal Oncology	6
Breast and Medical Oncology	5
Thoracic Oncology	3
Orthopedics	3
Neurosurgery	1
Thoracic Surgery	1
Esophageal Surgery	1
Total	34

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Journal

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Department of Pathology and Clinical Laboratories, Clinical Laboratory Division

Atsushi Ochiai, Koh Furuta

Introduction

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

Routine activities

Fifty full-time and 9 part-time medical technologists, 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 National Cancer Center Hospital (NCCH); and in the sections of phlebotomy and physiological examination in the Research Center for Cancer Prevention and Screening (RCCPS). The sections of 1) to 5) are supervised by Dr. Koh Furuta. The pathology section staff are supervised by the doctors in the Pathology Division, and the transfusion and phlebotomy staff are supervised by a doctor of the Department of Transfusion Therapy. In addition, the physiological examination staff are directly supervised by Dr. Yasunori Mizuguchi Department of Diagnostic Radiology, and Dr, Masaaki Syoji and Dr. Takeshi Iwasa, the General Internal Medicine Division* The bacteriology staff are members of the Infection Control Team (ICT) and participate in the activities of infection management in collaboration with the staff physicians.

An administrative meeting is held weekly, attending members of which consist of two chief doctors and three head doctors of this Department and the Department of Transfusion Therapy, and the head and vice-head medical technologists. The quality control meeting is regularly held twice a month, and an all-staff meeting is held once a month. The division also participates in several domestic and international programs for inter-laboratory standardization and external quality control including the College of American Pathologists (CAP) Survey. The actual number of laboratory tests performed in this Division in 2013 is shown in Table 1.

Table 1. Number of laboratory tests examined in the Clinical Laboratories Division (2013)

Section	Number
General laboratory medicine	506,790
Hematology	1,308,723
Biochemistry	2,928,640
Endocrinology, immunology, and tumor markers	372,534
Bacteriology	54,125
Physiology	87,188
Genetic diagnostics	739
Total	5,258,739

Research activities

An in-hospital bio-bank, which was established in 2002, has been maintained for use by various researchers, and more than 700,000 post clinical test blood samples have been cryo-preserved at -20 °C as of the end of 2013.

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

Using the Metafer system (an automated image analysis-assisted fluorescence in situ hybridization [FISH] system), the technique to evaluate the FISH imaging ofHER2 gene amplification was established. Furthermore, using the Metafer system, we tried to establish a method to evaluate FISH images of ALK-rearranged, ROS-rearranged, and RET-rearranged lung cancers.

The molecular pathology laboratory has been set up, FISH of epidermal growth factor receptor (tHoFR) in stomach cancer was performed, and

data are under acquisition. Many case reports with important ultrasound findings were presented in scientific meetings by the staff of the physiology section.

Under the education committee in the IS015189 scheme, a monthly seminar by the staff was started from this year for the purpose of promoting research activity in the Division.

List of papers published in 2013
Journal

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Office of Infection Control and Prevention

Minoru Esaki, Keiji Okinaka, Yasuko Ishida, Michi Shouji, Keiichi Koido, Yoshiko Nakayama

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, Infection control microbiological technologist, Board certified pharmacist in infection control, Office clerk, and Director. The team works very closely with staff from all areas of the hospital to prevent and control infection. The annual goals of our team for 2013 were

- to announce the 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 "ICT web"
- to collaborate with regional hospitals to keep cancer patient safe from healthcare-associated infections.
- to deliver 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

Our team provides

- Advice about the prevention and management of outbreaks, and delivering education programs to all staff including lectures by staff of 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 providing advice about building and refurbishment projects in the hospital from the infection control aspect.

Outpatient Treatment Center

Kenji Tamura

Introduction

The Outpatient Treatment Center deals with all kinds of malignant neoplasm. Our mission is to provide safe, smooth and high quality of standard chemotherapy regimens in the outpatient setting. Several groups collaborate to ensure the best chemotherapeutic approach, consisting of medical oncologists, nurses, pharmacists, medical social workers and clinical research coordinators. Our visions are 1) To provide findings based on evidenced based medicine, 2) To provide safe and efficient treatments, and 3) To maintain the quality of life of the patients.

Routine activities

From January to December 2013, The Outpatient Treatment Center supported at total of 22,162 patients who received anticancer drugs by intravenous administration (Table 1) and a total of 3678 patients whose drugs were administered by intramuscular or subcutaneous injection (Table 2, for example, endocrine therapy or interferon), making a grand total of 25,840 patients. The breakdown by cancer type was as follows: gastrointestinal (23%), breast (20%), gynecologic (15%), hepatobiliary and pancreatic (14%), hematology (10%), thoracic (10%) and other malignancies (6%). General infusions, general intramuscular or subcutaneous injections, blood transfusions, bone marrow punctures, lumbar punctures, intraperitoneal or chest drainage and blood gas analyses were conducted in the center.

Conference

A case conference is held biweekly on Monday with the participation of multidisciplinary specialists, including medical oncologists, nurses, and pharmacists. The monthly stuff meeting is held on the 2nd Tuesday of every month with the participation of physicians and nurses who are the main members in the center. The steering committee is held on the 3rd Thursday of every month.

Research Activities

- Efficacy of frozen gloves in the treatment of nail toxicities with docetaxel.
- Efficacy of frozen caps in the prevention of chemotherapy-mediated alopecia.
- Allergic reaction to oxaliplatin in outpatients.
- Telephone hot line for emergency for outpatients who are undergoing chemotherapy.

Education

We provide educational opportunities for multidisciplinary specialists, including medical oncologists, nurses, and pharmacists. We also provide an educational program for medical oncologists, nurses, pharmacists and medical social workers in designated hospital for cancer treatment in each prefecture.

Future Prospects

We continue to propose a near-future model of the clinical trials in outpatient style. We aim at shortening the waiting time, achieving smooth administration of novel molecular targeted drugs for outpatients, and to put into practice multidisciplinary care for cancer patients who received chemotherapy in the Outpatient Treatment Center.

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

	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Department	701	632	670	700	711	584	702	656	591	624	582	624	7777
Breast and Medical Oncology	458	430	423	384	458	389	453	459	423	504	439	444	5264
Hepatobiliary and Pancreatic Oncology	295	266	249	261	272	218	295	287	249	277	259	250	3178
Hematology	224	205	176	178	230	181	245	192	200	225	180	191	2427
Thoracic Oncology	202	185	191	210	195	179	182	148	166	163	157	173	2151
Others	87	90	95	97	101	110	174	133	122	129	115	112	1365
Total	1967	1808	1804	1830	1967	1661	2051	1875	1751	1922	1732	1794	22162

Table 2. Cumulative total number of patients who were treated except for intravenous administrations of anticancer drugs

	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Intramuscular or subcutaneous injection as anti-cancer drug	317	309	307	318	286	278	315	271	300	337	299	341	3678
General infusions-short	27	17	27	20	46	32	47	47	29	33	31	39	395
General infusions-long	2	4	0	2	0	0	1	1	3	0	5	1	19
General intramuscular or subcutaneous injections	195	167	212	234	223	192	223	203	231	217	208	195	2500
Blood transfusions	37	33	39	42	34	30	28	49	60	70	61	71	554
Bone marrow puncture	32	42	41	46	51	54	45	45	43	42	46	51	538
Lumbar puncture	3	1	3	3	4	2	1	0	1	1	1	0	20
Intraperitoneal drainage	3	2	0	1	0	2	1	2	0	2	4	0	17
Chest drainage	2	3	2	2	2	3	1	9	1	0	3	0	28
Blood gas analyses	35	30	28	42	26	32	26	34	28	27	27	21	356
Orientation	158	144	133	145	164	122	162	140	131	152	157	167	1775
Other treatments	38	28	37	32	38	21	23	22	19	30	38	40	366
Total	849	780	829	887	874	768	873	823	846	911	880	926	10246

Consultation, Counseling and Support Service Center

Masashi Kato, Yukiko Higuchi, Kayoko Miyata, Natsuko Moroi, Rieko Shimizu, Naoko Goto, Yasuko Arimoto, Mayumi Miura, Yuko Ogo, 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 cope with various problems of cancer patients and their families with the ultimate aim of helping patients feel relieved and to help them receive medical care. By putting ourselves in the patients' position, we can make real efforts to solve their problems.

Routine activities

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

We provide consultation, counseling and support to help 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 group for families of brain tumor patients
- CLIMB (Children's Lives Include Moments of Bravery) Support Program

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.

Table 1. The number of cases (April 2012 - March 2013)

1	Total	8,580
2	New cases	4,940
	New cases from NCCH	1,972
	New cases from other hospitals	2,968

Appearance Support Center

Keiko Nozawa, Naoya Yamazaki, Chikako Shimizu, Shu-ji Kayano, Shoko Toma, Kazuko Aoki

Introduction

The Appearance Support Centre is a new department of the National Cancer Center Hospital (NCCH), established on April 1, 2013. The outpatient consultation space is located on the first floor of the hospital, and it began operating from July 1st. We aim to support patients to be able to 'live in society' and to 'live as a human being', through clinical, research and educational practices regarding issues around the patients' physical appearance. In the current year, our goal is to establish the foundation of an organization and activities to fulfill our duty.

Routine activities

Our team consists of two Clinical Psychologists (1 full-time and 1 part-time) specialized in cosmetic knowledge, and they consult with both in- and outpatients as well as their families for questions and concerns regarding the patients' physical appearance. Examples of issues dealt with are the side effects of chemotherapy and radiotherapy on skin, nails and hair loss, scarring and post-surgery epitheses, and coping with mastectomies. 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 Monday-Thursday from 12-1 pm, providing a space in which patients can try on different products and consult staff. Despite limited hours for security reasons, we have had 445 users from July to December 2013. Additionally, we also run a patient support program titled *Cosmetic Information* every Tuesday and Thursday from 1 pm. Its main aim is the provision of information to patients through group sessions. We have conducted 51 sessions in which 229 patients participated.

For individual consultations for new patients, within six months there were a total of 287 consultations by 106 in- and outpatients. Main concerns were coping strategies with hair loss and specific symptoms of the skin and nails. Reasons for consultation 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, especially on account of the lack of evidence and increased risks of information regarding physical appearance that is currently available. Current research projects are: the multi-faceted examination of the efficacy of support programs for patients regarding physical appearance, research for establishment of guidelines for cancer patients' appearance support, and investigation and development of the appearance-care educational training system. Additionally, the study of patients' needs and the development and trials of products as possible solutions are carried out continuously through daily clinical practice.

Education

In order to foster medical staff that can practice appearance-care, a basic educational workshop was conducted for medical staff from designated regional cancer centers and hospitals. Additionally in order to enable implementation of the same program at the Kyushu Cancer Center and Shikoku Cancer Center, we conducted a special educational workshop as well.

We are contributing to the fostering of medical staff that possess understanding of physical appearance support by not only conducting workshops for nurses and pharmacists but also by allowing intern visits, holding hospital study sessions, and accepting internships as "Orange Casts" (Young patient volunteers) as well as from surviving student cancer patients.

Future prospects

We anticipate the emergence of new issues regarding physical appearance as the variety in treatment drugs increases, survival rates increase, cosmetic surgeries develop, and innovations continue in cosmetic products. Although responding to the

needs of all patients is difficult as fulltime workers are scarce, we hope to expand human resources and develop this emerging field based on research. Additionally in clinical practice, we aspire to conduct more workshops in order to improve cooperative networks within and outside the hospital.

List of papers published in 2013

Journal

1. Nozawa K, Shimizu C, Kakimoto M, Mizota Y, Yamamoto S, Takahashi Y, Ito A, Izumi H, Fujiwara Y. Quantitative assessment of appearance changes and related distress in cancer patients. Psychooncology, 22:2140-2147, 2013

Rare Cancer Center

Akira Kawai, Hirokazu Chuman, Eisuke Kobayashi, Motokiyo Komiyama, Satoshi Okada, Makoto Kodaira, Mayu Yunokawa, Shunsuke Kondo, Chitose Ogawa, Miyuki Sone, Minako Sumi, Akihiko Yoshida, Takuro Sakurai, Yoshitaka Narita, Naoya Yamazaki, Shigenobu Suzuki, Tadashi Kondo, Naohiro Higashi, Makiko Murase, Yoko Kato, Umio Yamaguchi, Naoto Gotohda, Toshihiko Doi, Yoichi Naito, Ako Hosono, Tetsuo Akimoto, Junya Ueno

The Rare Cancer Center was established in December 2013 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 no generally agreed definition of rare cancers. Rare diseases are often defined as those with a prevalence of < 50/100,000. In the US, the Orphan Drug Act defined rare diseases as those affecting < 200,000 persons. According to the definition of the project Surveillance 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 cancers is combined, it corresponds to up to 15% of all new cancer diagnoses.

Information (epidemiologic, medical, and social) 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.

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

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

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

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

Top enable the Center to play its role, a total of 27 doctors, nurses and researchers dealing with rare cancers have joined as members of the Center. They originate from the Departments of Musculoskeletal Oncology and Rehabilitation, Neurosurgery and Neuro-Oncology, Ophthalmic Oncology, Urology, Gynecology, Dermatologic Oncology, Gastric Surgery, Breast and Medical Oncology, Pediatric Oncology, Diagnostic Radiology, Radiation Oncology, Phase I Unit, Pathology, Nursing, Research Institute and the Center for Cancer Control and Information Services.

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. In addition to the daily clinical activities, the Center members supported "A workshop on the measures against rare cancers in Japan" which was held by the Center for Cancer Control and Information Services on February 16th 2014.

The Rare Cancer Center provides consultation to the patients and relatives with rare cancers on the telephone (Rare Cancer Hotline). The Center is now planning to provide comprehensive, scientifically based, up-to-date unbiased information about rare cancers to all patients, families and health professionals fighting against rare cancers via our website.

Surgical Center

Hitoshi Katai

Introduction

The Surgical Center deals with all kinds of malignant neoplasms. 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 2013, the Surgical Center supported more than 4,835 surgical cases and more than 4,193 general anesthesia surgical cases, a 2.9% increase in the number of cases and a 2.3% increase in the general anesthesia cases over 2012. 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.

The Da Vinci robotic surgical system has been introduced to provide less invasive surgery for the patients.

The Surgical Center staff work as part of a multidisciplinary team active in planning the best utilization of the 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.

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	1768
General and epidural	202	193	188	210	207	199	205	200	206	226	193	199	2428
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	4835

Table 2. Number of general anesthesia cases

	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Neurosurgery	12	10	11	11	11	11	13	8	9	11	11	7	125
Opthalmology	24	30	32	26	26	31	27	22	21	26	26	26	319
Head & Neck Surgery	12	13	15	16	12	13	16	14	13	16	16	11	168
Breast Surgery	42	42	41	37	43	28	34	32	30	32	32	29	427
Thoracic Surgery	49	52	45	55	55	54	56	55	50	60	60	57	643
Esophageal Surgery	9	9	13	12	5	10	8	11	10	10	10	8	119
Gastric Surgery	38	39	36	45	36	50	40	35	40	38	38	37	480
Colorectal Surgery	35	38	40	39	36	38	37	36	48	34	34	33	458
Hepatobiliary & Pancreatic Surgery	19	19	27	22	28	23	29	25	21	22	22	23	281
Gynecology	15	18	17	20	17	15	11	19	17	14	14	16	197
Urology	20	21	16	20	24	23	24	24	17	23	23	18	257
Dermatology	9	8	7	8	11	10	9	9	7	7	7	7	104
Orthopedic Surgery	21	21	14	18	21	23	23	23	20	23	23	23	264
Others	20	18	16	25	24	32	41	41	29	32	32	40	351
Total	325	338	330	354	349	361	354	354	332	348	348	335	4193

Physician Referral Service Office

Hidehito Horinouchi, Makiko Murase, Rieko Shimizu, Yukiko Higuchi, Hisako Tanaka, Keiko Tsutsumi, Kayoko Yamada, Hiroe Ishii

Introduction

The Physician Referral Service Office was established as an independent section directly under the Director of National Cancer Center Hospital (NCCH) and started its service in April 2013. The mission of this office is to provide appropriate access to best cancer practice for more patients and their physicians.

To help cancer patients with various needs to visit the NCCH, the Physician Referral Service Office consists of a physician, a nurse, a medical social worker and three clerks. This office also deals with inquiries for patients' medical records from their physician. Another important activity is to record and analyze the information concerning patients' referrals to the NCCH.

Routine activities

1. Physician referral service

Under strong collaboration with the reservation center, this office supports patients and their physicians to select the most appropriate doctor promptly.

2. Inquiries for patients' medical records

We receive and deal with inquiries regarding medical records from physicians who see patients from our hospital.

3. Relationship with affiliated hospitals and clinics

We send reminders to patients' physicians on the occasion of the patients' first visit to our hospital. To maintain the relationship, we hold regular meetings and invite physicians from affiliated hospitals and clinics.

4. Recording and analysis of clinical information

The information regarding all patients and their physicians is appropriately recorded in order to analyze the data and apply them for planning the subsequent strategies for a better service.

5. Cooperation with intramural departments and staff

To provide best practice, we make the utmost efforts to collaborate with intramural departments, sections and staff.

Table 1. Routine activities of Physician Referral Service Office

	Referral reply letters	Medical record inquiries	FAX	Reservation support
April	-	2	-	-
May	-	21	-	3
June	340	16	2	8
July	773	17	7	14
August	695	18	11	11
September	725	11	6	9
October	809	54	15	14
November	722	46	7	20
December	695	52	30	17
Total	4759	237	78	96

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 (the Clinical Research Coordinating Division and Administrating Division). The staff members, nurses, pharmacists and laboratory technologists, participate in this division independently from outpatient divisions, wards, the nursing division and pharmacy, thus breaking through the conventional framework of profession-based organizations.

Routine activities

The Clinical Trial Coordination (& Support) Office supports many of the industry-sponsored registration trials as well as the physician-initiated registration directed clinical trials. A total of 22 CRCs (clinical research coordinators) are supporting these trials. The number of the industry-sponsored registration trials is increasing year by year, and we supported 232 registration-directed clinical trials including 10 physician-initiated registration directed clinical trials in 2013 (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 2013

Phase	Ongoing	New (since 2013)	Total
I	41	25	66
I/II	16	5	21
II	27	18	45
II/III	2	1	3
III	51	23	74
POS	13	1	14
Medical device	2	2	4
In vitro diagnostics	0	1	1
IITs	8	5	13
Total	160	81	241

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

Nutrition Management Office

Mayumi Miyauchi, Tomoko Suzuki, Masahiro Sunaga, Hiroko Takashima, Noriko Aoki, Yasuko Muramatsu

Introduction

In 2013, we increased the number of staff exclusively engaged in the Nutrition Support Team and those almost exclusively engaged in the NST, resulting in enhancement of the NST activities.

The Metabolism and Clinical Nutritional Society released the results of an investigative study into the "Improvement of taste disorder through development of supportive care".

We started "An investigative commission regarding meal functional disorders in cancer medical treatment" in December.

We are creating an assessment sheet to enable nutritional management tailored for patients who have ingestion-retarding side effects. Through coordinating nutritional management with other appropriate hospitals, we believe that the completion of such assessment sheets and translating the results into dietary changes can help to improve the rate of improvement brought about by the medical treatment, and in the training of newly-starting dietitians.

Six years ago, the NST started working on a nutritional assessment of cancer patients, and measured resting metabolic changes in body constituents in the course of treatment, such as esophageal surgery and hepatobiliary-pancreatic surgery. This study has continued to accumulate data, and the results were released at The Clinical Nutrition meeting.

Routine activities

Dietary meals totaled 427,859 in 2013, and we gave nutrition-related dietary advice to 1,285 persons. There have been 951 requests for consultation to the NST, 79 per month on average, and this aspect of the Office has shown strong growth by 18% annually (Table 1).

Following release of our leaflet, "A hint when troubled at the time of food", We obtained the cooperation of the Foundation for Promotion of Cancer Research, and we have created "Hints for an appropriate diet before medical cancer treatment". These leaflets have been widely supplied to cancer treatment institutions all over the country and to many related organizations, with good utilization being seen by both medical staff and patients.

In the field of human resource development, we have a strong commitment to education and training and we conducted 10 University courses for registered dietitians within the University. By strengthening our cooperation with universities, our aim is to enhance research activities in the future through the development of human resources.

Research activities

1) The Nutritional Management Workshop for cancer patients has reached its the 32nd anniversary, and "Nutrition past, present and future" was delivered as the President's lecture in Kanazawa.
2) In cooperation with nutritionists of the Nutritional Management of Cancer Course we held lectures to help target the general public regarding a cancer-preventative diet (Ishikawa, Tokyo).
3) Research projects
   1. Survey of dysgeusia
   2. Studies on nutrition in the surgical treatment of esophageal cancer
   3. Perioperative nutritional assessment after pancreaticoduodenectomy

Future Prospects

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

Table 1. Number of NST consultations in 2013

Clinical Departments	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sept	Oct	Nov	Dec	Total
Esophageal Surgery	2	4	5	1	1	4	5	3	2	5	4	3	39
Head and Neck Surgery	5	6	4	2	5	1	7	7	4	8	5	5	59
Gastrointestinal Medical Oncology	10	15	9	13	18	12	20	15	14	17	9	11	163
Hematopoietic Stem Cell Transplantation	13	12	14	8	12	10	6	21	7	14	9	12	138
Thoracic Oncology	7	3	11	7	4	4	2	3	3	3	3	2	52
Thoracic Surgery		2		1	1		1	2	2	2			11
Hepatobiliary and Pancreatic Oncology	4	4	3	2	1	1	2	2		2	2	1	24
Hepatobiliary and Pancreatic Surgery	10	7	7	7	11	8	10	9	8	5	6	6	94
Breast Oncology and Mecal Oncology	2	4	8	4	10	7	6	7	4	5	5	4	66
Gynecology	4	2	1	1	2	1		2	2	2	3	1	21
Neurosurgery and Neuro-Oncology	1	1			1		1	1	1	2			8
Gastric Surgery	4	4	1	5	2	5	5	1	2	31	27	28	115
Colorectal Surgery		1	2	2	1	2	2	1	1			1	13
Urology	3	3	4	6	3	3	5	2	2	3	4	3	41
Pediatric Oncology		2		2	1					1			6
Orthopedic Surgery		1	2	2	1	4	2		1	1	1	2	17
Dermatologic Oncology	1		2	2	2		2		3			1	13
Hematology	2	1	1	5	6	4	2	2	2	2	4	2	33
Radiation Oncology			1	2		3	2	5	2	4	4	3	26
Diagnostic Radiology		3	4		1								8
Breast Surgery													0
Gastrointestinal endoscopy								1		1			
Respiratory Endoscopy									1	1			2
Total	68	75	79	72	83	69	80	84	61	109	86	85	951
												mean	67

Health Information Management Office

Hiroshi Nishimoto, Mieko Furumoto, Tomoko Takehara, Marika Noduki, Yukiko Sekimizu, Hisayo Nishizawa, Mari Samejima

Introduction

The Health Information Management Office was established in April, 2011. We are taking over several duties from the Cancer Information Services and Surveillance Division. One of them was the Audit of Discharge Summary, and another was the National Cancer Center Hospital (NCCH) Cancer Registry which is executed as a hospital-based cancer registry. Some statistical duties for the NCCH and Prognostic Investigation were taken over by the Medical Affairs Office, but since the main initiatives of the NCCH are activities against cancer, we will expand our role as the major statistics office of the NCCH.

Routine Activities

Auditing Discharge Summary (Quantitative inspection)

Data on discharge summaries should be entered by the attending physician. We inspected and checked about 12,000 summaries and, where required, gave some advice regarding correct input.

NCCH Cancer Registry (Hospital-based Cancer Registry)

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

Table 1. National Cancer Center Hospital Cancer Registry

Year of Diagnosis	Numbers of New Cancer Cases		
	Total	Male	Female
2009	6,721	3,895	2,826
2010	6,636	3,926	2,710
2011	6,471	3,721	2,750
2012	6,486	3,662	2,824

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 in keeping with the National Cancer Center Hospital's (NCCH) 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 electronic medical record system. The prescription order is then redirected to the medicine-package-printing system which provides drug information. The medicine-package information, instructions and explanations, which are easy to understand by patients, for the proper use of drugs, such as those regarding efficacy and effectiveness, precautions, and guidance concerning symptoms at the early stage of adverse reactions, are automatically printed out for patients when a prescription is ordered.

The injection-order is directly linked to an automatic "picking system" device, and this linkage ensures that injections are made properly and efficiently. This injection-ordering system contains an additional function, a regimen-ordering system for anti-cancer drugs which makes it possible to check the dose as well as the interval of chemotherapy. The Pharmacy has a robot which prepares injection preparations without human assistance.

Research activities

Since an important mission of the Pharmacy is to contribute to the development of new drugs, inventory control and handling of new investigative drugs are performed in accordance with Good Clinical Practice regulations. Research on the safety management of chemotherapy is conducted including handling of chemotherapeutic drugs, reduction of incidents regarding drugs, and improvement of pain control for patients who need palliative care through the use of guidance materials. A couple of studies on the pharmacokinetics and pharmacodynamics of cancer-related drugs have been performed and some of the results have been reported in international conferences and journals.

Information services

The mission of the Pharmacy Information Services is to provide an evidence-based foundation for safe and effective drug therapy for cancer patients. The internal online pharmacy journal is published monthly. Current safety information, newly adopted drugs, questions-and-answers, and topic of approvals are available for medical staff on the in-hospital computer network. The Pharmacy

also provides a variety of information on the internet to the general public and medical experts outside the hospital.

Education and Training

The NCCH offers a three-year postgraduate pharmacist residency in clinical oncology. In the first year, the program attaches the most importance to technical aspects of cancer care. In the second year, through required rotations in a variety of focused hematology/oncology services, the resident will refine his/her clinical problem-solving skills in cancer management and patient education. Moreover, residents provide pharmaceutical care to ambulatory care patients and participate in an oncology-focused Drug Information Program. This clinical acumen coupled with didactic training in the basic science of oncology will prepare the resident to investigate therapeutic questions related to the care of cancer patients. In the third year, residents participate in specialized pharmaco-clinical practice and research activities, which may be tailored to the resident's goals. There are also opportunities for educational activities, such as a training course for visiting expert pharmacists and post-graduate students of pharmacy, and participation in a multi-institutional TV conference.

Table 1. Number of Prescriptions in 2013

1) Oral and topical preparations	
Prepared in the hospital pharmacy	148,728
Inpatients	134,884
Outpatients	13,844
Taken to outside pharmacies	75,813
(% of prescription filled outside)	84.6
2) Injections	
Inpatients	279,808
Outpatients	39,509

Table2. Amounts of Drugs Consumed in 2013

	(including sales tax)	(%)
Total	4,819,668	100.0
Internal medicines	618,303	12.8
External	8,395	0.2
Injection	3,315,578	68.8
Narcotics	141,831	2.9
Blood	411,608	8.5
X-ray imaging	227,332	4.7
RI	47,896	1.0
Others	48,724	1.0

Unit:1000 yen

Table 3. Aseptic Preparation of Injectable Drugs in 2013

Anticancer Drugs	52,598
Others	33,521

Table 4. House Preparations in 2013

Sterilized	65
Non-sterilized	104

Table 5. Investigational Drugs

Newly registered	75
Ongoing study	148
Total	223

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

1) Continuous Nursing for Cancer Survivorship

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

We are accepting and meeting the challenge to provide many patient education programs produced by Certified Nurse Specialists and Certified Nurses. We have 6 patient education programs and consultation services, 3 outpatient clinics by nurses, and 2 support programs 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.

2) Educational Activities

(1) Assist and support new nurses

We have worked to reduce the gap between the technical skill level of new nurses and the clinical nursing required for actual cancer care by carrying out practical nursing training. During the first month, we provided training courses on basic nursing skills for new nurses. New nurses learn about clinical nursing practices by shadowing a senior nurse for the first one month. We ensure that new nurses can work in a favorable work-related stress-free environment.

(2) Development of knowledge and skills for cancer nursing

To develop the skills associated with 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 large-group training and small-group training was increased to implement the knowledge and techniques acquired from years of continuing education, which resulted in improved patient care.

We have 11 specialized nurse training courses: Cancer chemotherapy nursing I and II; Clinical trial nursing; Palliative care nursing I and II; Lymphedema care; Wound and skin care; Pressure ulcer care; Dysphagia nursing; Radiotherapy and IVR nursing; and Support for discharge and home care coordination nursing. A total of 202 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, 9 certified nurse specialists and 31 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, 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 members.

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

Research activities

We presented 20 studies on nursing at some annual conferences in 2013. We organized the Nursing Research Committee, the members of which must have a master's degree or a doctor's degree. They must also have sufficient experience regarding nursing research activities. They support nurses to challenge nursing research based on their clinical questions. We are making effort to improve the quality of nursing research through getting support from physicians and statisticians. We expect our nurses from the National Cancer Center Hospital to create and develop cancer nursing to even higher levels of proficiency and expertise.

List of papers published in 2013

Journal

1. Kubota K, Inoue A, Shimizu Y, Kagata S, Yong R, Hirama Y, Shiga M, Kawazoe T. Health-Related Problems after the Great East Japan Earthquake: An Evaluation Based on the Annual Health Examination. Journal of Nursing & Care, 2:134, 2013

Hospital East

Preface

Although past performance is usually written about in the Annual Report, in this particular Report I would rather describe the present and futuristic views of the National Cancer Center Hospital East (NCCHE). We're living in the present and the future is an extension of the present where the past is just for reference.

Twenty-two years have passed since the NCCHE was established. Meanwhile, there have been tremendous changes in the socio-economic states, demographic composition as well as science and medicine in Japan. We, the National Cancer Center (NCC) and NCCHE, had a leadership function and played an important role in cancer medicine. Today, the conventional and established way does not always work in medicine, which requires innovative changes in ourselves. We need a new vision of the NCC to be created over the following decades.

Six months ago, I came to Kashiwa and looked at everything through eyes of a freshman. At the beginning of this year, President Hotta has proposed a new vision of the NCC with novelty, challenge and change. A vision is considered to become a true vision only after being shared and practiced by everyone working in the NCC. Via MECE collaboration with the National Cancer Center Hospital (NCCH), We, NCCHE, have to create unprecedented values in medicine by reforming our mindset and organization to harmonize with brand-new future images.

We have three competitive edges which should be improved and developed even further.

The first is the drug development including NCC-EPOC and development of medical equipment for diagnosis and treatment. We are reshaping the management system of clinical trials and are constructing advanced laboratory medicine in and outside the institute to become a global leader of healthcare development over the next ten years.

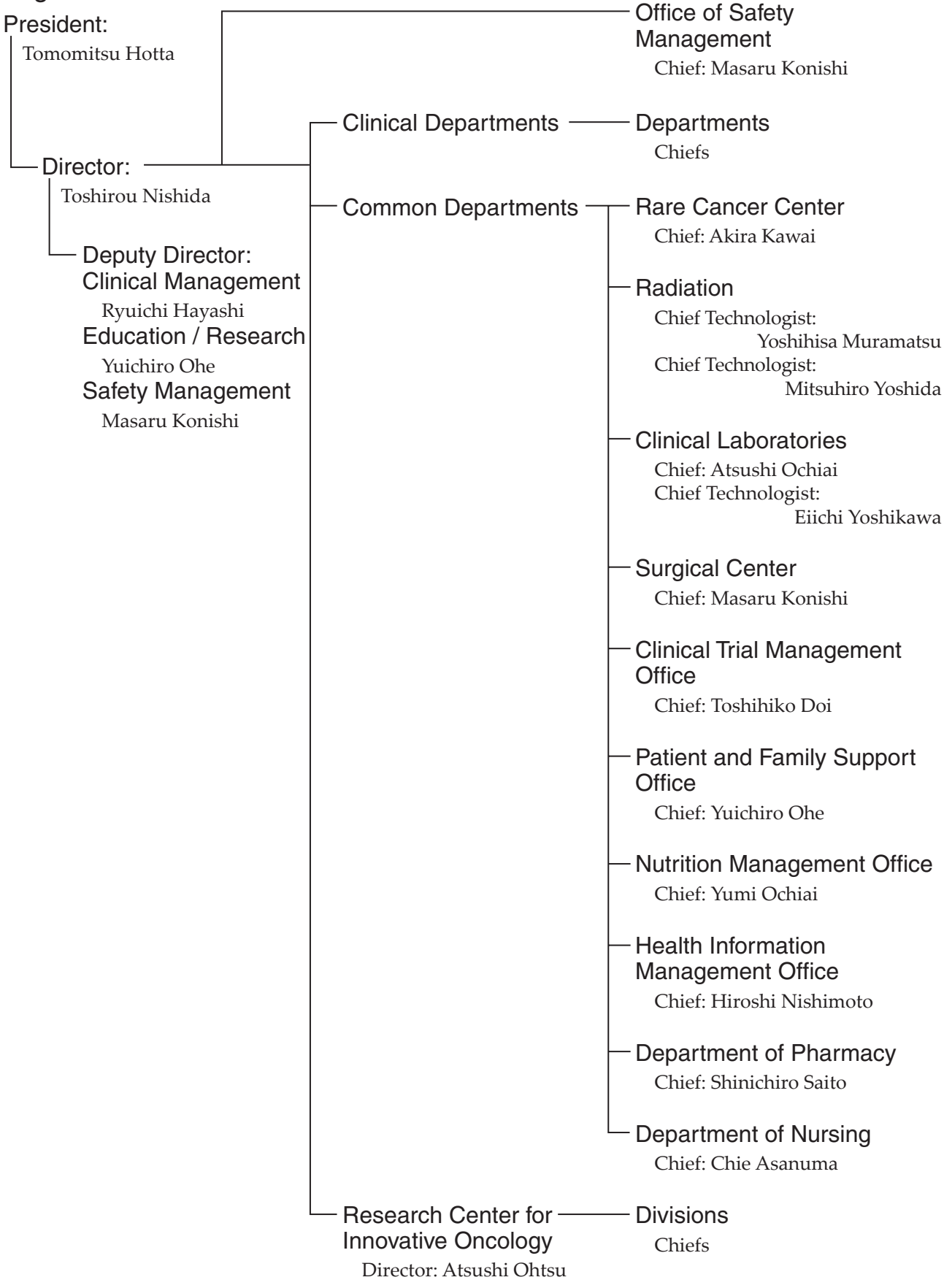
The second feature is minimally invasive therapy (MIT) for cancer patients. In this context, we have provided the highest quality of radiotherapy represented by the indication of proton beam therapy and endoluminal therapy as well as endoscopic surgery in Japan. Twenty years after our foundation, we need to renovate the soft and hard parts of MIT. The Institute of New Surgical and Endoscopic Development for Exploratory Technology (NEXT) project should be launched in near future to make the Kashiwa campus one of MIT centers in the world.

The third strength would be the Supportive Care Center under construction, where an interdisciplinary approach will be provided to cancer patients throughout all the stages of cancer treatment. We are building the cooperative system with regional hospitals, clinics and business enterprises to support and coordinate patients and families.

Hopefully, when we look back at the absolutely new and improved NCCHE after several decades from today, we would be able to find the seeds of the initial innovative trajectory in this Report.

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

Organization



Clinical Departments

Director:
Toshirou Nishida

Deputy Director:
Clinical Management
Ryuichi Hayashi
Education / Research
Yuichiro Ohe
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: Yuichiro Ohe
- Department of Thoracic Surgery
  Chief: Kanji Nagai
- Department of Thoracic Oncology
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- Department of Gastric Surgery
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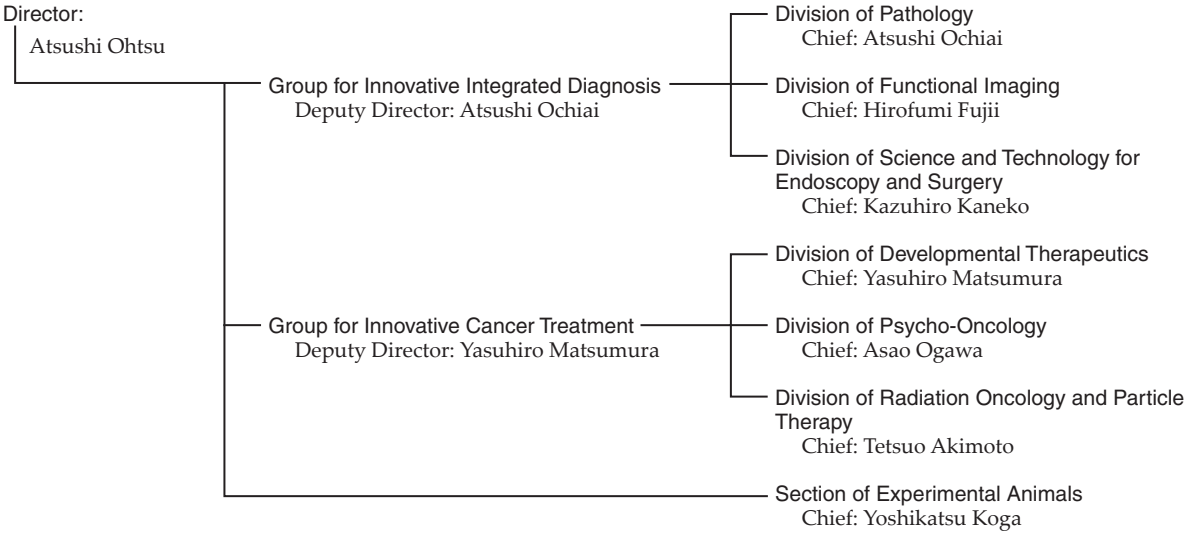
  Chief: Kazuhiro Kaneko
- Department of Hepatobiliary and Pancreatic Surgery
  Chief: Masaru Konishi
- Department of Hepatobiliary and Pancreatic Oncology
  Chief: Masafumi Ikeda
- Department of Urology
  Chief: Norio Saito
- Department of Gynecology
  Chief: Ryuichi Hayashi
- Department of Musculoskeletal Oncology and Rehabilitation
  Chief: Ryuichi Hayashi
- Department of Hematology
  Chief: Kunihiro Tsukasaki
- Departments of General Internal Medicine, Dentistry, Cardiovascular Medicine, Pediatric Oncology
  Chief: Yuichiro Ohe

- Department of Anesthesiology and Intensive Care Unit
  Chief: Vacant
- Department of Palliative Medicine, Palliative Care Service
  Chief: Hiroya Kinoshita
- Department of Psycho-Oncology Service
  Chief: Asao Ogawa
- Department of Diagnostic Radiology
  Chief: Mitsuo Satake
- 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

Masakazu Miyazaki, Ryuichi Hayashi, Takeshi Shinozaki, Toshifumi Tomioka, Takao Hamamoto, Hideaki Nishi

Introduction

Surgical treatment of head and neck cancer must meet two contradictory requirements: (1) the resection volume must be sufficiently large to remove all cancer cells, and (2) the resection volume should be sufficiently small to preserve important functions such as swallowing, speech, vision, and cosmetic appearance. The Head and Neck Surgery Division resolves these conflicting requirements mainly by two distinct approaches: (1) conservative surgery and (2) extensive resection with microsurgical reconstruction. The most successful approach for voice preservation has been conservative surgery. This procedure includes a vertical partial laryngectomy which is indicated for T1/T2 glottic carcinoma, recurrent glottis carcinoma after radiotherapy, and early false cord carcinoma. Another example of conservative surgery is partial hypopharyngectomy with preservation of the vocal cords for hypopharyngeal carcinoma with limited extension. On the other hand, extensive resection with microsurgical reconstruction is designed to minimize loss of function following ablative surgery by employing microsurgical transfer of various flaps.

Routine activities

The current treatment policy for head and neck cancer is multimodal therapy. To effectively implement available therapeutic modalities, 4 staff surgeons at the Division work closely with plastic surgeons, radiotherapists, medical oncologists, pathologists, dentists, psycho-oncologists, nurses, and other hospital staff. To facilitate regular communication among the members of this large team, several weekly conferences are conducted. In 2013, 410 patients underwent surgery under general anesthesia and 18 patients under local anesthesia. 102 patients underwent major surgery with microsurgical reconstruction. The number of surgically treated high-risk patients, including elderly patients aged over 80, is currently increasing owing to the recent advances in surgical techniques and perioperative care. Technically difficult operations, such as surgical resection of advanced oropharyngeal carcinoma with immediate reconstruction and salvage surgery after chemoradiation, are also being increasingly performed. We saw the first case of hypopharyngeal carcinoma who was treated with larynx preservation surgery as a salvage operation. The outpatient service of the Division is available from Monday to Friday. Endoscopic, radiographic, and ultrasonic examinations are routinely performed. The dental service is also available to improve the quality of life after ablative surgery using maxillofacial prostheses, to prevent severe odontogenic infection during chemotherapy and /or radiotherapy, and to reduce local infection after major surgery for head and neck cancer.

Research activities

1. Mucosal Defect Repair with a Polyglycolic Acid Sheet

Early-stage oral or oropharyngeal carcinomas are often treated with surgical resection. Resulting wounds that are too large for primary closure can be covered with skin grafts or patches made from various biomaterials. Recently, polyglycolic acid sheets have been used for this purpose. We treated six patients with large wounds resulting from the resection of oral or oropharyngeal squamous cell carcinoma with polyglycolic acid sheet patch grafting. Grafting of a polyglycolic acid sheet patch is effective and provides good pain control for patients with large, open wounds after mucosal resection of oral or oropharyngeal squamous cell carcinoma. We plan to evaluate tissue contraction and oral intake after polyglycolic acid patch grafting.

2. Observation as an Option for an Epithelial Positive Margin after Partial Glossectomy in Stage I and II Squamous Cell Carcinoma: Analysis of 365 Cases

This study was conducted to assess local recurrence and clinical prognosis in patients diagnosed as having a positive margin in the epithelial layer after a partial glossectomy treated with close observation. A total of 365 cases of squamous cell carcinoma of the tongue diagnosed as being at clinical Stage I or II, treated by partial glossectomy in the National Cancer Center Hospital East between 1992 and 2006, were studied retrospectively. We suggest careful observation as one option for cases diagnosed as having an epithelial positive margin.

Clinical trials

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

A prospective observation study was conducting and 68 cases were 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 was conducted to evaluate the swallowing function after treatment for oropharyngeal cancer. This study is related to standardizing the assessment of the swallowing function.

Table 1. Type of surgical procedures

Glossectomy	56
Resection of oral cavity	59
Oropharyngectomy	20
Hypopharyngectomy	36
Cervical esophagectomy or hypopharyngectomy	3
Laryngectomy	16
Resection of the nasal and/or paranasal sinuses	21
Thyroidectomy	48
Parotidectomy	23
Submandibulectomy	3
Endoscopic resection	47
Neck dissection	72
Others	6
Total	410

Table 2. Survival rates

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

n.v. : not verified

List of papers published in 2013
Journal

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Department of Head and Neck Medical Oncology

Makoto Tahara, Hiroto Ishiki, Hisao Amatsu, Tomoko Yamazaki, Tomohiro Enokida

Introduction

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

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

Routine activities

Our Department consists of two physicians, two senior residents and one resident. We manage the treatment of HNC patients who receive chemotherapy, including concurrent chemoradiotherapy, induction chemotherapy and palliative chemotherapy. An estimated 60% of HNC patients will present with locally advanced disease (stage III/IV) and require a multidisciplinary approach, including surgery, radiotherapy, and chemotherapy. Furthermore, HNC patients are at risk of injury and impairment of vital organs, including the eyes, ears, nose, mouth, pharynx, and larynx, both from the cancer itself and from the series of treatments provided to cure it. In treating patients, we therefore carefully assess both the curability of the condition and possible subsequent complications, such as swallowing dysfunction and cosmetic changes. Given the increasing complexity of the management of HNC, recommended treatment for patients who are referred to our institution is decided at weekly head and neck cancer conferences attended by a multidisciplinary team, which includes head and neck surgeons, radiation oncologists, plastic surgeons, dentists, pharmacists, and medical oncologists. Treatment option for locally advanced/metastatic RAI-refractory differentiated thyroid cancer (DTC) has been limited. Recently, development of molecular targeted drugs has been emerged in the treatment of thyroid cancer. Several molecular targeted drugs demonstrated significant clinical activity in phase II trials for RAI-refractory DTC, which has led to NCI guidelines recommending patients with RAI-refractory DTC to participate in clinical trials. Therefore, we have also participated in such clinical trials.

A total of 237 patients were treated in our Department from April 2012 to March 2013 (Table 1). The outpatient service of our Department is available from Monday to Friday. We carefully follow patients during and after treatment and provide palliative chemotherapy as an outpatient service.

Research activities

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

1) Development of new treatments

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

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

2) Biomarker analysis

An analysis of gene expression profiles in head and neck cancer is being carried out to determine biomarkers that could predict treatment outcomes. High levels of gene expression including MMP1, IGHA1/IGHA2, IGLC1, MMP13 and INHBA were observed in 36 HNC patients who received radical surgery. Recently, the existence of circulating microRNAs (miRNAs) in the blood of cancer patients

has raised the possibility that miRNAs may serve as a novel diagnostic marker. 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 24 miRNAs was significantly changed.

Clinical trials

A feasibility study of a combination with docetaxel, cisplatin and 5-FU (TPF) as an induction chemotherapy for locally advanced SCCHN has been completed and the results will be open soon.

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

To facilitate the timely approval of new drugs and eliminate the drug lag, we have also participated in the following global trials: 1) a randomized, open-label, phase III study to evaluate the efficacy and safety of oral afatinib (BIBW 2992) versus intravenous methotrexate in patients with R/M-SCCHN who progressed after platinum-based therapy; 2) a randomized, double-blinded, placebo-controlled, phase III study to evaluate the efficacy and safety of oral afatinib (BIBW 2992) as adjuvant therapy after chemoradiotherapy in patients with primary unresected SCCHN; 3) a double-blinded, randomized phase III study evaluating the efficacy and safety of sorafenib compared to a placebo in patients with locally advanced/metastatic RAI-refractory differentiated thyroid cancer (DECISION study) ; and 4) a double-blinded, randomized phase III study evaluating the efficacy and safety of Lenvatinib(E7080) compared to a placebo in patients with locally advanced/metastatic RAI-refractory differentiated thyroid cancer (SELECT study). The DECISION study demonstrated that sorafenib significantly improved progression-free survival (PFS) compared with a placebo (HR: 0.587,$p<0.001$). Based on these results, sorafenib will be approved for thyroid cancer soon in Japan. Our institution was ranked number one in the world for patient enrollment in the SELECT study. Recently, a press release announced that lenvatinib demonstrated significant improvement in PFS compared with a placebo.

Table 1. Number of patients

Primary site	No. of patients (N=269)
Nasal cavity	27
Nasopharynx	26
Oropharynx	52
Hypopharynx	52
Oral cavity	33
Larynx	27
Salivary	14
Thyroid	29
Other	9

Table 2. Type of procedure

	No. of patients (N=269)
Induction chemotherapy followed by CRT	41
CRT	50
Palliative chemotherapy	43
Study drug	9
Others	126

Table 3. Survival rates

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

n.v. : not verified

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1. Zenda S, Ishi S, Kawashima M, Arahira S, Tahara M, Hayashi R, Kishimoto S, Ichihashi T. A Dermatitis Control Program (DeCoP) for head and neck cancer patients receiving radiotherapy: a prospective phase II study. Int J Clin Oncol, 18:350-355, 2013
2. Yoshino T, Hasegawa Y, Takahashi S, Monden N, Homma A, Okami K, Onozawa Y, Fujii M, Taguchi T, de Blas B, Beier F, Tahara M. Platinum-based chemotherapy plus cetuximab for the first-line treatment of Japanese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: results of a phase II trial. Jpn J Clin Oncol, 43:524-531, 2013
3. Okano S, Yoshino T, Fujii M, Onozawa Y, Kodaira T, Fujii H, Akimoto T, Ishikura S, Oguchi M, Zenda S, de Blas B, Tahara M, Beier F. Phase II study of cetuximab plus concomitant boost radiotherapy in Japanese patients with locally advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol, 43:476-482, 2013
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5. Fuse N, Nagahisa-Oku E, Doi T, Sasaki T, Nomura S, Kojima T, Yano T, Tahara M, Yoshino T, Ohtsu A. Effect of RECIST revision on classification of target lesions and overall response in advanced gastric cancer patients. Gastric Cancer, 16:324-328, 2013
6. Vermorken JB, Stohlmacher-Williams J, Davidenko I, Licitra L, Winquist E, Villanueva C, Foa P, Rottey S, Skladowski K, Tahara M, Pai VR, Faivre S, Blajman CR, Forastiere AA, Stein BN, Oliner KS, Pan Z, Bach BA. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. Lancet Oncol, 14:697-710, 2013
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8. Fujii S, Uryu H, Akashi K, Suzuki K, Yamazaki M, Tahara M, Hayashi R, Ochiai A. Clinical significance of KRAS gene mutation and epidermal growth factor receptor expression in Japanese patients with squamous cell carcinoma of the larynx, oropharynx and hypopharynx. Int J Clin Oncol, 18:454-463, 2013
9. Suzuki K, Hayashi R, Ebihara M, Miyazaki M, Shinozaki T, Daiko H, Sakuraba M, Zenda S, Tahara M, Fujii S. The effectiveness of chemoradiation therapy and salvage surgery for hypopharyngeal squamous cell carcinoma. Jpn J Clin Oncol, 43:1210-1217, 2013

Department of Plastic and Reconstructive Surgery

Minoru Sakuraba, Masahide Fujiki, Azusa Oshima, Junichi Nakao, Yutaka Fukunaga, Shogo Azumi, Shusaku Maeda

Introduction

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

Routine activities

Five plastic surgeons cover reconstructive operations both in the National Cancer Center Hospital (NCCH) East in Kashiwa and the NCCH in Tokyo, and train = residents in both hospitals. These reconstructive surgeries are performed in cooperation with the surgeons of another department of the hospital, such as Head and Neck Surgery, Breast Surgery, Orthopedic Surgery, Esophageal Surgery, Colorectal and Urological Surgery and so on. In the NCCH East, Head and Neck reconstruction is the most frequently performed operation accounting for 65% of the reconstructive surgical procedures. In the head and neck region, the 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, and since then patients' needs for breast reconstruction have been increasing. Additionally, lymphatico-venulo anastomosis as a surgical treatment for lymphedema of the extremities has been introduced since June 2013.

Research activities

The Department has focused on the following four aspects in the surgical treatment of cancer, for the purpose of contributing to the improvement of the QOL of patients.

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

With the objective of addressing these four aspects, establishing a standard of reconstructive surgery and developing new techniques of reconstructive surgery are the most important aims of our studies. A multi-institutional analysis of postoperative complication and swallowing function after total pharyngolaryngo-esophagectomy and reconstruction with a free jejunal graft is performed continuously. This study is supported by a Grant in-Aid for Cancer Research. The aim of the study is to clarify the relationship between surgical procedures and postoperative complications and function. Another multi-institutional analysis of postoperative complication after microsurgical head and neck reconstruction has been started to clarify the risk factor of postoperative vascular thrombosis.

Clinical trials

No clinical trial is currently under way.

Table 1. Cooperation with other divisions

NCCH East	No. of patients
Head & Neck surgery	122
Orthopedic surgery	6
Esophageal surgery	8
Breast surgery	46
Dermatology	----
Urologic surgery	1
HB&P surgery	3
Ophthalmic surgery	----
Colorectal surgery	7
Gastric surgery	0
Thoracic surgery	4
Gynecology	----
Plastic & Reconstructive	12
Total	209

Table 2. Operative Procedures

NCCH East	No. of flaps
Microvascular free flap	115
Jejunum	40
RAMC (DIEP)	38(11)
Anterolateral thigh	22
Fibula bone	12
Latissimus Dorsi	0
Radial Forearm	1
Other flaps	2
Other Microsurgery	11
Supercharge	1
Nerve Graft	0
Limb Salvage	1
Hepatic Artery	2
Lymphatico-Venulo Anast	5
Others	2
Subtotal	126
Pedicled flaps	23
PMMC	12
Latissimus Dorsi	7
RAMC	0
Other flaps	4
Other Procedures	49
Total	198

List of papers published in 2013

Journal

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3. Sakuraba M, Miyamoto S, Kimata Y, Nakatsuka T, Harii K, Ebihara S, Hayashi R. Recent advances in reconstructive surgery: head and neck reconstruction. Int J Clin Oncol, 18:561-565, 2013

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 three staff surgeons and one resident, and is committed to providing the latest, most comprehensive breast treatments for our patients. The multidisciplinary approach to the diagnosis and treatment of cancer are carried out 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. Indeed, our multidisciplinary team approach to breast cancer treatment sets the quality of care we provide for our patients well apart from the norm.

Changes in the annual number of patients with breast cancer who underwent surgery are shown in Table 1. A total of 306 patients with primary breast cancer and 24 patients with recurrence or other breast disease were operated on. Fourteen immediate breast reconstruction surgeries were included. Of the patients with primary breast cancer, 84 (28%) underwent primary systemic therapy. The types and number of operative procedures performed in 2013 are shown in Table 2. The rate of breast-conserving surgeries (including two radiofrequency ablation alone cases) was 71% (218/306). Sentinel node biopsy was performed in 255 patients, and 236 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 planning to omit ALND even in SLN positive patients.

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

γ-glutamyl hydroxymethyl rhodamine green (gGlu-HMRG) is a small-molecule aminopeptidase probe which was enzymatically cleaved, revealing a bright fluorescent region of cancer cells which overexpress the enzyme γ-glutamyltranspeptidase

(GGT). Visualized tiny cancerous nodules may allow us to delineate the border of tumors and confirm that there are no residual tumors.

Clinical trials

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

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

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

Table 1. Number of primary breast cancer patients operated on during 2004-2013

Clinical stage	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Stage 0	14	29	34	27	23	38	39	43	28	25
Stage I	100	89	79	94	84	86	80	86	91	112
Stage II	97	94	103	87	87	122	137	112	128	138
Stage III	24	35	34	25	33	42	32	43	49	29
Stage IV, unknown	2	2	1	4	0	3	1	1	4	2
Total	237	249	251	237	227	291	289	285	300	306

Table 2. Types of operative procedures performed in 2013 for primary breast cancer

Type of operation	N
BT+SNB	53
BT+SNB→ALND	10
BT+ALND	23
BT alone	2
BP+SNB	181
BP+SNB→ALND	9
BP+ALND	24
BP alone	2
RFA+SNB	2
Total	306

Total mastectomy with immediate 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 2007

Clinical stage	N	5 yr. OS	10 yr. OS
Stage 0	200	98.5%	95.2%
Stage I	877	96.1%	93.1%
Stage II	1435	90.5%	80.4%
Stage III	312	67.9%	55.7%
Stage IV, unknown	32	40.4%	15.1%
Total	2856	89.7%	81.7%

Median follow up period: 101 months [0-237]

List of papers published in 2013
Journal

1. Hojo T, Kinoshita T, Imoto S, Shimizu C, Isaka H, Ito H, Imi K, Wada N, Ando M, Fujiwara Y. Use of the neo-adjuvant exemestane in post-menopausal estrogen receptor-positive breast cancer: a randomized phase II trial (PTEX46) to investigate the optimal duration of preoperative endocrine therapy. Breast, 22:263-267, 2013
2. Matsubara N, Mukai H, Fujii S, Wada N. Different prognostic significance of Ki-67 change between pre- and post-neoadjuvant chemotherapy in various subtypes of breast cancer. Breast Cancer Res Treat, 137:203-212, 2013
3. Ishihara M, Mukai H, Nagai S, Onozawa M, Nihei K, Shimada T, Wada N. Retrospective analysis of risk factors for central nervous system metastases in operable breast cancer: effects of biologic subtype and Ki67 overexpression on survival. Oncology, 84:135-140, 2013

Department of Breast and Medical Oncology

Hirofumi Mukai, Nobuaki Matsubara, Yoichi Naito, Masaoki Sasaki, Ako Hosono, Mariko Masumoto, Yoko Yamada, Tetsuya Urasaki, Yujiro Ueda

Introduction

Patients with different types of cancer, including those with breast and genitourinary tract cancers, are treated with standard chemotherapy and/or managed in clinical trials in daily medical practice at the Division of Breast/Medical Oncology. Gynecological malignancies and soft tissue sarcomas are also treated with chemotherapy. Another major target of the Division is cancer of unknown primary origin. The clinical and research activities of the Division primarily focus on the following fields: Standard chemotherapeutic treatment in medical practice, disease-oriented clinical trials, developmental therapeutics of new anticancer agents sponsored by pharmaceutical companies and development of combination chemotherapy involving newly developed drugs or new combinations of currently available drugs.

Routine activities

The major and specific target disease of the Division comprised breast cancer. Eligible patients were invited to participate in large phase II/III studies. The Division also treated cancers of the genitourinary tract, cancer of unknown primary origin, soft tissue sarcomas and gynecological cancers including uterine and ovarian cancers. For patients with diseases treated with established standard chemotherapeutic regimens, standard chemotherapy was administered in routine medical practice. Patients in whom standard chemotherapy had failed and those with cancers for which standard chemotherapy was unavailable were invited to participate in clinical studies on experimental drugs and regimens. In 2013, 567 patients with different types of cancer visited the Division for consultation. Approximately 400 patients per month received routine chemotherapy as an outpatient service by the Division. The overall inpatient care system of the Division is held on every morning. A weekly educational review on oncology and hematology is conducted on Thursday mornings. Moreover, a biweekly joint conference is held on Wednesday evenings and on Monday evenings with breast surgeons and with urologists, respectively. Morning journal clubs also meet on Mondays and Fridays at the Division in collaboration with the Division of Hematology.

Research activities and clinical trials

Phase I 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; cabazitaxel (a new taxane derivative) for patients with hormone refractory prostate cancer [JNJ212082 (abiraterone acetate, a CYP17 inhibitor for androgen antagonist) for patients with castration-resistant prostate cancer who have not received chemotherapeutic agents] and NK105 (paclitaxel-incorporating micellar nanoparticle formulation) for patients with advanced or metastatic cancer for which standard chemotherapy was unavailable. Phase I/II studies of new anticancer agents for specific disease targets are conducted in collaboration with pharmaceutical companies. A phase II study of E7389 for treated patients with soft tissue sarcomas is also ongoing.

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

with operable HER2-positive primary breast cancer (APHINITY: Adjuvant Pertuzumab and Herceptin IN Initial Therapy); a randomized phase III study on NK105 versus paclitaxel in patients with recurrent or metastatic breast cancer; and a randomized phase III study on lapatinib, trastuzumab, and both lapatinib and trastuzumab, combined with an aromatase inhibitor in patients with HER-2 overexpressed breast cancer who received neo-/adjuvant therapy with trastuzumab and endocrine therapy.

Table 1. Number of patients

Breast cancer	277
Genitourinary cancers	165
Gynecological cancers	28
Cancer of unknown primary	45
Sarcoma	32
Others	20
Total	567

List of papers published in 2013
Journal

1. Mukai H. The current status and future perspectives of clinical trial groups in Japan. Breast Cancer, 20:285-286, 2013
2. Matsubara N, Mukai H, Naito Y, Itoh K, Komai Y, Sakai Y. First experience of active surveillance before systemic target therapy in patients with metastatic renal cell carcinoma. Urology, 82:118-123, 2013
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6. Matsubara N, Mukai H, Fujii S, Wada N. Different prognostic significance of Ki-67 change between pre- and post-neoadjuvant chemotherapy in various subtypes of breast cancer. Breast Cancer Res Treat, 137:203-212, 2013
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Department of Thoracic Surgery

Kanji Nagai, Junji Yoshida, Tomoyuki Hishida, Keiju Aokage, Yuki Matsumura, Nao Aramaki

Introduction

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

Since its establishment in 1992, the Division has been one of the most active leaders in the field of lung cancer in Japan. Moreover, it has been an active participant in international and national scientific venues. This year, in addition to 21 scientific papers published in English, the Division made 44 presentations: 8 international, 31 national, and 5 regional.

Routine activities

The Division is presently composed of 4 consultant surgeons and 5 or 6 residents. The Division has adopted a team approach in patient treatment and resident training. Potential surgical intervention candidate cases are presented every Tuesday evening at a multidisciplinary team conference of thoracic surgeons, oncology physicians, radiologists and residents. Each case is thoroughly and vigorously reviewed and discussed. To improve the English fluency of staff members and residents in preparation for international presentations, and to better involve visiting physicians from other countries, treatment modality discussions are conducted in English. Moreover, selected patients' records are radiologically and cytopathologically reviewed every Friday morning. These reviews aim to improve the interpretation of radiologic indications to pathology findings, accurately evaluate surgical indications, and upgrade knowledge on rare histologies. The Division believes that these activities improve the knowledge base, treatment indications, and surgical treatment.

For non-small cell histology, primary pulmonary carcinomas in clinical stages I/II and IIIA without bulky 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 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 tumors is attempted based on the modified Thomfold's criteria after consultation with the patient. The majority of these cases are metastases from colorectal carcinomas, while most of the mediastinal tumors are thymic epithelial tumors.

The surgical procedures of the Division have generally remained similar for the past decade, but we have employed port-access thoracoscopic surgery more often for the past 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 Division have improved and have become shorter, 3 days being the shortest with a median of 7 days for cases of primary lung cancer. These shorter hospital stays are achieved with a slightly better complication rate than the normal rate. This year, no 30-day operative mortality occurred in any patient undergoing surgery for primary lung cancer.

Research activities and Clinical trials

1. Surgical margin lavage cytology examination in limited resection for primary and metastatic lung cancer patients [observational].
2. Member of an organized trial of TS-1 vs. UFT adjuvant chemotherapy for completely resected pathologic stage I (> 2 cm) non-small cell lung cancer [phase III, 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]
6. Member of an organized trial of recMAGE-A3 + AS15 antigen-specific cancer immunotherapeutic as adjuvant therapy in patients with completely resected MAGE-A3 positive stage IB-IIIA non-small cell lung cancer [phase III, patient accrual completed].
7. Member of an organized trial of WT1 peptide vaccination as adjuvant therapy in patients with completely resected WT1/HLA-A*2402 positive stage IB-II non-small cell lung cancer [randomized phase II, inauguration awaited].

Table 1. Number of patients

Lung cancer	358
Metastatic lung tumor	71
Mediastinal tumor	21
Others	54
Total	504

Table 2. Type of procedure – primary lung cancer

Pneumonectomy	12
Lobectomy	296
Segmentectomy	17
Wedge resection	22
(Combined resection)	(17)
Others	11
Total	358

Table 3. Overall survival rates

Diagnosis (primary lung cancer)	No. of pts	MST (mo)	5-yr survival (%)
Pathologic stage			
IA	1260	NR	85.8
IB	511	NR	67.9
IIA	309	67.4	55.6
IIB	214	42.7	41.3
IIIA	436	37.5	35.6

Surgery between 2000 and 2010; stages according to the TNM Classification 7th edition; NR, not reached.

List of papers published in 2013
Journal

1. Aokage K, Yoshida J, Ishii G, Matsumura Y, Haruki T, Hishida T, Nagai K. Identification of early t1b lung adenocarcinoma based on thin-section computed tomography findings. J Thorac Oncol, 8:1289-1294, 2013
2. Zenke Y, Ishii G, Ohe Y, Kaseda K, Yoshida T, Matsumoto S, Umemura S, Yoh K, Niho S, Goto K, Ohmatsu H, Kuwata T, Nagai K, Ochiai A. Aldehyde dehydrogenase 1 expression in cancer cells could have prognostic value for patients with non-small cell lung cancer who are treated with neoadjuvant therapy: identification of prognostic microenvironmental factors after chemoradiation. Pathol Int, 63:599-606, 2013
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Department of Thoracic Oncology

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

Introduction

The Thoracic Oncology Division provides care for patients with primary lung cancer, mediastinal tumors, and pleural tumors. The Division aims to provide the highest quality treatment and establish new effective treatments against lung cancer and other thoracic malignancies through innovative clinical and translational research. To provide assistance to our patients through multidisciplinary care, the staff members of the Division work closely with thoracic surgeons, radiation oncologists, pharmacists, clinical research coordinators, and psychiatrists who have expertise in these areas. Moreover, residents and trainees from other institutions have joined the Thoracic Oncology Program.

Routine activities

Our Outpatient Clinic, managed by the staff members and senior residents, is open from Monday to Friday for the examination of all new referred patients and the evaluation of returning patients. Returning patients are also receiving oral chemotherapy and/or intravenous chemotherapy in the Ambulatory Care Center. Bronchoscopy for diagnosis is performed on Monday and Thursday afternoons. EBUS was introduced in 2013. Fluoroscopic-CT guided needle lung biopsies are carried out on Tuesday afternoons. For patient management, we use approximately 70 beds in wards 8F, 6A, 5A and 5B.

Case conferences on thoracic surgery and medical oncology are scheduled on Tuesday evenings and Wednesday evenings, respectively. The staff members and residents of the Division participate in a journal club on Monday and Wednesday mornings. At monthly meetings with physicians in private practice, the staff members and residents teach methods of reading chest X-ray and CT scan films.

Research activities

Our research activities are focused on four areas: 1) development of new and effective diagnosis and treatment modalities; 2) detection, diagnosis, and treatment of peripheral-type minute lung cancers that are not visible in plain chest X-rays; 3) collaborative studies with the Research Center for Innovative Oncology in the following areas: detection of driver mutation for small cell lung cancer; development of 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.

Whole 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 ROS fusion gene and BRAF mutation are especially under investigation in collaboration with the Research Center for Innovative Oncology.

Clinical trials

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

Recently, the usefulness of continuation and switch maintenance chemotherapy using pemetrexed for non-squamous non-small cell lung cancer (NSCLC) has been established. An in house feasibility study of maintenance chemotherapy of TS-1 for stage IV NSCLC is ongoing. Patients received TS-1 as a maintenance chemotherapy after 3 or 4 cycles of platinum-based 1st line chemotherapy and the target number of the patients is 78 in this study. The patient accrual will be complete within the next few months. A randomized phase 2 study of cisplatin + S1 + thoracic radiothetrapy vs cisplatin + pemetrexed + thoracic radiotherapy for stage 3 non-squamous NSCLC was started this year.

CH5424802 is a newly developing selective ALK inhibitor and very effective for ALK fusion positive NSCLCs, although 4-5% of NSCLCs are

positive for ALK fusion protein. A phase I /II study of CH5424802 demonstrated a durable response and a response rate of higher than 90% without severe toxicity. A phase I study of AZD9291, 3rd generation EGFR-TKI which is also effective for T790M resistant mutation is ongoing. Patients were treated at a dose of 20 mg to 240 mg, and up to 240 mg no DLTs were observed. Very good responses for T790M positive patients were observed with minimal toxicities.

Patient accrual was completed in this year for JCOG1011, a randomized phase 2 study for LD-SCLC comparing cisplatin and amurubicin with a CODE regimen (weekly cisplatin, vincristine, Adriamycin, etoposide) after induction chemoradiotherapy with cisplatin and etoposide.

LC-SCRUM (Lung Cancer Genomic Screening Project for Individualized Medicine in Japan), a nation wide screening project of lung cancer patients with rare driver gene alteration such as ALK, RET and ROS fusion gene and BRAF mutation, was stared this year. As of January 31st 2014, 524 patients were enrolled and 21 (5%) RET and 18 (4%) ROS1 fusion gene positive were detected. Eight of 21 RET and 6 of 18 ROS1 fusion gene positive patients have already been entered into a clinical trial of vandetanib or crizotinib, respectively. Multiple mutation screening in LC-SCRUM also started this year and as of Feburuary 5th 5 BRAF mutated patients were detected in 115 patientrs.

Table 1. Number of patients in 2013

Lung Cancer		460
	Small cell lung cancer	64
	Adenocarcinoma	243
	Squamous cell carcinoma	75
	Large cell carcinoma	5
	NSCLC NOS	56
	Others	17
Thymic cancer		2
Thymoma		3
Malignant pleural mesothelioma		6

Table 2. Initial treatment of lung cancer in 2013

Chemotherapy	256
Chemoradiotherapy	87
Surgery followed by chemotherapy	46
Radiotherapy	13
Palliative care	54
Others	4

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

Disease	Stage	Treatment	N	Survival rate (%)				
				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

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Journal

1. Zenke Y, Ishii G, Ohe Y, Kaseda K, Yoshida T, Matsumoto S, Umemura S, Yoh K, Niho S, Goto K, Ohmatsu H, Kuwata T, Nagai K, Ochiai A. Aldehyde dehydrogenase 1 expression in cancer cells could have prognostic value for patients with non-small cell lung cancer who are treated with neoadjuvant therapy: identification of prognostic microenvironmental factors after chemoradiation. Pathol Int, 63:599-606, 2013
2. Kirita K, Ishii G, Matsuwaki R, Matsumura Y, Umemura S, Matsumoto S, Yoh K, Niho S, Goto K, Ohmatsu H, Ohe Y, Nagai K, Ochiai A. Identification of biological properties of intralymphatic tumor related to the development of lymph node metastasis in lung adenocarcinoma. PLoS One, 8:e83537, 2013
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Department of Esophageal Surgery

Hiroyuki Daiko, Takeo Fujita

Introduction

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

Routine Activities

The Esophageal Surgery Division consists of 2 staff surgeons and 2 residents. An Esophageal Conference is held every Tuesday evening to discuss the diagnosis, staging, and treatment strategy for each patient and is attended by surgeons, medical oncologists, endoscopists, radiologists, radiation oncologists, and head & neck surgeons. Approximately 4 patients are operated upon every week. In 2012, 151 patients underwent esophagectomy. Transthoracic esophagectomy with extended lymph node dissection was performed on 54 nontreated cases. Thoracoscopic esophagectomy in the prone position with radical lymph node dissection was undertaken in 84 cases and transhiatal esophagectomy without thoracotomy was performed in 3 cases. Two-stage surgical procedures divided into resection and reconstruction for patients of more than 80 years old or with multiple complications was undertaken in 10 cases. Postoperatively, within 30 days, 1 patient died due to complications after a salvage operation.

Clinical Activities

Currently, the Division is examining the role of thoracolaparoscopic esophagectomy as a minimally invasive esophagectomy comprising thoracoscopic esophagectomy and laparoscopic reconstruction. For patients who are not undergoing radical chemoradiotherapy, thoracoscopic esophagectomy is performed in the prone position with radical lymph node dissection, and laparoscopic reconstruction after esophagectomy is performed for the patients with no history of laparotomy: our aim is for these to become standard surgical procedures for esophageal cancer.

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

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

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

Table 1. Type of Procedure

1 stage operation	141
2 stage operation	10
Total number of esophagectomy	151
Rt-Transthoracic Esophagectomy	54
Thoracoscopic Esophagectomy	84
Transhiatal Esophagectomy	3
Thoracoscopic enuclation for GIST	3
Emergency Operation	7
Others	10
Total	171

List of papers published in 2013
Journal

1. Suzuki K, Hayashi R, Ebihara M, Miyazaki M, Shinozaki T, Daiko H, Sakuraba M, Zenda S, Tahara M, Fujii S. The effectiveness of chemoradiation therapy and salvage surgery for hypopharyngeal squamous cell carcinoma. Jpn J Clin Oncol, 43:1210-1217, 2013
2. Makuuchi Y, Honda K, Osaka Y, Kato K, Kojima T, Daiko H, Igaki H, Ito Y, Hoshino S, Tachibana S, Watanabe T, Furuta K, Sekine S, Umaki T, Watabe Y, Miura N, Ono M, Tsuchida A, Yamada T. Soluble interleukin-6 receptor is a serum biomarker for the response of esophageal carcinoma to neoadjuvant chemoradiotherapy. Cancer Sci, 104:1045-1051, 2013
3. Nakamura K, Kato K, Igaki H, Ito Y, Mizusawa J, Ando N, Udagawa H, Tsubosa Y, Daiko H, Hironaka S, Fukuda H, Kitagawa Y. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). Jpn J Clin Oncol, 43:752-755, 2013

Department of Gastric Surgery

Takahiro Kinoshita, Hidehito Shibasaki, Masaru Konishi, Shinichiro Takahashi, Naoto Gotohda, Yuichiro Kato, Kenji Sakai, Masayuki Honda

Introduction

Patients with gastric tumors are treated by the Gastric Surgery Division in the Upper Abdominal Surgical Oncology Group. Our group consists of six staff surgeons, two senior residents and ten resident surgeons. The gastric tumors managed by the Division include not only common gastric adenocarcinomas but also adenocarcinomas of the esophagogastric junction (AEG), the incidence of which is increasing recently, probably due to reduction of *Helicobacter pylori* (HP)-infection rates, and gastric submucosal tumors (GIST etc.). Annually 260-300 patients are operated on either 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. The recent availability of the high-definition laparoscope has enabled more meticulous and accurate maneuvers. In 2013, about 70% of gastrectomies were performed under laparoscopy. The basis of our surgery is radical extirpation of cancer lesions, but at the same time organ functions and better QOL should be maintained. In addition, we attempt to obtain better clinical outcomes for patients with disease with dismal prognoses (scirrhous gastric cancer or with progressive lymph nodes metastasis) by surgery combined with recent advanced chemotherapy regimens, including molecular-targeting drugs (Trastuzumab).

Routine activities

Usually 16-18 patients are hospitalized and 5-7 patients undergo operations per week. A weekly film conference is held every Monday from 17:00 with doctors of the Department of Diagnostic Radiology and the Department of Gastrointestinal Oncology, discussing the diagnosis of patients with gastric tumors from oncological, surgical, endoscopic and radiologic aspects, and to determine the optimal treatment strategy for each patient. In principle, patients with superficial gastric cancer lesions (cT1a) of the intestinal histologic type showing clear margin are treated with endoscopic submucosal dissection (ESD). Some are required to undergo subsequent completion laparoscopic surgery with nodal dissection based on the pathological findings of the specimen obtained by ESD. Laparoscopic surgery with nodal dissection is indicated in other patients of c-stage I gastric cancer as the initial intervention. Not only distal gastrectomy but also total gastrectomy or function preserving procedures (pylorus-preserving gastrectomy or proximal gastrectomy) are performed laparoscopically. Basically, all of the procedures, mobilization, lymphadenectomy and reconstruction, are carried out under laparoscopy, which are referred to as total laparoscopic procedures. Currently D2 radical dissection is also performed under laparoscopy with much less blood loss, therefore its indication has been expanded with our experience of this procedure. When the tumor infiltrates adjacent organs (liver, pancreas, etc.), extended radical operations (pancreaticoduodenectomy, plus hepatectomy) are chosen. For AEGs, when the tumor involves the distal esophagus exceeding 3 cm in long, the left thoraco-abdominal approach is selected. Otherwise, the abdominal approach is chosen according to the results of JCOG 9502, and recently the transhiatal approach can be also employed laparoscopically with a better surgical view. When the patients are diagnosed as having p-stage II or III in the final pathological findings after operation, postoperative adjuvant chemotherapy with S-1 is recommended for these patients according to Gastric Cancer Treatment Guidelines, but now its duration for p-stageII is estimated by a phase-III JCOG trial, and the feasibility of XELOX and SOX therapy is under review in a phase-II trial.

We place importance on education of the gastric surgeons, including those from other institutions as well as hands-on training for resident surgeons in our hospital. Surgeons from domestic or foreign hospitals have visited our Division to 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 the Japan Clinical Oncology Group (JCOG)-Gastric Surgery Study Group. 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 as follows:

1. JCOG 0501 A phase III randomized study to investigate the effectiveness of neoadjuvant chemotherapy (CDDP+S-1) for resectable gastric cancer with appearances of large-sized type 3 or type 4. In this trial, a neoadjuvant chemotherapy arm is compared to a surgery preceding arm, both of which are followed by adjuvant chemotherapy (S-1).
2. JCOG 0705 A phase III randomized study to investigate the efficacy and feasibility of palliative gastrectomy for non-resectable advanced gastric cancer. (REGATTA trial, in collaboration with Korea) In this trial, a palliative gastrectomy arm is compared to a chemotherapy arm.
3. JCOG 0912 A phase III randomized study of laparoscopy-assisted versus open distal gastrectomy with nodal dissection for clinical stage IA and IB gastric cancer.
4. JCOG 1001 A phase III randomized study to evaluate the clinical benefits of bursectomy for patients with SS/SE gastric cancer.
5. JCOG 1002 A phase II study of systemic chemotherapy with Docetaxel, CDDP, and S-1 followed by surgery in advanced gastric cancer with extensive lymph node metastasis
6. JCOG 1009/1010 A phase II trial of ESD for expand indication to early gastric cancer of the undifferentiated type
7. JCOG 1104 A phase II trial to define the optimal period of adjuvant S-1 chemotherapy for pathological stage II gastric cancer patients who have undergone a D2 gastrectomy
8. JCOG 1108 A randomized phase II/III study of 5-fluorouracil /l-leucovorin vs. 5-fluorouracil /l-leucovorin plus paclitaxel in gastric cancer with severe peritoneal metastasis

Table 1. Number of patients

Gastric cancer	281
Others (GIST etc.)	6

Table 2. Type of procedure

Open gastrectomy	81
Distal Gastrectomy	29
Pylorus-preserving Gastrectomy	0
Proximal Gastrectomy	3
Total Gastrectomy	39
Pancreaticoduodenectomy	0
Partial Gastrectomy	1
Others (bypass, exploration, etc.)	4
Laparoscopic Surgery	206
Distal Gastrectomy	108
Pylorus-preserving Gastrectomy	16
Proximal Gastrectomy	18
Total Gastrectomy	26
Partial Gastrectomy	3
Others (bypass, exploration, etc.)	35

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 2013

Journal

1. Sugimoto M, Kinoshita T, Shibasaki H, Kato Y, Gotohda N, Takahashi S, Konishi M. Short-term outcome of total laparoscopic distal gastrectomy for overweight and obese patients with gastric cancer. Surg Endosc, 27:4291-4296, 2013
2. Kinoshita T, Gotohda N, Kato Y, Takahashi S, Konishi M, Kinoshita T. Laparoscopic proximal gastrectomy with jejunal interposition for gastric cancer in the proximal third of the stomach: a retrospective comparison with open surgery. Surg Endosc, 27:146-153, 2013

Department of Colorectal Surgery

Norio Saito, Masanori Sugito, Masaaki Ito, Akihiro Kobayashi, Yusuke Nishizawa, Nobuhiro Sugano, Mitsuru Yokota, Yu Sato

Introduction

The Colorectal and Pelvic Surgery Division was established 15 years ago. Its main purpose is to bring together the divisions that are composed of colorectal surgeons and urologists. Cooperation between these divisions contributes not only to the establishment of effective operative techniques but also to an oncological consensus including consensus on the quality of life (QOL) and the various functions of patients with pelvic malignancies. New surgical procedures, such as nerve-sparing surgery, sphincter-saving surgery, bladder-sparing surgery, pouch surgery and minimally invasive surgery, are being developed to prevent postoperative dysfunctions. These new approaches will contribute to better curability and QOL among patients with pelvic malignancies

Routine activities

The Colorectal and Pelvic Surgery Division comprises 7 consultants (5 colorectal surgeons and 2 urologists) and 11 residents. The outpatient clinic is open 5 days a week. More than 350 new patients with colorectal carcinomas and more than 150 new patients with other pelvic malignancies visited this Division during the last year. Treatment plans are discussed at a weekly conference on GI malignancies and at another weekly conference on pelvic malignancies. Many treatment modalities, such as local excision with or without adjuvant chemo- or radiotherapy and other minimally invasive forms of surgery using laparoscopy, have been introduced for the treatment of patients in the early stages of cancer. Laparoscopy-assisted operations (Lap-Ops) with wider lymphadenectomy of up to more than D2 are also increasingly being performed in patients with advanced colorectal carcinomas. Abdominoperineal resection (APR) has, in the past, been the standard surgery in patients with very low rectal cancer; however, partial anal sphincter preserving surgery such as intersphincteric resection (ISR) has been performed in about 400 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). The criteria for inclusion into this trial include (1) T3 and T4 tumors located at C, A, and S in the colon and Rs in the rectum; (2) stage N0-2; (3) stage M0; and (4) a maximum tumor size ≤8 cm. A total of 77 patients has been registered in this Division. This study is currently in progress.
2) Intersphincteric resection study (ISR Study). APR has been the standard surgery for very low rectal cancer located within 5 cm of the anal verge. However, 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 by performing ISR in patients with very low rectal cancer. However, patients need to be informed preoperatively regarding the potential functional adverse effects after ISR. This study is in progress, and 43 patients have been registered. The final results will be obtained soon.
3) Bladder-sparing surgery for locally advanced rectal cancer involving the prostate and/or seminal vesicles. Total pelvic exenteration (TPE) is the standard procedure in patients with locally advanced rectal cancer involving the prostate and seminal vesicles. This study aims to evaluate the feasibility of bladder-sparing surgery as an alternative to TPE. This procedure has been performed in 34 patients with primary or recurrent tumors and permits conservative surgery in selected patients with advanced rectal cancer involving the prostate and/or seminal vesicles without compromising local control. The QOL of these patients appears to be better. This study is also in progress.
4) A prospective randomized trial for the feasibility and effect of lateral node dissection in low rectal cancer–(Total) Mesorectal Excision (ME) vs. Lateral Node Dissection with preservation of autonomic nerves (D3 with nerve-sparing) [JCOG0212 CRC Surg.]. This study aims to evaluate the feasibility and effects of lateral node dissection in patients

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

5) Local excision with postoperative chemoradiotherapy for T1·T2 rectal cancer. This study aims to evaluate preoperatively the feasibility and the oncologic outcome of local therapy for T1 and a part of T2 rectal cancer without lymph node metastases. In this study, 82 patients have been registered. This study is currently in progress.

Clinical trials

Other clinical trials are also in progress as follows.

- The role of diverting stoma in low anterior resection for rectal cancer – A prospective multi-center study under the Japanese Society for Cancer of the Colon and Rectum (JSCCR)
- Comparing surgical site infection rates in colorectal surgery following closure of abdominal wounds with metallic skin staples or subcuticular absorbing-monofilament suture; A prospective randomized trial
- A phase I study of preoperative chemoradiotherapy with S-1+L-OHP for locally advanced rectal cancer
- A phase I/II trial of chemoradiotherapy concurrent with S-1 plus MMC in patients with clinical stage II/III squamous cell carcinoma of the anal canal. (JCOG0903)
- A randomized study of conventional technique vs. no-touch isolation technique. (JCOG1006)
- A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer (JCOG1007)
- 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 Phase II/III randomized multicenter trial of intersphincteric resection (ISR) with or without preoperative chemotherapy for very low-lying rectal cancer.
- A prospective cohort study of Reduced Port Surgery for colorectal cancer
- 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

Table 1. Number of patients (2013.1-2013.12)

Colorectal cases			Other cases	
Colon	Rectum	Sub-total	Gastro-intestinal	Others
144	196	340	10	126

Table 2. Type of procedure
Operative Procedures (2013.1-2013.12)

Colon N = 144 Laparoscopic(LAP) : 112 Open : 32		
Sigmoidectomy	65	(LAP:62)
Right (hemi) colectomy	34	(LAP:30)
Ileocecal resection	13	(LAP:13)
Limited colectomy	19	(LAP:5)
Hartmann procedure	1	
Low anterior resection	3	(LAP:0)
Left (hemi) colectomy	4	(LAP:32)
Stoma	4	
Other	1	

Rectum N = 196 Laparoscopic (LAP): 126 Open : 70		
Low anterior resection	72	(LAP:50)
*Abdominoanal resection(AAR)	59	(LAP:44)
High anterior resection	21	(LAP:19)
Abdominoperineal resection (APR)	20	(LAP:11)
Hartmann procedure	5	(LAP:2)
Local excision	2	
Total pelvic exenteration	1	
Stoma	10	
Others	6	
*Conventional coloanal anastomosis	10	
Partial intersphincteric resection (ISR)	24	
Subtotal ISR	8	
Total ISR	12	
Partial external sphincter resection (ESR)	5	

Table 3. Survival rates

Stage	Colon			Rectum		
	No. of pts	5-yr survival (%)		No. of pts	5-yr survival (%)	
		overall	cancer specific		Overall	cancer specific
Stage 0	7	100	100	10	100	100
Stage I	199	96.4	100	161	95.0	98.7
Stage II	275	92.0	95.6	192	84.0	88.9
Stage IIIa	186	85.1	88.8	158	80.5	82.3
Stage IIIb	64	68.4	71.3	114	60.3	64.9
Stage IV	154	25.7	27.0	92	26.8	26.7

OP:1991.1-2006.12

List of papers published in 2013
Journal

1. Nakajima K, Sugito M, Nishizawa Y, Ito M, Kobayashi A, Nishizawa Y, Suzuki T, Tanaka T, Etsunaga T, Saito N. Rectoseminal vesicle fistula as a rare complication after low anterior resection: a report of three cases. Surg Today, 43:574-579, 2013
2. Nakajima K, Takahashi S, Saito N, Sugito M, Konishi M, Kinoshita T, Gotohda N, Kato Y. Efficacy of the predicted operation time (POT) strategy for synchronous colorectal liver metastasis (SCLM): feasibility study for staged resection in patients with a long POT. J Gastrointest Surg, 17:688-695, 2013
3. Watanabe K, Saito N, Sugito M, Ito M, Kobayashi A, Nishizawa Y. Incidence and predictive factors for pulmonary metastases after curative resection of colon cancer. Ann Surg Oncol, 20:1374-1380, 2013

Department of Gastrointestinal Oncology

Atsushi Ohtsu, Toshihiko Doi, Takayuki Yoshino, Nozomu Fuse, Takashi Kojima, Kohei Shitara, Wataru Okamoto, Hideaki Bando

Introduction

In 2013, approximately 550 patients were treated by 8 medical oncologists and some residents in the Gastrointestinal (GI) Oncology Division, which focuses on the use of chemotherapy with or without radiation for the treatment of GI malignancies.

Routine activities

Inter-Divisional tumor board conferences with the Surgical/Radiation Oncology Divisions are held regularly to review and direct treatment for each patient or to discuss treatment strategies. Chemotherapy on an outpatient basis for probable candidates was managed passively, and usually approximately 1508 patients are hospitalized and the hospital stay with chemotherapy or palliative therapy was short. Our activities for each type of GI cancer in 2013 are shown in Table 1 (Number), Table 2 (Treatment), and Table 3 (Efficacy). In clinical trials, both 72 sponsored initiated trials which consisted of 38 phase I trials including first-in-human, first-in-class drugs in a global fashion and 34 phase2/3 global trials to approve investigational new drugs (INDs) were conducted.

Research activities

Phase I

Our division has focused more on early stage clinical development of investigational agents. The numbers of patients enrolled for phase I trials have been increasing recently. During April to November 2013, 111 patients were enrolled for phase I trials. Importantly, the number of first-in-human trials and trials around the same time as Western countries is increasing. We organize a weekly meeting of phase I trials ("phase I meeting") to share the updated information of each trial and to allocate patients to adequate phase I trials. The median interval from registration to "phase I meeting" to actual enrollment for trials was 28 days. We also routinely hold teleconferences with the National Cancer Center Hospital (NCCH) to efficiently recruit patients. Several results of phase I trials, such as a angiopoietin-1/2 antagonist (trebananib, AMG 386), an IGF-1R inhibitor (ganitumab, AMG 479), a histone deacetylase inhibitor (vorinostat) for GI cancer, PI3K inhibitor (BAY 80-6946), MEK inhibitor (BAY 86-9766), p70S6 kinase inhibitor (LY2584702), and a fully human antibody against ALK-1 receptor (PF-03446962) were published or presented at international meetings and published. The preliminary results of an investigator initiated phase I trial of sulfasalazine, an xCT inhibitor targeting cancer stem-like cells, will be presented at the upcoming Annual Meeting of the American Association for Cancer Research 2014.

Esophageal Cancer (EC)

The results of a multicenter phase I/II study of biweekly docetaxel in combination with fixed-dose cisplatin plus fluorouracil in patients with advanced esophageal cancer (JCOG0807), and safety profile of thoracoscopic esophagectomy for esophageal cancer compared with traditional thoracotomy from the results of JCOG0502: A randomized trial of esophagectomy versus chemoradiotherapy, were presented at the ASCO meeting, 2013. The results of a multicenter phase I/II trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by concurrent chemoradiotherapy in locally advanced esophageal squamous cell carcinoma were presented at the ASCO meeting, 2013.A multicenter phase III trial comparing surgery with CRT concurrent with 5-FU and cisplatin in stage I EC (JCOG0502) has been completed.

Gastric Cancer (GC)

The results of a global randomized phase III trial comparing ramucirumab with paclitaxel to placebo with paclitaxel (RAINBOW) were presented at the 2014 Gastrointestinal Cancers Symposium. Ramucirumab has become the second of the molecular targeting agents that showed survival benefit in advanced GC patients. The results of a multicenter phase III trial (G-SOX) comparing S-1 plus oxaliplatin to S-1 plus cisplatin were presented at the 2013 Gastrointestinal Cancers Symposium. This trial showed non-inferiority of oxaliplatin to cisplatin in terms of progression-free survival and the follow-up of overall survival is ongoing. Based on the promising results from a randomized phase II

trial in colorectal cancer, we have conducted a phase II trial of TAS-102 in advanced GC, which was the first investigator-initiated trial using an unapproved agent for us, and we reported the results at the European Cancer Congress 2013.

We have investigated if the status of HER2, EGFR and c-Met could be an independent prognostic factor for advanced GC patients who have undergone standard chemotherapy, and the correlation between the status of these factors and clinicopathological features, and reported the results at the American Society of Clinical Oncology Annual Meeting 2013 and the European Cancer Congress 2013. We have conducted a comprehensive molecular analysis of advanced GC using next-generation sequencing and immunohistochemistry to profile both gene alterations and conventional biomarkers for potential molecular targeted therapy. We identified several possible candidate genes that could be targets for personalized therapy and will present the results at an upcoming meeting.

Colorectal Cancer (CRC)

Based on our promising results from a randomized phase II trial comparing TAS-102 with BSC (best supportive care) published in Lancet Oncology, an international phase III trial, called the RECOUSE trial, to confirm the clinical benefit of TAS-102 is ongoing as a company-sponsored trial. We have started the phase1b/2 trial of the novel combination of TAS-102 plus bevacizumab as an investigator-initiated trial. We reported the results of the CORRECT trial to show the clinical benefit of regorafenib published in the Lancet, which has been approved in this indication in the USA, Europe, and Japan. We have started a randomized phase II study of regorafenib followed by cetuximab versus reverse sequence for Wild-Type KRAS metastatic CRC called the REVERCE trial. We have developed a consortium of 7 cancer centers to collect strictly selected archived samples as the first-step in a trial called the BREAC trial (Biomarker Research for Anti-EGFR Monoclonal Antibodies by Comprehensive Cancer Genomics), from colorectal cancer patients who had received anti-EGFR therapy; the selection of 92 cases of super-responders and those of non-responders. We have started whole exon mutation analyses to find the specific gene candidates potentially related to the efficacy of anti-EGFR therapy. As the second step to validate the specific gene candidates, we will investigate the association between the specific gene candidates and the efficacy for another consecutive 150 colorectal cancer patients who had received anti-EGFR therapy. We identified several possible candidate genes that could be targets for personalized therapy and will present the results at an upcoming meeting. A nationwide screening project called GI-SCREEN 2013-01 has been started to identify several key gene mutations including NRAS, BRAF and PIK3CA. We also conducted a prospective multicenter clinical validation study of a novel multiplex kit for all RAS mutations called RASKET as the registration trial and have already submitted the results to the Japanese authorities.

Clinical trials

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) and a three-arm randomized phase III study comparing preoperative CDDP+5-FU versus docetaxel+CF versus CF-radiation followed by esophagectomy with D2-3 lymphadenectomy for locally advanced esophageal squamous cell cancer (JCOG1109) is ongoing. In addition, a multicenter phase II trial of BKM120 in patients with advanced esophagus cancer has been opened.

Gastric Cancer (GC)

The enrollment for a multicenter global phase III trial comparing pertuzumab with chemotherapy to placebo with chemotherapy in HER2-positive advanced GC patients (JACOB), a multicenter global phase III trial comparing nimotuzumab with irinotecan to irinotecan alone in EGFR-positive advanced GC patients (ENRICH), a multicenter phase III trial comparing weekly or triweekly ABI-007 to weekly paclitaxel in non-selected advanced GC patients and a multicenter phase II trial of c-MET inhibitor in c-MET-positive advanced GC patients have been opened.

The enrollment for a multicenter phase II trial of neoadjuvant chemotherapy using docetaxel with cisplatin plus S-1 (DCS; JCOG 1002), a phase II trial of adjuvant chemotherapy with capecitabine plus oxaliplatin in stage II/III GC patients and a phase II trial of adjuvant chemotherapy with S-1 plus oxaliplatin in stage II GC patients have been completed and the follow-up is ongoing.

The enrollment for a multicenter global phase II/III trial comparing trastuzumab emtansine to taxane in HER2-positive GC patients (GATSBY) and a multicenter phase III trial comparing 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.

Colorectal Cancer (CRC)

An international phase III trial called the

RECOUSE trial, to confirm the clinical benefit of TAS-102 with a placebo in a salvage setting is ongoing. Based on the Western and our phase I trials of the first-in-class cancer stemness inhibitor BBI608, an international phase III trial called the NCIC CTG CO.23 trial to confirm the clinical benefit of BBI608 with a placebo in a salvage setting is ongoing. We have conducted a phase I study of the selective BRAFV600 inhibitor combined with cetuximab and with or without the α-specific PI3K inhibitor in patients with advanced BRAF mutant CRC. We also have conducted several phase II trials including ziv-aflibercept and PI3K inhibitor for mCRC. In order to achieve a personalized medicine approach, we are conducting an Analysis of Biopsy samples for Cancer genomics called the ABC study, using target sequencing from pre-treatment biopsy samples for advanced solid tumors including CRCs. We have conducted two randomized, multicenter, phase III studies called the ACHIEVE and ACHIEVE-2 trial to compare 6 months of either mFOLFOX6 or XELOX with 3 months of the same regimen as adjuvant chemotherapy in patients with completely resected stage III and high-risk stage II colon cancer, together with other nations' collaborative groups in the US, UK/Australia, Italy, Greece and France. We also have conducted a confirmatory study called the SUNRISE trial of an Oncotype DX Colon Cancer assay to assess the relationship between the continuous recurrence score and the likelihood of recurrence in patients with resected stage II and stage III colon cancer.

Table 1. Number of new patients

Esophageal	279
Gastric	260
Colorectal	340
Other type of tumors	79
Total	960

Table 2. Treatment

Esophageal Cancer	Chemotherapy (include CRT*)	153
Gastric Cancer	Chemotherapy	171
Colorectal Cancer	Chemotherapy	233

Table 3. Survival rates

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

List of papers published in 2013
Journal

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Department of Digestive Endoscopy

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Introduction

The Digestive Endoscopy Division covers the fields of the gastrointestinal (GI) tract and head and neck regions. In 2013, a total of 11,696 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, A Blue LASER imaging (BLI) system was installed 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 of cancer patients, or cancer prevention 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 and prevention of cancer, or prediction of prognosis for treatment. These projects are conducted in collaboration with not only commercial companies but also with university faculties of Technology and Science.

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 used for the detection of neoplastic lesions of the head and neck and alimentary tracts, with blue visualized images. A first in-human clinical trail 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 using this system with an InGaAs CCD has been developed, since nanoparticles of rare earth act as fluorescent agents. With a low-

temperature atmospheric pressure plasma system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnostic system using photosensitizing agents, such as hypericin and aminolevulinic acid (5-ALA), has been constructed. Moreover, a new clinical trial of a biodegradable (BD) stent has been performed for patients with benign esophageal stricture after curative treatment, such as ESD, surgery, and chemoradiotherapy.

Clinical trials

A wide range of many prospective clinical trials is ongoing into the endoscopic treatment of cancers of the esophagus, stomach, and colorectum, as follows: a first in-human clinical trial of hypoxia imaging for neoplasia of alimentary tract in a single unit; a phase II clinical trial for BD stent implantation for benign esophageal stricture; a clinical trial for photodynamic diagnosis using 5-ALA; a 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 with endoscopic mucosal resection and chemoradiotherapy for clinical stage I esophageal carcinoma (JCOG0508); a multicenter clinical study on enrollment of early gastric cancer following endoscopic treatment with an 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.

Table 1. Number of Patients Examined in 2009-2013

Section	2009	2010	2011	2012	2013
Upper gastrointestinal endoscopy	5,545	5,720	6,350	6,647	6,846
Endoscopic ultrasonography	86	78	70	54	43
Endoscopic mucosal resection (esophagus)	130	145	181	168	220
Endoscopic mucosal resection (stomach)	231	211	205	215	203
Endoscopic balloon dilation	866	613	644	711	824
Percutaneous endoscopic gastrostomy	173	218	215	171	196
Photodynamic therapy (esophagus)	23	47	48	39	32
Colonoscopy	2,027	2,250	1,550	2,302	2,368
Polypectomy/EMR	791	744	800	912	832
Narrow Band Imaging (head and neck)	194	147	95	106	80
Endoscopic mucosal resection (head and neck)	21	41	41	46	52

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

Table 2. Endoscopic procedures in 2013

		2011	2012	2013
Esophagus	EMR	100	89	65
	ESD	45	79	155
Stomach	EMR	9	3	0
	ESD	202	212	203
Colon and rectum	EMR*	744	834	725
	ESD	17	78	98
Head and neck	EMR	6	7	1
	ESD	35	33	51

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

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Journal

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Department of Hepatobiliary and Pancreatic Surgery

Masaru Konishi, Shinichiro Takahashi, Naoto Gotohda, Yuichiro Kato, Eiji Higaki, Yatuka Sahara, Masayuki Honda, Gentaro Hirokata, Yusuke Ome

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, 4 chief residents, and 4–6 residents. The outpatient clinic is open 5 days a week. Staff meetings are held 3 times a week during which treatment strategies from the medical and surgical points of view are discussed. A case conference on imaging diagnosis is conducted every Tuesday in cooperation with radiologists and medical oncologists, and a pathology conference is held every month with pathologists. In 2013, 254 patients with hepatobiliary and pancreatic diseases underwent surgical treatment including 52 laparoscopic hepatectomies and 8 laparoscopic distal pancreatectomies. Because surgical treatment after chemoradiotherapy for borderline or locally advanced pancreatic cancer has been aggressively indicated since 2012, the number of pancreatectomies has been increasing.

Research activities

1) Pancreatic cancer

JASPAC-01 is a randomized phase III trial to compare orally administered S-1 with intravenous gemcitabine as adjuvant chemotherapy for patients with curatively resected pancreatic cancer. In this study, adjuvant chemotherapy with S-1 has been shown superior to gemcitabine.

JSAP-04 is a randomized phase III study on adjuvant chemotherapy using combination therapy with gemcitabine and S-1 vs. gemcitabine alone in patients with resected pancreatic cancer. Recruitment is complete and follow-up is on-going.

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

Prep02/JSAP05 is a randomized phase III study on neoadjuvant chemotherapy using combination therapy with gemcitabine and S-1 vs. surgery first in patients with resected pancreatic cancer. Recruitment started in 2013.

2) Biliary tract cancer

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

JCOG1202 (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.

3) Hepatocellular carcinoma

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

Recruitment in a phase III trial on adjuvant chemoprevention with Peretionin for HCC patients following curative local treatment is on-going.

4) Liver metastasis from colorectal cancer

JCOG trial 0605 is a randomized phase III trial to compare FOLFOX with surgery alone as adjuvant chemotherapy for patients with curatively resected liver metastasis from colorectal cancer. Recruitment is on-going.

5) Immune-enhancing enteral diet (IED)

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

6) Surgical device efficacy

EPL is a randomized phase III trial to evaluate the impact of the use of an energy-based device during parenchyma transaction of the liver. Based on the results of this study, using energy devices became the standard method during liver parenchymal transection.

Table 1. Number of patients

Invasive pancreatic cancer	65
Other pancreatic neoplasms	13
Hepatocellular carcinoma	45
Hepatic metastases	60
Intrahepatic cholangiocarcinoma	6
Bile duct cancer	23
Gallbladder cancer	10

Table 2. Type of procedure

Pancreaticoduodenectomy	62
Distal pancreatectomy	22
Total pancreatectomy	1
Laparoscopic distal pancreatectomy	8
Hepatectomy with biliary reconstruction	9
Hepatectomy without biliary reconstruction	67
Laparoscopic hepatectomy	52
Other procedures	33
Total	254

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	89	37.3
Extrahepatic bile duct cancer	254	47.2
Papilla Vater cancer	96	54.2
Gallbladder cancer	116	44.8

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Journal

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Department of Hepatobiliary and Pancreatic Oncology

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Introduction

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

Routine activities

Our Department is composed of 5 staff oncologists, 1 senior resident and 1 resident, with 35-50 beds in the hospital, and we conduct clinical rounds for admitted patients every morning and evening. Most new patients with unresectable hepatobiliary and pancreatic tumors are hospitalized for tumor diagnosis and treatment. Individual patient treatment strategies are discussed in weekly tumor board conferences attended by medical oncologists, surgeons, radiologists, radiation oncologists, and pharmacists. Furthermore, we are also responsible for external or endoscopic abdominal ultrasonographic examinations, percutaneous or endoscopic ultrasound-guided biopsies of abdominal masses, local ablative therapy for liver cancer, percutaneous or endoscopic biliary drainage and stenting for obstructive jaundice.

Research activities

Hepatocellular carcinoma (HCC)

The efficacy of sorafenib for HCC patients refractory to transcatheter arterial chemoembolization (TACE) has been investigated and retrospectively compared to the results with those of patients treated with hepatic arterial infusion chemotherapy using cisplatin (cisplatin group). Sorafenib showed favorable treatment results in patients refractory to TACE. When compared with a cisplatin group, sorafenib demonstrated a significantly higher disease control rate and a longer time to progression and overall survival. Thus, sorafenib, rather than hepatic arterial infusion chemotherapy, should be considered as the first-line therapy for patients who are refractory to TACE.

The following studies have been also investigated for advanced HCC patients: the relationship between treatment efficacy and adverse events in patients treated with sorafenib, the comparative evaluation of efficacy and safety in sorafenib-treated patients with hepatitis B and C viral infection, and the prognostic factors in patients with HCC refractory or intolerant to sorafenib. In addition, the results have been also reported of a multi-institutional phase II trial of hepatic arterial infusion chemotherapy with cisplatin in advanced HCC patients with portal vein tumor thrombosis, and the results of an Asian cooperative study between Japan and Korea on TACE for unresectable HCCs. Both of these studies were published in the English literature.

Pancreatic cancer (PC)

Gemcitabine (Gem) plus erlotinib was one of the standard chemotherapy regimens for advanced PCs, and our hospital was No.1 regarding the number of advanced PC patients who were treated with this regimen in Japan. The treatment efficacy has been investigated retrospectively and the results in clinical practice have been reported. In addition, the efficacy of prophylactic minocycline treatment against the skin toxicities induced by erlotinib has been investigated as compared to deferred minocycline treatment in advanced PC patients treated with erlotinib plus Gem. This study clarified that prophylactic minocycline treatment should be recommended for the management of erlotinib-related acneiform rash and xerosis during chemotherapy in advanced PC patients. The following studies have also been reported in the English literature: the results of a multicenter phase II trial of S-1 with concurrent radiation therapy has been reported for locally advanced PC, and the usefulness of serum levels of IL-6 and IL-1β on prediction of the efficacy of Gem in patients with advanced PCs.

Biliary tract cancer (BTC)

A total of 1,047 BTC patients have been investigated to evaluate the patient characteristics and treatment efficacy in BTC patients, and the clinical features of recent BTC patients and prognostic factors have been clarified.

Hepatitis B viral (HBV) reactivation following chemotherapy

HBV reactivation has often been reported as a fatal complication, such as acute hepatitis, during or following chemotherapy. The Japanese guidelines from the research team of the Ministry of Health, Labour and Welfare recommend that the high risk patient group should be identified by measuring HBsAg, anti-HBc and anti-HBs before the commencement of chemotherapy. We investigate the present status of screening of HBV in patients who underwent chemotherapy for malignancy in Japan, and we concluded that the proportion of screening of HBV was not sufficient and the enlightenment for "HBV reactivation by chemotherapy" was warranted.

Clinical trials

Forty eight clinical trials (sponsored: 30 trials, investigator-initiated: 18 trials) are ongoing, and 11 clinical trials (sponsored: 7 trials, investigator-initiated: 4 trials) are being planned for the upcoming year.

HCC

The enrollment for a randomized controlled trial comparing the combined administration of sorafenib with intra-arterial cisplatin with sorafenib alone for highly advanced HCCs has been completed, and the final analyses will be planned for next year. Among sponsored trials, the enrollments for a phase III trial of orantinib vs. a placebo in combination with TACE, 2 randomized phase II trials of dovitinib vs. sorafenib in the first-line setting and of GC33 vs. a placebo in the second-line setting, and 2 phase I trials of a Stat-3 inhibitor (OPB-31121) and tivantinib have already been completed. Some phase III trials of peretinoin vs. a placebo in the adjuvant setting after resection or ablation, of lenvatinib vs. sorafenib in the first line setting, and of regorafenib vs. a placebo in the second line setting are underway. Two randomized phase II trials comparing sorafenib vs. observation in combination with TACE, and of ALK-1 inhibitor (PF-03446962) vs. best supportive care in the second-line setting and 1 single arm phase II trial of rafametinib are also underway. Some phase I trials of nintedanib, pimasertib, and a peptide vaccine including glypican-3 (ONO-7268MX1), sorafenib plus resminostat, a stat 3 inhibitor (AZD9150), etc. are ongoing.

BTC

The enrollment for a randomized phase III trial comparing adjuvant S-1 with observation has been opened to determine whether adjuvant chemotherapy with S-1 might improve the outcomes of patients with resected biliary tract cancer. Furthermore the enrollment for a randomized phase III trial comparing Gem plus S-1 with Gem plus cisplatin has also been opened as a first line treatment for advanced BTC. A phase I investigators-initiated trial of combined Gem, cisplatin and S-1 therapy is ongoing to determine the recommended doses for subsequent trials. A single arm, sponsored, multicenter phase II trial of trametinib is underway for advanced BTCs refractory to Gem.

PC

The enrollment for a randomized phase II trial of S-1 and concurrent radiotherapy with versus without induction chemotherapy for locally advanced pancreatic cancer (JCOG1106) has been completed. As sponsored trials, the enrollments for a phase II trial of Gem plus nab-paclitaxel for untreated metastatic PC and a phase III trial of a peptide vaccine (OCV-C01) for Gem refractory PC have been completed. A multicenter phase II trial of neoadjuvant S-1 and concurrent radiotherapy for borderline resectable pancreatic cancer (JASPAC05) is ongoing. 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.

Thus, a many clinical trials will be planned for hepatobiliary and pancreatic cancer in the coming year.

Table 1. Number of patients

Hepatocellular carcinoma	117
Biliary tract cancer	
Intrahepatic cholangiocarcinoma	25
Extrahepatic cholangiocarcinoma	33
Gallbladder cancer	31
Papilla of vater carcinoma	5
Pancreatic cancer	
Locally advanced disease	47
Metastatic disease	145
Other	29
Total	432

Table 2. Type of procedure

Hepatocellular carcinoma	
Radiofrequency ablation	85
Transarterial chemoembolization	200
Intra-arterial chemotherapy	47
Systemic chemotherapy	68
Proton beam radiotherapy	29
Biliary tract cancer	
Systemic chemotherapy	53
Radiotherapy	1
Pancreatic cancer	
Systemic chemotherapy	193
Chemoradiotherapy	10
Total	686

Table 3. Survival rates

Hepatocellular carcinoma	No. of pts	MST(mo)	2-yr survival(%)
Radiofrequency ablation	191	57.2	83.0
Transcatheter arterial chemoembolization	292	22.7	46.9
Intra-arterial chemotherapy	75	6.5	21.9
Period:	1992/11-2005/12		
Systemic chemotherapy	127	10.6	20.7
Period:	2009/06-2011/12		
Biliary tract cancer	No. of pts	MST(mo)	2-yr survival(%)
Systemic chemotherapy	410	6.5	6.1%
Period:	1992/11-2013/5		
Pancreatic cancer	No. of pts	MST(mo)	1-yr survival(%)
Locally advanced disease	369	10.6	43.8
Metastatic disease	798	5.8	21.0
Post-ope recurrence	121	9.3	37.1
Period:	1992/11-2013/5		

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Journal

1. Suyama K, Ikeda M, Suzuki E, Kojima M, Mitsunaga S, Shimizu S, Ohno I, Takahashi H, Okuyama H, Kuwahara A, Okusaka T, Furuse J. Early relapse of unresectable gallbladder cancer after discontinuation of gemcitabine monotherapy administered for 5 years in a patient who had complete response to the treatment. Case Rep Oncol, 6:531-537, 2013
2. Nakayama Y, Ikeda M, Kojima M, Goto K, Hara M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Okusaka T. Successful everolimus treatment in a patient with advanced pancreatic neuroendocrine tumor who developed everolimus-induced interstitial lung disease on two occasions: a case report. Chemotherapy, 59:74-78, 2013
3. Ikeda M, Okusaka T, Furuse J, Mitsunaga S, Ueno H, Yamaura H, Inaba Y, Takeuchi Y, Satake M, Arai Y. A multi-institutional phase II trial of hepatic arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Cancer Chemother Pharmacol, 72:463-470, 2013
4. Morizane C, Okusaka T, Mizusawa J, Takashima A, Ueno M, Ikeda M, Hamamoto Y, Ishii H, Boku N, Furuse J. Randomized phase II study of gemcitabine plus S-1 versus S-1 in advanced biliary tract cancer: a Japan Clinical Oncology Group trial (JCOG 0805). Cancer Sci, 104:1211-1216, 2013
5. Inagaki M, Akechi T, Okuyama T, Sugawara Y, Kinoshita H, Shima Y, Terao K, Mitsunaga S, Ochiai A, Uchitomi Y. Associations of interleukin-6 with vegetative but not affective depressive symptoms in terminally ill cancer patients. Support Care Cancer, 21:2097-2106, 2013
6. Asai M, Akizuki N, Fujimori M, Shimizu K, Ogawa A, Matsui Y, Akechi T, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Impaired mental health among the bereaved spouses of cancer patients. Psychooncology, 22:995-1001, 2013
7. Otsuka T, Morizane C, Nara S, Ueno H, Kondo S, Shimada K, Kosuge T, Ikeda M, Hiraoka N, Okusaka T. Gemcitabine in patients with intraductal papillary mucinous neoplasm with an associated invasive carcinoma of the pancreas. Pancreas, 42:889-892, 2013
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9. Sawada Y, Yoshikawa T, Fujii S, Mitsunaga S, Nobuoka D, Mizuno S, Takahashi M, Yamauchi C, Endo I, Nakatsura T. Remarkable tumor lysis in a hepatocellular carcinoma patient immediately following glypican-3-derived peptide vaccination: an autopsy case. Hum Vaccin Immunother, 9:1228-1233, 2013
10. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, Fukutomi A, Sugimori K, Baba H, Yamao K, Shimamura T, Sho M, Kitano M, Cheng AL, Mizumoto K, Chen JS, Furuse J, Funakoshi A, Hatori T, Yamaguchi T, Egawa S, Sato A, Ohashi Y, Okusaka T, Tanaka M. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol, 31:1640-1648, 2013
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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 (NCHHE) 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 the BCG vaccine into the bladder. Advanced urogenital cancers including stage D2 prostate cancer are referred to the Medical Oncology Division for chemotherapy or hormone therapy. Extrinsic obstructions of the upper urinary tract that directly result from invasion of an adjacent malignancy or peritoneal metastasis are also treated. In most cases, internal stenting is better tolerated than percutaneous nephrostomy. Fifty-three patients newly received ureteral stents and 23 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 31 combination surgeries with colorectal surgeons. In the Department of Urology, 102 general anaesthesia surgeries, 76 spinal anesthesia surgeries and 42 prostate biopsies were performed.

Other: We have a conference on urogenital cancers every other week among medical oncologists, radiation oncologists and one pathologist. Neoadjuvant chemotherapy for invasive bladder cancer, combination therapy of hormone and radiation for prostate cancer, treatment strategies for metastatic renal cell carcinoma and testicular cancer, and so on, are determined in the meeting.

Research activities

Minimum incision endoscopic surgery was introduced from 2011, which comprises a gasless, single-port access, cost-effective, and minimally invasive surgery. We intend to make this operation more sophisticated in coordination with the Department of Urology, Tokyo Medical and Dental University. 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 assisted 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 with the da Vinci S/Si Surgical System

Table 1. Number of patients

Renal cell carcinoma	23
Upper urinary tract urothelial cell carcinoma	15
Bladder cancer	41
Prostate cancer	21
Testicular cancer	2

Table 2. Type of procedure

Radical nephrectomy	9
Partial nephrectomy	14
Nephroureterectomy	15
Radical cystectomy	16
TURBT	69
Radical prostatectomy	21

Table 3. Survival rates

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

List of papers published in 2013
Journal

1. Matsubara N, Mukai H, Naito Y, Itoh K, Komai Y, Sakai Y. First experience of active surveillance before systemic target therapy in patients with metastatic renal cell carcinoma. Urology, 82:118-123, 2013

Department of Musculoskeletal Oncology and Rehabilitation

Umio Yamaguchi

Introduction

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

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

Clinical Department	2011	2012	2013
Hematology oncology	29	39	24
Thoracic oncology	24	35	44
Thoracic surgery	18	29	13
Head and neck oncology	12	21	10
Gastrointestinal oncology	12	21	23
Esophageal surgery	18	19	34
Musculoskeletal oncology	2	17	52
Palliative medicine	9	15	18
Colorectal surgery	8	13	2
Hepatobiliary and pancreatic oncology	7	12	15
Breast and Medical oncology	-	-	27
Head and neck surgery	-	-	13
Others	7	24	19
Total	146	245	294

Routine activities

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

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

List of papers published in 2013
Journal

1. Lin F, Yamaguchi U, Beppu Y, Kawai A, Chuman H. Massive ossification around the prosthesis after limb salvage treatment for osteosarcoma. J Orthop Sci, 18:667-670, 2013
2. Lin F, Yamaguchi U, Matsunobu T, Kobayashi E, Nakatani F, Kawai A, Chuman H. Minimally invasive solid long segmental fixation combined with direct decompression in patients with spinal metastatic disease. Int J Surg, 11:173-177, 2013
3. Yamaguchi U, Chuman H. Overview of medical device regulation in Japan as it relates to orthopedic devices. J Orthop Sci, 18:866-868, 2013

Department of Hematology

Kunihiro Tsukasaki, Masahiko Nezu, Kuniaki Itoh, Hiromi Yuasa

Introduction

The staff physicians and residents of this Department carry out clinical and research activities related to multi-disciplinary treatment of patients with hematological malignancies which consist of more than 100 disease entities in the WHO classification (version 2008). The Department focuses on the early and late phases of clinical trials in collaboration with the Research Center for Innovative Oncology and the Japan Clinical Oncology Group (JCOG), respectively, especially on lymphoid malignancies.

Routine Activities

The number of patients 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 for this year (Table 1). The Department is currently providing routine chemotherapy as an outpatient service to an increasing number of relatively aged patients with hematological malignancies. All patients undergoing intensive chemotherapy and autologous peripheral blood hematopoietic stem cell transplantation (APBSCT) (Table 2) are managed in laminar airflow rooms in the designated ward on the eighth floor. Besides managing patients, the Department also provides consultation on hematological abnormalities detected in the Department of Clinical Laboratories. A 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. A morning journal club is held on Mondays and Fridays jointly for our Department of ours and the Department of Breast and Medical Oncology.

Research activities

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

Clinical trials

Clinical trials on hematological malignancies performed by our Department comprise protocols prepared in-house and participation in the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG-LSG), the Japan Adult Leukemia Study Group (JALSG) and others. The Department participated in pharmaceutical company-sponsored new-agent trials including international ones for hematological malignancies. The following JCOG clinical trials are ongoing: a randomized phase III trial of rituximab administered weekly or tri-weekly with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in patients with newly diagnosed CD20+ diffuse large B cell lymphoma (DLBCL) (JCOG0601) in which a dose-intense schedule of rituximab is evaluated; a randomized phase II trial comparing biweekly rituximab-CHOP or biweekly rituximab-CHOP/cyclophosphamide, cytarabine, dexamethasone, etoposide and rituximab (CHASER) followed by high dose melphalan, cyclophosphamide, etoposide and dexamethasone (LEED) with APBSCT in patients with newly diagnosed poor risk CD20+ DLBCL (JCOG0908); a randomized phase II trial comparing dexamethasone with bortezomib or thalidomide in patients with relapsed/refractory multiple myeloma (JCOG0904); a randomized phase II study of two

induction treatments of melpharan, 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 controls in JCOG9801 to evaluate the promising efficacy of allo-HSCT, possibly associated with a graft-versus-ATL effect, especially in view of a comparison with intensive chemotherapy (JCOG0907). A phase III study evaluating the efficacy of the combination of interferon-alpha (IFN) and zidovudine (AZT) as compared to watchful-waiting for indolent ATL (JCOG1111) has been initiated at our Department and the Department of Hematology at the National Cancer Center Hospital at Tsukiji under the highly advanced medical technology assessment system because IFN and AZT are not covered for ATL by the National Health Insurance system in Japan.

Table 1. Number of patients

Non-Hodgkin's lymphoma	170
Hodgkin's lymphoma	16
Multiple myeloma	8
Acute leukemia	11
Chronic leukemia	3
Others	39
Total	247

Table 2. Type of procedure

PBSCT for non-Hodgkin's lymphoma in relapse	3
PBSCT for myeloma in remission	5
Total	8

List of papers published in 2013

Journal

1. Ogura M, Itoh K, Ishizawa K, Kobayashi Y, Tobinai K, Kinoshita T, Hirano M, Ueda R, Shibata T, Nakamura S, Tsukasaki K, Hotta T, Shimoyama M, Morishima Y. Phase II study of ABV (doxorubicin with increased dose, bleomycin and vinblastine) therapy in newly diagnosed advanced-stage Hodgkin lymphoma: Japan Clinical Oncology Group study (JCOG9705). Leuk Lymphoma, 54:46-52, 2013
2. Tsukasaki K, Tobinai K. Biology and treatment of HTLV-1 associated T-cell lymphomas. Best Pract Res Clin Haematol, 26:3-14, 2013
3. Yoshida N, Nishikori M, Izumi T, Imaizumi Y, Sawayama Y, Niino D, Tashima M, Hoshi S, Ohshima K, Shimoyama M, Seto M, Tsukasaki K. Primary peripheral T-cell lymphoma, not otherwise specified of the thyroid with autoimmune thyroiditis. Br J Haematol, 161:214-223, 2013

Book

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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 the 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 osteoclast-modifying agent-related osteonecrosis of the jaw (OMAONJ) as a result of contamination of the oral cavity and tooth extraction; we are therefore 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 2013, the numbers of new and revisiting patients were 841 and 7108, respectively, and the total number of patients was 7949. 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 dental care in cancer has been recognized.

Research activities

We are participating in a multicenter study being conducted to evaluate the effectiveness of the 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 the National Cancer Center-East (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 Groups. 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 conferences with the Orthopedic Surgery, Thoracic Surgery and Urology Divisions at any time.

Research activities

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

Clinical trials

Three clinical trials described below are currently active.

(1) A randomized phase II study on two cross-over sequences comprising vinorelbine/cyclophosphamide and temozolomide/etoposide in the outpatient setting for relapsed or refractory solid tumors in children and young adults.
(2) A phase I trial of immunotherapy using HLA-A2 and A24-restricted glypican-3 peptide vaccine for pediatric tumors.
(3) Phase 1 study of a peptide cocktail vaccine for patients with refractory pediatric sarcomas.

Table 1. Number of patients

Bone tumor	7
Soft tissue sarcoma	7
Rhabdomyosarcoma	2
Ewing sarcoma	1
Osteosarcoma	1
Hepatoblastoma	1
Retinoblastoma	1

Department of Anesthesiology and Intensive Care Unit

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

Introduction

The Department of Anesthesiology and Intensive Care Unit (ICU) consists of 5 staff members, including 4 JSA (Japan Society of Anesthesiologists) board certified anesthesiologists and two or three rotating residents. Each year, we provide more than 2,500 anesthesia services in 8 operating rooms and over 1200 patients are admitted to the ICU. A large number of operations in the Head and Neck Surgery Division and procedures involving a thoracotomy for lung and esophageal cancer are one of the features of this hospital. Accordingly a special anesthesia induction method for a 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

Five staff members (4 full-time and one visiting anesthesiologists), two or three rotating residents and 10 part-time anesthesiologists cover 8 operating rooms. A preanesthesia case presentation is held every morning to examine the case of the day and discuss the anesthesia strategy for patients with various complications. A Journal club is also held once a week. We provided 2,825 anesthesia services and annual number of patients admitted to the ICU was 1,458 in 2013.

Research activities

Dr. Torigoe presented "The effect of intraoperative vasopressors on free flap in microsurgical head and neck reconstruction" at the 33rd Annual Meeting of the Japan Society for Clinical Anesthesia.

Table 1. Number of Anesthesia Cases

Type of Surgery	2009	2010	2011	2012	2013
Head and Neck	474	515	424	454	470
Thoracic	503	488	466	473	505
Esophageal	-	137	126	182	201
Gastric, Hepatobiliary, Pancreatic	566	542	-	-	
Hepatobiliary and Pancreatic	-	-	269	231	284
Gastric	-	-	286	308	292
Colorectal	418	491	426	453	486
Urology	79	88	78	107	173
Orthopedic	-	-	-	22	56
Breast	282	297	291	309	328
Plastic and Reconstructive	-	-	-	3	30
Total	2322	2558	2366	2542	2825

Table 2. Number of Patients Admitted to the ICU

	2009	2010	2011	2012	2013
Number of Patients	1167	1435	1228	1412	1458

Department of Palliative Medicine

Hiroya Kinoshita, Yoshihisa Matsumoto, Kazuaki Hiraga, Yoichiro Higashi

Introduction

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

Routine activities

1. Palliative care unit

This unit is the main designated inpatient setting unit for palliative care in the Toukatu-Hokubu region. Before 2007, the registry system for admittance was adopted wherein patients were admitted in the order of their application. This system was abolished because patients with severe symptoms had to wait for a long time before being admitted. In line with this, the criteria for admitting patients were changed to ensure optimal use of limited resources and provide appropriate care to patients with severe physical symptoms and psychological problems. The waiting time for admission and the mortality rate in this unit were reduced to approximately 4 days and approximately 70%, respectively. In 2013, the total number of inpatients was more than 400 for the first time since the hospital's opening.

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

2. Outpatient clinic

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

3. Supportive care team

To deal with the various levels of suffereing of the inpatients and their families, the Department participates with the Supportive Care Team through an interdisciplinary approach.

Research activities

The Department is actively studying a regional model of palliative care. The construction of a regional palliative care model prepared for large scale disasters and the information sharing with home clinic physicians via information and communication technology (ICT) are ongoing in the Department. In addition, the Department participates in the Outreach Palliative care Trial of Integrated regional Model (OPTIM), which is an intervention study for the purpose of dispersing palliative care in four typical regions in Japan..

The Department is studying a feasibility study on early specialty palliative care.

Table 1. New referrals to the outpatient clinic (n=360, January - December 2013)

		N (%)
Age	Mean±SD (median, range) (yr)	68.4±10.8 (70, 23-92)
Gender	(male/female)	188/172
Survivors or receiving anticancer therapy		77 (21.4)
Cancer site	Lung	100 (27.8)
	Breast	43 (11.9)
	Pancreas	38 (10.6)
	Colorectal	32 (8.9)
	Head and Neck	30 (8.3)
	Kidney/Bladder	23 (6.4)
	Stomach	19 (5.3)
	Others	75 (20.8)

Table 2. Admission to the palliative care unit (n=409, January - December 2013)

		N (%)
Age	Mean±SD (median, range) (yr)	66.6±11.3 (68, 20-92)
Gender	(male/female)	235/174
Cancer site	Lung	129 (31.5)
	Pancreas	52 (12.7)
	Colorectal	37 (9.0)
	Breast	32 (7.8)
	Stomach	27 (6.6)
	Head and Neck	26 (6.4)
	Kidny/Bladder	24 (5.9)
	Others	82 (20.0)
Wating time for admission	Mean±SD (median, range) (days)	4.1±5.2 (2, 0-25)

List of papers published in 2013
Journal

1. Asai M, Akizuki N, Fujimori M, Shimizu K, Ogawa A, Matsui Y, Akechi T, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Impaired mental health among the bereaved spouses of cancer patients. Psychooncology, 22:995-1001, 2013
2. Morita T, Sato K, Miyashita M, Akiyama M, Kato M, Kawagoe S, Kinoshita H, Shirahige Y, Yamakawa S, Yamada M, Eguchi K. Exploring the perceived changes and the reasons why expected outcomes were not obtained in individual levels in a successful regional palliative care intervention trial: an analysis for interpretations. Support Care Cancer, 21:3393-3402, 2013

Department of Psycho-Oncology Service

Asao Ogawa, Daisuke Fujisawa, Kensuke Higa, Junko Ueda, Harumi Koga, Natsuki Hori

Introduction

The Psycho-Oncology Division (Psycho-Oncology Service), established in July 1996, aims to manage and alleviate emotional distress of cancer patients, their families and the caring staff. The division, adjunctive to the Psycho-oncology Division of the Research Center for Innovative Oncology, also aims to study the influence of psychosocial issues upon the 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 1 psychiatry resident. The clinical activities include psychiatric consultation, involving comprehensive assessment and addressing of psychiatric problems of cancer patients. The patients are either self-referred or referred by their oncologists in charge. The consultation data are shown in the Table. Psychiatric diagnosis is based on the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria. Consultation data also imclude individuals who are family members of cancer patients.

A conference with the Supportive Care Team is held on Wednesdays, and a multicenter joint clinical teleconference involving 6 cancer center hospitals and 3 university hospitals is held on Thursdays. In August 2008, the Comprehensive Support Center for Cancer Patients and Families was developed outside the hospital as a part of the regional palliative care project.

Table 1. Psychiatric consultation data (n=1020; January-December, 2013)

Section		N (%)
Age	Mean ± SD (median, range) (yr)	64.9±13.2 (68, 15-93)
Gender	(male/female)	621 (60.9%) / 399 (39.1%)
Inpatient / Outpatient		694 (68.0%) / 326 (32.0%)
Cancer patient / Family member		991 (97.1%) / 26 (2.5%)
Cancer site	Lung	183 (17.9%)
	Head and Neck	173 (16.9%)
	esophagus	109 (10.3%)
Stage	I/II/III/IV/Recurrent	84 (8.4%) /75 (7.5%) /131 (13.2%) /405 (40.9%) /149 (15.0%)
PS	0/1, 2/3, 4	260 (25.5%) /520(50.9%)/536(52.5%)
Psychiatric diagnosis	Delirium	335 (32.8%)
	Adjustment disorders	81 (7.9%)
	Major depression	29 (2.8%)
	Dementia	58 (5.7%)
	No diagnosis	229 (22.5%)

List of papers published in 2013
Journal

1. Kondo K, Fujimori M, Shirai Y, Yamada Y, Ogawa A, Hizawa N, Uchitomi Y. Characteristics associated with empathic behavior in Japanese oncologists. Patient Educ Couns, 93:350-353, 2013
2. Asai M, Akizuki N, Fujimori M, Shimizu K, Ogawa A, Matsui Y, Akechi T, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Impaired mental health among the bereaved spouses of cancer patients. Psychooncology, 22:995-1001, 2013
3. Fujisawa D, Suzuki Y, Kato TA, Hashimoto N, Sato R, Aoyama-Uehara K, Fukasawa M, Tomita M, Watanabe K, Kashima H, Otsuka K. Suicide intervention skills among Japanese medical residents. Acad Psychiatry. 37:402-7, 2013
4. Umene-Nakano W, Kato TA, Kikuchi S, Tateno M, Fujisawa D, Hoshuyama T, Nakamura J. Nationwide survey of work environment, work-life balance and burnout among psychiatrists in Japan. PLoS One, 8:e55189, 2013
5. Deno M, Miyashita M, Fujisawa D, Nakajima S, Ito M. The influence of alexithymia on psychological distress with regard to the seriousness of complicated grief and the time since bereavement in the Japanese general population. J Affect Disord, 149:202-208, 2013
6. Miyajima K, Fujisawa D, Hashiguchi S, Shirahase J, Mimura M, Kashima H, Takeda J. Symptoms overlooked in hospitalized cancer patients: Impact of concurrent symptoms on overlooked by nurses. Palliat Support Care, 19:1-6, 2013

Supportive Care Team

Hiroya Kinoshita, Asao Ogawa, Daisuke Fujisawa, Yoshihisa Matsumoto, Hiroyuki Takei, Yoichiro Higashi, Tomofumi Miura, Kensuke Higa, Yasuhiro Hirano, Junko Ueda, Harumi Koga, Natsuki Hori, Chiyuki Sasaki, Kumi Nakamura, Shinya Motonaga, Asuka Iwamoto, Kanae Sato, Aya Matsumaru, Hatoe Sakamoto

Introduction

The Supportive Care Team (SCT), established in October 2005, primarily aims to improve care for cancer patients and families facing a life-threatening illness. The role of the SCT is to implement comprehensive cancer care by assessing unrelieved symptoms (physical and psychiatric) and unattended needs, as well as efficiently managing physical symptoms, providing psychological support, and coordinating services.

Routine activities

The SCT is an interdisciplinary team composed of palliative care physicians, psycho-oncologists, certified nurse specialists, certified nurses, clinical psychologists, pharmacy practitioners, registered dietitians and social workers. The SCT keeps regular contact with clinician-teams in charge, discusses patients' needs, and refers patients and families to the appropriate services. Interdisciplinary team conferences and SCT rounds are held on Wednesdays. The SCT consultation data are shown in the table.

Research activities and Clinical trials

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

Table 1. Supportive Care Team consultation data (n = 869; January-December, 2013)

		N (%)
Age	Mean ± SD (range) (yr)	65.1 ± 13.1
Gender	(male/female)	587 (67.5%) / 282 (32.5%)
Service	Palliative care/ Psycho-oncology	175 / 694
Cancer site	Lung	200 (23%)
	Head and Neck	129 (15%)
	Esophagus	98(11%)
	Pancreas	82(9%)
	Stomach	70 (8%)
Stage	I / II / III / IV	61 (7%) / 49 (6%) / 97 (11%) / 426 (49%)
	/ recurrence / unknown / others	/ 156 (18%) / 45 (5%) / 1 (0%)
Performance status	0/ 1/ 2/ 3/ 4	108 (12%) / 173 (20%) / 245 (28%) / 236 (27%) / 107 (12%)
Physical symptoms	Pain	433 (50%)
(moderate - severe)	Appetite loss	347 (40%)
	Fatigue	376 (43%)
	Respiratory distress	225 (26%)
Psychiatric diagnosis	Delirium	310 (36%)
(primary diagnosis)	Adjustment disorders	17 (2%)
	Dementia	34 (4%)
	Major Depressive Disorder	9 (1%)
Outcome	Discharge/ Hospital transfer	607 (65%) / 55 (6%)

List of papers published in 2013
Journal

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

Department of Diagnostic Radiology

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

Introduction

The Diagnostic Radiology Division is committed to improving health through excellence in image-oriented patient care and research. Our Division performs more than 84,000 inpatient and outpatient procedures annually. The Division also conducts clinical scientific research as well as basic scientific studies, with the results translated directly into better patient care.

Routine activities

Our division has four multi-slice CT scanners, including one area detector CT scanner and one Dual Source CT, two MRI systems (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 ^{18}F-FDG (fluorodeoxyglucose) has been performed. These all-digital image systems enhance the efficacy of routine examinations.

This division has 7 consulting radiologists and 35 technologists. As part of our routine activities, every effort is made to produce an integrated report covering almost all examinations, such as MMG, contrast radiologica1 procedures, CT, MRI, RI, PET, angiography and IVR, mainly transarterial chemo-embolization (TACE).

The number of cases examined in 2013 is shown in the Table below.

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

Table 1. Number of Cases Examined

	2009	2010	2011	2012	2013
Plain X-ray examination	33,841	34,330	35,032	39,128	38,722
Mammography (MMG)	2,388	2,595	2,434	2,380	2,354
Fluoroscopic Imaging (GI-series, etc.)	3,781	3,478	3,903	4,029	4,628
CT	19,543	21,128	21,967	24,101	28,963
MRI	5,723	5,830	5,708	5,619	5,657
RI	1,718	1,676	1,582	1,586	1,363
PET	1,670	2,048	2,239	2,284	2,208
Angiography	711	728	656	742	511
Total	69,375	71,813	73,521	79,869	84,406

Research activities and Clinical trials

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

(1) Development of new Nuclear Medicine tracers

Small interfering RNAs (siRNAs) were discovered as a promising gene silencing tool in research and in the clinic, and we succeeded in radiolabeling siRNAs. Briefly, The 3'-end of double strand 21-nucleotide oligoribonucleotides 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 gene-silencing ability of the siRNA did not change after radiolabeling.

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

(2) Development of new CT technology

Diagnostic imaging is an area gathered for Advanced Science and Technology. The advances of CT/MRI are particularly remarkable, such as a 320-row area-detector CT, Dual-energy CT and 3-Tesla MR images. The accurate evaluation of tumor invasion is essential for deciding upon appropriate treatment strategies for cancer. In dual-energy CT (DECT), two data sets acquired with different tube voltages can be fused to generate weighted-average CT images that have a similar image impression to conventional CT images obtained at 120 kV, in addition to generating images of the distribution of iodinated contrast medium alone. For these applications, the material-specific X-ray energy dependence of the absorption coefficient is used in image postprocessing to mathematically extract iodine and separately calculate color-coded iodine images and virtual non-contrast images. 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 decrease the overestimation of laryngeal cartilage invasion. This is particularly important for treatment strategy decisions, especially when function-preserving therapy is being considered.

(3) Construction of a cancer image reference database

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

List of papers published in 2013

Journal

1. Kuno H, Fujii S. A case of adenoid cystic carcinoma arising from the nasopharynx. Jpn J Clin Oncol, 43:942, 2013
2. Ikeda M, Okusaka T, Furuse J, Mitsunaga S, Ueno H, Yamaura H, Inaba Y, Takeuchi Y, Satake M, Arai Y. A multi-institutional phase II trial of hepatic arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Cancer Chemother Pharmacol, 72:463-470, 2013

Department of Radiation Oncology

Tetsuo Akimoto, 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 retain the severity of radiation-related complications within acceptable levels.

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

Routine activities

At present, the staff of the Radiation Oncology Division consists of 7 consultant physicians (radiation oncologists), 15 radiation technologists, 3 medical physicists, 1 nurse, and 1 clerk. We have more than 1000 new cases for conventional RT and 2000 new patients for proton beam therapy every year, and the quality assurances of both conventional RT and PBT is 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 the precise radiation dose to the targeted tumors. Respiratory-gating has been applied especially in radiotherapeutic management for patients with lung, esophagus and liver cancers.

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

The section is responsible for conventional (photon-electron) RT with equipment consisting of 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 with 6 operating staff members and 1 technician for fabricating the compensator and aperture; they are sent from the system manufacturers and work in collaboration with the other staff members of the Division. The PBT system is housed in 2 treatment rooms and both rooms are routinely used for rotational gantry treatment. The Division ensures quality assurance and regular maintenance of the PBT machines for precise dose delivery and safe treatment.

Research activities

In the Radiation Oncology Division, the following research activities are 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.
2) Establishment of the clinical usefulness of IMRT for head and neck cancer and localized prostate cancer.
3) Hypofractionated IMRT for localized prostate cancer.
4) Hypofractionated PBT for localized prostate cancer.
5) Evaluation of the feasibility of PBT combined with chemotherapy for inoperable locally advanced non-small cell lung cancer and locally advanced esophageal cancer.
6) Evaluation of long-term complications after PBT for pediatric malignancies.
7) The role of gene polymorphism in the development of acute and late radiation-related complications.

8) Exploration of biomarkers for head and neck cancer.

Clinical trials

The following in-house and multi-institutional clinical trails 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 the 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) A phase II study of PBT for malignant melanoma of the nasal cavity.
5) A phase II trial of concurrent chemoradiotherapy with 5-FU plus cisplatin for resectable squamous cell carcinoma of the cervical esophagus.
6) A JROSG phase II trial of IMRT with concurrent chemoradiotherapy for resectable squamous cell carcinoma of the cervical esophagus.

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

Number of patients treated with radiotherapy during 2008-2012

	2008	2009	2010	2011	2012
New patients	1084	1230	1248	1305	1470
Head and neck cancers	211	281	220	223	183
Lung and mediastinal cancers	220	230	280	329	413
Breast cancers	264	281	283	325	362
Gastrointestinal cancers	203	202	219	176	188
Hepatobiliary tract cancers	47	46	54	38	69
Urological cancers	89	120	151	174	151
Bone and soft tissue cancers	8	6	15	2	10
Hematological cancers	33	27	6	19	24
Others	9	35	20	19	70

List of papers published in 2013
Journal

1. Kawashima M, Ariji T, Kameoka S, Ueda T, Kohno R, Nishio T, Arahira S, Motegi A, Zenda S, Akimoto T, Tahara M, Hayashi R. Locoregional control after intensity-modulated radiotherapy for nasopharyngeal carcinoma with an anatomy-based target definition. Jpn J Clin Oncol, 43:1218-1225, 2013
2. Matsubara K, Kohno R, Nishioka S, Shibuya T, Ariji T, Akimoto T, Saitoh H. Experimental evaluation of actual delivered dose using mega-voltage cone-beam CT and direct point dose measurement. Med Dosim, 38:153-159, 2013
3. Kiyozuka M, Akimoto T, Fukutome M, Motegi A, Mitsuhashi N. Radiation-induced dimer formation of EGFR: implications for the radiosensitizing effect of cetuximab. Anticancer Res, 33:4337-4346, 2013
4. Okano S, Yoshino T, Fujii M, Onozawa Y, Kodaira T, Fujii H, Akimoto T, Ishikura S, Oguchi M, Zenda S, de Blas B, Tahara M, Beier F. Phase II study of cetuximab plus concomitant boost radiotherapy in Japanese patients with locally advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol, 43:476-482, 2013
5. Sugimoto M, Gotohda N, Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Kojima M, Ochiai A, Zenda S, Akimoto T, Konishi M. Pancreatic resection for metastatic melanoma originating from the nasal cavity: a case report and literature review. Anticancer Res, 33:567-573, 2013

Department of Pathology and Clinical Laboratories

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

Introduction

The Department of Pathology and Clinical Laboratories (DPCL) is composed of two divisions; the Pathology Division (PD) and the Clinical Laboratory Division (CLD). Both divisions play a fundamental role in routine hospital service and support research activities at National Cancer Center Hospital East (NCCHE). In 2013, the CLD received ISO15189 accreditation ensuring the quality control of the laboratory tests performed in the department.

Seven pathologists, including 6 pathologists board-certified by the Japanese Society of Pathology are assigned to the PD. Also working in the Division are 6 clinical laboratory technicians. Two doctors and 3 technicians are cytology experts and cytoscreeners, respectively, board-certified by The Japanese Society of Clinical Cytology.

The CLD consists of 6 subsections for i) general laboratory medicine, ii) hematology, iii) biochemistry/serology, iv) Physiology, v) Bacteriology and vi) blood transfusion. A total of 13 full-time clinical laboratory technicians and 1 secretary are working at the CLD. From April in 2013, under the contract between the NCCHE and SRL, the role of three subsections (general laboratory medicine, hematology and biochemistry/serology) has been undertaken by an intramural referee laboratory, where 8 clinical technicians are working.

Routine activities

Primarily, the routine activities of the PD comprise surgical pathology. In 2013, 9168 biopsy specimens, including 852 frozen sections, and 2358 surgical specimens, were examined and pathologically diagnosed (see Table 1 for details). Three thousand nine hundred and thirty eight (3938) cytology specimens were evaluated (Table 2). Four autopsies were performed, and all cases were presented and discussed in clinicopathological conferences. Conference-style training sessions are open every Thursday morning for the residents.

The CLD provides accurate and reliable data to understand the patients' conditions and support prompt decision making for all clinicians working at the NCCHE (see Table 3 for details). The most of essential laboratory test services are available on a round-the-clock basis. Most of the general laboratory tests for hematology, biochemistry, serology and urinalysis were automatically performed by an automated analyzer, which enable the division to provide the results within one hour after samples submission. A special computer-based ordering system is equipped for ensuring sample-processing and data-transfer to and from outside commercial laboratories.

Research activities

All of the pathologists were involved in research activities at RCIO. All the technicians working in the Department are also highly motivated to develop advanced diagnostic technology and some results have been presented in several meetings including the one organized by the Japanese Society of Laboratory Medicine.

Clinical trials

The CLD participated practically in almost all of the clinical trials carried out at the NCCHE through the provision of laboratory data.

Table 1. Number of pathology samples examined at Pathology Division in 2013

Department	Biopsy	Surgical	Autopsy
Digestive Endoscopy	3828	0	0
Gastrointestinal Oncology	1083	2	0
Breast Surgery	652	330	0
Head and Neck Surgery	595	365	0
Thoracic Surgery	547	472	0
Thoracic Oncology	490	3	1
Hematology and medical oncology	481	4	1
Hepatobiliary and Pancreatic Oncology	372	1	2
Urology	241	82	0
Upper Abdominal Surgery	221	493	0
Radiation Oncology	204	0	0
Lower Abdominal Surgery	168	358	0
Orthopedics	90	36	0
Ambulant Treatment Center	80	9	0
Esophageal Surgery	39	186	0
Head and Neck Oncology	32	0	0
Obstetrics and Gynecology	16	0	0
Dental division	10	0	0
Anesthesiology	8	0	0
Dermatology	6	0	0
Plastic Surgery	3	16	0
Others	2	1	0
Total	9,168	2,358	4

Table 2. Number of cytology samples examined at the Pathology Division in 2013

Department	
Urology	835
Thoracic Oncology	793
Thoracic Surgery	706
Head and Neck Surgery	395
Hepatobiliary and Pancreatic Oncology	338
Upper Abdominal Surgery	247
Obstetrics and Gynecology	216
Hematology and medical oncology	131
Breast Surgery	115
Lower Abdominal Surgery	71
Gastrointestinal Oncology	41
Orthopedics	10
Head and Neck Oncology	10
Esophageal Surgery	8
Digestive Endoscopy	4
Ambulant Treatment Center	3
Radiation Oncology	2
Dermatology	1
Plastic Surgery	1
Others	11
Total	3,938

Table 3. Number of laboratory tests examined at the Clinical Laboratory Division in 2009-2013

Section	2009	2010	2011	2012	2013
General laboratory medicine	230,610	265,517	264,452	282,716	306,136
Hematology	560,110	589,144	622,666	676,889	712,962
Biochemistry	1,493,858	1,569,963	1,648,755	1,811,244	1,834,169
Serology	136,127	139,759	146,104	141,224	175,102
Bacteriology	22,466	21,978	21,657	25,112	26,870
Blood transfusion	24,181	22,441	21,895	20,550	19,853
Physiology	39,232	43,215	43,275	45,408	45,555
Total	2,506,584	2,652,017	2,768,804	3,003,143	3,120,647

Clinical Trial Coordination (& Support) Office

Toshihiko Doi, Miyuki Hara, Yumiko Uchiyama

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 mission of the Clinical trials management office (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 40 staff members support the CTMO:12 Clinical Research Coordinators(CRCs) (9 nurses and 3 pharmacists), 7 data managers, 6 medical technologists, and 15 secretaries.

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 personnels 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 164 registration-directed clinical trials including 21 phase1 trials in 2013 (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 pre-clinical and clinical development of investigational anti-cancer agents.

Table 1. Supported Trials in Clinical Trial Coordination (& Support) Office in 2013

Phase	New (since 2013)	Ongoing
I	21	56
I/II	4	8
II	17	38
II/III	0	1
III	19	61
POS	0	3
Total	61	164

POS: post marketing study

Consultation, Counseling and Support Service Center

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Introduction

Our Center staff members form "Cancer Counseling and Support Specialists". We provide psycho-social and spiritual support for cancer patients, families and caregivers with various anxieties and burdens during their course of illness. In our Division, Cancer counseling and support specialists deliver the various forms of support though the following four services: 1) counseling services; 2) coordination of community resources; 3) managing support group; and 4) information service.

Patients and Families Care Coordination

1. Patients and families counseling
   - Counseling Services face-to-face and telephone counseling
     In 2013, we received 4782 new consultations (Table 1). As for the patient's condition in the case of new consultations, an increasing numbers of patients have either not yet received initial treatment or are in the stage of receiving anti-cancer therapy (Table 2). Our services are available to patients and families throughout all phases of the caner continuum, including prevention, diagnosis, survivorship, terminal care, and bereavement.

2. Support group
   - Pancreatic Cancer Support Group
     This support group focuses on various pancreatic cancer-related topics including education, emotional support and pancreatic cancer treatments. This support group was held 7 times in 2013, with a total of 49 participants.

3. Community healthcare coordination

In the coordination function, cancer counseling and support specialists provide discharge planning and case management, linking patients with a variety of services necessary to meet each person's multiple needs.

During 2013, we had 3156 cases of community resources coordination. Other coordination-related events were as follows:

- Official Publication of *Kokuganhigashi News*
  This publication aims to provide information about our center and to gather new patients from other hospitals. We have published "*Kokuganhigashi News*" 4 times from January 2013 to December 2013. The publications were sent to 1800 hospitals in Japan.

- Meetings for regional collaboration
  The meetings were held twice in the year with a total of 288 participants.

- Medical pathway
  We developed a medical pathway to collaboration with the regional Tujinaka hospital, which resulted in increasing the numbers of patient referrals. As an example of collaboration, the doctors in our hospital worked at Tujinaka Hospital.

Training and Education of Cancer Counseling and Support Specialists

- Training Sessions for Cancer Consultation Worker in Chiba
  With the theme "Support for cancer patient employment", two training sessions were held in 2013 for Cancer counseling and support specialists. Cancer counseling and support specialists from 20 hospitals attended the sessions.

Table 1. Numbers of cases

	2010	2011	2012	2013
Total	8091	8604	9412	11940
New cases	4260	4700	4760	4782
The contents of consultation (New cases)				
Finding community resources	2032	2250	2475	2796
Coping with life changes	857	1046	990	588
Adjustment to diagnosis and treatment	547	570	499	525
Family counseling	148	124	85	57
Spiritual or religious concerns	60	36	38	27
Other	616	674	673	386

Table 2. New consultation data (N=4782, January_December,2013)

		N	%
Age	Mean±SD (median, range)	62.7±12.3(1-94)	
Inpatient/Outpatient	Inpatient	3518	73.6%
	Outpatient	1135	23.7%
	Other	129	2.7%
Cancer Site	Lung	969	20.3%
	Head and Neck	508	10.6%
	Colon	485	10.1%
	Stomach	347	7.3%
	Pancreas	335	7.0%
	Esophagus	329	6.9%
	Brest	287	6.0%
	HCC	210	4.4%
	Other	1312	27.1%
Treatment Profile	No diagnosis	80	1.7%
	Before first time cancer treatment	936	19.6%
	Receiving anti-cancer therapy	1302	27.2%
	Post-treatment/Monitored	814	17.0%
	No anti-cancer therapy (palliative care)	1327	27.8%
	Deaths (Bereaved family)	10	0.2%
	Other	312	6.5%

Health Information Management Office

Hiroshi Nishimoto, Tokiko Inagaki, Chie Ogura, Maiko Miura, Yayoi Otsuka

Introduction

The Health Information Management Office was established in April, 2011. We have established the following processes, the Audit of Discharge Summary, and the National Cancer Center Hospital (NCCH) Cancer Registry which is executed as a hospital-based cancer registry. Some statistical duties for the NCCH-East (NCCHE) and Prognostic Investigation were taken over by the Medical Affairs Office, but since the main initiatives of the NCCHE are activities against cancer, we will expand our role as the major statistics office of the NCCHE.

Routine Activities

Auditing Discharge Summary (Quantitative inspection)

Data on discharge summaries should be entered by the attending physician. We inspected and checked about 7,000 summaries and, where required, gave some advice regarding correct input.

NCCH Cancer Registry (Hospital-based Cancer Registry)

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

Table 1. NCCHE Cancer Registry

Year of Diagnosis	Numbers of New Cancer Cases		
	Total	Male	Female
2009	4,613	3,029	1,584
2010	4,679	3,053	1,626
2011	4,878	3,145	1,733
2012	5,184	3,435	1,749

Department of Pharmacy

Shinichiro Saito, Kunio Takahashi, Yasuhiko Ichida, Reiko Matsui, Sonoko Kobayashi, Hisanaga Nomura, Akihito Kibune, Yasuaki Ryushima, 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

Introduction

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

Our residents' training program started in 2006. In 2013, 9 residents joined our department. Presently, we have a total of 19 residents. In addition, our department has accepted 6 trainees from other institutions for our oncology pharmacist training programs. Through 2013, 3 terms of the training courses, we have educated 14 pharmacy students and 3 advanced-training pharmacy students.

The Department of Pharmacy provides various important services: controlling inventory; dispensing medications; preparing i.v. solutions for chemotherapy, which include the aseptic mixing of antineoplastic agents; collecting and providing drug information; managing therapeutic drug monitoring; checking treatment regimens for each patient's chemotherapy; and providing pharmaceutical management and counseling.

Our department reviews the drugs taken by patients before and during their hospitalization. In inpatient care, the department assigns pharmacists to provide medication counseling and drug information for healthcare providers and patients, to pursue effective pharmaceutical care. In outpatient care, the department provides a pharmacy outpatient service in which pharmacists check patients for adverse reactions and doses of antineoplastic agents, especially in the case of oral anticancer medications. We then assess the necessity of supportive-care medications and suggest them to physicians. The pharmacy outpatient service also reviews the drugs taken by all patients to evaluate when patients have to stop their anticoagulants before their operation or when they have to stop to take metformin before examinations with iodinated-contrast material. Pharmacists are on duty at the Outpatient Chemotherapy Center as dedicated staff members. The pharmacists provide a Chemotherapy Hotline Service, which is a direct line for our outpatients who have any problems concerning their chemotherapy treatment. In the Outpatient Chemotherapy Center, pharmacists are always available to provide drug information for healthcare providers and patients. We also manage investigational drugs.

New developments

Over the years, the services of our Department of Pharmacy have been under continuous expansion and development. We used to place pharmacists in 3 wards only. Finally our department has successfully assigned pharmacists as dedicated staff members to all wards (10 wards including the surgical unit) on a full time basis since May 2013. These dedicated pharmacists have evaluated high-risk medications, drug interactions, and drug compatibilities. They also have monitored prescriptions and suggested medications through medical conferences or by attending multi-disciplinary team rounds. At the surgical unit, in addition to the above work, we have perfectly controlled the whole medication inventory that includes narcotic drugs and muscle relaxants.

Table 1. Pharmacy Achievement

	2010	2011	2012	2013
Number of Prescriptions				
Prepared in hospital pharmacy				
Total	84,492	86,643	90,392	97,444
Inpatients	78,327	80,837	84,800	91,549
Outpatients	6,165	5,806	5,592	5,895
Taken to outside pharmacies	50,731	55,826	59,722	64,123
(% of prescription filled outside)	(89.2%)	(90.6%)	(91.4%)	(91.6%)
Injections				
Total	157,958	159,730	160,105	158,557
Inpatients	132,407	132,969	126,428	125,106
Outpatients	25,551	26,761	33,677	33,451
Number of Prescriptions				
(Investigational new Drugs)	4,435	4,676	4,584	5,110
Aseptic Preparation of Injection Mixture				
Anticancer drugs	32,007	35,386	38,663	42,735
Others	4,689	3,320	3,994	4,204
Number of medication counseling (for inpatients)				
Patients	5,063	5,067	6,418	7,248
counselings which earned the counseling fee	6,522	6,645	7,139	5,005
Number of medication counseling (for outpatients)				
in the Outpatient Chemotherapy Center	5,705	6,701	8,965	10,073
in the pharmacy outpatient service	479	738	1,782	2,375
in the ‘Nexavar’ outpatient service	416	583	381	202
Number of calls on the Chemotherapy Hotline	980	1,468	1,665	2,087
Number of checking home medications	5,422	5,364	6,017	6,506
Number of insurance-reimbursement claims for dedicated clinical-pharmacist services				8,094

Department of Nursing

Chie Asanuma

Introduction

The Department of Nursing has been promoting several actions for team healthcare not only through the activities of the Department of Nursing, but also through collaboration with doctors, pharmacists, *etc*., in order to improve and to maintain the quality of medical cares for out-patients and in-patients the number of whom has been increasing on an annual basis.

In a consensus of the hospital, the chief nurse has been authorized to control the bed for hospitalization, which establishes a hospitalization management system in cooperation with the doctor and it contributes to improvement of annual bed occupancy rate. We promoted the effective management of the hospital ward with collaboration between the ward and related sections, and we integrated two nursing units (5A and 5B) into one unit with a chief nurse in order to equalize Nursing services, to correct the gap between quantity and content of work in the ward, and to allow the effective performance of ward activities.

We plan to open the Supportive Care Center, in collaboration with relevant departments, which will provide patients with the continuous services of mental, psychical, and social support through the environmental changes experienced by patients from the out-patient and in-patient settings to home medical care. Additionally, a full-time chief nurse has been allocated in order to collect information, to develop the organization framework, to strengthen of support for patient discharge and partnership with home visit nursing stations.

A Delirium Care program has been started in order to provide early intervention in the development and prevention of delirium in collaboration with the Department of Psycho-Oncology, nurses and relatives, and it provides screening for all hospitalized patients, enables extraction of high-risk patients, and provides unification of treatment orders and appropriate practice for patients with delirium.

We have been authorized as an institution providing educational courses towards nurse certification by the Japan Nursing Association in order to promote palliative care for the development of the quality of life (QOL) of patients and to encourage human resources development for improvement of the quality of nursing, and in June, an educational course for certification of palliative care nurses was opened with 12 participants. In addition, the role of the certified expert nurse course in the hospital for intravenous anticancer drug delivery was described and the training framework was established.

We set these following goals for our activities in 2013 based on the policy of the national Cancer Center (NCC)

1. To secure human resources for safety care services and patient satisfaction.
2. To collaborate with the relevant of outpatient and inpatient sections to offer seamless palliative care.
3. To enhance the study of Nursing for the improvement of the quality of Nursing, ability in Nursing practice.
4. To get accreditation from the JCQHC (Japan Council for Quality Health Care) for improvement of health care.
5. To take part in the hospital's administration in order to implement strategic hospital management.
6. To manage the educational course for certification of the palliative care nurse

Routine Activities

In 2013, of the current 349 nurses, 35 were newly employed. The average number of outpatients per day was 933.5, while that of inpatients was 370.6. The average hospitalization term was 13.8 days. The number of chemotherapy treatments in The Medical Treatment Center per day was 104.4. We provided educational services for patients undergoing chemotherapy on how to deal with the side effects, and also provided telephone-follow-up servicers and hot-line-telephone services to solve patient problems and relieve anxiety once they had returned home. The number of operations conducted was 2,829 and the average of per day was 11.6.The Division aims to improve nurse education to provide proper quality nursing services. Four courses have been initiated (1) an introductory course for new employees; (2) a practical course; (3) a specialized cancer nursing course; and (4) a "power up" course, and we prepared the post of head nurse in charge of nursing education to help nurses to study and to to support their mental health.

There are 6 expert nurses,1 psychiatric mental health nurse and 24 certified expert nurses specializing in wound ostomy care (3), cancer pain (6), cancer chemotherapy (6), palliative care (1), infection control (2), breast care (2), swallowing and eating (2) and

radiation (2). They are in charge of the specialized cancer nursing course education programs. We have subsequently accepted trainees participating in the expert nurse course and certified expert nurse course. As for nursing-related research projects, not only expert nurses and certified nurses, but also registered nurses in our hospital have both participated and attended external training programs. We gave 24 presentations at academic conferences in 2013.

Table 1. The number of trainee (< 1 week)

	2008	2009	2010	2011	2012	2013
Postgraduate Nurse	8	6	14	6	5	5
Certified Expert	12	13	12	17	25	11
Total	20	19	26	23	28	16
Nursing student	208	172	156	141	139	154

Preface

The Research Center for Innovative Oncology (RCIO) was originally funded as a branch of the Research Institute in 1994 at the Kashiwa campus. For the purpose of focusing more on translational researches (TR) and mutual collaborations between basic and clinical researchers, the National Cancer Center (NCC) Kashiwa campus was reorganized Under which the RCIO belonged to the NCC Hospital East (NCCE) in 2005. With the launch of the Exploratory Oncology Research & Clinical Trial Center (EPOC), some divisions in the RCIO were incorporated into EPOC. A large number of studies in collaboration with the NCCE EPOC, and the Research Institute have been conducted for TR and support for hospital services.

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, which are now being optimized for preclinical study and will be incorporated into clinical study within a few years. They will participate 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 the Pathology Division, the investigators play a central role in various types of TR and standardized a procedure in pathological sample analysis. With many collaboration studies with the EPOC and commercial companies to establish companion diagnosis, they are acting as the central pathology diagnostic function in an international randomized control trial. Various TRs are also on-going in collaboration with the EPOC TR division. Large amounts of 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. With a grant support from Japan Science and Technology Agency (JST), they are investigating new predictive markers for an anti-EGFR antibody using a large number of samples from the collaborative institutions.

In 2012, our hospital was also selected as "a designated center for new endoscopic instrument development" by the Ministry of Health, Labour and welfare (MHLW) 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. They conducted a first in human clinical trial of hypoxia imaging 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 models. Furthermore, a clinical trial for biodegradable (BD) stent implantation for benign esophageal strictures after curative treatment, and a clinical trial for photodynamic diagnosis using 5ALA have been started. A new generation surgical device/technique development (NEXT) project is also being planned to establish 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 these fields. In the Particle Therapy Division, the investigators 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 the patients who received proton-beam irradiation has been rapidly increasing in recent years and multi-institutional clinical trials with proton beam radiation will start soon. 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. A supportive care center with the collaboration of psycho-oncology, palliative care, nursing, pharmacy, and social worker divisions has also been organized for a variety of patient support systems. With these activities, we eagerly aim to establish a world-leading innovative cancer center with the best amenities for cancer patients.

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Division of Pathology

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Introduction

The contribution of the members of the Division of Pathology to both the Research Center for Innovative Oncology (RCIO) and the National Cancer Center Hospital East [NCCH-E] comprises 4 major activities: 1) Pathological diagnoses for the NCCH-E; 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 diagnoses for NCCH-E with the collaboration of the staff pathologists of the Department of Pathology and Clinical Laboratories of 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 research activities of the Division of Pathology currently focus on the application of the morphological study of cancer tissue to the clinical course of the patient. These activities aim I) to elucidate new biological roles for cancer epigenetics and cancer-stromal interaction; II) to develop a new cancer diagnosis and treatment strategy (Preclinical study); and III) to design and perform experimental and clinicopathological studies on cancer. Prognostic factors and clinicopathological characteristics of various cancers have also been investigated in collaboration with the NCCH-E Diagnostic Pathology Section and other institutions. I) To elucidate new biological roles for cancer epigenetics and cancer-stromal interaction: in addition to adenocarcinoma of the lung, podoplanin (PDPN) expressing cancer associated fibroblasts (CAFs) correlated with a poor prognosis of the stage-I squamous cell carcinoma of the lung (14). II) Development of a new cancer diagnosis and treatment strategy (Preclinical study): 1) Pathological diagnosis of blood and lymphatic vessel invasion (BLI) of colon adenocarcinomas was reported to be subjective and inconsistent among pathologists. In order to create an objective pathological diagnostic system for BLI, a framework for pathological diagnostic criteria was developed by reviewing concordance and using the Delphi method. The criteria developed may serve as the basis for creating a standardized procedure for pathological diagnosis (8). 2) To characterize the impact of pro-inflammatory cytokines on the outcomes of gemcitabine monotherapy (GEM) in patients with pancreatic cancer (PC). Treatment-naive patients with advanced PC and no obvious infections were eligible for enrolment. All of the patients were scheduled to undergo systemic chemotherapy. Serum pro-inflammatory cytokines were measured using an electro-chemiluminescence assay method before chemotherapy. High IL-6 and IL-1β levels were poor prognostic factors for overall survival in a multivariate analysis (P=0.011 and P=0.048, respectively). Patients with both a high IL-6 level and a high IL-1β level exhibited shortened overall and progression-free survival, a reduction in the tumor control rate, and a high dose intensity of GEM compared with patients with low levels of both IL-6 and IL-1β (9). III) Experimental and clinicopathological studies on cancer: The histological predictive and prognostic factors for in various cancers including lung cancers (1,5,6,10,11,13,17-19,21-26), colon cancers (12,15,16,29), hepatocellular carcinoma (31), head and neck cancer (3,27,28,30,32,34) and other tumors (7,33) are also being investigated and reported in collaboration with the clinical divisions of the NCCH-E and other institutions. Other basic studies which have elucidated cancer biology have been published (2,4,20)

List of papers published in 2013
Journal

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Division of Functional Imaging

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

Introduction

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

Research activities

Tumor hypoxia imaging is important for the optimization of cancer therapy because hypoxic lesions in tumors are closely related with their resistance to radiation therapy and chemotherapy. We have been developing several hypoxia imaging probes with capacities for clinical application in nuclear medicine diagnosis. During 2013 we investigated ^{99m}Tc-labeled hypoxia imaging probes with a novel retention mechanism. By modifying their molecular structures, promising probes were synthesized and we determined that they were able to reach the tumor after intravenous injection and specifically accumulated in the tumor hypoxic lesions. We applied for a patent for a series of these compounds.

The liposome project to apply radionuclide-encapsulated liposomes for diagnostic imaging and radionuclide therapy is also ongoing. This year, we developed some new liposomes containing radionuclides and it was revealed that one of them was useful for arteriosclerosis nest imaging. In apolipoprotein E-deficient mice, the aorta was successfully visualized with SPECT imaging using ^{111}In-labeled liposomes.

Lung cancer is one of the leading causes of cancer-related deaths worldwide. Although computed tomography (CT) can detect small lung lesions such as ground glass opacity (GGO), it cannot differentiate between malignant and non-malignant lesions. ^{111}In-DOTA-c(RGDfK) could clearly visualize lung nodules, though we failed to detect small lung nodules like adenomas and hyperplasias (adenocarcinomas: 66.7%, adenoma:s 33.6%, hyperplasias: 0.0%). Histopathological examination using human lung tissue samples revealed clear up-regulation of $\alpha_v\beta_3$ integrin in well-differentiated adenocarcinomas rather than atypical adenomatous hyperplasia. SPECT with ^{111}In-DOTA-c(RGDfK) might be a useful non-invasive imaging approach for evaluating the characteristics of lung tumors.

Magnetic resonance (MR) imaging can provide anatomical images of experimental animals with high spatial resolution and high tissue contrast, however its long examination time (typically 1hr per animal) affects the efficiency of experiments when a large number of animals need to be examined. To increase the throughput, we have developed multiple-animal MR imaging techniques, constructing a dedicated radiofrequency coil to receive signals from several animals, applying a data acquisition method which is less susceptible to motion artifacts, and programming new post-processing software to promote precise interpretation of multi-animal MR images. At present, we can complete MR imaging of the liver for a group of hepatoma-bearing rats in under 10 min per rat, and can measure two important markers to determine tumor response to therapy; the tumor volume and the apparent diffusion co-efficient (ADC) levels. The latter reflects diffusion of water molecules and provides information regarding tumor cell density and membrane stability.

Delayed hepatic signal recovery on ferucarbotran-enhanced MR images is another topic. Ferucarbotran is carboxydextran-coated iron oxide and has a superparamagnetic property. After intravenous administration, ferucarbotran particles are trapped by Kupffer cells (KCs) and reduce the signal intensity of the liver. While hepatic signals are normally restored within one week as the particles are degraded to ferric iron by KCs, the recovery was delayed when we administered a compound that impaired this KC function. It is thought that hepatic signal recovery is a potential MRI marker to monitor KC function *in vivo*.

Clinical trials

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.

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Division of Science and Technology for Endoscopy and Surgery

Kazuhiro Kaneko, Masaaki Ito, Takahiro Kinoshita, Tomonori Yano, Mari Takahashi, Atsushi Yagishita

Introduction

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

One of the characteristic natures of 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 are highly absorbed in circulating hemoglobin, narrow band imaging (NBI) endoscopy may provide better images of the capillaries in the mucosal surface.

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

Routine activities

The present research activities mainly focus on the development of new instruments for endoscopic diagnosis and new endoscopic treatment modalities. Since posing a problem in the present condition is required in endoscopy-related research and development, our Division collaborates with the Endoscopy Division. Therefore, endoscopic diagnoses are routinely performed for cancer patients, and endoscopic procedures, such as EMR or ESD, are performed in patients with early GI tract cancers. We deliver lectures to resident doctors regarding individual projects. Furthermore, meetings are constantly conducted with various university faculties, including Technology and Science.

Research activities

Patient-related research studies have been conducted in various fields: endoscopic diagnosis and treatment, or cancer prevention in the GI tract and head and neck. In addition, studies are currently being performed to develop new devices or procedures in innovative and 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 university faculties of Technology and Science. of the university.

Research into developing novel endoscopy systems is being performed. Hypoxia imaging is being used to detect neoplastic lesions of the head and neck and alimentary tracts, with two types of visualized images, such as a pseudocolor StO_2 image overlaid with an StO_2 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 has been planned for this year. With a low-temperature atmospheric pressure plasmas system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnostic system using photosensitizing agents, such as hypericin, has been constructed. A novel tattooing system under endoscopy has been developed, and a patent is currently being applied for. Ongoing projects are to develop needle graspers, and a needle ultrasonic coagulator in the surgical field. A clinical trial regarding confocal laser endocytoscopy using fluorescein has been planned and has been classified into a new category.

Clinical trials

A first in human clinical trial of hypoxia imaging was finished on the endoscopic diagnosis of neoplasia of the esophagus, stomach, and colorectum. We conducted a proof-of-the-concept trial for 40 patients with neoplastic lesions in the esophagus including the pharynx, stomach and colorectum. In this first in human trial (UMIN 000004983), two types of StO_2 images were used. One was a pseudocolor StO_2 image that showed StO_2 levels as different hues, and the other was a StO_2 overlay image that overlapped StO_2 levels in blue on a white light illumination image to detect background mucosa. A system has been developed using near-infrared light with nanoparticles which act as fluorescent agents. Nanoparticles in a probe attach themselves to the surface of cancer cells and fluoresce when activated with near-infrared light, which can penetrate through target organ walls. Molecular imaging endoscopy for the use of this system with an InGaAs CCD is currently in development in collaboration with a university Faculty of Technology. Preclinical animal model studies are under way, such as a low-temperature atmospheric pressure plasma system and photodynamic diagnosis with hypericin. Furthermore, clinical trials are ongoing on biodegradable (BD) stent implantation for benign esophageal stricture after curative treatment, and on photodynamic diagnosis (PDD) using aminolevulinic acid (5-ALA).

List of papers published in 2013
Journal

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3. Kaneko K, Yano T, Minashi K, Kojima T, Ito M, Satake H, Yajima Y, Yoda Y, Ikematsu H, Oono Y, Hayashi R, Onozawa M, Ohtsu A. Treatment strategy for superficial pharyngeal squamous cell carcinoma synchronously combined with esophageal cancer. Oncology, 84:57-64, 2013
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Division of Developmental Therapeutics

Yasuhiro Matsumura, Masahiro Yasunaga, Yoshikatu Koga

Introduction

Our Division has been involved in basic research on drug delivery systems (DDS) including anticancer agent incorporating micelle systems and antibody drug conjugates and in the clinical development of drugs used in DDS. We also investigated a mechanism of cancer induced blood coagulation and are developing a new cancer diagnosis based on cancer specific monoclonal antibodies (mAbs). In addition to the research work, we are operating the Japan Clinical Oncology Group Tumor Repository.

Routine activities

Examination of clinical trials as an IRB member

Operation of the JCOG Tumor Repository

Management of personal information protection in the NCC East Hospital

Research activities

(Drug Delivery System in Cancer Chemotherapy)

Tumor-targeted delivery of therapeutic agents is a longstanding pharmacological goal to improve the treatment selectivity and therapeutic index. Most scientists have sought to use 'active' receptor-mediated tumor-targeting systems. However, the 'passive' targeting afforded by the "Enhanced Permeability and Retention (EPR) effect" provides a versatile and non-saturable approach for tumor-selective delivery. Polymeric micelles are ideally suited to exploit the EPR effect, and have been used for the delivery of a range of anticancer drugs in preclinical and clinical studies.

A phase 3 study of NK-105, a paclitaxel incorporating micelle, is now underway in Japan, Taiwan, and Korea in patients with metastatic breast cancer. Phase 2 trials of NC-6004, a cisplatin incorporating micelle, A Phase 1 study of K-912, an epirubicin incorporating micelle has begun (1). We also reported for the first time, the precise distribution of a non-radiolabelled DDS drug using the imaging mass spectrometry (IMS) technique (2). In addition to clinical trials, we have published a reflection paper on the development of micelle medical products in collaboration with the European Medicines Agency (EMA) (Reflection paper 1)

(Cancer Stromal Targeting (CAST) Therapy)

In spite of the recent success of mAb drug conjugate (ADC) therapy in patients with hypervascular and special tumors recognized by a particular mAb, there are several issues to be solved before ADC can be recognized as a universal therapy for any type of cancer. A particular problem is that most human solid tumors possess abundant stroma that hinders the distribution of any ADC. To overcome these drawbacks, we developed a unique strategy, known as cancer-stromal targeting (CAST) therapy through the application of cytotoxic immunoconjugate bound to the collagen 4 or fibrin network in the tumor stroma, from which the payload is released gradually and distributed throughout the tumor, resulting in the arrest of tumor growth due to induced damage of tumor cells and tumor vessels. During this study, we discovered an unexplored hole in fibrin clots occurring only when insoluble fibrin clots formed, and we also found that our monoclonal antibodies developed against structures inside the hole recognized only insoluble fibrin and not fibrinogen, soluble fibrin, or D-dimer (fibrin degradation products). Finally, we assessed the clinical significance of these mAbs (3, 7).

(Noninvasive Diagnostic Test for Colorectal or Uterus Cancer)

In our laboratory, simple and non-invasive methods for detecting colorectal and endometrial cancers have been investigated for the last decade. Regarding colorectal cancer (CRC), we investigated the applicability of the fecal miRNA test (FmiRT) to fecal samples used for previous fecal occult blood tests (FOBTs) stored under various conditions (4). We subsequently investigated a new colorectal cancer screening method combining FOBT and FmiRT to improve the sensitivity compared with FOBT alone (5). For endometrial cancer diagnosis, we prepared immuno-magnetic beads conjugated with anti-human EpCAM rat mAb to isolate exfoliated endometrial cells including endometrial cancer cells in the vaginal discharge (6).

List of papers published in 2013

Journal

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2. Yasunaga M, Furuta M, Ogata K, Koga Y, Yamamoto Y, Takigahira M, Matsumura Y. The significance of microscopic mass spectrometry with high resolution in the visualisation of drug distribution. Sci Rep, 3:3050, 2013
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Book

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Reflection paper

8. Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products. 19 December 2013 EMA/CHMP/13099/2013. Committee for medicinal Products for Human Use (CHMP)

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 as having lung cancer and clinical factors associated with incapacity. Over an 11-month period, we recruited 135 patients newly diagnosed as having lung cancer. All patients were receiving a combination of treatments (e.g., chemotherapy, chemoradiotherapy, or targeted therapy). The MacArthur Competence Tool for Treatment was administered to participants, in addition to a neurocognitive test battery and the Vulnerable Elders Survey-13 (VES-13) to help us identify clinical factors associated with incapacity in lung cancer patients. Twenty-seven (24%, 95% CI, 16–31%) patients were judged not to have consent capacity. In contrast, clinical teams only identified 6 (22.2%) patients who did not 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. A substantial portion of patients diagnosed as having lung cancer showed impairments in their capacity to consent to treatment. Results suggest that many advanced lung cancer patients fail to fully understand physicians' recommendations due to age-related functional cognitive impairment. Future studies should investigate brief and effective assessments of capacity and determine whether specific interventions can improve informed consent.

Division of Radiation Oncology and Particle Therapy

Tetsuo Akimoto, Sadatomo Zenda, Teiji Nishio, Ryosuke Kohno, Tomoko Kawagishi, Kenji Hotta

Introduction

The aim of the research performed in the Radiation Oncology and Particle Therapy Department at the National Cancer Hospital East (NCCHE) 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.

Research activities

(a): PBT as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study. The aim of this pilot study was to assess the clinical benefit of PBT for mucosal melanoma of the head and neck. Patients with mucosal melanoma of the head and neck with histologically confirmed malignant melanoma and N0 and M0 disease were enrolled. PBT was delivered three times per week with a planned total dose of 60 Gy equivalents (GyE) in 15 fractions. Fourteen consecutive patients were enrolled from January 2004 through February 2008. Patient characteristics were as follows: median age 73 years old (range, 56 to 79 years); male/female ratio, 7/7; and T stage 1/2/3/4, 3/2/0/9. All patients were able to receive the full dose of PBT. The most common acute toxicities were mucositis (grade 3, 21%) and mild dermatitis (grade 3, 0%). As for late toxicity, 2 patients had a unilateral decrease in visual acuity, although blindness did not occur. No treatment-related deaths occurred throughout the study. The initial local control rate was 85.7%, and, with a median follow-up period of 36.7 months, median progression-free survival was 25.1 months, and 3-year overall survival rates were 58.0%. The most frequent site of first failure was the cervical lymph nodes (6 patients), followed by local failure in 1 patient and lung metastases in 1 patient. On follow-up, 5 patients died of disease, 4 died due to cachexia caused by distant metastases, and 1 patient by carotid artery perforation caused by lymph nodes metastases. PBT showed promising local control benefits and would benefit from ongoing clinical study.

(b): Phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer: To evaluate the feasibility of proton beam therapy (PBT) for stage III non-small cell lung cancer, especially focusing on acute toxicities and related dose volume histogram (DVH) parameters for the organ at risk. (Preliminary results) Twenty-three of the patients (96%) completed the planned treatment course except one patient who developed distant metastases during PBT. Regarding acute toxicities, grades of radiation pneumonitis were grade 0-1 in 23 (96%) and grade 2 in one patient, respectively. Those of esophagitis were grade 0-1 in 16 (62%), grade 2 in 6 (25%) and grade 3 in 2 patients (13%), respectively. All patients who developed grade 2-3 esophagitis were treated with concurrent chemotherapy. No other severe acute radiation-related toxicities were observed. The DVH parameters of all patients were as follows: average lung V20 Gy; 23% (16 to 32%), V10 Gy; 30% (19% to 50%), V5 Gy; 34% (20 to 52 %), mean whole lung dose; 16 GyE (6 to 19 GyE), mean dose to the heart; 7 GyE (4.9 to 22.5 GyE), esophagus V50 GyE; 11 GyE (0 to 47.2 GyE), mean whole esophageal dose; 22 GyE (1.9 to 30.4 GyE), the maximum dose to the spinal cord; 37 GyE (34.7 to 48 Gy). The lung V20 Gy and whole lung dose of the one patient who developed grade-2 radiation pneumonitis were 29% and 16.4 Gy, respectively. There was no statistical difference in the esophageal V50 Gy ($p=0.97$) and esophageal whole mean dose ($p=0.76$) between the patients with grade 0-1 esophagitis and those with grade 2-3.

(c): Proton dose distribution measurements using a MOSFET detector with a simple dose-weighted correction method for LET effects.

We experimentally evaluated the proton beam dose reproducibility, sensitivity, angular dependence and depth-dose relationships for a new Metal Oxide Semiconductor Field Effect Transistor (MOSFET) detector. The detector was fabricated with a thinner oxide layer and was operated at high-bias voltages. In order to accurately measure dose distributions, we developed a practical method for correcting the MOSFET response to proton beams. The detector was tested by examining lateral dose profiles formed by protons passing through an L-shaped bolus. The dose reproducibility, angular dependence and depth-dose response were evaluated using a 190 MeV proton beam. Depth-output curves produced

using the MOSFET detectors were compared with results obtained using an ionization chamber (IC).

Since accurate measurements of proton dose distribution require correction for LET effects, we developed a simple dose-weighted correction method. The correction factors were determined as a function of proton penetration depth, or residual range. The residual proton range at each measurement point was calculated using the pencil beam algorithm. Lateral measurements in a phantom were obtained for pristine and SOBP beams. The reproducibility of the MOSFET detector was within 2%, and the angular dependence was less than 9%. The detector exhibited a good response at the Bragg peak (0.74 relative to the IC detector). For dose distributions resulting from protons passing through an L-shaped bolus, the corrected MOSFET dose agreed well with the IC results. Absolute proton dosimetry can be performed using MOSFET detectors to a precision of about 3% (1 sigma). A thinner oxide layer thickness improved the LET in proton dosimetry. By employing correction methods for LET dependence, it is possible to measure absolute values with a thinner oxide layer which was operated at high-bias voltages. In order to accurately measure dose distributions, we developed a practical method for correcting the MOSFET response to proton beams. The detector was tested by examining lateral dose profiles formed by protons passing through an L-shaped bolus. The dose reproducibility, angular dependence and depth-dose response were evaluated using a 190 MeV proton beam. Depth-output curves produced using the MOSFET detectors were compared with results obtained using an ionization chamber (IC).

Since accurate measurements of proton dose distribution require correction for LET effects, we developed a simple dose-weighted correction method. The correction factors were determined as a function of proton penetration depth, or residual range. The residual proton range at each measurement point was calculated using the pencil beam algorithm. Lateral measurements in a phantom were obtained for pristine and SOBP beams. The reproducibility of the MOSFET detector was within 2%, and the angular dependence was less than 9%. The detector exhibited a good response at the Bragg peak (0.74 relative to the IC detector). For dose distributions resulting from protons passing through an L-shaped bolus, the corrected MOSFET dose agreed well with the IC results. Absolute proton dosimetry can be performed using MOSFET detectors to a precision of about 3% (1 sigma). A thinner oxide layer thickness improved the LET in proton dosimetry. By employing correction methods for LET dependence, it is possible to measure absolute values.

Clinical trials

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

1) A phase II study of PBT for malignant melanoma of nasal cavity.
2) A phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.
3) A 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 radiotherapy during 2007-2011				
	2008	2009	2010	2011	2012
New patients	52	57	107	200	245
Head and neck cancers	13	24	39	49	49
Lung and mediastinal cancers	22	13	12	24	24
Hepatocellular carcinoma	6	6	12	27	27
Prostate cancer	11	14	42	93	93
Others	0	0	2	7	7

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Journal

1. Tansho R, Takada Y, Kohno R, Hotta K, Hara Y, Mizutani S, Akimoto T. Experimental verification of dose calculation using the simplified Monte Carlo method with an improved initial beam model for a beam-wobbling system. Phys Med Biol, 58:6047-6064, 2013
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4. Kiyozuka M, Akimoto T, Fukutome M, Motegi A, Mitsuhashi N. Radiation-induced dimer formation of EGFR: implications for the radiosensitizing effect of cetuximab. Anticancer Res, 33:4337-4346, 2013
5. Okano S, Yoshino T, Fujii M, Onozawa Y, Kodaira T, Fujii H, Akimoto T, Ishikura S, Oguchi M, Zenda S, de Blas B, Tahara M, Beier F. Phase II study of cetuximab plus concomitant boost radiotherapy in Japanese patients with locally advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol, 43:476-482, 2013
6. Sugimoto M, Gotohda N, Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Kojima M, Ochiai A, Zenda S, Akimoto T, Konishi M. Pancreatic resection for metastatic melanoma originating from the nasal cavity: a case report and literature review. Anticancer Res, 33:567-573, 2013

Section of Experimental Animals

Yoshikatsu Koga

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 2013, 58 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 2013

Journal

1. Yamazaki N, Koga Y, Yamamoto S, Kakugawa Y, Otake Y, Hayashi R, Saito N, Matsumura Y. Application of the fecal microRNA test to the residuum from the fecal occult blood test. Jpn J Clin Oncol, 43:726-733, 2013
2. Koga Y, Katayose S, Onoda N, Kasamatsu T, Kato T, Ikeda S, Ishikawa M, Ishitani K, Hirai Y, Matsui H, Matsumura Y. Usefulness of immuno-magnetic beads conjugated with anti-EpCAM antibody for detecting endometrial cancer cells. J Cancer Ther, 4:1273-1282, 2013
3. Yasunaga M, Furuta M, Ogata K, Koga Y, Yamamoto Y, Takigahira M, Matsumura Y. The significance of microscopic mass spectrometry with high resolution in the visualisation of drug distribution. Sci Rep, 3:3050, 2013
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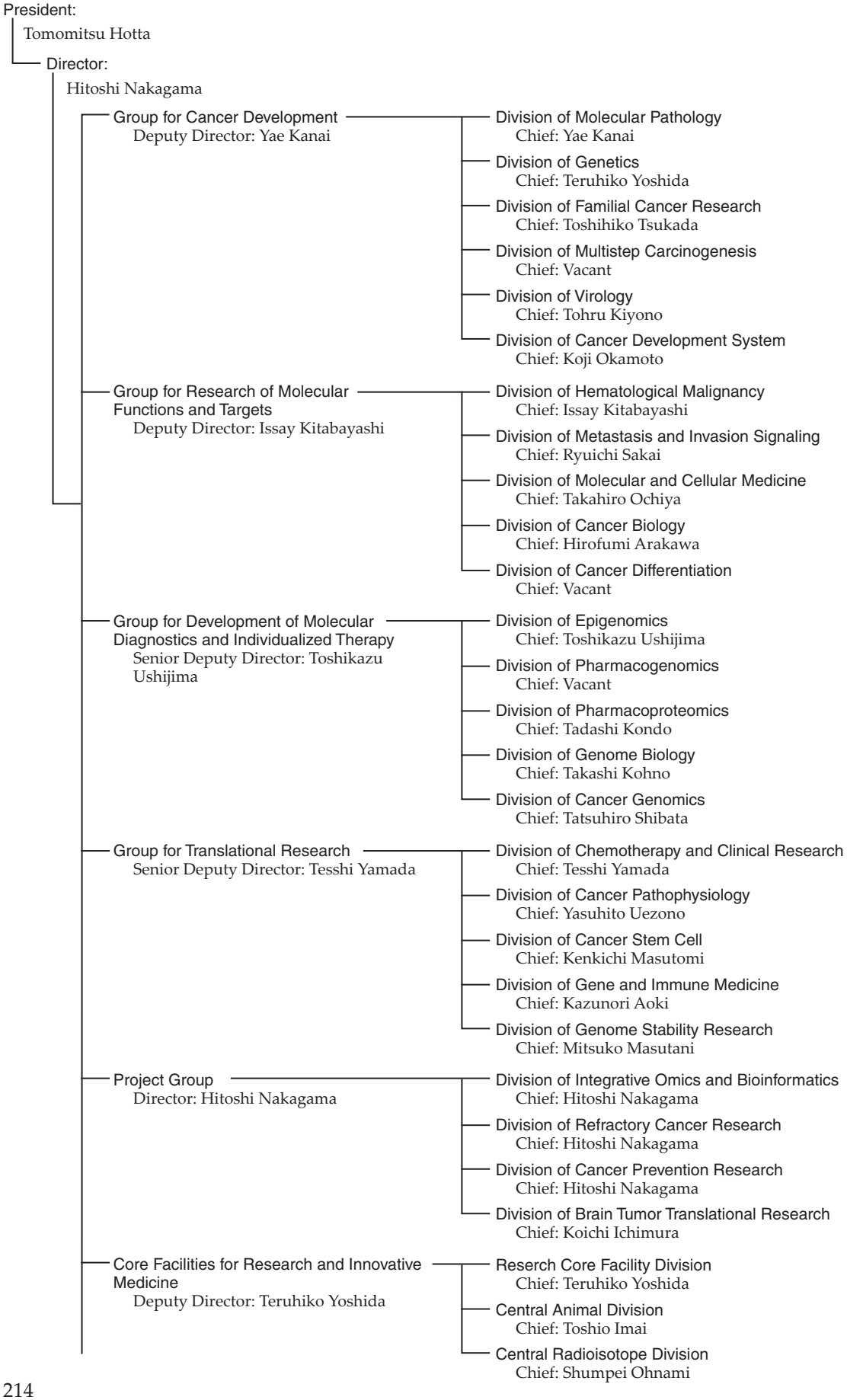
Research Institute

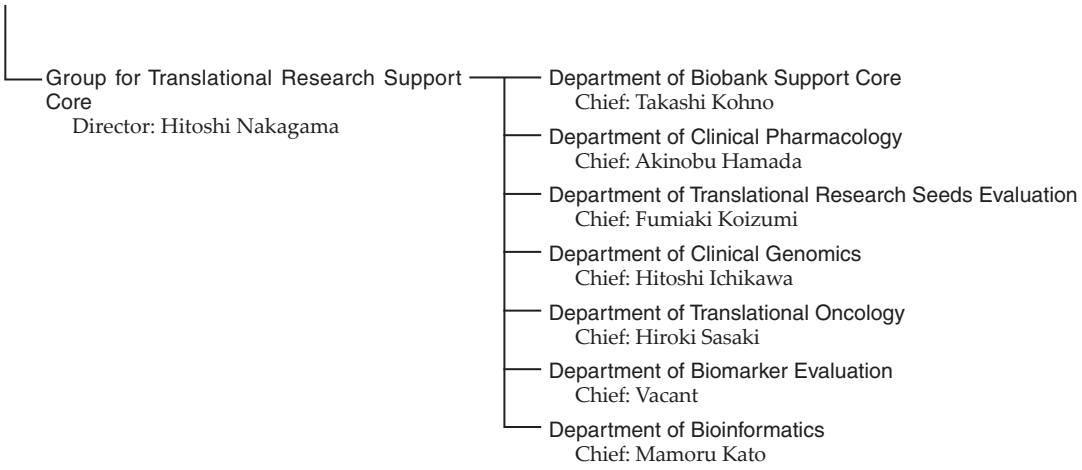
Preface

The National Cancer Center Research Institute (NCCRI) was established in 1962 as a department of the National Cancer Center (NCC), and has been the nation's leading cancer research institute for more than 50 years. The NCCRI is now internationally recognized for its major contributions to various aspects of cancer research worldwide. The mission of the NCCRI is to advance our knowledge of cancer prevention, diagnosis and therapy, toward the ultimate goal of cancer control. Collaborative research integration between other departments of the NCC, including NCC Hospitals, and the Research Institute is highly encouraged. The NCCRI is now composed of 25 divisions, and they are sub-grouped into four major Research Groups and one Project Group; namely, the Group for Cancer Development and Progression, Group for Research into Molecular Functions and Targets, Group for Development of Molecular Diagnostics and Individualized Therapy and Group for Translational Research and Project Group. Core Facilities for Research and Innovative Medicine, which consist of the Central Animal Division, Central Radioisotope Division and Core Facility Division, provide several kinds of technical support for molecular biology, high-throughput omics-type analyses, biological analysis and animal experiments for researchers in both the Research Institute and Hospitals to further encourage and facilitate the development of translational-type studies in our Institute. The NCCRI currently has approximately 90 research staff, around 30 postdoctoral fellows, and more than 180 supporting staff. Foreign scientists and research fellows are also welcomed on a regular basis. We launched the Group for Translational Research Support Core (consisting of 5 departments) to further facilitate and support the activities of TR projects, conducted between Hospital, Research Institute and other internal sections. The "Annual Report" of the NCCRI summarizes the recent research activities of each division, which cover the following areas: (i) environmental human carcinogens and cancer chemoprevention, including the use of animal models; (ii) clarification of molecular mechanisms underlying cancer development, invasion and metastasis; (iii) investigation of genetic and epigenetic alterations in a variety of cancers; (iv) clarification of the molecular bases underlying the susceptibility to cancer development; (v) exploration of novel biomarkers with diagnostic, therapeutic and prognostic value; and (vi) functional analyses of various cancer-related genes. We have also been participating in worldwide research consortia, such as the International Cancer Genome Consortium (ICGC), International Human Epigenome Consortium (IHEC), and International Cancer Biomarker Consortium (ICBC). We further encourage our members to develop international collaborative research projects in various other areas. The activities of the research institute can also be viewed on the home page: http://www.ncc.go.jp/en/nccri/index.html.

Hitoshi Nakagama, M.D., D.M.Sc.
Director, National Cancer Center Research Institute

Organization




Group for Translational Research Support Core
Director: Hitoshi Nakagama
Department of Biobank Support Core
Chief: Takashi Kohno
Department of Clinical Pharmacology
Chief: Akinobu Hamada
Department of Translational Research Seeds Evaluation
Chief: Fumiaki Koizumi
Department of Clinical Genomics
Chief: Hitoshi Ichikawa
Department of Translational Oncology
Chief: Hiroki Sasaki
Department of Biomarker Evaluation
Chief: Vacant
Department of Bioinformatics
Chief: Mamoru Kato

Activities of the Divisions

Division of Molecular Pathology

Yae Kanai, Nobuyoshi Hiraoka, Shigeki Sekine, Masahiro Gotoh, Hidenori Ojima, Eri Arai, Taisuke Mori, Ying Tian, Masumi Tanaka, Takashi Sato, 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.

Multilayer omics analysis in human cancers for personalized and preemptive 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. Based on a single-CpG-resolution genome-wide DNA methylation analysis (methylome analysis) using the Infinium BeadChip system in 240 renal tissue specimens, we identified the CpG island methylator phenotype (CIMP) of clear cell renal cell carcinomas (RCCs), which is characterized by accumulation of DNA hypermethylation of CpG islands, clinicopathological aggressiveness and poorer patient outcome (Figure 1). We also have identified 17 RCC-specific CIMP marker genes. In order to establish the criteria for CIMP diagnosis, DNA methylation levels at 299 CpG sites of entire promoter CpG islands in the RCC-specific CIMP marker genes were evaluated quantitatively using a MassARRAY system. Receiver operating characteristic curve analysis showed that the area under the curve values for the 32 CpG sites were larger than 0.95. Criteria combining the 32 CpG sites discriminated CIMP-positive from CIMP-negative RCCs with 100% sensitivity and specificity in the learning cohort. Cancer-free and overall survival rates of patients with CIMP-positive RCCs were significantly lower than those of patients with CIMP-negative RCCs in the validation cohort consisting of the 100 patients. Patients with CIMP-positive RCCs in the validation cohort had a higher likelihood of both recurrence and disease-related death (hazard ratios 10.7 and 77.1, respectively). We have filed patent applications for prognostication of RCC patients using the established criteria (US61/646,044, PCT/JP2013/62650). We are now developing a new device, which is specialized to DNA methylation diagnosis and widely applicable for clinical use, in collaboration with a medical device company (Figure 1).

To reveal the molecular pathways significantly participating in 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 RCCs was identified as the potential therapeutic target (Figure 1). The effectiveness of the inhibitor of the identified pathway is now being examined in CIMP-positive RCC cell lines. Since the potential therapeutic target has been identified for clinically aggressive CIMP-positive RCCs, our criteria for CIMP diagnosis may be useful for not only prognostication but also companion diagnosis for personalized medicine.

With respect to lung carcinogenesis, a single-CpG-resolution methylome analysis in 414 lung tissue specimens reveled that DNA methylation profiles reflecting carcinogenetic factors, *i.e.*, smoking and chronic obstructive lung disease, are established even at the precancerous stage and DNA methylation alterations at the precancerous stages may determine tumor aggressiveness and patient outcome. Multilayer omics analysis identified *ADCY5 and EVX1* as potential therapeutic targets of lung adenocarcinomas. With respect to gastric carcinogenesis, a single-CpG-resolution methylome analysis in 220 gastric tissue specimens revealed that DNA methylation profiles at the precancerous stages associated with *Helicobacter pylori* infection and/or chronic atrophic gastritis were inherited by gastric cancer tissues themselves and determined tumor aggressiveness and patient outcome.

Activities in The International Human Epigenome Consortium (IHEC)

In 2010, the IHEC was established to comprehensively characterize the heterogeneity of standard epigenome profiles of multiple normal cell lineages from different human populations and to construct the epigenome database as an international research basis. Researchers and founding agencies from Canada, the EU, Italy, Germany, Japan, South Korea and the USA currently participate in the IHEC to decipher at least 1000 epigenomes (epigenome maps of 1000 cell lineage-person) within the next

7-10 years. 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 (JST) Agency. In collaboration with research groups in the National Cancer Center (NCC) and the University of Tokyo, we perform whole-genome sequencing, 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.

As a contribution to the IHEC program, we first focused on epigenome mapping in hepatocytes purified from normal liver tissue and diseased liver tissue with hepatitis C virus (HCV) or hepatitis B virus (HBV)-infection. Hepatocytes were purified by collagenase perfusion via canulated hepatic veins in partial hepatectomy specimens followed by low-velocity centrifugation. More than 95% purity was immunocytochemically confirmed. Personal differentially methylated regions (pDMRs) and DMRs associated with HCV or HBV infection were identified. We are examining genome-epigenome crosstalk, *i.e.* correlations among pDMR, single-nucleotide variation and copy number variation. Under the supervision of the IHEC, we intend to disclose the data through the National Bioscience Database Center supported by the JST. Accurate standard epigenomic profiles of digestive and urogenital organ epithelial cells obtained through IHEC activities will be used to explore more useful biomarkers of and drug targets for cancers.

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 NCC Biobank and contribute to collaborative studies through providing clinicopathological information. In addition, from surgically resected materials, cancer cell lines and mouse xenograft models have been established.

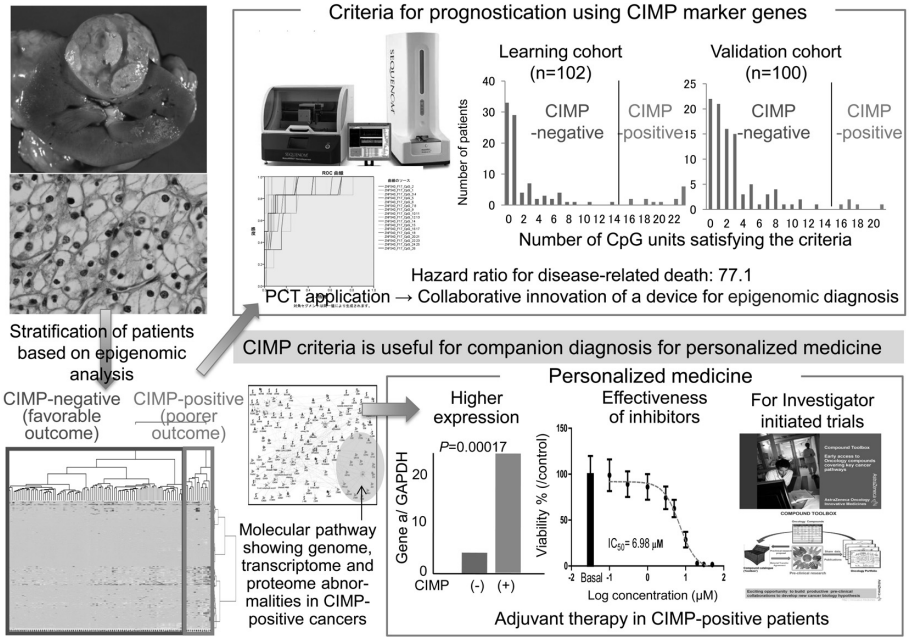


Figure 1. Personalized medicine based on epigenomic analysis of renal cell carcinomas

List of papers published in 2013
Journal

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2. Nishikawa G, Sekine S, Ogawa R, Matsubara A, Mori T, Taniguchi H, Kushima R, Hiraoka N, Tsuta K, Tsuda H, Kanai Y. Frequent *GNAS* mutations in low-grade appendiceal mucinous neoplasms. Br J Cancer, 108:951-958, 2013
3. Matsubara A, Sekine S, Yoshida M, Yoshida A, Taniguchi H, Kushima R, Tsuda H, Kanai Y. Prevalence of *MED12* mutations in uterine and extrauterine smooth muscle tumours. Histopathology, 62:657-661, 2013
4. Matsubara A, Sekine S, Kushima R, Ogawa R, Taniguchi H, Tsuda H, Kanai Y. Frequent *GNAS* and *KRAS* mutations in pyloric gland adenoma of the stomach and duodenum. J Pathol, 229:579-587, 2013
5. Yamazaki H, Mori T, Yazawa M, Maeshima AM, Matsumoto F, Yoshimoto S, Ota Y, Kaneko A, Tsuda H, Kanai Y. Stem cell self-renewal factors Bmi1 and HMGA2 in head and neck squamous cell carcinoma: clues for diagnosis. Lab Invest, 93:1331-1338, 2013
6. Matsuzaki J, Suzuki H, Tsugawa H, Watanabe M, Hossain S, Arai E, Saito Y, Sekine S, Akaike T, Kanai Y, Mukaisho K, Auwerx J, Hibi T. Bile acids increase levels of microRNAs 221 and 222, leading to degradation of CDX2 during esophageal carcinogenesis. Gastroenterology, 145:1300-1311, 2013
7. Saito Y, Suzuki H, Imaeda H, Matsuzaki J, Hirata K, Tsugawa H, Hibino S, Kanai Y, Saito H, Hibi T. The tumor suppressor microRNA-29c is downregulated and restored by celecoxib in human gastric cancer cells. Int J Cancer, 132:1751-1760, 2013
8. Chihara Y, Kanai Y, Fujimoto H, Sugano K, Kawashima K, Liang G, Jones PA, Fujimoto K, Kuniyasu H, Hirao Y. Diagnostic markers of urothelial cancer based on DNA methylation analysis. BMC Cancer, 13:275, 2013
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11. Yoshida N, Esaki M, Kishi Y, Shimada K, Ojima H, Kanai Y, Hiraoka N. Bile duct carcinoma involving the common channel associated with pancreaticobiliary maljunction shows an extension pattern similar to ductal carcinoma of the pancreas. Pathol Int, 63:415-418, 2013
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20. Maruyama M, Kobayashi M, Sakai Y, Hiraoka N, Ohya A, Kageyama S, Tanaka E, Nakayama J, Morohoshi T. Periductal induction of high endothelial venule-like vessels in type 1 autoimmune pancreatitis. Pancreas, 42:53-59, 2013
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22. Sekiguchi M, Suzuki H, Oda I, Abe S, Nonaka S, Yoshinaga S, Taniguchi H, Sekine S, Kushima R, Saito Y. Favorable long-term outcomes of endoscopic submucosal dissection for locally recurrent early gastric cancer after endoscopic resection. Endoscopy, 45:708-713, 2013
23. Kobayashi S, Tsuta K, Sekine S, Yoshida A, Sasaki N, Shibuki Y, Sakurai H, Watanabe S, Asamura H, Tsuda H. Pulmonary neuroendocrine tumors with nuclear inclusion. Pathol Res Pract, 209:574-577, 2013
24. Kushima R, Sekine S, Matsubara A, Taniguchi H, Ikegami M, Tsuda H. Gastric adenocarcinoma of the fundic gland type shares common genetic and phenotypic features with pyloric gland adenoma. Pathol Int, 63:318-325, 2013
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27. Makuuchi Y, Honda K, Osaka Y, Kato K, Kojima T, Daiko H, Igaki H, Ito Y, Hoshino S, Tachibana S, Watanabe T, Furuta K, Sekine S, Umaki T, Watabe Y, Miura N, Ono M, Tsuchida A, Yamada T. Soluble interleukin-6 receptor is a serum biomarker for the response of esophageal carcinoma to neoadjuvant chemoradiotherapy. Cancer Sci, 104:1045-1051, 2013
28. Sekiguchi M, Sekine S, Oda I, Nonaka S, Suzuki H, Yoshinaga S, Taniguchi H, Tsuda H, Kushima R, Saito Y. Risk factors for lymphatic and venous involvement in endoscopically resected gastric cancer. J Gastroenterol, 48:706-712, 2013
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30. Yamada M, Sekine S, Matsuda T. Demo-type carcinoma of the colon masquerading a submucosal tumor. Clin Gastroenterol Hepatol, 11:A30, 2013
31. Kitagawa N, Ojima H, Shirakihara T, Shimizu H, Kokubu A, Urushidate T, Totoki Y, Kosuge T, Miyagawa S, Shibata T. Downregulation of the microRNA biogenesis components and its association with poor prognosis in hepatocellular carcinoma. Cancer Sci, 104:543-551, 2013
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33. Yazawa M, Mori T, Kishi K. A comparison of malignant bone treatments for reuse. Surg Sci, 4: 49-52, 2013
34. Kubota D, Mukaihara K, Yoshida A, Suehara Y, Saito T, Okubo T, Gotoh M, Orita H, Tsuda H, Kaneko K, Kawai A, Kondo T, Sato K, Yao T. The prognostic value of pfetin: a validation study in gastrointestinal stromal tumors using a commercially available antibody. Jpn J Clin Oncol, 43:669-675, 2013

Division of Genetics

Teruhiko Yoshida, Hiromi Sakamoto, Fumiaki Koizumi, Hiroki Sasaki, Hitoshi Ichikawa, Norihisa Saeki, Kazuhiko Aoyagi, Kazuyoshi Yanagihara, Sumiko Ohnami, Mineko Ushiama, Yoko Odaka, Misuzu Okuyama, Sachiyo Mitani,YousukeTomokuni, Akiko Takahashi, Masumi Shimizu, Mika Shioya, Sayaka Mito, Hiroo Takahashi, Hiroe Sakuyama, Nozomi Nakata,Noriko Koyama

Introduction

In 2013, 2 laboratory heads of the Division of Genetics, Drs. Koizumi and Sasaki were promoted to Department chiefs, and whose research activities are shown separately. The 2 major research themes of the Division were 1) molecular understanding of cancer susceptibility; and 2) development of personalized cancer diagnosis and treatment of gastric cancer.

Routine activities

We have maintained our participation in the biobanking project of the Tsukiji campus of the National Cancer Center (NCC), particularly for the peripheral blood samples.

Research activities

1) Molecular understanding of cancer susceptibility

Our previous genome-wide associated study (GWAS) identified the PSCA and MUC1 gene polymorphisms as the 2 major genetic factors for diffusetype gastric cancer. Although the associations have been successfully replicated by several laboratories, we believe that the functional understanding of the genes is important for the development of reliable preventive methods. The function of the PSCA protein has been explored by its expression pattern in other cancers and tissues and by searching the molecules associated with the PSCA protein. Whereas PSCA is up-regulated in many types of cancer, the protein was found to be down-regulated in both gallbladder and gastric cancers. In gallbladder cancer cells, the risk allele of the rs2294008 missense SNP attenuated the anti-tumor effects of the PSCA gene. However, the binding protein for PSCA has not been identified yet, and the PSCA signaling pathway still remains unknown in spite of several experimental approaches. So far, it has not been an easy task to unveil a signaling pathway and functional role of PSCA in carcinogenesis. Nonetheless, we would like to keep challenging, because the association per se appears to be solid in several ethnic groups, and the risk allele has a high frequency in the Japanese population (0.62); the combination of the PSCA and MUC1 polymorphisms would give a strong starting point to develop a combined genetic and life-style/environment profile to identify the high-risk group for diffuse-type gastric cancer, which may be less prone to decrease along with the decline of the *Helicobacter pylori* infection than the intestinal-type counterpart.

In the study on a neuroblastoma susceptibility gene, LMO1, which encodes a transcriptional regulator, several target genes of the LMO1 regulation have been identified through chromatin immunoprecipitation and DNA sequencing (ChIP-Seq).

Through collaboration with Dr. Haruhiko Sugimura at Hamamatsu University, School of Medicine, familial and/or young-onset gastric cancer cases have been analyzed with germline whole-exome sequencing (WES). We have been actively involved in the peripheral blood collection and DNA/RNA extraction in the NCC biobank project to accumulate further validation cases. Eighteen patients from 16 pedigrees with familial and/or early-onset gastric cancer were analyzed as cases with WES and SNP array analyses for structural variations. The candidate gene search from the WES data is underway based on several informatics criteria. The crucial step of the whole-exome/genome sequencing for the germline variations is an effective filtering and selection of the candidates and their validation. Two critical fundamentals for the further investigation are the large-scale Japanese reference genome sequence database and a biobank of germline DNA. We ourselves obtained the WES data of 165 control subjects from the participants of the population-based cohort study led by Dr. Shoichiro Tsugane at the NCC Research Center for Cancer Prevention and Screening. However, the reference data from several thousand members of the Japanese general population will be obtained by the Tohoku Medical Megabank project and other population-based genome cohorts, with whom we

would like to keep collaborating in the genome analyses.

2) Development of personalized cancer diagnosis and treatment of gastric cancer.

Next generation sequencer analysis has been shown to be a powerful tool to identify driver mutation candidates for the development of specific and sensitive biomarkers and therapeutics targeted to molecular aberrations. However, the proof that the observed mutation is actually a viable target of a therapeutic intervention needs a functional evaluation. Moreover, the frequency of each mutation in a particular type of cancer is often less than 5%. Therefore, establishment of cell lines from each patient with specific mutations is an important step for the functional selection of drug targets. Specifically, the Division has been analyzing clinical samples of malignant ascites from the patients with gastric cancer to identify somatic mutations and fusion genes through WES and whole transcriptome sequencing (WTS), respectively, as a part of the Integrated Disease Omics Project by NiBio. A large multi-center collaborative study on 10 malignant and non-malignant diseases has been organized, and the integrative database has been designed (Figure 1). We are in charge of the WES and SNP array analyses of 4 types of solid cancers and pediatric leukemia. The samples are being analyzed in order of the cancer types as agreed. While waiting in the queue, we successfully established 43 cancer cell lines by December 2013 from the ascites of 21diffuse-type gastric cancer patients by plate-culturing and intraperitoneal injection into SCID mice of retrieved cells (Figure 2). Our newly established cell lines can benefit the functional analyses of mutated genes and promote the preclinical study for developing new molecular target drugs.

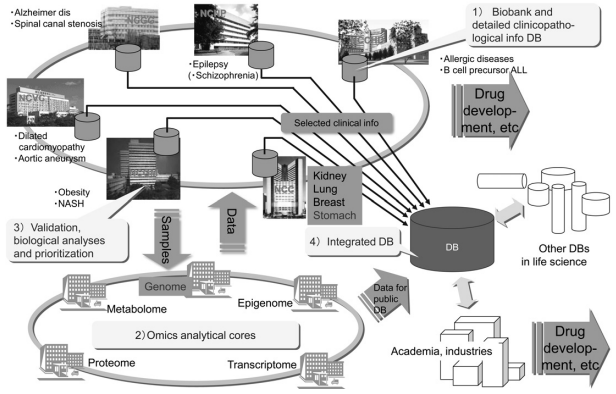

Figure 1. NiBio Integrated Disease Omics Project (FY2010-2014)

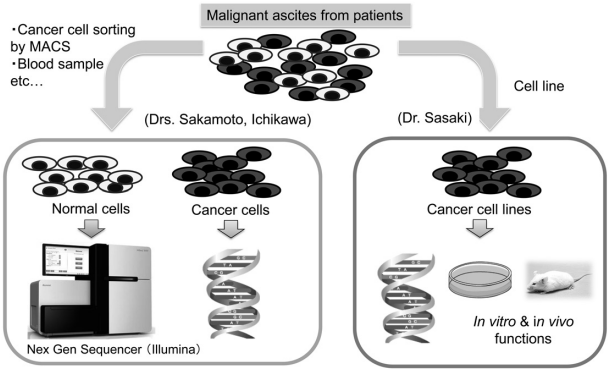

Figure 2. Functional Screening of Mutated Genes Identified by NGS Integrative Disease Omics Project Supported by NIBIO

List of papers published in 2013
Journal

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Division of Familial Cancer Research

Toshihiko Tsukada, Yuko Nagamura

Introduction

The Division of Familial Cancer Research is focusing its research activities on the development of new methods for diagnosis and treatment of familial cancer syndromes. A new diagnostic DNA test for multiple endocrine neoplasia type 1 (MEN1) was evaluated for clinical usefulness. Pharmacological actions of rikkunshito, a traditional Japanese herbal medicine, were also investigated.

Research activities

DNA diagnosis of MEN1

MEN1 is a familial cancer syndrome characterized by the multiple occurrences of endocrine tumors in the pituitary, parathyroid, and enteropancreatic endocrine tissues. MEN1 is caused by heterozygous germline mutations of the causative gene *MEN1*, which encodes a tumor suppressor protein named menin. Because the optimal therapies for MEN1-associated tumors, especially for multicentric parathyroid and pancreatic tumors, are different from those for sporadic, non-hereditary endocrine tumors, accurate differential diagnoses are mandatory before planning treatment. Germline mutation analysis of the *MEN1* gene is a powerful tool for the differential diagnosis of patients with endocrinopathy suggestive of MEN1. However, it is often difficult to distinguish a disease-causing mutation from a rare benign polymorphism especially when a novel missense mutation is identified in a patient with incomplete forms of MEN1. We previously found that mutant menin proteins associated with MEN1 were unstable and were rapidly degraded by the ubiquitin-proteasome pathway. A diagnostic test for predicting the prognosis of missense *MEN1* mutant gene carriers has been developed by exploiting this reduced stability. This method was evaluated for its clinical usefulness in collaboration with many hospitals in Japan. A missense *MEN1* mutation found in a new patient was evaluated for its pathogenicity by this method. The results indicated that the mutation will cause familial isolated primary hyperparathyroidism rather than typical MEN1 because of its residual biological activities.

The clinical characteristics and survival outcome of 32 patients with MEN1 were examined in relation to the *MEN1* gene mutation. Premature deaths related to MEN1 are suggested to be due to the development of malignant pancreatic neuroendocrine, pituitary or thymic tumors associated with mutations in exon 2, 3 and a large gene deletion (1).

Effects of rikkunshito on endocrine cells

Rikkunshito is widely used to treat appetite loss associated with various disorders, and may be a useful regimen for cancer cachexia. In order to examine possible effects of rikkunshito on hormone production in endocrine cells, we measured intracellular cAMP, which is a major regulator of biosynthesis and initiates the release of several hormones. A growth hormone-producing pituitary cell GH3 and an ACTH-producing pituitary cell AtT-20 were treated with rikkunshito with or without forskolin, a direct adenylate cyclase activator. Intracellular cAMP levels increased in both cell lines following the treatment with rikkunshito and/or forskolin in a dose-dependent manner. Release of ACTH and growth hormone from AtT-20 and GH3 cells, respectively, were suppressed by rikkunshito. These findings suggest that rikkunshito acts directly on endocrine cells and modulates secretion of hormones.

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Division of Virology

Tohru Kiyono, Takashi Yugawa, Nagayasu Egawa, Tomomi Nakahara, Kenji Yamada, Satomi Kikawa, Shin-ichi Ohno, Takako Ishiyama, Katsuyuki Tanaka, Yuki Inagawa, Kasumi Ohtsubo, Hikaru Tanaka, 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 Virology 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 tumour suppressors, p53 and retinoblastoma protein (pRB), respectively. By using an *in vitro* multistep carcinogenesis model for cervical cancer, we are elucidating the roles of E6, E7 and cellular oncogenes in multistep carcinogenesis (Figure 1).

A Novel function of NOTCH1 in keratinocyte differentiation

We previously elucidated that the NOTCH1 gene is transcriptionally activated by p53 and repressed by ΔNp63α. Since NOTCH1 is a key inducer of keratinocyte differentiation, ΔNp63α maintains the self-renewing capacity of normal human keratinocytes and cervical cancer cells partly through transcriptional repression of the Notch1 gene and imply a novel pathogenetic significance of frequently observed overexpression of ΔNp63α together with p53 inactivation in SCCs. ROCK, an effector of the small GTPase RHO, is also implicated in keratinocyte differentiation, and its inhibition efficiently potentiates immortalization of human keratinocytes and greatly improves the survival of dissociated human pluripotent stem cells. However, the molecular basis for ROCK activation is not fully established in these contexts. We elucidated that the intracellular forms of NOTCH1 trigger the immediate activation of ROCK1 independent of its transcriptional activity, promoting differentiation and resulting in decreased clonogenicity of normal human keratinocytes (Figure 2). Knock-down of NOTCH1 abrogated ROCK1 activation and conferred sustained clonogenicity upon differentiation stimuli. Treatment with a ROCK inhibitor, Y-27632, or ROCK1 silencing substantially rescued the growth defect induced by activated NOTCH1. Furthermore, we revealed that impaired self-renewal of human induced pluripotent stem cells upon dissociation is, at least in part, attributable to NOTCH-dependent ROCK activation. Thus, the present study unveils a novel NOTCH-ROCK pathway critical for cellular differentiation and loss of self-renewal capacity in a subset of immature cells (1).

Isolation of a novel type of HPV

E7 proteins of most HPVs as well as animal papillomaviruses conserve the Leu-X-Cys-X-Glu pRB-binding motif. However, some of the HPVs causing flat warts do not. In collaboration with dermatologists, a novel type of HPV, HPV160, belonging to the Alpha-PV species 2 was isolated from a flat wart of an immunocompetent patient (2).

Immortalization of Normal and Precancerous Human cells

We have immortalized various types of normal and precancerous human cells. Among them, immortalized ovarian endometrioma cells were used for analyzing the molecular mechanisms of progestin to inhibit their growth (5). A novel cell line, AM-3, was established from an ameloblastoma patient to analyze a pathway to induce osteoclastogenesis (4). Immortalized skin fibroblasts from severe combined immunodeficiency (SCID) patients with mutations in the Artemis gene were used for identifying a novel function of Artemis as a molecular switch that converts stalled replication forks harboring single-stranded gap DNA lesions into DSBs, thereby activating the ATM signaling pathway following prolonged replication fork stalling (8). From normal human amniotic tissues, epithelial cells and mesenchymal stem cells were newly immortalized (6, 9). By using several immortalized human cells as tools for cellular biology, Ser99 on Plk1 was identified as a novel mitosis-specific phosphorylation site, which operates

independently of Plk1-Thr210 phosphorylation (3) and beta1,4-galactosyltransferase 6 (B4galt6) in addition to B4galt5 was confirmed to play a role as a lactosylceramide synthase (7).

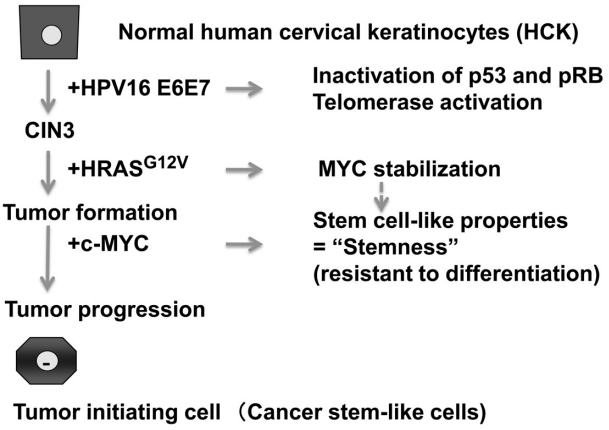

Figure 1. An *in vitro* multistep carcinogenesis model for cervical cancer

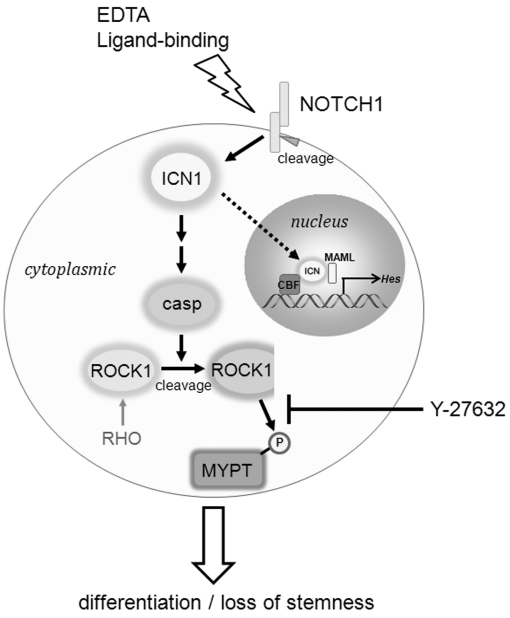

Figure 2. Proposed model for the NOTCH-ROCK pathway and its biological signif

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Division of Cancer Development System

Koji Okamoto, Yoshitaka Hippou, Yukari Totsuka, Daisuke Shiokawa, Masako Ochiai, Mitsuyoshi Yoshimoto, Hirokazu Ohata, Masanori Gotoh, Kazuhiro Shiizaki, Noriyuki Yokomichi, Tetsuya Matsuura, Emi Fukai, Akira Baba, Toshihiro Tsujita, Waka Kato, Yuki Yokoi, Naoko Osada, Sachiko Dobashi, Ai Sato, Hiroaki Sakai, Emiko Yamamoto, Mayumi Mizuta, Yumi Miyamoto, Kaoru Orihashi, Yukie Matumura

Introduction

Cancer stem cells (CSCs) play important roles during the development of refractory cancer with highly metastatic potential. Our group mainly focuses on studying CSCs from various refractory tumors. In particular, we cultivate CSCs *in vitro* from various clinical specimens, and attempt to understand how CSCs contribute to metastatic capability and chemo-resistance of cancer through our research on the biological properties of CSCs.

Routine activities

A weekly conference is held with members of Division of Cancer Development System.

Research activities

In vitro cultivation and characterization of cancer stem cells from human refractory cancer

Accumulating reports indicate that CSCs are responsible for metastatic processes as well as the tumorigenicity and chemoresistance of cancer. In our previous studies, we isolated cancer stem cells from human colon cancer, and established the conditions that allow stable *in vitro* propagation of colon CSCs in a spheroid form. We expanded our studies to cultivate CSCs not only from the primary tumor but also from metastatic foci in the liver. The CSCs from metastatic foci are likely to show higher metastatic capability. We are comparing the metastatic and non-metastatic CSCs through a series of 'Omics' data analyses, in order to elucidate the biological feature that is linked to the capability of CSCs to metastasize. Similar studies on CSCs from ovarian cancer and glioma are in progress.

In addition to the systematic Omics studies, we continued to investigate the regulation of CD44, whose induction after suppression of Rho-associated protein kinase is linked to the stemness (stem-like qualities) of colon CSCs. We demonstrated that mTOR is responsible for the induction of CD44, and in fact the upregulation of mTOR is indispensable for the stemness of colon CSCs.

Functional identification and characterization of a regulatory factor of cancer metastasis

In our previous studies, miR-493 was functionally isolated as an inhibitor of liver metastasis of colon cancer cells, and the following studies indicated that up-regulation of miR-493 during carcinogenesis prevents liver metastasis via the induction of cell death of metastasized cells. We demonstrated that MKK7, a MAP-related kinase, was identified as a direct target of miR-493, and its inhibition partially phenocopied the anti-metastatic effects. Thus, in combination with IGF-1R, a previously identified target of miR-493, MKK7 functions to promote liver metastasis of colon cancer, presumably in response to surviving signals from the liver microenvironment, and the inhibition of such signals by miR-493 blocks liver metastasis.

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.

Identification of Novel Mutagens/Carcinogens

Nanomaterials are commonly used in various industrial fields. Because the genotoxicity and safety of nanomaterials are of serious concern, we examined the genotoxicity of magnetite nanoparticles (MGT) on human A549 and Chinese hamster ovary (CHO) AA8 cells. Treatment with MGT increased the frequency of micronuclei (MN), DNA double strand

breaks (DSB), sister chromatid exchange (SCE), and production of reactive oxygen species (ROS) in *in vitro* systems. These findings suggested that MGT, through induction of ROS, induces DSB, which is followed by clastogenic events including MN and SCE. Reports related to other environmental mutagens/carcinogens are listed in the attached references.

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Division of Hematological Malignancy

Issay Kitabayashi, Kazutsune Yamagata, Takuo Katsumoto, Yutaka Shima, Yoko Ogawara, Emi Takamatsu, Yukiko Aikawa, Mika Shino, Akiko Kittaka, Rieko Furuya, Miu Adachi, Mariko Saito

Introduction

Acute myeloid leukemia (AML) is the most common leukemia in Japan and the U.S. With current standard chemotherapy, Approximately 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. However, many of the AML patients relapse and only 25-30% of young adults and fewer than 10% of older patients survive longer than 5 years, suggesting the presence of AML stem cells that are resistant to chemotherapy. AML stem cell eradication is therefore thought to be crucial to effect a cure for AML. Chromosome abnormalities, which results in a generation of specific fusion genes, are observed in ~50% of AML patients. In cases of AML associated with fusion genes involving *MLL, MOZ, CALM* or *NUP98* the outcome is extremely poor. Normal cytogenetics portend average-risk AML. Recent genome analyses revealed that mutations in NPM, IDH1/IDH2/TET2, DNMT3a and FLT3 genes are often simultaneously observed in patients with normal cytogenetics. The purpose of our research is to establish new therapeutic methods by identifying molecular targets that are essential for the maintenance of AML cells, especially AML stem cells.

Research activities

Chromosomal translocations that involve the monocytic leukemia zinc finger (MOZ) gene are typically associated with human AML and often predict a poor prognosis. Overexpression of HOXA9, HOXA10, and MEIS1 were 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. An immunoprecipitation analysis showed that MOZ-TIF2 forms a stable complex with BRPF1, and a chromatin immunoprecipitation analysis showed that MOZ-TIF2 and BRPF1 interact 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 the MOZ-TIF2/BRPF1 complex upregulates HOX genes mediated by MOZ-dependent histone acetylation, leading to the development of leukemia. We suggest that activation of the BRPF1/HOX pathway through MOZ HAT activity is critical for MOZ-TIF2 to induce AML.

AML1/RUNX1 is a frequent target of chromosome translocations and mutations in myeloid and B-cell leukemias, and upregulation of AML1 is also observed in some cases of T-cell leukemias and lymphomas. Our study showed that the incidence of thymic lymphoma in p53-null mice is less frequent in the Aml1+/- than in the Aml1+/+ background. AML1 is upregulated in p53-null mouse bone-marrow cells and embryonic fibroblasts. In the steady state, p53 binds to and inhibits the distal AML1 promoter. When the cells are exposed to stressors, p53 is released from the distal AML1 promoter, resulting in upregulation of AML1. Overexpression of AML1 stimulates T-lymphocyte proliferation. These results suggest that upregulation of AML1 induced by loss of p53 promotes lymphoid-cell proliferation, thereby inducing lymphoma development.

The PML gene is frequently fused to the retinoic acid receptor α (RARα) gene in acute promyelocytic leukemia (APL), generating a characteristic PML-RARα oncogenic chimera. PML-RARα disrupts the discrete nuclear speckles termed nuclear bodies (NBs) which are formed in PML, suggesting that NB disruption is involved in leukemogenesis. NB formation that relies upon PML oligomerization and its stabilization of the hypoxia-inducible protein kinase HIPK2 is disrupted by expression of the PML-RARα chimera. We reported that disruption of NBs is also mediated by PML-RARα inhibition of PML oligomerization. The PKA-mediated phosphorylation of PML-RARα blocked its ability to inhibit PML oligomerization and destabilize HIPK2. Our results established that both PML oligomerization and HIPK2 stabilization at NBs are important for APL cell differentiation, offering insights into the basis for the most common pro-

differentiation therapies of APL used clinically.

Monocytic leukemia zinc finger (MOZ)/KAT6A is a MOZ, Ybf2/Sas3, Sas2, Tip60 (MYST)-type histone acetyltransferase that functions as a coactivator for acute myeloid leukemia 1 protein (AML1)- and Ets family transcription factor PU.1-dependent transcription. We previously reported that MOZ directly interacts with p53 and is essential for p53-dependent selective regulation of p21 expression. We showed in a subsequent study that MOZ is an acetyltransferase of p53 at K120 and K382 and colocalizes with p53 in promyelocytic leukemia (PML) nuclear bodies following cellular stress. The MOZ–PML–p53 interaction enhances MOZ-mediated acetylation of p53, and this ternary complex enhances p53-dependent p21 expression. Moreover, we identified an Akt/protein kinase B recognition sequence in the PML-binding domain of MOZ protein. Akt-mediated phosphorylation of MOZ at T369 has a negative effect on complex formation between PML and MOZ. As a result of PML-mediated suppression of Akt, the increased PML–MOZ interaction enhances p21 expression and induces p53-dependent premature senescence upon forced PML expression. Our study demonstrated that MOZ controls p53 acetylation and transcriptional activity via association with PML.

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Division of Metastasis and Invasion Signaling

Ryuichi Sakai, Hitoyasu Futami, Hideki Yamaguchi, Takamasa Uekita, Takuya Shirakihara, Katsuhiko Nakashima

Introduction

The invasive and metastatic nature of cancers is the major threat for cancer patients and is a serious problem during cancer treatment. It has also been recently highlighted that unique interactions of cancer cells with neighboring cells such as stromal fibroblasts have critical roles in the invasion and metastasis of cancers. Numerous types of genetic and epigenetic alterations found in cancers might utilize several common pathways responsible for these malignant characteristics. An understanding of the signal pathway regulating these cancer-specific properties could lead to the development of new therapeutic targets specific to cancers. One of our approaches to identify these cancer-specific pathways is to investigate aberrant phosphotyrosine-containing proteins during cancer development and progression. As substrates of tyrosine kinases, these protein might include the mediators of cancer-specific signals and potential targets of therapeutics. The main object of our research is to establish models of the novel therapy for progressive cancer by regulating phosphotyrosine-dependent signals in cancer cells and their microenvironments.

Mediators of cancer invasion and metastasis signaling

Resistance to cell death caused by detachment (so-called anoikis) is one of the properties that cancer cells need to acquire for metastasis to distant organs. We have identified a transmembrane protein CDCP1 (CUB-domain-containing protein 1) from metastatic lung cancer cells as a key molecule responsible for resistance to anoikis. Expression of CDCP1 is detected in a number of cancer cell lines and tissues and is closely correlated with a poor prognosis. We demonstrated that CDCP1 is induced by activation of the Ras-Erk pathway and phosphorylated at tyrosines by activated Src family kinases (SFKs) in cancer cells. In other words, CDCP1 is a functional link between Ras and Src signaling during the multistage progression of human malignant tumors, highlighting CDCP1 as a potent target for treatment in the broad spectrum of human cancers associated with activation of the Ras pathway. Inhibition of CDCP1 expression using small interfering RNA (siRNA) induced cell death of suspended cancer cells without generating cleaved caspase-3, a marker of apoptosis, and the cell death was not inhibited by a general caspase inhibitor, suggesting that loss of CDCP1 induced a caspase-independent cell death. Instead, the loss of CDCP1 induced the LC3-II protein and the formation of autophagosomes. Moreover, the cell death of suspended lung cancer cells induced by the CDCP1 siRNA was reduced by an autophagy inhibitor 3-Methyladenine. These results indicated that CDCP1 signaling plays a critical role in the inhibition of autophagy which contributes to the anoikis resistance of lung cancer cells.

We have revealed that CDCP1 is required for ECM degradation by invadopodia in human breast cancer and melanoma cells. CDCP1 was localized to caveolin-1-containing vesicular structures and lipid rafts and was detected in close proximity to invadopodia. Invadopodia are actin-based protrusions on the surface of invasive cancer cells that promote the degradation of the extracellular matrix (ECM) via localized proteolysis, which is mainly mediated by membrane-type 1 matrix metalloproteinase (MT1-MMP). Further biochemical analysis revealed that CDCP1 is an essential regulator of the trafficking and function of MT1-MMP- and invadopodia-mediated invasion of cancer cells.

Investigation of molecular targets for scirrhous gastric carcinoma

Scirrhous gastric carcinoma (SGC) has the worst prognosis among various types of gastric cancers, owing to its rapid expansion through progressive invasion, peritoneal dissemination and frequent metastasis to lymph nodes. Because massive proliferation of stromal fibroblasts (SF) occurs within SGC lesions, interaction between SGCs and SF cells might play a role in the invasive properties of SGC cells. When SGC cells were cocultured with SF cells on three-dimensional Matrigel, they were attracted together to form large cellular aggregates that invaded the Matrigel. A myosin II inhibitor, blebbistatin, blocked the invasion and ECM remodeling by SGC and SF cells. These results indicated that SGC cells promote actomyosin-mediated contractility of SF cells to remodel the ECM during invasion. The

formation of these invasive foci was monitored by fluorescent imaging, and utilized for screening of inhibitor libraries. Several regents such as Rho inhibitors and Src inhibitors were picked up as candidate drugs targeting cancer-stromal interaction in SGCs.

Oncogenic Signals in Neuroblastomas

Activation of anaplastic lymphoma kinase (ALK) either by mutation or overexpression, has been indicated as a significant oncogenic factor in neuroblastoma formation. Investigation of phosphotyrosine-containing proteins associated with ALK in neuroblastomas was performed using mass-spectrometry analysis to elucidate the unique signals associated with neuroblastomas. Among various types of novel and known binding partners of ALK, Flotillin-1 (FLOT1), a plasma membrane protein known to be involved in endocytosis, was identified by mass-spectrometry analysis. Knockdown of FLOT1 in neuroblastoma cells caused dissociation of ALK from endosomes along with membrane accumulation of ALK, which resulted in activation of ALK and downstream signals. Suppression of FLOT1 expression also enhanced the oncogenic properties of neuroblastoma cells both *in vitro* and *in vivo*. On the other hand, oncogenic ALK mutants showed less binding affinity to FLOT1 than wild-type ALK. Lower expression levels of FLOT1 were observed in highly malignant subgroups of human neuroblastoma tissues. Taking these findings together, the results suggested that decreased levels of FLOT1 or defects in the binding affinity between ALK mutants and FLOT1 may cause malignant phenotypes of neuroblastoma through the activation of ALK signaling.

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Division of Cancer Biology

Hirofumi Arakawa, Yasuyuki Nakamura, Hiroki Kamino, Hitoya Sano, Yuri Saito, Ryuya Murai, Izumi Hyo

Introduction

The scope of the research at the Division of Cancer Biology is broad, covering numerous areas including the cloning of genes involved in carcinogenesis, biological and structural analyses of proteins, analyses of animal models, and the development of new strategies for cancer therapy. In particular, the tumor suppressor p53 and the genes that are directly regulated by p53 have been studied to uncover the mechanism of p53-mediated tumor suppression, based on which new cancer preventive, diagnostic, and therapeutic strategies could be developed.

Research activities

Identification and characterization of p53-target genes

Using a combination of a microarray analysis and a chromatin immunoprecipitation assay, identification of p53-target genes in the human genome has been conducted. Thus far, a number of p53-target genes including *DFNA5*, *SEMA3F*, *BLNK*, *UNC5A*, *NEEP21*, and *TMPS* have been identified and characterized at the Division. Along the 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 mitochondria

Mieap controls mitochondrial quality via two distinct novel mechanisms. One of the mechanisms has been designated MALM for Mieap-induced accumulation of lysosome-like organelles within mitochondria (*PLoS ONE* 6: e16054, 2011). In this mechanism, Mieap induces the accumulation of intramitochondrial lysosomal proteins in order to eliminate oxidized mitochondrial proteins in response to mitochondrial damage. This leads to a decrease in reactive oxygen species generation and an increase in mitochondrial ATP synthesis activity, implying 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 the cytosol into the 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-induced 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 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 pancreatic and gastric cancer patients.

Aerobic glycolysis is a common feature of human cancers, which is also known as the Warburg effect. Although the nature of cancer cells has been applied to the development of positron emission tomography (PET) for the whole body screening of human cancers, the mechanism for the phenomenon remains to be elucidated. The p53-Mieap pathway is frequently inactivated in human cancers because of p53 mutations and/or Mieap methylation. This leads to the accumulation of unhealthy mitochondria and consequently the Warburg effect (Figure 2). The accumulated unhealthy mitochondria in cancer cells also produce high levels of reactive oxygen

species (ROS). The increased mitochondrial ROS dramatically enhance cancer migration and invasion (Figure 2).

New therapeutic strategies for cancer therapy

Adenovirus-mediated gene transfer of *Mieap* has been found to strongly suppress tumor growth, suggesting that normalization of unhealthy mitochondria could be a novel strategy to suppress cancers *in vivo*. Toward the development of new strategies for cancer therapy, the *in vitro* and *in vivo* antitumor effects of these genes are being examined in this Division.

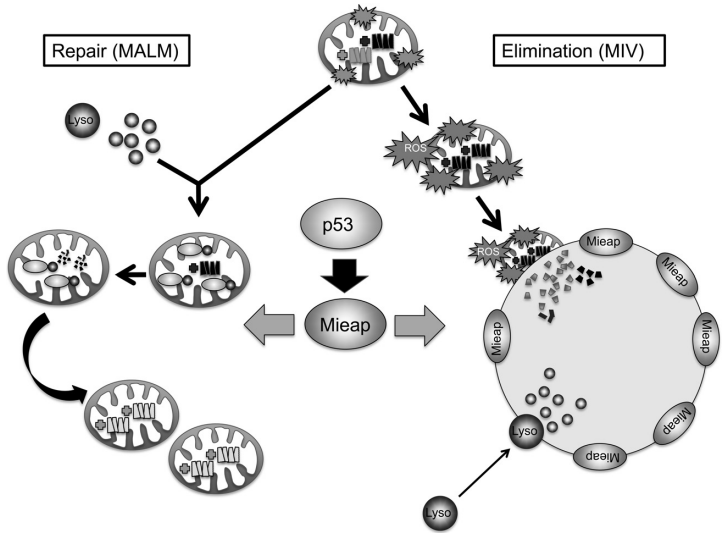

Figure 1

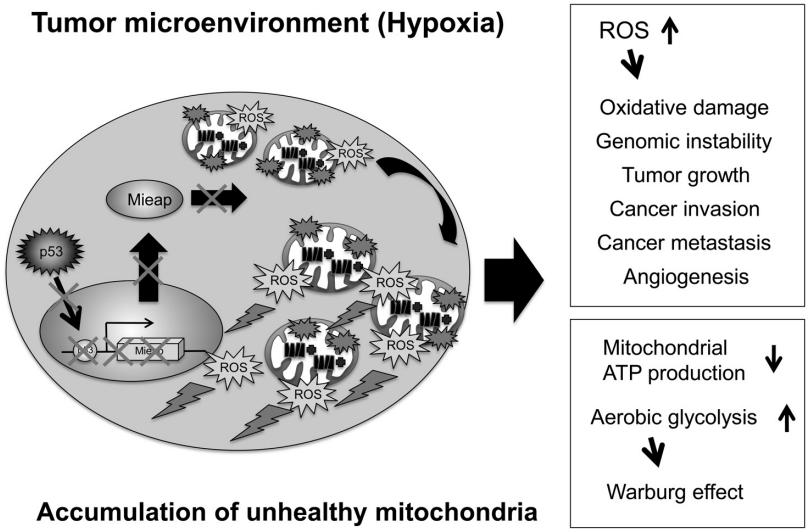

Figure 2

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Division of Molecular and Cellular Medicine

Takahiro Ochiya, Fumitaka Takeshita, Masaki Kawamata, Nobuyoshi Kosaka, Ryou-u Takahashi, Ayako Inoue, Wakako Kobayashi, Maki Abe, Yu Fujita, Hiroaki Miyazaki, Takeshi Katsuda, Makiko Ono, Yusuke Yoshioka, Luc Gailhouste, Muriel Thirion, Yuki Konishi, Kurataka Ootsuka, Yutaka Nezu, Keitaro Hagiwara, Naoomi Tominaga

Introduction

The focus of the Division of Molecular and Cellular Medicine lies in the development of novel treatments and diagnosis to advance cancer therapy. The specific activities were as follows: 1) Studies on microRNA (miRNA) regulation in cancer cells and development of RNA interference (RNAi) -based therapeutics; 2) An exosome as a novel diagnosis and therapeutic tool against cancer; 3) Study of stem cells and their therapeutic applications.

1) Studies on miRNA regulation in cancer cells and development of RNAi-based therapeutics.

RNAi-based therapeutics is a promising approach as novel and potentially more effective treatments for cancer and miRNA are one of the targets involved in the regulation of tumor-related genes (1-5, 31). We show miRNA (miR)-582-5p and -3p, which are strongly decreased in high-grade bladder cancer clinical samples (6). The overexpression of miR-582-5p or -3p reduced the proliferation and invasion of human bladder cancer cells. Furthermore, transurethral injections of miR-582 suppressed tumor growth and metastasis in an animal model of bladder cancer. Thus, local treatment with RNAi is anticipated to become available for clinical use. We have developed novel RNAi agents (PnkRNA™, nkRNA®) that show knockdown of the target gene in tumor cells on lung tissues through inhalation without any sophisticated delivery technology in mice (7).

Our group also identified miR-148a as a liver-specific miRNA highly expressed in the adult liver and found that miR-148a was critical for hepatic differentiation through the direct targeting of DNA methyltransferase (DNMT) 1, a major enzyme responsible for epigenetic silencing (8, 32). We also found that miR-148a directly targeted the c-Met oncogene in human liver cancer. Therefore, our study suggests that miR-148a plays an important dual role in hepatic maturation and liver tumor suppression.

We previously identified Ribophorin-2 (RPN2) as a novel regulator for drug resistance. We also found that RPN2 played an important role in the regulation of breast cancer stem cell (CSC) properties such as tumorigenic and metastatic activities via stabilizing p53 mutants (9). These findings reveal a previously undescribed molecular mechanism for mtp53 stabilization in breast cancer and suggest that the RPN2/mtp53 regulatory network could be a promising target for anti-CSC therapy. For clinical application of siRNA targeting RPN2, pre-clinical trials with naturally occurring breast cancer in dogs have been performed. The first clinical trials of siRNA in Japan will be started next year at the National Cancer Center Hospital (NCCH).

2) An exosome as a novel diagnostic and therapeutic tool against cancer

Circulating exosomes have been found in a variety of body fluids including serum, plasma, urine, saliva, and breast milk (10). The existence of circulating exosomes in the blood of cancer patients has raised the possibility that exosomes may serve as a novel diagnostic marker (11-12, 33). For this reason, a new method for a highly sensitive method of identifying circulating exosomes has been developed (13,14). Cell-cell communication of cancer cells and microenvironmental cells is critical for the acquisition of malignancy in human cancer, however, the precise molecular mechanisms of this cell-cell communication remain unclear (15,16). We have demonstrated that a tumor-suppressive miRNA secreted from non-cancerous cells via the neutral sphingomyelinase 2 (nSMase2)-mediated exosomal pathway could be transported between cells and exert gene silencing in the recipient cancer cells, thereby leading to an inhibition of cancer cell growth. We recently showed the contribution of nSMase2-mediated exosomes from cancer cells to the cancer cell metastasis *in vivo* via the induction of angiogenesis in the tumor (17). These findings prompted us to consider the idea for the application of the exosome in the diagnosis of and therapy against cancer development (18, 19).

3) Study of stem cells and their therapeutic applications

We are interested in the therapeutic potential of stem cells, including induced pluripotent stem

(iPS) cells, embryonic stem (ES) cells (20-24), and mesenchymal stem cells (MSCs) (25-28). Our main focus is particularly on the realization of the clinical application of adipose tissue derived-mesenchymal stem cells (ADSC) in liver diseases (25, 26). We have also reported that a stem or progenitor cell-based approach is beneficial in the regeneration of functional liver tissue (23, 24). Recently, MSCs are attracting much attention not only for their own potential as cells, but also for their secretory capacity of exosomes that can have therapeutic benefits (27). We recently reported the novel therapeutic potential of exosomes secreted from human ADSCs against Alzheimer's disease (AD) (28). We found that hADSCs secrete exosomes carrying enzymatically active neprilysin, the most important β-amyloid peptide (Aβ)-degrading enzyme in the brain. We have also studied the relationships between infection with the hepatitis viruses and cancer pathogenesis (29, 30).

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Division of Epigenomics

Toshikazu Ushijima, Eriko Okochi-Takada, Satoshi Yamashita, Kiyoshi Asada, Tohru Niwa, Hideyuki Takeshima, Naoko Hattori, Yukie Yoda, Takamasa Takahashi, Yasuyuki Shigematsu, Satoshi Yoshida, Emil Rehnberg, Akiko Mori, Naoko Kobayashi, Yuko Miyaji, Aya Nakajima, Zong Liang

This Division has been focusing on the epigenetic mechanisms of carcinogenesis, and has identified many aberrantly methylated CpG islands (CGIs) in various cancers, *i.e.*, gastric cancers, breast cancers, pancreatic cancers, lung cancers, ovarian cancers, neuroblastomas, and melanomas. This has led to the identification of novel tumor-suppressor genes (TSGs) in gastric cancers, development of a powerful prognostic marker in neuroblastomas, and establishment of the concept of an "epigenetic field for cancerization". This Division continues its activity through revealing epigenetic alterations in various cancers, and by developing clinically useful biomarkers, a novel approach of cancer prevention, and epigenetic therapy.

Identification of novel epigenetic alterations

Identification of TSGs inactivated by aberrant DNA methylation is important. During 2013, by focusing on genes on chromosome X that can be inactivated only by a single hit, *FHL1* was identified as a TSG inactivated in gastrointestinal cancers by either aberrant DNA methylation or somatic mutation. Inactivation of *FHL1* in normal-appearing tissues was suggested to be involved in the formation of an epigenetic field for cancerization (1).

The recent development of personal sequencers and bead array technology has made it possible to obtain integrated pictures of genetic and epigenetic alterations on the same set of cancer samples. This Division showed that the number of aberrantly methylated genes was highly variable among individual gastric cancers, and that the CpG island methylator phenotype (CIMP) was associated with mutations of oncogenes, such as *ERBB2* and *PIK3CA* (2).

Development of biomarkers

This Division previously revealed that neuroblastomas with CIMP have a worse prognosis than those without (3). At the same time, aberrant DNA methylation of individual TSGs has also been reported to be associated with a poor prognosis. During 2013 it was revealed that CIMP had a stronger prognostic power than methylation of individual genes (Figure 1) (4). The clinical usefulness of CIMP in neuroblastomas is currently being analyzed using materials collected in a prospective manner. In gastric cancers, levels of accumulated methylation in normal-appearing tissues are expected to be useful as a cancer risk marker, and a prospective study is being conducted to bring this concept into clinical practice. The degree of aberrant methylation in gastric mucosae was correlated with the severity of *Helicobacter pylori (H. pylori)*-related gastritis (5).

Contamination of normal cells is almost always present in tumor samples and affects their molecular analyses, and development of a biomarker that can estimate the fraction of cancer cells in a tumor DNA sample is important. Using esophageal squamous cell carcinoma (ESCC) as an example, this Division isolated three genomic regions, *TFAP2B*, *ARHGEF4*, and *RAPGEFL1*, whose DNA methylation levels reflected the fraction of cancer cells in a tumor DNA sample (6).

Development of cancer prevention

Suppression of aberrant DNA methylation is a novel approach to cancer prevention that has the potential to reverse risk once accumulated. This Division revealed that suppression of aberrant DNA methylation by a DNA demethylating agent, 5-aza-2'-deoxycytidine (5-aza-dC), can prevent *H. pylori*-induced gastric cancers using a Mongolian gerbil model (7). It was also shown that *Il1b* induced by *H. pylori* infection enhanced mouse gastric carcinogenesis (8). It was suggested that removal of aberrant DNA methylation and/or suppression of DNA methylation induction could become a novel target for cancer prevention.

Development of a novel technique to detect a combination of epigenetic modifications

A combination of epigenetic modifications specifically present in cancer cells is a possible target in developing cancer cell-specific epigenetic therapy.

Regardless of the importance of combinations of epigenetic modifications, techniques to detect combinations are limited. This Division developed a novel technique to visualize a combination of epigenetic modifications (designated as imaging of a combination of histone modifications, iChmo) (9). This technique was able to visualize a combination of epigenetic modifications not only in cultured cells but also in tissue samples, and offered advantages in the detection of combinations in samples with heterogeneous cell population and also in tissue samples.

Other activities

This Division assisted other research groups with the epigenetic analysis in *UNC5D* in neuroblastoma (10), that of *PTEN* in colorectal cancer (11), and those in various animal models (12-14).

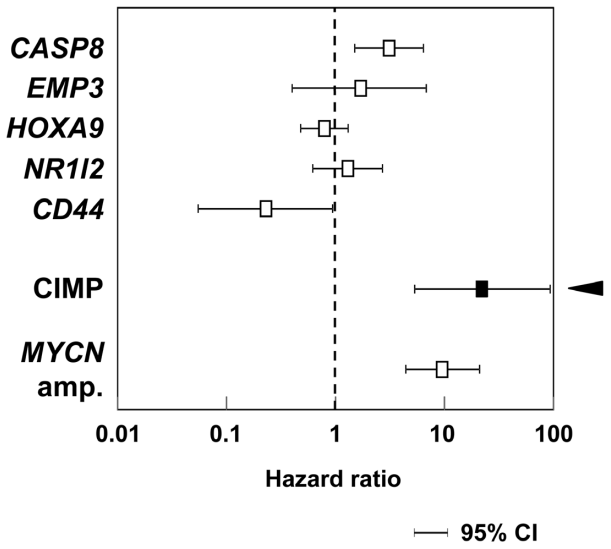

Figure 1. Stronger prognostic power of the CpG island methylator phenotype (CIMP)

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Journal

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Division of Pharmacoproteomics

Tadashi Kondo, Takashi Tajima, Fusako Kito, Marimu Sakumoto, Kazutaka Kikuta, Kenta Mukaihara, Naofumi Asano, Yuta Kurota, Daisuke Kubota, Hiroshi Ichikawa, Yutaka Sugihara, Yuki Tani

Introduction

Our research goal is to contribute to the development of effective anti-cancer therapy. To achieve this goal, we have developed our current research plan, which is aimed at the discovery of biomarkers and drug targets, on the basis of interdisciplinary collaborative projects. All malignancies are the research subjects, and recently we focused more on sarcomas.

Research activities

In sarcomas, we investigated biomarker candidates for personalized medicine and therapeutic targets for additional indications. In osteosarcomas, we discovered novel protein and miRNA biomarkers to predict the response to neo-adjuvant treatments, and launched a collaboration with diagnostic companies. We aim to commercialize our discovery over the next few years. One protein was considered as a candidate for a drug target, and we confirmed the inhibitory effects of the small molecule approach on osteosarcoma cells. In gastrointestinal stromal tumors, we discovered pfetin as a novel prognostic biomarker, achieved multi-institutional validations, and commercialized our original antibody as a research tool in partnership with a domestic company. We plan to reveal the clinical usefulness of measuring pfetin expression in a prospective clinical study. In alveolar soft tissue sarcomas, we surveyed all tyrosine kinases using specific antibodies, identified over-expressed kinases in tumor tissues, and started to find specific inhibitors for additional indications. In mixoid liposarcomas, we examined the protein complex of the fusion gene products of sarcomas with a proteomic approach, and revealed the functional properties of complex components. In epithelioid sarcomas and rhabdomyosarcomas, we identified proteins with specific expression in tumor tissues, and started molecular characterization of their properties. We also applied our approach to other malignancies. In gastric cancer, we identified proteins associated with lymph node metastasis. In renal cancer, we found prognostic biomarkers. In metastatic bone tumors, we identified proteins and miRNAs with unique expression in metastatic tumors, and characterized their functional properties *in vitro*. A novel protein fractionation system for proteomic analysis has been under development in collaboration with an industrial company. To reveal the molecular backgrounds of biomarkers, *in vitro* experiments were extensively performed.

Education

Four young doctors and two students had training in translational research. The doctors who stayed in our laboratory were supervised regarding their presentations, papers, and grant applications. One student started his professional career in the field of translational research. The Division Chief has given lectures in various universities as a visiting professor or lecturer.

Perspectives

Using clinical materials and comprehensive analysis, we are identifying various promising biomarkers and drug targets. Through functional experiments and independent validations, we are selecting candidates for further research. In each stage we have several candidates, and examine more malignancies using the same approach. For pfetin and the several other biomarkers, we have reached the stage of commercialization. We will soon clarify the clinical utility of our biomarkers and their targets in future clinical studies.

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Division of Genome Biology

Takashi Kohno, Naoto Tsuchiya, Hideaki Ogiwara, Kouya Shiraishi, Motonobu Saito, Yoko Shimada, Mariko Sasaki, Ayaka Otsuka, Yuko Fujiwara, Tatsuji Mizukami, Reika Iwakawa-Kawabata, Masaki Takenaka, Takashi Nakaoku, Hideyuki Hayashi, Takashi Mitachi, Yujin Ishihara, Shino Kasuga, Daisuke Kurioka, Momoyo Nishida, Tomoyo Kobayashi, Yoshiaki Onozato, Mei Tanabe

Introduction

Somatic mutations in the cancer genome and inter-individual variations in the human genome are critical keys to improving the efficacy rate of cancer clinics. The aim of our division is to find "seeds" that improve the treatment and prevention of cancer by identifying and elucidating the biological significance of somatic mutations in cancer genomes and genetic polymorphisms of cancer patients. We are working together with National Cancer Center (NCC) staff from hospitals, the Research Center for Cancer Prevention and Screening, and the Center for Cancer Control and Information Service to fight lung cancer, the most common cause of cancer-related deaths in Japan and worldwide.

Research activities

1. Genes for personalized therapy

Whole RNA sequencing of 30 lung adenocarcinomas (LADCs) led us to identify the RET fusion gene as a new druggable driver oncogene present in 2% of LADCs. A phase II clinical trial, which is investigating the therapeutic effect of a RET-tyrosine kinase inhibitor, vandetanib, has been started as described below (Figure 1). Future personalized therapies including all druggable oncogene targets will cover >60% and >30% of Japanese and US/European LADC patients, respectively.

SMARCA4/BRG1, encoding an ATPase functioning as a catalytic subunit of the SWI/SNF chromatin remodeling complex, is deficient by genetic and epigenetic alterations in 10% of lung cancers, preferentially in those without driver oncogene aberrations. Our functional studies, including that on DNA double strand break repair, revealed that ablation of the ATPase activity of SMARCA2/BRM, another SWI/SNF catalytic subunit, specifically causes senescence of BRG1-deficient cancer cells based on synthetic lethality. BRM-ATPase inhibitory therapy is a promising approach for the treatment of BRG1-deficient cancers, including lung cancers without mutations in known therapeutic target genes (Figure 1). Specific inhibitors against BRM-ATPase are searched for by conducting a collaborative study with a pharmaceutical company. Patients with BRG1-deficient cancers will benefit from the BRM-ATPase inhibitory therapy.

2. Genes for personalized prevention

Our genome-wide association study (GWAS) verified two previously reported loci, TERT and TP63, and identified two new susceptibility loci, BPTF (Bromodomain PHD finger transcription factor), encoding a chromatin remodeling protein, and BTNL2 (Butyrophilin-like 2), encoding an immune-modulating protein. All the defined SNPs were common ones with minor allele frequencies >0.25 and per allele odds ratios of 1.1-1.4. Associations of these four loci were validated in an independent sample set. International and pan-Japan collaborative GWASs are underway to further identify genetic factors involved not only in the susceptibility to but also in the prognosis of lung cancer.

3. Biological roles of microRNAs in cancer development

A tumor-suppressive microRNA, miR-22, is a regulator for intrinsic tumor-suppressor networks organized by p53. Through the miR-22 target screening, we recently identified NIMA-related kinase 9, NEK9, as a novel factor required for cell cycle progression in p53-mutated cancer cells. NEK9 depletion repressed cell proliferation selectively in p53 deficient cancer cells *in vitro* and *in vivo*, suggesting its inhibition could be a novel strategy for the development of cancer therapy. Furthermore, based on the detailed analysis of exosomal miRNAs that were circulating in the serum, we have successfully identified several 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, and positive therapeutic responses have been

observed. For the purpose, >300 nonsmall cell lung carcinoma cases have been screened by an all-Japan consortium consisting of >125 hospitals, LC-SCRUM-Japan (Lung Cancer Genomic Screening Project for Individualized Medicine in Japan), using RT-PCR and FISH assays developed by us. LC-SCRUM-Japan will shortly include the screening of two more driver oncogenic aberrations, ROS1 fusion and BRAF mutation, for clinical trials of corresponding kinase inhibitors.

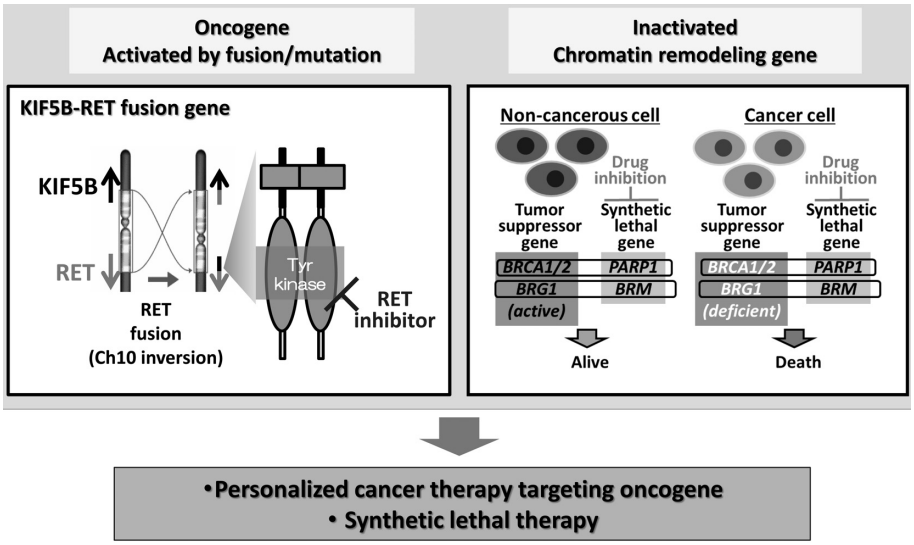

Figure 1. Personalized cancer therapy based on genetic aberrations

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Division of Cancer Genomics

Tatsuhiro Shibata, Fumie Hosoda, Yasushi Totoki, Yasuhito Arai, Hiromi Nakamura, Tomoki Shirota, Hirofumi Rokutan, Naoko Okada, Tomoko Urushidate, Hiroko Shimizu, Shoko Ohashi, Wakako Mukai, Isao Kurosaka, Arisa Hara, Yasuko Konagai, Momoko Nagai, Asmaa M. Elzawahry

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 representing heterogeneous and interconnected "biological systems" that contribute to the pathogenesis of cancer. This Division has also organized the facility and developed new informatics methodologies for the analysis of a next-generation high-performance sequencer.

Research activities

Whole genome/exome sequencing of liver cancer and the International Cancer Genome Project

We have participated in the International Cancer Genome Consortium to generate a comprehensive high-resolution catalog of genomic changes for major cancer types (1-3). We performed whole genome sequencing of 31 Japanese liver cancers and identified high accurate sets of somatic mutations. We provided this dataset for the analysis of mutational signatures between various cancer types (1). We also performed whole exome sequencing of 213 Japanese liver cancers and executed the joint collaboration of two large-scale cancer genome projects (ICGC and TCGA) and comparatively analyzed the trans-ethnic liver cancer genome data of 608 cases.

Novel druggable fusion genes in cholangiocarcinoma

Cholangiocarcinoma is an intractable cancer, with limited therapeutic options, in which the molecular mechanisms underlying tumor development remain poorly understood. We performed whole transcriptome sequencing (WTS) analysis in eight specimens from cholangiocarcinoma patients without KRAS/BRAF/ROS1 alterations, and identified two fusion kinase genes, FGFR2-AHCYL1 and FGFR2-BICC1. In reverse transcriptase polymerase chain reaction (RT-PCR) screening, the FGFR2 fusions were detected in 9 patients with cholangiocarcinoma, exclusively in the intrahepatic subtype (9/66, 13.6%). The rearrangements were mutually exclusive with KRAS/BRAF mutations. Expression of the fusion kinases in NIH3T3 cells activated MAPK, and conferred anchorage-independent growth and in vivo tumorigenesis of subcutaneous transplanted cells in immune-compromised mice. Treatment with FGFR kinase inhibitors, BGJ398 and PD173074, effectively suppressed transformation. The expression pattern of these fusions in association with sensitivity to FGFR inhibitors warrant a new molecular classification of cholangiocarcinoma and suggest a new therapeutic approach to the disease.

Oncogenic ROS1 rearrangement in lung cancer

Non-small-cell lung cancer (NSCLC) has recently been undergoing extensive molecular subclassification. We performed a histological analysis, WTS and RT-PCR analysis of 799 surgically resected NSCLC samples and identified 15 cases of ROS1-rearranged cancer. Half of the cases harbored mucinous cribriform or signet ring cell features similar to the ALK-rearranged type (4). We established a transgenic mouse model for ROS1-rearranged lung cancer, and revealed a pivotal role of the ROS1-fusion gene in lung carcinogenesis (5).

Transcriptome sequencing analysis for other tumor types

To understand the genetic basis and to identify new drug targets in sarcomas and other cancer types, a transcriptome sequencing approach has been undertaken (6-8). WTS and a verification experiment with the RT-PCR method identified more than a hundred in-frame fusion genes in 68 gastric cancers examined. Those fusion genes include good candidates for therapeutic targets: two oncogenic protein kinase gene fusions, two oncogenic pathway-activating gene fusions, and four recurrent promoter-swapping gene fusions. Functional analyses of these fusion genes are in progress.

Metabolomic analysis of the GLO1 oncogene in gastric cancer

We have identified a frequent amplification of chromosome 6p21 in gastric cancer and six potential

cell growth-activating genes in this region. Among them, GLO1 that encodes glyoxalase I, a detoxifying enzyme of a cytotoxic methylglyoxal, exhibited the strongest oncogenic activity. Downregulation of GLO1 resulted in growth inhibition of gastric cancer cells. A metabolomic analysis of GLO1-downregulated gastric cancer cells revealed that GLO1 functions in the activation of the central carbon metabolism: glycolysis, the pentose phosphate pathway, and TCA cycle. These data indicated that GLO1 is a multifunctional metabolic oncogene and could be an important therapeutic target for gastric cancer.

Bioinformatics platform and support for other cancer research

We developed highly efficient and accurate in-house algorithms to detect and analyze somatic mutations, structural alterations including fusion genes, virus integrations, transcriptome and small RNAs. Using them, we supported a bioinformatics analysis for non-coding RNAs and gene expression (9-12). As an expert pathological function, further collaborative clinical research with the Division and hospital groups has been performed (13). We also developed a somatic mutation caller for low tumor purity samples and subclonal mutations.

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Division of Chemotherapy and Clinical Research

Tesshi Yamada, Masaya Ono, Kazufumi Honda, Mari Masuda, Nami Miura, Ayako Mimata, Masahiro Kamita, Tomoko Umaki, Yuko Miyamoto, Hiroko Ito, Haruyo Tozaki, Akihiko Miyanaga, Takafumi Watanabe, Yukio Watabe, Nobuhiko Nishijima

Introduction

Even for cancers having the same origin and histology, their clinical courses may vary among individuals. Accurate prediction of disease progression and therapeutic efficacy is therefore essential for optimization of therapy in individual patients. The Division has shifted its main focus from basic research to the identification and clinical application/translation of biomarkers applicable for therapy personalization. We reported 2 prognostic and 1 predictive biomarkers during 2013.

Distinct outcome of stage I lung adenocarcinoma with ACTN4 cell motility gene amplification

Even if detected at an early stage, a substantial number of lung cancers relapse after surgery. Patients with such tumors are likely to benefit from adjuvant therapy, but no method for discriminating among them has been established. We identified that amplification of a single metastasis-related gene was able to recognize a small (8-16%) but substantial subset of stage I lung adenocarcinomas with a markedly unfavorable outcome. Actinin-4 is an actin-binding protein that we originally identified as being associated with enhanced cell motility and cancer invasion. Overall survival was significantly worse for patients with stage I lung adenocarcinoma harboring actinin-4 (ACTN4) gene amplification than for those whose tumors showed no such gene amplification (P<0.001, log-rank test). Multivariate analysis revealed that ACTN4 gene amplification in stage I lung adenocarcinoma was an independent factor associated with a higher risk of death (hazard ratio, 6.78; P<0.001, Cox regression analysis) (Table 1). The result was first astonishing to us, because to the best of our knowledge no single biomarker has yet been identified as having such a high prognostic significance for early-stage lung cancer. We carefully confirmed its reproducibility in multiple cohorts totaling 1774 patients. We may say that ACTN4 gene amplification in lung adenocarcinoma is equivalent to HER2/CERBB2 gene amplification in breast cancer.

Diagnostic and prognostic significance of the alternatively spliced ACTN4 variant in high-grade neuroendocrine pulmonary tumors

High-grade neuroendocrine tumors (HGNT) of the lung manifest a wide spectrum of clinical behavior, and patients whose prognosis is predicted to be unfavorable might benefit from intense adjuvant chemotherapy. So far, however, no prognostic biomarker for HGNT has been established.

In a study, we demonstrated that the variant form of actinin-4 is a novel biomarker predictive of an unfavorable postsurgical outcome in HGNT patients. We established a monoclonal antibody specifically recognizing the product of the alternatively spliced *ACTN4* transcript, and used it to examine the expression of variant actinin-4 immunohistochemically in a total of 609 surgical specimens of various histological subtypes of lung cancer. Variant actinin-4 was expressed in 55% (96/176) of HGNTs. Expression of variant actinin-4 was significantly associated with poorer overall survival in HGNT patients ($P < 0.001$, log-rank test). Multivariate analysis using the Cox proportional hazards model showed that expression of variant actinin-4 was the most significant independent negative predictor of survival in HGNT patients (hazard ratio, 2.18; $P < 0.001$) after the presence of lymph node metastasis.

Soluble Interleukin-6 receptor is a serum biomarker that predicts the response of esophageal squamous cell carcinoma to neoadjuvant chemoradiotherapy

Preoperative chemoradiotherapy (PCRT) has been shown to improve the outcome of patients with esophageal caner, but response to the therapy varies among patients. Esophageal squamous cell carcinoma (ESCC) patients with high levels of serum vascular endothelial growth factor and C-reactive protein have been reported to respond poorly to PCRT, but no reliable biomarker that can predict the efficacy of PCRT has yet been established.

We performed comprehensive profiling of 84 serum cytokines in 37 ESCC patients who were able to receive neoadjuvant PCRT. We found that the baseline level of soluble interleukin-6 receptor (sIL6R) was significantly higher in 30 patients who failed to achieve a histological complete response to PCRT ($P = 0.005$). Multivariate analysis revealed that the increased level of sIL6R was one of several

significant independent predictors of an unfavourable outcome (hazard ratio, 2.87; $P = 0.017$). The increased level of sIL6R in patients who did not obtain a complete response was reproducibly observed in an independent cohort of 34 patients. These findings were further subjected to independent validation using retrospective and prospective cohorts.

Table 1. Hazard Ratios for Death in 284 Stage I Cases of TMA, According to Prognostic Factors

Characteristics		Univariate analysis			Multivariate analysis		
		Hazard Ratio	[95% CI¶]	*P* Value*	Hazard Ratio	[95% CI¶]	*P* Value*
Sex	(Female vs. Male)	2.98	[1.06-8.36]	**.04**	1.73	[0.40-7.47]	.16
Age	(<65 yr vs. ≥65 yr)	3.24	[1.28-8.23]	**.01**	3.61	[1.31-9.94]	**.01**
Smoking history	(Never smoked vs. Current and former smokers)	3.23	[1.25-8.34]	**.02**	1.31	[0.32-5.26]	.71
Pathological stage†	(IA vs. IB)	6.88	[2.26-21.0]	**< .001**	3.53	[1.11-11.2]	**.03**
Histological differentiation	(Well differentiated§ vs. Moderately and poorly differentiated)	4.83	[1.72-13.6]	**.003**	2.55	[0.86-7.59]	.09
EGFR mutation	(Absent vs. Present)	0.20	[0.07-0.62]	**.005**	0.43	[0.12-1.49]	.18
KRAS mutation‡	(Absent vs. Present)	1.57	[0.45-5.41]	.48			
ACTN4 gene amplification	(Negative vs. Positive)	10.53	[4.15-26.7]	**< .001**	6.78	[2.59-17.7]	**< .001**

¶ Abbreviation: CI, confidence interval.
* Cox regression analysis. *P* values of < .05 are shown in bold
† According to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours, 6th edition (2002).
§ Includes bronchioloalveolar carcinoma [World Health Organization (WHO) Histological Typing of Lung and Pleural Tumours, 3rd edition (1995)].
‡ Six cases for whom *KRAS* mutaion data were not avilable were excluded.

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Division of Cancer Pathophysiology

Yasuhito Uezono, Seiji Shiraishi, Masami Suzuki, Kanako Miyano, Yumi Sawada, Yuka Sudo, Junko Ezuka, Yukiko Araki, Katsuya Morita, Kiyoshi Terawaki, Katsuya Ohbuchi, Koichiro Minami, Tohru Yokoyama, Naofumi Oyanagi, Yohei Kashiwase, Akinobu Yokoyama, Hitomi Nishimura

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.

Research activities

Translational research to innovate and develop new strategies to improve pain analgesia in cancer patients

The purpose of our studies is to develop new therapies for both refractory cancer pain and chemotherapy-induced peripheral neuropathy, which make the quality of life of cancer patients even worse. One of the targets is severe pain with bone-metastasized patients and patients undergoing cancer chemotherapy. A second target is stomatitis induced by chemotherapy and/or radiotherapy.

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 and streptozotocin-induced diabetes model (5). 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 (Morita and Shiraishi et al., PLOS ONE (2014), in press). The pain-relieving action of PAF antagonists were found to be effective in neuropathic pain animal models (5), and patent was issued covering the compounds; "COMPOSITION FOR TREATMENT OF CANCER PAIN AND USE THEREOF WO/2012/077775 PCT/JP2011/078508".

The cancer patients who undergo chemotherapy, radiotherapy and terminal paliative care often have a wide range of stomatitis, which induces severe pain and limits the fundamental basics of life, namely “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 blocks selectively 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, and have elucidated the effects of the compound X on oral pain indueced by stomatitis. We estabilised the method to evaluate the intensity of oral pain using stomatitis model animals. With the model, lidocaine inhibited not only the pain but also caused numbness in normal oral mucosa. On the other hand, 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 a more superior analgesic drug than lidocaine.

In a basic study with cultured cell models, we have been elucidating the pharmacological actions of the compound X (*e.g.*, how does it block only the pain-related neurons?). By connecting such a basic study to a clinical study, we want to develop "the new pain-killer the compound X, which can remove the oral pain without changing the texture and taste of food" for the cancer patients with severe painful stomatitis.

Prevention, and decrease the cachexic symptoms that make the quality of life of caner patients even worse

We established novel cancer cachexia animal models (2). We 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 (1, 2, 4). We then established a novel cancer cachexic model by inoculating human gastric

cancer cells (85As2) (2), and 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 (Terawaki K et al., Am J Physiol Endocrinol Metab, 306:E373-E387, 2014). We summarize the mechanisms of traditional Japanese Kampo medicines and their potential use for improvement of the symptoms of cancer cachexic patients and the side effects in cancer patients who take anticancer agents. We further try to elucidate novel methods to overcome cancer cachexic symptoms and make them clinically available, in additional to rikkunshito, in collaboration with several clinical groups in Japan.

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Division of Cancer Stem Cell

Kenkichi Masutomi, Yoshiko Maida, Satoko Yamaguchi, Mami Yasukawa, 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 to develop novel therapeutic approaches to treating cancer through targeting cancer stem cells. In particular, the Division studies the molecular links between a) telomerase and RNA dependent RNA polymerase; b) telomerase and cancer stem cells; and c) telomerase and epigenetics.

Telomerase and RNA dependent RNA polymerase

Telomerase is a ribonucleoprotein complex that elongates telomeres. Human TERT (hTERT) 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 (ncRNA) template, human *TERC* (*hTERC*). In addition to *hTERC*, we found that hTERT binds a second ncRNA, *RMRP*, the RNA component of RNase MRP, and TERT and *RMRP* act as an RNA-dependent RNA polymerase (RdRP) and produce double-stranded *RMRP* that can be processed into an endogenous small interfering RNA (siRNA) to regulate *RMRP* expression levels (Figure 1). To further investigate the biological functions of hTERT RdRP, we generated a new anti-hTERT monoclonal antibody and established a RdRP assay using hTERT immune complexes isolated from cell lysate (IP-RdRP assay). We confirmed that both hTERT levels and hTERT-associated RdRP activity are increased during mitosis while telomerase activity is upregulated in S phase. These observations indicate a non-telomere directed function of hTERT during mitosis.

Telomerase and cancer stem cells

Previous studies indicated that hTERT has activities beyond telomere maintenance, and it is speculated that the constitutive expression of hTERT not only stabilizes telomere length and facilitates cell immortalization but also contributes to tumor susceptibility and alters stem cell cycling *in vivo* even when telomere lengths are not limited. We showed that hTERT forms a protein complex with the SWI/SNF component, Brahma-related gene 1 (BRG1) and the nucleolar GTP-binding proteins, nucleostemin (NS), and the complex composed of hTERT, BRG1 and NS (TBN complex) participates in the regulation of tumor initiating cells (TICs) phenotypes through telomere-independent mechanisms (Figure 2). We also confirmed that the cells that constitutively express NS exhibited increased beta-catenin signaling and elevated MYC, OCT3/4, KLF4 and TWIST (master regulator of epithelial mesenchymal transition [EMT]) expression. Moreover, cells that constitutively express elevated levels of hTERT, BRG1 and NS 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.

TERT, BRG1 and NS are upregulated in malignant cells. We found that the expression levels of BRG1 and NS as well as hTERT are increased in the cells arrested in M phase. We further confirmed that the hTERT, BRG1 and NS complex assembles specifically in mitosis. Because hTERT exerts RdRP activity in mitotic cells, we hypothesized that the TBN complex may function as a RdRP complex. To investigate the hypothesis, we performed an IP-RdRP assay using either BRG1 immune complexes or NS immune complexes and found RdRP activity in both of the immune complexes as observed with the hTERT immune complexes. The results indicate a novel function of the TBN complex as a RdRP.

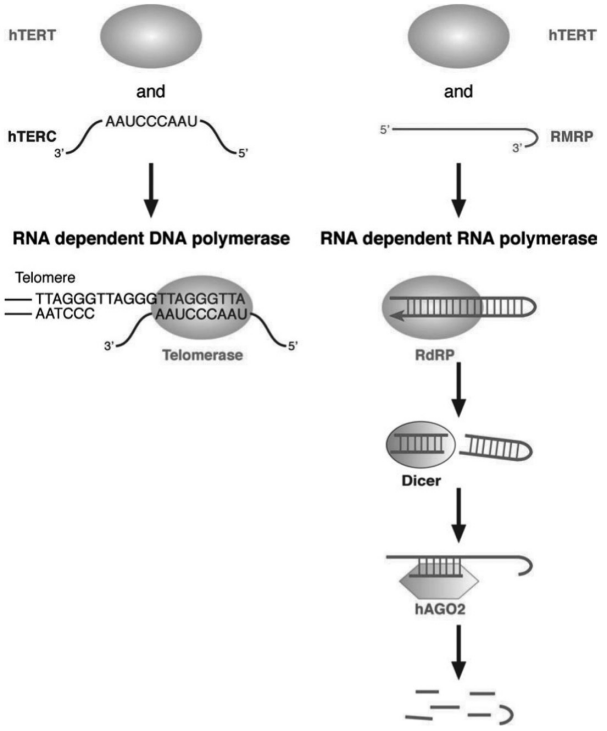

Figure 1. hTERT exerts RdRP activity

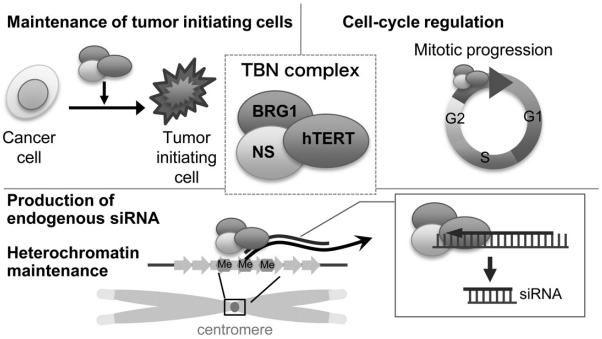

Figure 2. Various functions of the TBN complex

Telomerase and epigenetics

Previously reports have shown that functional non-coding RNA synthesized via RdRP is involved in the physiology of model organisms through its epigenetic regulation. RdRP regulates centromeric heterochromatin formation and it is required for proper chromosome segregation in mitosis. The RNA-directed RNA polymerase complex (RDRC) and the RDRC-like complex maintain heterochromatin in yeast and worms, respectively, and both complexes contain RdRP and RNA helicase. Because hTERT has RdRP activity, and BRG1 has helicase activity, we speculated that the TBN complex might have similar functions with the RDRC and the RDRC-like complex. We therefore focused on studying the molecular basis of maintenance of the heterochromatin formation by RNAs, especially by non-coding RNAs such as siRNAs, and RdRP in human cells. It is widely known that epigenetic abnormalities contribute to tumor progression, but the detailed mechanisms are unclear. It is thus important to understand the detailed mechanisms of epigenetics regulation. We found that hTERT localizes not only at centromeres but also on mitotic spindles in M phase. We further found that the TBN complex contributes to heterochromatin maintenance at centromeres and transposons. Acting as a RdRP, the TBN complex produced double stranded RNAs homologous to centromeric repeat elements and transposons that were processed into small interfering RNAs targeted heterochromatin regions. These small interfering RNAs promoted heterochromatin assembly in a manner dependent on the RNA interference pathway. These observations indicated that the mammalian homologue of RdRP (TERT) regulates heterochromatin formation through its epigenetic regulation. We further confirmed that suppression of hTERT, BRG1 or NS increases the cells arrested in mitosis, suggesting a regulatory effect of the TBN complex on mitotic progression (Figure 2). Our findings suggest that inhibitors for the novel functions of hTERT may prove useful in targeting cancer stem cells.

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Division of Gene and Immune Medicine

Kazunori Aoki, Kenta Narumi, Naoko Goto, Yoko Kobayashi, Kouichirou Aida, Yuki Yamamoto, Reina Miyakawa, Yosei Rin, Tsukasa Shinohara, Kei Nakano

Introduction

Research programs in the Division of Gene and Immune Medicine consist of the development of gene and cell therapies for solid cancers based on the analysis of host-immune response against cancer, and the development of novel cancer-targeting vectors by the peptide-displaying viral library approach. The specific activities in 2013 were as follows: 1) Combination of hematopoietic stem cell transplantation and immune gene therapy against solid cancers; 2) Cancer-targeting vectors using the peptide-display adenovirus library.

Research Activities

Combination of hematopoietic stem cell transplantation and immune gene therapy against solid cancers

Lymphopenia-induced homeostatic proliferation (HP) of T cells following autologous hematopoietic stem cell transplantation (HSCT) skews the T-cell repertoire by engaging tumor-associated antigens (TAAs), leading to an induction of antitumor immunity. Since the tumor-reactive lymphocytes preferentially proliferate under the condition of HP, the Division examined whether the priming of donor lymphocytes to TAAs could enhance HP-induced antitumor immunity in autologous HSCT recipients. Since type I interferon (IFN) maturates the dendritic cells and promotes the priming of T cells, the Division investigated whether the further priming of donor cells by IFN-α could strengthen the antitumor effect of HSCT. The intratumoral IFN-α gene transfer significantly increased the number of IFN-γ-positive lymphocytes in response to CT26 cells but not the syngeneic lymphocytes in donor mice. The infusion of primed donor lymphocytes markedly suppressed the tumor growth in recipient mice, and cured 64% of the treated mice (Figure 1) (1). Autologous HSCT with the infusion of primed donor lymphocytes is a promising strategy to induce an effective antitumor immunity for solid cancers.

On the other hand, how HSCT alters the immunosuppressive microenvironment in the tumors is unknown. The Division analyzed the kinetics of regulatory T cells (Tregs) in the tumors after syngeneic HSCT. Unexpectedly, the frequency of $CD4^+$ cells expressing Foxp3 was increased in the spleen, whereas the frequency was clearly decreased in the tumors after HSCT. Next, to examine the mechanism of Treg suppression after HSCT, dendritic cells were isolated from tumors. A large amount of the Treg-inhibitory cytokine IL-6 was secreted from the dendritic cells in the tumors but not in the spleens in the recipient mice. Furthermore, to understand what factor affected the activity of dendritic cells in the tumors after HSCT, we analyzed the expression of various cytokines/chemokines with mouse cytokine antibody arrays, and noticed that VEGF-D concentration was increased in the tumors in the early period after HSCT. The dendritic cells produced IL-6 in response to VEGF-D stimulation, and an administration of VEGFR-3 neutralizing antibody significantly suppressed the production of IL-6 from dendritic cells accompanied with the increase of Tregs in the tumors of HSCT recipients (Figure 2)(2). Autologous HSCT creates an environment strongly supporting the enhancement of antitumor immunity in reconstituted lymphopenic recipients through the suppression of Tregs. In fact, the Division previously reported that in osteosarcoma mouse models, intratumoral IFN gene transfer markedly suppressed the growth of vector-injected tumors and inhibited formation of spontaneous lung and liver metastases in syngeneic HSCT mice, and an infiltration of many immune cells was recognized in metastatic tumors of the treated mice. To translate the basic research to a clinical setting, the Division collaborates with the Central Hospital, and is planning a Phase I clinical trial on intratumoral injection of IFN-β plasmid/liposome complex in patients with sarcoma at advanced stages.

Development of cancer-targeting vectors using the peptide-display adenovirus library

Recently, adenovirus vectors have been applied for oncolytic virotherapy and in vivo imaging technology (3). Although a conditionally replicative adenovirus is an efficient anticancer agent designed to replicate selectively in tumor cells, the addition of a targeting strategy is necessary to enhance oncolysis and secure safety. However, redirection of the adenovirus vectors by engineering the capsid-

coding region has shown limited success because proper targeting ligands are generally unknown. To overcome this limitation, the Division constructed an adenovirus library displaying random peptides on the fiber knob, and its screening led to successful selections of several particular targeted vectors (4). In the previous library construction method, the procedures were complicated and time-consuming, and some of the vectors in the library were defective with no displaying peptide. To resolve these problems, the Division developed a novel method employing an in-cell Cre recombination and fiberless adenovirus, which greatly simplified the library-making steps. The high quality live adenovirus library may be able to facilitate the development of targeted adenovirus vectors for a variety of applications in medicine.

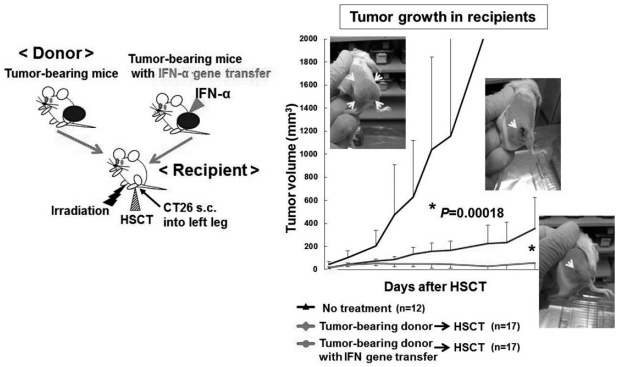

Figure 1. Donor priming enhances the antitumor immunity of HSCT

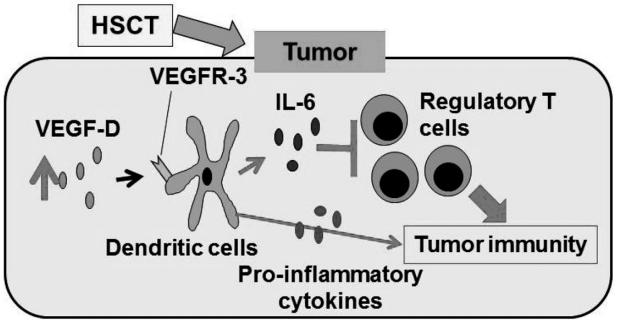

Figure 2. Breakup of the immunotolerant microenvironment by HSCT

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Division of Genome Stability Research

Mitsuko Masutani, Ken-ichi Yoshioka, Hiroaki Fujimori-Sakuma, Akira Asto, Kengo Inoue, Takahisa Hirai, Hiromi Harada, Junhui Wang, Soichiro Saito, Yuko Atsumi, Yuko Kudo, Tomoyuki Osawa, Hiroaki Mukai, Tasuku Itoh, Miyuki Hozumi, Sota Kikuhara, Motoharu Kohata, Masako Yamazaki, Tsubasa Sekiguchi

Introduction

This Division has been focusing on the biology of genome stability and trying to apply the evidence towards the development of strategies in cancer therapy and prevention. One of the pathways we focus on is the poly (ADP-ribosylation) pathway. Poly (ADP-ribose) polymerases (PARPs) and poly (ADP-ribose) glycohydrolase (PARG) are the major enzymes of poly (ADP-ribosylation) and are involved in DNA damage response and chromatin regulation. This pathway is being studied at molecular/cellular levels, and furthermore in animal models to pursue the development and evaluation of the inhibitors of poly (ADP-ribosylation) for cancer treatment. Radiation biology is also being studied to establish biological radiosensitization strategies in tumor radiotherapy and to elucidate the mechanisms of carcinogenesis.

Involvement of Parp-1 in germ cell tumor development

Parp-1 deficient embryonic stem (ES) cells showed preferential differentiation into a trophoblast lineage during tumorigenesis when grafted subcutaneously. This was demonstrated to associate the overexpression of *H19*, a non-coding gene, under *Parp-1* deficiency. The forced expression of the *H19* triggered the differentiation of ES cells into trophoblasts. The *H19* overexpression was able to promote trophoblast lineage commitment even under the suppressive pressure by the transcription factor Oct3/4. It is necessary to clarify whether aberrant *H19* overexpression induced during human carcinogenesis is related to PARP-1 dysfunction. When *Parp-1* deficient ES cells were grafted into uteri, trophoblasts were only present in the induced *Parp-1* deficient tumors and these tumors were associated with higher frequencies of invasive and metastatic lesions.

Intervention of the poly (ADP-ribosylation) pathway in cancer treatment

PARP inhibitors are reported to be effective against cancer cells, which are defective in homologous recombination pathways. Clinical trials suggested that further studies on factors that affect the effectiveness of inhibitors should be carried out. By screening with a shRNA library, candidate genes that affect the lethal effects of PARP inhibitors were identified and are being evaluated.

PARG inhibition in cancer cells induced S-phase arrest and PAR accumulation, inhibited DNA repair after alkylation damage and induced cell death. Therefore, PARG has also been suggested as a potential anti-cancer target. However, useful and specific PARG inhibitors are not currently available. A collaboration study with other institutions aimed at developing PARG inhibitors has therefore been conducted. From random and focused library screening, PARG inhibitors were identified and structural optimization is ongoing.

We also studied PAR metabolism *in vivo* using mouse models. PAR is rapidly converted into metabolites in the bloodstream. Dynamic states of these metabolites are currently being analyzed.

Radiation damage response and radiosensitization

For optimization of radiation therapy from basic biology, strategies for radiosensitization of various forms of radiation, including low and high linear-transfer (LET) radiation should be developed and evaluated. PARG functional inhibition augmented the level of PAR, blocked repair of DNA double-strand breaks (DSBs) and enhanced cell death caused by γ- and carbon-ion irradiation. Accumulated levels of PAR, which has been indicated to cause cell death, were particularly higher after carbon-ion irradiation compared with γ-irradiation, suggesting that PARG inhibition may be beneficial, especially for sensitization to particle-ion radiation.

Using shRNA libraries, around 100 candidate target genes of various categories for radiosensitization were selected and are being validated using siRNA. The radiosensitization effect for several cell lines was confirmed by knocking down gene A, resulting in increased S-phase arrest.

Boron-captured neutron therapy

The project of introduction of accelerator-based BNCT (boron-captured neutron therapy) system in NCC is ongoing. To support the biological evaluation of this new system, a collaborative study of BNCT with other institutes was initiated in 2012. Along

with a supporting study for biological evaluation, the study to understand the mechanisms of tumor cell death induced by BNCT and biomarkers for damage response is being pursued. For this purpose, transcriptome and proteome analyses after boron-captured neutron reaction in human cancer cell lines have been conducted. Transcriptome analysis after BNCT in cancer cells revealed that several particular transcription factors and immune-response-related genes were upregulated. Proteome analysis also revealed augmented levels of several proteins specifically after BNCT irradiation. The biological significance of these genes in monitoring of BNCT effectiveness will be evaluated in cellular or animal models.

Role of Arf/p53, and H2AX in the maintenance of genomic stability

Aging is a risk factor for cancers that develop with genomic instability and mutations, such as in the ARF/p53 module. Immortality is developed after abrogation of the H2AX-diminished state, which is associated with genomic instability (often with tetraploidy) and the induction of mutations in either the Arf or p53 gene. Although the involvement of p53 for the protection from immortalization is firmly established, the dependence of ARF has remained unclear. Both Arf and p53 were shown to be required for the down-regulation of H2AX and formation of the growth-arrested state. This observation is consistent with the previous reports that show the immortality development with the mutations in either ARF or p53 and the resulting recoveries of H2AX and cell growth. Notably, whereas tetraploidization was essential for immortalization of wild-type MEFs, this event was not required for immortalization of MEFs containing mutations in Arf/p53 and these cells still underwent mitotic catastrophe-associated cell death to get rid of their octaploid population. The Arf/p53-dependent down-regulation of H2AX was also shown to contribute to the selective survival of normal cells against treatment with anticancer drugs.

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Division of Integrative Omics and Bioinformatics

Hitoshi Nakagama, Tsutomu Ohta, Akinobu Hamada, Masaru Katoh, Mamiko Miyamoto, Yuuki Yamamoto, Teruaki Tsuji, Shuichi Shimma, Yuki Takashima

Introduction

This division consists of Ohta's Unit, Hamada's Unit and Katoh's Unit. Our goal is the development of innovative diagnostics and therapeutics for cancer based on an integrative omics approach.

Ohta's Unit

Oxidative and electrophilic stresses are sensed by Keap1, which activates transcription factor Nrf2 to achieve cytoprotection by regulating the expression of drug-metabolizing and anti-oxidative stress enzymes/proteins. The constitutive activation of Nrf2 leads to resistance against anti-cancer drugs and growth stimulation in lung cancer. This suggests that inhibition of *NRF2* may provide a new direction for therapeutic approaches in lung cancers with activation of Nrf2. The inhibitors for NRF2 are investigated and identified using *in vitro* and *in vivo* analyses.

Failure to expeditiously repair DNA at sites of double-strand breaks (DSB) ultimately leads to human disorders including cancer. NBS1 plays an important role in the cellular response to DSB damage. A rare polymorphic variant of *NBS1* that resulted in an isoleucine to valine substitution at amino acid position 171 (I171V) was first identified in childhood acute lymphoblastic leukemia. The *NBS1* polymorphic variant locates in the N-terminal region that is a protein interaction region with DNA repair factors. An aplastic anemia (AA) patient (a Japanese child) with a homozygous polymorphic variant of *NBS1*-I171V was previously described. The chromosomes of lymphoblastic cell lines derived from this patient contained a remarkable number of structural chromosomal aberrations. However, it was unclear whether the *NBS1*-I171V polymorphic variant affected DSB repair activity and chromosomal instability. The reduced DSB repair activity of *NBS1*-I171V polymorphic variant was detected.

Hamada's Unit

The activity of Hamada's Unit is described in the report from the Department of Clinical Pharmacology.

Katoh's Unit

Omics medicine, producing large amounts of omics data on genetics, genomics, epigenomics, transcriptomics, proteomics and metabolomics, consists of three layers (Figure 1). The first layer corresponds to clinical medicine that is involved with clinical sampling of blood and tissues or bio-banking. The second layer corresponds to basic medicine that produces large amounts of omics data from clinical samples and generates curated databases by using algorithms. The third layer corresponds to translational medicine that develops novel diagnostics and therapeutics and generates a knowledgebase from manuscripts and curated databases (Reference 1). Katoh's Unit has been involved in translational medicine since 2002.

WNT, FGF, Hedgehog, Notch and TGFβ signaling cascades are the major themes of Katoh's Unit (Reference 1), while human genes that had been first discovered in the Katoh's Unit are sub-themes of Katoh's Unit (References 2-4). Forkhead-box (FOX) family members are DNA-binding proteins with a FOX domain. Germ-line mutations in the *FOX* family of genes cause hereditary diseases, because FOX proteins are involved in transcriptional regulation and DNA repair. Somatic mutations in the *FOX* family of genes, including gene amplifications, point mutations, and translocations, occur in a variety of human cancers (Reference 2). The *Drosophila Asx* gene encodes an epigenetic regulator that is associated with the Polycomb-group repressor complex and the trithorax-group activator complex. ASXL1, ASXL2 and ASXL3 are human homologs of the *Drosophila* Asx. ASXL family members are epigenetic

scaffolding proteins that assemble epigenetic regulators and transcription factors to specific genomic loci with histone modifications. Germline mutations in *ASXL1* occur in Bohring-Opitz syndrome, while somatic mutations in *ASXL1* occur in colorectal cancer with microsatellite instability, hematological malignancies and castration-resistant prostate cancer (Reference 3). GIPC1, GIPC2 and GIPC3 are GIPC family members that consist of GH1, PDZ and GH2 domains. GIPC1 is an adaptor protein with a dimerizing ability that loads PDZ ligands as cargoes for MYO6-dependent endosomal trafficking. GIPC1 is required for the cell-surface expression of IGF1R and TGFβR3. GIPC1 is also required for integrin recycling during cell migration, angiogenesis and cytokinesis. GIPC1 upregulation in breast, ovarian and pancreatic cancers promotes tumor proliferation and invasion, whereas GIPC1 downregulation in cervical cancer with human papillomavirus type 18 infection leads to resistance to cytostatic TGFβ signaling. GIPC2 is downregulated in acute lymphocytic leukemia owing to epigenetic silencing, while Gipc2 is upregulated in estrogen-induced mammary tumors. Somatic mutations of GIPC2 occur in malignant melanoma, and colorectal and ovarian cancers (Reference 4).

Extracellular DNA and circulating miRNAs are key topics in translational medicine, and epigenetics play a key role in cancerous and non-cancerous diseases. Katoh underlined diagnostic techniques utilizing circulating miRNAs in exosomes and microvesicles, therapeutics utilizing siRNAs in polymer-based hydrogel nanoparticles and therapeutics targeted to a field of epigenetic alterations (Reference 5).

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 82 times in 2013. Katoh is an Academic Editor of *PLoS ONE*, and has carried out editorial decision 160 times in 2013 that resulted in 51 final decisions for manuscripts submitted to PLoS ONE. Masaru Katoh was inaugurated as the Chief Editor of *Frontiers in Molecular Medicine* that aims to address the gap between cell and developmental biology and clinical medicine and to promote development of novel diagnostics and therapeutics for various types of cancers and non-cancerous diseases (http://www.frontiersin.org/Molecular_Medicine).

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 548 times by others in 2013.

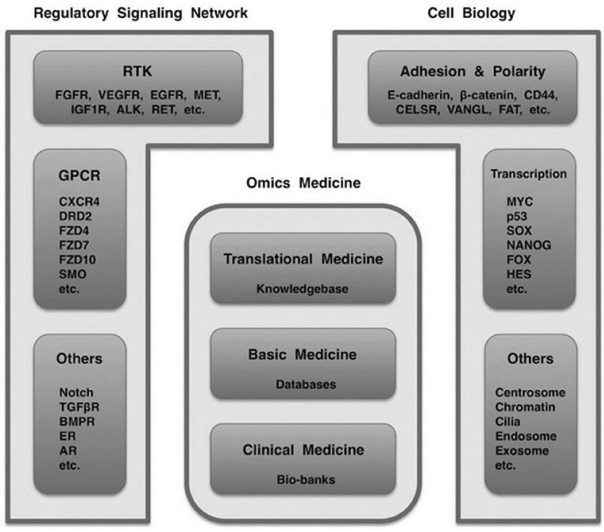

Figure 1. Three layer structure of omics medicine (http://www.frontiersin.org/Journal/10.3389/fcell.2013.00001/full)

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5. Katoh M. Therapeutics targeting angiogenesis: Genetics and epigenetics, extracellular miRNAs and signaling networks. Int J Mol Med, 32:763-767, 2013

Division of Refractory Cancer Research

Hitoshi Nakagama, Masato Enari, Shinichi Yachida, Rieko Ohki, Erina Takai, Yuko Hibiya, Yukie Aita, Chika Shima, Keiko Igarashi, Ryo Otomo, Makoto Miyazaki, Yoshinori Asano, Issei Ezawa, Kozue Saito, Miku Shimizu, Shiori Suzuki, Chen Yu, Yuhei Takano, Junko Ohtsuka, Raira Saigawa, Maiko Minegishi, Shu Matsushita, Haruka Takigawa

Introduction

Our main focus is to clarify the molecular mechanisms of tumor progression in refractory cancers including lung cancers, pancreatic cancers and brain tumors, and to develop various novel therapeutic strategies for cancer prevention. In particular, the Division studies how cancer cells acquire invasiveness, metastatic activity and drug resistance, which are characteristics of refractory cancers. The specific activities in 2013 were as follows: 1) Requirement of NuMA for the selective induction of p53-target genes; 2) PHLDA3 is a p53-regurated repressor of Akt and a novel suppressor of neuroendocrine tumors; 3) New Approaches of Early Detection of Pancreatic Cancers; and 4) Metagenomics: Role of the Human Gut Microbiome in Colorectal Carcinogenesis.

Routine activities

A weekly conference is held with the members of the Division of Refractory Cancer Research, and a biweekly conference is held with the members of the Division of Cancer Development System. In addition, a monthly progress report is held with the members of the research institute.

Research activities

1) Requirement of NuMA for the selective induction of p53-target genes

The p53 tumor suppressor protein is a transcription factor controlling various outcomes, such as growth arrest and apoptosis, through the regulation of a different set of target genes. The Mitotic Apparatus protein (NuMA) plays important roles in spindle-pole organization during mitosis and in chromatin regulation in the nucleus during interphase. Although NuMA has been shown to co-localize with several nuclear proteins including high-mobility group proteins I/Y and GAS41, a role for NuMA during the interphase remains unclear. We have reported that NuMA binds to p53 to modulate p53-mediated transcription. The acute and partial ablation of NuMA attenuates induction of the pro-arrested p21 gene following DNA damage, subsequently causing impaired cell-cycle arrest. Interestingly, the NuMA knockdown had little effect on induction of the p53-dependent pro-apoptotic PUMA gene. Furthermore, NuMA is required for the recruitment of Cdk8, a component of the Mediator complex and promoter of the p53-mediated p21 gene function. These data demonstrate that NuMA is critical for the target selectivity of p53-mediated transcription (Ohata H. et al. *Molecular and Cellular Biology* 2013).

2) PHLDA3 is a p53-regulated repressor of Akt and a novel suppressor of neuroendocrine tumors

p53 and Akt are critical players regulating tumorigenesis with opposite effects: whereas p53 transactivates target genes to exert its function as a tumor suppressor, Akt phosphorylates its substrates and transduces downstream oncogenic signals. In addition, p53 and Akt negatively regulate each other to balance oncogenic and tumor-suppressive signals within a cell. We have identified PHLDA3 as a p53 target gene, which encodes a PH domain-only protein. We found that PHLDA3 competes with the PH domain of Akt for binding of membrane lipids, thereby inhibiting Akt translocation to the cellular membrane and activation (Kawase T. et al. *Cell* 2009). We demonstrated the suppression of anchorage-independent cell growth by PHLDA3, and furthermore, frequent loss of the PHLDA3 genomic locus in primary endocrine tumors. In addition, we demonstrated hyperactivation of Akt and hyperplasia in endocrine tissues in PHLDA3 deficient mice. These results collectively indicate that PHLDA3 is a novel tumor suppressor of endocrine tumors. Our results reveal a new mode of coordination between the p53 and Akt pathways, and show that PHLDA3 is an important downstream mediator of p53 to regulate Akt activity.

3) New Approaches of Early Detection of Pancreatic Cancers

We previously estimated that the time from tumor initiation to metastatic dissemination is at

least a decade in pancreatic ductal adenocarcinomas (Yachida S. et al. *Nature* 2010; Yachida S. et al. *Oncogene* 2013). This finding indicates that there is a large window of opportunity for medical intervention before the cancer spreads to distant organs. The goal of this project is to establish novel methods to detect the early stages of pancreatic ductal adenocarcinomas, for which we use two approaches: 1. The Genomic approach: *KRAS* and other mutations in plasma samples using next-generation sequencing technology; and 2. The Metabolomic approach: Applications of the metabolism characteristic to pancreatic ductal adenocarcinoma to develop a new tracer on PET.

4) Metagenomics: Role of the Human Gut Microbiome in Colorectal Carcinogenesis

Recent evidence based on metagenomics has highlighted the potential contribution of the microbiome in the maintenance of host homeostasis. In this project, we will clarify the relationships between the luminal microbiota and colorectal cancers and the mechanisms of potential contribution of the microbiome towards colorectal cancer development. The study is conducted with patients who undergo total colonoscopy in the National Cancer Center Hospital. Their lifestyle, such as dietary habits, is obtained from detailed questionnaires. Fecal samples are collected before colonoscopy, frozen immediately and DNA is purified by standard methods. Sequencing is carried out by whole-genome shotgun using standard protocols.

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7. Okano K, Asano E, Oshima M, Yamamoto N, Yachida S, Nishizawa Y, Akamoto S, Fujiwara M, Deguchi A, Mori H, Masaki T, Suzuki Y. Omental flap wrapping with fixation to the cut surface of the liver for reducing delayed gastric emptying after left-sided hepatectomy. Surg Today, 43:1425-1432, 2013
8. Okano K, Oshima M, Kakinoki K, Yamamoto N, Akamoto S, Yachida S, Hagiike M, Kamada H, Masaki T, Suzuki Y. Pancreatic thickness as a predictive factor for postoperative pancreatic fistula after distal pancreatectomy using an endopath stapler. Surg Today, 43:141-147, 2013
9. Takai E, Tsukimoto M, Kojima S. TGF-β1 downregulates COX-2 expression leading to decrease of PGE2 production in human lung cancer A549 cells, which is involved in fibrotic response to TGF-β1. PLoS One, 8:e76346, 2013.

Division of Cancer Prevention Research

Hitoshi Nakagama, Michihiro Mutoh, Gen Fujii, Rikako Ishigamori, Masami Komiya, Ruri Nakanishi

Introduction

We are investigating mechanisms of carcinogenesis, searching for early diagnostic markers for cancer, and developing practicable cancer chemopreventive agents. Abnormal activation of β-catenin signaling, including TCF/LEF transcription factor activation, is a well-known cause of many carcinogeneses. On the other hand, dyslipidemia, alterations of adipocytokine balance and pro-inflammatory status have been suggested to be involved in the development of many cancers. In animal studies, improvement of dyslipidemia, adipocytokine imbalance and inflammation status suppressed carcinogenesis. However, underlying suppressive mechanisms are not known in detail, such as lipid metabolism changes in the cancer cells and cross-talk changes between the epithelial cells, adipocytes and macrophages. Investigations clarifying the mechanisms of dyslipidemia-, obesity- and inflammation-related carcinogenesis may lead us to develop early diagnostic markers for cancer. Based on the molecular findings, cancer chemopreventive agents were selected from clinically used medicines. Drug repositioning will be a clue to the development of effective approaches for human cancer prevention.

Research activities

Apc-deficient mouse model: P-glycoprotein (P-gp; encoded by *Mdr1a* gene) has been shown to be associated with intestinal tumorigenesis through activation of the TCF/LEF transcription factor. We examined inhibition of the P-gp function with verapamil (a clinically used antihypertensive drug), and found that verapamil could decrease the number of intestinal polyps which developed in the mice with loss of function of the *Apc* gene product.

Mouse lung carcinogenesis model: We have shown that *in vivo* SPECT imaging with ^{111}In-DOTA-c(RGDfK) is a useful method to detect early pancreatic cancer in a hamster pancreatic carcinogenesis model. Thus, we aimed to demonstrate the great potential for detecting urethane-induced A/J mice lung cancer by a combination of SPECT/CT imaging. ^{111}In-DOTA-c(RGDfK) was clearly visualized in small lung nodules, suggesting that SPECT/CT is a useful non-invasive imaging approach for evaluating the characteristics of lung tumors in mice, linking to a human imaging approach.

Hp-induced gastritis model: *Helicobacter pylori* (*Hp*) infection causes gastritis and is considered a gastric cancer risk. We have reported that codfish meal markedly enhanced *Hp*-induced gastritis in Mongolian gerbils. Thus, we examined the effects of components in codfish meal in the model, and found that intake of calcium compounds, such as hydroxyapatite and calcium carbonate, may contribute to enhance *Hp*-induced gastritis. These findings of novel risk factors may link to the development of new chemopreventive agents

Clinical trials: A double-blind, randomized, placebo-controlled clinical study was performed to evaluate the influence of low-dose aspirin enteric-coated tablets (100 mg/day for 6-10 months) in 34 familial adenomatous polyposis subjects (17 each in the aspirin and placebo groups). The sizes of colorectal polyps tended to be greater in the placebo as compared to the aspirin group, and subgroup analysis revealed that subjects with a mean baseline polyp diameter of ≤ 2 mm showed a significant reduction of mean polyp sizes in the aspirin group.

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Journal

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2. Fujimoto K, Fujii G, Mutoh M, Yasunaga M, Tanaka H, Wada M. Suppression of intestinal polyp development in *Apc*$^{Min/+}$ mice through inhibition of P-glycoprotein using verapamil. Eur J Cancer Prev, 22:8-10, 2013
3. Iimuro M, Nakamura S, Arakawa T, Wakabayashi K, Mutoh M. Effects of dietary calcium on *Helicobacter pylori*-induced gastritis in Mongolian gerbils. Anticancer Res, 33:3667-3674, 2013
4. Hayakawa T, Mutoh M, Imai T, Tsuta K, Yanaka A, Fujii H, Yoshimoto M. SPECT/CT of lung nodules using ^{111}In-DOTA-c(RGDfK) in a mouse lung carcinogenesis model. Ann Nucl Med, 27:640-647, 2013
5. Komiya M, Fujii G, Takahashi M, Iigo M, Mutoh M. Prevention and intervention trials for colorectal cancer. Jpn J Clin Oncol, 43:685-694, 2013

Division of Brain Tumor Translational Research

Koichi Ichimura, Shintaro Fukushima, Taishi Nakamura, Hirokazu Takami, Emiko Yamamoto, Hideyuki Arita, Yuko Matsushita

Introduction

Our laboratory focuses on translational research into various types of malignant brain tumor. Brain tumors are a rare form of cancer, however some of them remain as one of the most difficult cancers to cure in humans. There are more than 130 different types of brain tumors, each developing through a distinct molecular pathogenesis. To facilitate an effective personalized therapy, elucidating the molecular basis of each individual tumor is essential. We therefore set our aim as follows: 1) Conduct comprehensive investigational research into the molecular basis of key malignant brain tumors such as gliomas, primary central nervous system lymphomas (PCNSL) and intracranial germ cell tumors (iGCT) to identify novel tumor markers for making a more accurate diagnosis or predicting the outcome of the patients as well as therapeutic targets; 2) Establish an optimal assay for molecular marker testing to utilize in clinical trials and routine clinical practice ; and 3) Organize and/or participate in a multicenter study to collect a large number of tumor materials to facilitate the above research and to validate the findings.

Research activities

1. Investigation for novel biomarkers in adult gliomas

Through a genetic analysis of 546 gliomas, we identified that somatic mutations at two hotspots (C228T, C250T) in the promoter region of *TERT*, the reverse-transcriptase subunit of telomerase, occur very frequently among adult gliomas. We found that *TERT* promoter mutations were particularly common among primary glioblastomas (70%), making it the most frequently mutated gene in glioblastomas. We showed that *TERT* promoter mutations invariably upregulate *TERT* expression while *TERT* promoter methylation alone did not. Thus, we showed for the first time that *TERT* promoter mutations are the main driver of telomerase upregulation, the phenomenon which has been widely known over the decades while its mechanism remained unknown up until now. *TERT* mutations are also common among oligodendroglial tumors and strongly associated with the presence of 1p19q loss and *IDH1/2* mutations, however they are uncommon in astrocytic tumors with concurrent *IDH1/2* and *TP53* mutations. These findings make *TERT* promoter mutations an ideal diagnostic marker. We are currently validating the efficacy of *TERT* promoter mutations as a biomarker in a large independent cohort of adult gliomas. We have also established a novel pyrosequencing-based assay for *MGMT* methylation testing. The presence of *MGMT* methylation has been established as a prognostic marker in glioblastomas, as well as a predictive marker for the response to temozolomide in elderly glioblastoma patients. We are currently utilizing the assay for a clinical trial to validate whether the postoperative treatment of the patients could be determined based on the *MGMT* methylation status (see below).

2. A comprehensive genome analysis on intracranial germ cell tumors

Intracranial germ cell tumors (iGCT) are the second most common brain tumors among the patients under the age of 14, however they are rare in the Western population. iGCTs are one of the few pediatric brain tumors that remain largely unexplored. We have established an Intracranial Germ Cell Tumor Genome Analysis Consortium to centrally collect surgical specimens of iGCTs nationwide and conduct a comprehensive genome analysis on them. Our current iGCT sample cohort consists of 125 iGCTs, 65 testicular germ cell tumors and 8 metastatic GCTs, which is by far the largest iGCT series in the world. We analyzed 41 iGCTs with exome sequencing and identified about 40 candidate genes, for which all the remaining tumors are being investigated using the IonTorrent system.

3. Establishment of the Japanese Pediatric Molecular Neuro-oncology group (JPMNG)

Numerous large-scale genome analyses have uncovered the molecular pathogenesis of various types of pediatric brain tumor in the last few years. A novel molecular classification which can better predict the outcome of the patients has already been developed in several tumor types such as medulloblastomas and ependymomas. To establish a standardized molecular classification system in Japan based on the international consensus and to

utilize it for better prognostication of the patients or stratification for personalized target therapy, a Japanese Molecular Neuro-Oncology Group (JPMNG) has been established as a joint project between the Japan Society for Neuro-Oncology and the Japanese Society for Pediatric Neurosurgery. As one of the core members of JPMNG, we are jointly in charge of performing molecular tests for medulloblastomas and ependymomas that are currently being collected nationwide.

Clinical trials

We are in charge of the methylation testing in the EGGTRIAL on newly diagnosed elderly glioblastomas. This clinical trial has been set to validate the earlier reports that elderly glioblastoma patients with *MGMT*-methylated tumors respond to temozolomide better than those with *MGMT*-unmethylated tumors. Patients at the age of 70 or more with newly diagnosed glioblastoma are eligible for enrollment in the EGGTRIRAL. We perform and report the results of the *MGMT* methylation test within three weeks after the operation. The patient will be treated with temozolomide alone when *MGMT* is methylated while they will receive radiation therapy alone when *MGMT* is unmethylated. The registration to the trial started in May 2013 and is scheduled to continue until 2015.

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Journal

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5. Fukushima S, Narita Y, Miyakita Y, Ohno M, Takizawa T, Takusagawa Y, Mori M, Ichimura K, Tsuda H, Shibui S. A case of more than 20 years survival with glioblastoma, and development of cavernous angioma as a delayed complication of radiotherapy. Neuropathology, 33:576-581, 2013

Research Core Facility Division

Teruhiko Yoshida, Yasuhito Arai, Toshio Imai, Yoshinori Ikarashi, Hitoshi Ichikawa, Tetsuya Ishikawa, Shumpei Ohnami, Masaya Ono, Takahiro Ochiya, Koji Okamoto, Yae Kanai, Takuo Katsumoto, Issay Kitabayashi, Tadashi Kondo, Hiromi Sakamoto, Hiroki Sasaki, Tatsuhiro Shibata, Fumie Hosoda, Tesshi Yamada

Introduction

The Research Core Facility (CF) 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 thus establishing a bidirectional translational bridge (Figure 1). Ample collection of high quality clinical samples combined with advanced and reliable analytical power should be a crucial asset of our Institute, especially in light of international collaboration and competition. However, the latest genome and other omics technologies demand heavy investments from our researchers both in hardware, its maintenance and human expertise, which are increasingly difficult if not impossible to afford by individual laboratories, especially those staffed by young PIs and physician scientists. Animal histopathology, reproductive engineering and advanced cell biology are other areas where the availability of highly skillful CF support would make a huge difference in the progress and outcome of the research. As a consequence, the CF has become an essential component integrated in many leading biomedical research institutes in the world.

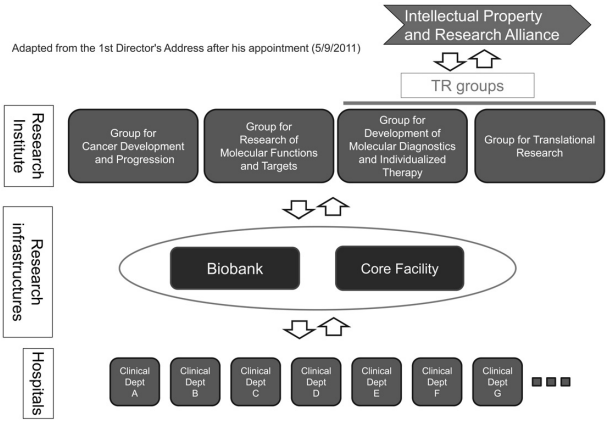


Figure 1. Concept of CF: Director's Initiative

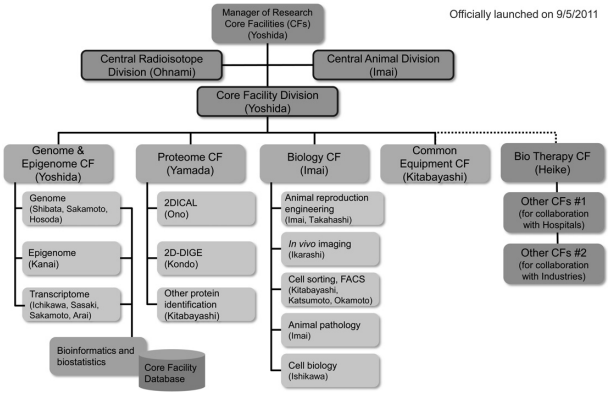


Figure 2. CF Organization

Routine activities

Following the Director's lecture, the CF was officially started on September 5, 2011 with the organization shown in Figure 2. The important point is that the CF is a virtual facility, putting together and further facilitating the existing collaborative effort by the individual research scientists and laboratories, each engaging in their own competitive research. The CF has 4 major arms to share technical expertise, *i.e.*, 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 mission of the CF is not restricted to the mutual support and collaboration inside the NCCRI, but extends to other sectors of the 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. Some CF staff are also involved in the NCC EPOC (Exploratory Oncology Research & Clinical Trial Center) and its translational research. The CF is also supporting a transitional zone between research and clinical practice, such as genetic diagnosis of hereditary cancer syndromes. One of the major uses of the CF is the large-scale analysis of clinical samples, and thus, the CF is closely related with several Biobank-based projects (Figure 3).

Research activities

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. As shown on the rightmost columns, some of the projects supported by CF were directed by PIs outside of the NCCRI. Although not apparent in the table, one of the most important contributions of the CF may be the discussion and consultation BEFORE offering the actual CF service.

The activities of the Biology arm of the CF can be found in the report of the Central Animal Division.

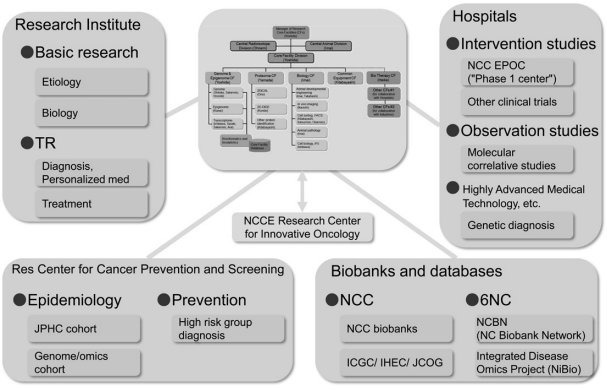


Figure 3. CF Interactions and Participations

Table 1. CF Activities in FY 2011-2013 (excluding the self-service type)

CF Area	Applications	# projects			# samples			PIs outside RI	
		FY 2011	FY 2012	FY 2013	FY 2011	FY 2012	FY 2013	Hosp	RCCPS
Genome	Next Generation Sequencer	18	19	11	739	995	346	○	○
	SNP array/TagMan assay	10	9	9	1993	1574	1777	○	○
	Agilent array and others	5	9	4	366	652	123		○
Epigenome	NGS	2	2	1	102	14	8		
	Infinium array	7	6	9	1646	569	801		○
Transcriptome	NGS	5	9	1	148	169	8		
	Affymetrix GeneChip	5	4	2	97	76	110	○	
	Agilent array	5	3	4	58	56	68		
Proteome	2DICAL	7	2	2	524	112	54	○	
	2D-DIGE	0	7	4	0	308	83		
Animal reproduction engineering	Embryo/ sperm freezing stock	2	5	5	9	36	17		
	Microbiological cleaning	1	1	5	0	1	5		
In vivo imaging	IVIS	10	2	4	-	-	-		
	OV110	2	2	0	-	-	-		
Animal histopathology	FFPE, frozen sections	12	12	11	1743	2974	1778		
	Examination and diagnosis	4	4	6	-	-	-		
Cell biology	Cell line establishment	1	1	0	5	2	0		
Total		96	97	78	7,430	7,538	5,178		

Central Animal / Radioisotope Divisions

Toshio Imai, Mami Takahashi, Tetsuya Ishikawa, Yoshinori Ikarashi, Kotomi Otsubo, Naoaki Uchiya, Momoko Kobayashi, Teruo Komatsu, Masashi Yasuda, Manabu Tsuchida, Ayami Kawashima, Satoshi Ikeda, Junichi Zukeyama, Fukase Masashi, Seki Yudai, Takuya Matsuyama, Junya Asahira, Shumpei Ohnami

Introduction

The Central Animal Division belongs to the Core Facilities for Research and Innovative Medicine, and a pivotal role of this division is supportive actions for basic/clinical/public health researchers on the basis of biological resources in the National Cancer Center.

The Central Radioisotope Division provides advanced technical training and education for researchers in the fields of molecular genetics and radiology. This division is equipped with separate laboratories where registered users can conduct experiments safely with various types of radioisotopes.

Routine activities

The important role of the Central Animal Division is health management of the experimental animals and maintenance of the animal experimentation facility in the National Cancer Center Research Institute. Some researchers and technical staff act also in the Core Facilities for Research and Innovative Medicine, and several support services are provided based on their biological skills, such as reproductive technologies for animal cleaning/embryo-sperm preservation, histopathological techniques for animal tissues and establishment of expandable cells/xenograft transplantable models from clinical cancer tissues.

Research activities

Research activities of the Central Animal Division have focused on studies of chemical carcinogenesis using laboratory animals and genetically modified cancer developing animal models, the process of graft-versus-host disease using *in vivo* imaging technologies and human induced hepatic stem cells for anti-cancer drug screening. Research activities of the Central Radioisotope Division have been performed in collaboration with the Division of Genetics and the Division of Gene and Immune Medicine.

1) Promotion of colorectal and pancreatic carcinogenesis by A^y allele

Epidemiologically, obesity has been associated with colorectal and pancreatic cancer risks, but the underlying mechanisms are not clearly understood. The A^y mice possessing the agouti yellow allele expresses ectopically the agouti gene product, which regulates energy metabolism, and become obese. We reported that A^y allele promotes colorectal tumor development in diabetic KK mice. We also found that the A^y allele promoted pancreatic carcinogenesis in *K-ras* mutant mice. These results suggest involvement of the agouti/melanocortin receptor pathway in obesity-associated cancer.

2) Pancreatic Ductal Carcinogenesis and Epithelial Mesenchymal Transition in Hamsters

Elevations in mucin 1 (MUC1) mRNA levels were found to be prominent among the up-regulated genes in atypical hyperplasias in a hamster model. Immunohistochemistry for the MUC1 cytoplasmic domain (MUC1-CD), which was not detected in normal-like pancreatic ducts, was positive in apical surfaces of the epithelia of atypical hyperplasias and invasive ductal carcinoma (IDC) areas with distinct tubular patterns. In contrast, its translocation to cytoplasmic/nuclear positivity was observed in the invasive front of IDCs. The co-expression of epithelial-mesenchymal transition (EMT)-related proteins, such as slug and vimentin, with cytoplasmic/nuclear MUC1-CD was also found. These results indicate that the alteration in the expression level and subcellular localization of MUC1 is a biphasic phenomenon and the latter may be associated with EMT in pancreatic carcinogenesis in hamsters.

3) Mechanisms of Promotion/progression of Mammary Carcinogenesis associated with a High-fat Diet

The effects of a high-fat diet (HFD) during prepubertal and pubertal stages were investigated in 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in female F344 rats. The results obtained indicated that HFD promoted carcinogenesis, and, in addition, affected aggressive phenotypes of the induced carcinomas. The molecular mechanisms of the promotion/progression as assessed with DNA microarray analysis for the carcinoma tissues were speculated to be associated

with increased expression of a couple of cell cycle/differentiation-related genes, which were reported to be up-regulated in human breast carcinoma cell lines.

4) *In Vivo* Fluorescence Imaging of Donor Cells after Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Visualizing the *in vivo* dynamics of donor cells after allogeneic HSCT could be useful for an understanding of the process of graft-versus-host disease (GVHD) and donor cell engraftment. The *in vivo* fluorescence imaging technique can visualize GFP donor cells in small animals in a whole-body manner. Furthermore, the combination with *in vivo* imaging and immunohistochemistry simultaneously visualize both proliferating and apoptotic cells and their origin, donor or host. These techniques enable a great deal of understanding regarding the mechanism of GVHD.

5) Human Induced Hepatic lineage-oriented Stem Cells for Drug Discovery and Regenerative Medicine in Cancer Therapy

We generated human induced hepatic lineage-oriented stem (iHS) cells from fibroblasts by gene transfer (OCT3/4, SOX2, and KLF4). The human iHS cells self-renewed during more than 80 passages. They were differentiated in a chemically defined medium without any differentiation growth factors through 12-days-culture. The almost all *in vitro*-differentiated cells were strongly positive for albumin, and negative for neuroectodermal and mesodermal marker proteins. The cells expressed hepatic genes such as *ALB*, *AFP*, *AAT*, *TTR*, *FABP1*, cytochrome P450 enzymes, and conjugating enzymes. The hepatocyte-like cells were functional for the uptake of indocyanine green, storage of glycogen, and production of urea. A protocol for fully functional hepatic differentiation of iHS cells is under investigation.

List of papers published in 2013
Journal

1. Imai T, Cho YM, Takahashi M, Kitahashi T, Takami S, Nishikawa A, Ogawa K. High susceptibility of heterozygous (+/*fa*) lean Zucker rats to 7,12-dimethylbenz(*a*)anthracene-induced mammary carcinogenesis. Oncol Rep, 29:1914-1922, 2013
2. Ito K, Ishigamori R, Mutoh M, Ohta T, Imai T, Takahashi M. A^y allele promotes azoxymethane-induced colorectal carcinogenesis by macrophage migration in hyperlipidemic/diabetic KK mice. Cancer Sci, 104:835-843, 2013
3. Takahashi M, Mutoh M, Ishigamori R, Fujii G, Imai T. Involvement of inflammatory factors in pancreatic carcinogenesis and preventive effects of anti-inflammatory agents. Semin Immunopathol, 35:203-227, 2013

Department of Biobank Support Core

Takashi Kohno, Izumi Kobayashi, Mari Tomoda

Introduction

The Department of Biobank Support Core was established in May 2013 to support the management of the National Cancer Center (NCC) Biobank. This Department supports committees and working groups of this Biobank and the National Center Biobank Network (NCBN).

Routine activities

1. Support of the NCC Biobank

This Department functions as a secretariat for the NCC Biobank Coordination Committee and has held coordination committee conferences eight times. The consent ratio of NCC patients for cooperation in Biobanking in 2013 was 86.4%. Information on the NCC Biobank is being published through the periodical updating of the NCC-internal website and also by tours (16 including the ones for the Ministries, University Hospitals and National Institutes abroad), interviews and answering queries. The Department also functions as a contact window to researchers who need NCC Biobank samples.

2. Support of NCBN

This Department supported several conferences of NCBN committees. The topics discussed included how we should disclose research findings, including incidental ones, to patients, and how banked samples and clinical information should be provided to researchers who need them. The Department also supported the construction and publication of a catalog database on the NCBN webpage.

3. Support for translational research in the NCC

The Department supported 10 monthly Research Conferences (Table 1) inviting 28 researchers as presenters. In total, 1,694 discussants participated in the conferences. The Department also held 3 conferences for discussion on TR (Table 2) inviting three researchers as presenters. A conference is being held to promote "seeds push" and "needs pull" TRs through discussion among Group for Translational Research Support Core staff, NCC hospitals staff and EPOC staff (Figure 1).

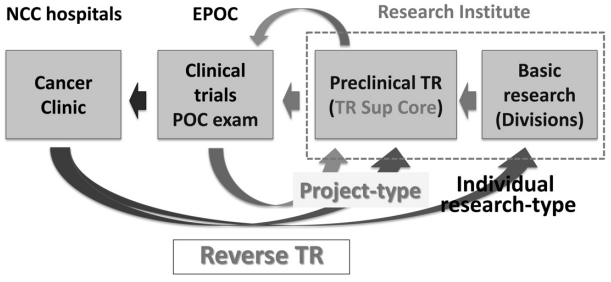


Figure 1. "Seeds Push" & "Needs-Pull" translational research approaches in the NCC

Table 1. Research conferences in 2013

Date	Topic	Presenter	No.of participant
Jan8,2013	Molecular imaging	Kenji Tamura, Hirofumi Fujii, Akinobu Hamada	215
Feb12,2013	Biobank	Yae Kanai, Izumi Kobayashi, Kazufumi Honda, Teruhiko Yoshida	173
Mar12,2013	Surgery & Medical device	Masaaki Ito, Kiyokazu Nakajima, Ichiro Sakuma	134
Apr16,2013	Clinical sequencing	Takayuki Yoshino, Takashi Kohno	231
May14,2013	Adverse event	Yoshiro Saito, Ken Kato, Teruhiko Yoshida	157
Jun11,2013	Liquid biopsy	Takahiro Ochiya, Shintaro Kanda	200
Jul16,2013	Biomarker	Shoichiro Tsugane, Motoki Iwasaki, Atsushi Goto	136
Sep10,2013	Liquid biopsy	Makiko Ono, Fumiaki Koizumi, Tsuchiya Naoto	172
Oct8,2013	Sarcoma	Akira Kawai,Tadashi Kondo	125
Dec10,2013	Familial cancer	Noriyuki Katsumata, Teruhiko Yoshida, Yoichi Naito	153

Table 2. Monthly discussion on translational research (TR) in 2013

Date	Topic	Presenter
25-Sep	Clinical sequencing in TOPICS-1	Kenji Tamura
23-Oct	TR of novel FGFR fusion in cholangiocarcinoma	Tatsuhiro Shibata
27-Nov	Reverse TR & Clinical benefit	Yasuhide Yamada

Department of Clinical Pharmacology

Akinobu Hamada, Shuichi Shimma, Yoichi Kurata, Satoko Osawa, Yu Yamanoi, Yuki Takashima, Masanobu Nishidate, Toshiyuki Hata

Introduction

The Clinical Pharmacology Group is focused on the development of pharmacokinetic analyzing system. This system provides the drug exposure in blood and tissues using a high-sensitivity triple-quadrupole mass spectrometer and mass microscope for non-label imagining mass spectrometry. Imaging mass spectrometry (IMS) is now widely used in several research fields. For pharmacokinetic studies in particular, IMS can provide novel visualization information that differs from conventional imaging technologies such as autoradiography and positron emission tomography due to its non-labeled feature.

Research activities

Our aim is to provide evaluation methods for novel drugs in clinical trial. In 2013, we started to evaluate IMS using animal models and clinical samples obtained from surgical operations and biopsies. During this evaluation, we have developed standard operational procedures from tissue sampling to obtained ion imaging analysis. The most important breakthrough was the development of a new matrix application method to provide higher ionization efficiency and tissue surface protection. Using this method, the ionization efficiency was improved by 40 times compared with previous techniques. We found this new sample preparation method was essential for IMS. In addition to the matrix application method, a tissue sectioning procedure for small specimens such as biopsies also had to be developed. In general, small tissue specimens are embedded in a polymer-based compound for sectioning. However, the compound is a well-known contaminant in IMS. The tissue surface is directly analyzed in IMS, hence the residual polymers on the tissue surface are preferentially ionized. The cluster of polymer peaks is usually detected at a high intensity compared to the target molecules. We developed a sectioning procedure without embedding, and we confirmed the feasibility of IMS for small specimens. Due to our developments in sample preparations, we started to apply IMS for a few clinical trials of molecular targeting drugs (Figure 1).

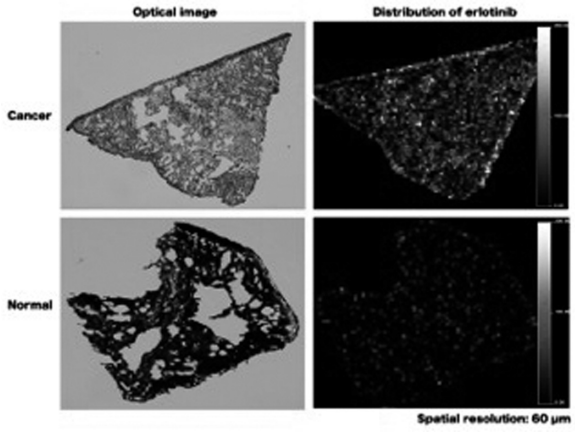


Figure 1.

List of papers published in 2013
Journal

1. Shimma S, Takashima Y, Hashimoto J, Yonemori K, Tamura K, Hamada A. Alternative two-step matrix application method for imaging mass spectrometry to avoid tissue shrinkage and improve ionization efficiency. J Mass Spectrom, 48:1285-1290, 2013
2. Hashiguchi Y, Hamada A, Shinohara T, Tsuchiya K, Jono H, Saito H. Role of P-glycoprotein in the efflux of raltegravir from human intestinal cells and CD4+ T-cells as an interaction target for anti-HIV agents. Biochem Biophys Res Commun, 439:221-227, 2013
3. Tomita Y, Yuno A, Tsukamoto H, Senju S, Kuroda Y, Hirayama M, Irie A, Kawahara K, Yatsuda J, Hamada A, Jono H, Yoshida K, Tsunoda T, Kohrogi H, Yoshitake Y, Nakamura Y, Shinohara M, Nishimura Y. Identification of promiscuous KIF20A long peptides bearing both CD4+ and CD8+ T-cell epitopes: KIF20A-specific CD4+ T-cell immunity in patients with malignant tumor. Clin Cancer Res, 19:4508-4520, 2013
4. Tsubata Y, Okimoto T, Miura K, Karino F, Iwamoto S, Tada M, Honda T, Hamaguchi S, Ohe M, Sutani A, Kuraki T, Hamada A, Isobe T. Phase I clinical and pharmacokinetic study of bi-weekly carboplatin/paclitaxel chemotherapy in elderly patients with advanced non-small cell lung cancer. Anticancer Res, 33:261-266, 2013

Department of Translational Research Seeds Evaluation

Fumiaki Koizumi, Takeshi Sawada, Shigehiro Yagishita, Yoshitaka Seki, Satoshi Kitazono, Jun Hashimoto, Takayuki Sasaki, Yuka Kitamura, Misaki Ono, Mayumi Akitaya, Rumi Koyama, Yukiko Ito

Introduction

The Department of Translational Research Seeds Evaluation is a newly established section of the Translational Research Support Group. The main goal of our team is to develop safe and effective cancer biomarkers for molecular targeted cancer drugs. We have two main projects ongoing to achieve this goal: the "ADCC project" and the "CTC project".

Research activities

Objective

1. CTC project (Figure 1.)

The aim of this project is to develop a novel flow-cytometry-based circulating tumor cell (CTC) detection and sorting system (On-Chip Sort) independent of the tumor cell EpCAM expression. The system is expected to provide useful clinical information on prognosis, cancer staging, drug choice, and therapeutic efficacy.

2. ADCC project (Figure 2.)

This project's goal is to develop a new assay system for predicting the antibody-dependent cellular cytotoxicity (ADCC) activity and the clinical outcome in patients receiving antibody therapy.

Approach

1. CTC project

In our assay, 4 mL of samples is hemolyzed and CD45+ leucocytes are eliminated using magnetic beads coated with an anti-CD45 antibody. After negative CTC enrichment, samples are fixed and labeled with FITC-cytokeratin, PE-EpCAM and Alexa700-CD45 antibodies, and analyzed with our flow-cytometry-based CTC detection and sorting system. In a preclinical study, various kinds of cell line were spiked into human blood. The sensitivity in detection and the possibility of mutation analysis from captured cells were evaluated. In a clinical study, 40 advanced lung cancer patients, 40 advanced breast cancer patients and 5 healthy donors were recruited at the National Cancer Center Hospital (NCCH). The results of the CTC enumeration were compared with those from CellSearch®.

2. ADCC project

We used the peripheral blood mononuclear cells (PBMCs) of eight healthy volunteers (HVs) to examine the degree of ADCC with the calcein assay. To identify molecular markers that might be correlated with ADCC activity, we adopted an *ex vivo* gene expression analysis in which changes in the mRNA expression after exposure to IgG can be measured quantitatively.

Current Research Outcomes

1. CTC project

Enumeration of the spiked tumor cells was linear over a range of 10 to 1000 cells, with a recovery rate of ≥ 90%. A significantly higher recovery rate was observed with our system (90 - 102%) than with CellSearch® (0%) when EpCAM-negative PC-14 cells were spiked, suggesting a superior sensitivity of our system in capturing EpCAM-negative tumor cells. A mutation analysis of captured cells from spiked cultured cells in peripheral blood was successfully performed. In 22 blood samples from lung cancer patients, CTCs detected by our system ranged from 0 - 18 CTCs (median, 6.5), and 77.3% (17/22) of the samples were above the threshold level (≥ 4 / 4 mL). On the other hand, with CellSearch®, only 27% of the samples had a ≥ 2 / 7.5 mL threshold level. In 2 blood samples from healthy donors, our system detected 0 and 3 CTCs, and CellSearch® detected 0 and 1 CTC. In 24 blood samples from breast cancer patients, CTCs detected by FISHMAN-R ranged from 0 - 829 CTCs (median, 4.5), and 86.3% (19/22) of the samples were above the threshold level (≥ 2 / 4 mL). On the other hand, CellSearch® detected CTCs in only 22.7% (5/22) of the samples which had a CTC threshold level (≥ 2 CTCs / 7.5 ml PB). In 2 blood samples from healthy donors, 1 CTC was detected by On-Chip Sort and the CellSearch detected none. These results of a clinical feasibility study showed our system to be significantly more sensitive for CTC enumeration in lung and breast cancer. Isolation of CTCs is achieved in lung cancer and breast cancer patients by our novel CTC system. We also demonstrated mutation detection (EGFR and PIK3CA mutations) from isolated CTCs.

2. ADCC project

We demonstrated that the inter-individual differences in trastuzumab-mediated ADCC activities of the PBMCs were consistent and reproducible. Using this technology, we tested 14 candidate genes

and found that the increase (expressed as a fold increase (FI)) in the expressions of several cytokines were significantly correlated with the ADCC activity. Next, we conducted a prospective evaluation in 18 patients who were receiving trastuzumab-based neoadjuvant chemotherapy, to determine whether the FIs in the expressions of these 14 genes were associated with a pathological complete response (pCR). Patients who showed a pCR showed higher FIs in the expressions of four genes (among the four selected genes, two were also selected in an *in vitro* ADCC association experiment). than those who did not show a pCR ($p = 0.004$, $p = 0.015$, $p = 0.0495$, and $p = 0.014$, respectively).

Future Perspectives

1. CTC project

We plan to apply this approach in the assay of clinical samples from patients with a variety of cancer types and investigate the correlation among gene mutations in sorted CTCs, circulating free DNA and primary lesions.

2. ADCC project

A prospective clinical trial to validate our results and use this system in the clinical setting is now in the planning stage. In the near future, we will also propose conducting clinical trials for rituximab and cetuximab.

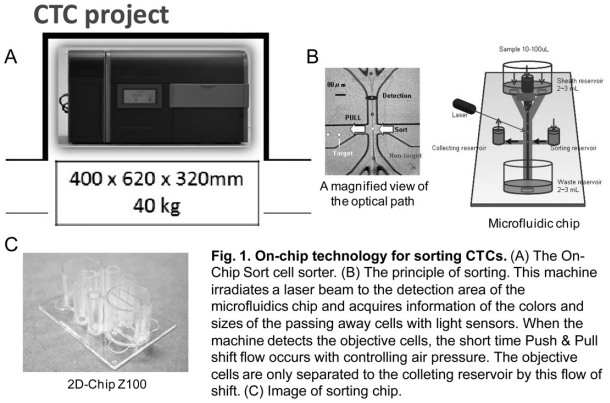
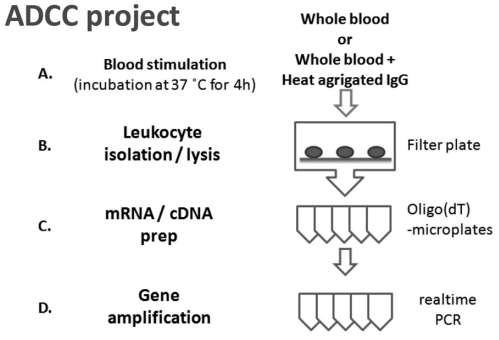


Fig. 1. On-chip technology for sorting CTCs. (A) The On-Chip Sort cell sorter. (B) The principle of sorting. This machine irradiates a laser beam to the detection area of the microfluidics chip and acquires information of the colors and sizes of the passing away cells with light sensors. When the machine detects the objective cells, the short time Push & Pull shift flow occurs with controlling air pressure. The objective cells are only separated to the colleting reservoir by this flow of shift. (C) Image of sorting chip.

Figure1.



Assay principle and procedure

A blood stimulation.
B Thawed sample is transferred to filter plate to trap leukocytes on membrane, then lysis buffer is added into a well.
C Lysate is transferred to oligo(dT)-immobilized microplate for poly(A)$^+$ mRNA isolation, followed by cDNA synthesis on the same plate.
D The cDNA solution is transferred to 384-well plate for real time PCR.

Figure2.

List of papers published in 2013
Journal

1. Katanasaka Y, Kodera Y, Kitamura Y, Morimoto T, Tamura T, Koizumi F. Epidermal growth factor receptor variant type III markedly accelerates angiogenesis and tumor growth via inducing c-myc mediated angiopoietin-like 4 expression in malignant glioma. Mol Cancer, 12:31, 2013
2. Kondo S, Ueno H, Hosoi H, Hashimoto J, Morizane C, Koizumi F, Tamura K, Okusaka T. Clinical impact of pentraxin family expression on prognosis of pancreatic carcinoma. Br J Cancer, 109:739-746, 2013
3. Nishio M, Horai T, Horiike A, Nokihara H, Yamamoto N, Takahashi T, Murakami H, Koizumi F, Nishio K, Yusa W, Koyama N, Tamura T. Phase 1 study of lenvatinib combined with carboplatin and paclitaxel in patients with non-small-cell lung cancer. Br J Cancer, 109:538-544, 2013
4. Nakadate Y, Kodera Y, Kitamura Y, Tachibana T, Tamura T, Koizumi F. Silencing of poly(ADP-ribose) glycohydrolase sensitizes lung cancer cells to radiation through the abrogation of DNA damage checkpoint. Biochem Biophys Res Commun, 441:793-798, 2013

Department of Clinical Genomics

Hitoshi Ichikawa, Fumie Hosoda, Sachiyo Mitani, Shizuka Shinohara

Introduction

The Department of Clinical Genomics was organized in 2013 in order to support genome, epigenome and transcriptome analyses of clinical samples in translational research with the aim of realizing personalized cancer treatment based on those omics data. For this purpose, small-scale next generation sequencers, Illumina MiSeq and Ion Proton, have been set up in this department, and sequencing services are provided which can detect base-substitution and insertion/deletion mutations, gene amplifications, and gene fusions from cancer tissues including formalin-fixed paraffin-embedded (FFPE) samples.

Research activities

Target sequencing analysis from FFPE cancer tissues

Next generation sequencing technology has enabled us to unravel most of the genetic alterations generated in cancer genomes. However, in actual research projects, available cancer tissue samples are often limited and not enough for typical next generation sequencing analysis. This Department accepts FFPE tissue samples which are easier to access than frozen tissue samples, and supports target sequencing of tens to hundreds of cancer genes on commercial or in-house cancer panels using the small-scale next generation sequencers. This year thymic cancer and pancreatic cancer were analyzed upon request from researchers in Hospital and Research Institute.

Development of clinical sequencing system

Individual cancers harbor a set of genetic aberrations such as mutations, gene amplifications and gene fusions, and some of them are expected to become informative biomarkers to predict the therapeutic response in molecular targeted therapies. Next generation sequencers have the potential to become an important tool in diagnosis and therapeutic decision-making in cancer treatment because of their ability to sequence a large number of clinically relevant cancer genes in a single test and to detect mutations with high sensitivity. As the basis of realizing omics data-driven personalized cancer treatment in the National Cancer Center (NCC), we have developed a clinical sequencing system which can identify genetic alterations of targetable or actionable cancer genes with next generation sequencers. 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 were captured and sequenced for detection of mutations/gene amplifications and gene fusions, respectively. By using a novel algorithm developed by researchers of the Department of Bioinformatics, mutations, gene amplifications and gene fusions could be called out. This sequencing system was adopted in the TOPICS-1 (Trial of Onco-Panel for Introduction into Clinical Study-Phase 1) study, a clinical study to investigate the feasibility and utility of clinical sequencing in early phase clinical trials, and the performance of this system in the clinical setting is now under investigation.

Department of Translational Oncology

Hiroki Sasaki, Kazuhiko Aoyagi, Masashi Tamaoki, Rie Komatsuzaki, Fumiko Chiwaki, Shinzo Mayuzumi, Akio Ashida

Introduction

In 2013, the two 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 770 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 were established many years ago. Only insufficient clinical and pathological information is attached. The establishment of new GC cell lines, especially from metastatic sites after therapy, has been urgently required. Peritoneal metastasis is most frequent in GCs, especially diffuse-type GCs. In collaboration with the Division of Genetics, we have newly established 43 diffuse-type GC derived cell lines from the cancer ascites of 21 patients. Now we possess 74 GC cell lines including 66 diffuse-type (new 43 and existing 23) and 8 intestinal-type. We have also established peritoneal metastasis model mice (1). In collaboration with two pharmaceutical companies, *in vitro* and *in vivo* preclinical studies of 4 molecular-targeted drugs using 39 representative cell lines (33 diffuse- and 6 intestinal-type) expressing luciferase and GFP 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 in this category: 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. We recently developed a mini DNA chip assay by using 98 retrospectively-collected peritoneal washings (Ann Surg Oncol 14:1694-1702, 2007). Next, we conducted a prospective study on 189 advanced cancers with more than 4 years of follow up. Prognoses of 36 CY0/DNA chip+ cases were found to be as poor as those of 34 CY1 cases. In 140 P0CY0 patients, LN+/DNA chip+ cases showed the highest recurrence (83%, 19/23), while LN-/DNA chip- cases showed the lowest (4%, 2/45). Our collaborating company prepared many supporting data for submitting the mini DNA chip to the Pharmaceuticals and Medical Devices Agency (PMDA) for marketing approval as an IVD. Second, we successfully identified 5 intrinsic subtypes of esophageal squamous cell carcinomas by gene expression-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 chemoradiotherapy (CRT) or surgery) and a validation set (167 cases containing 90 and 77 cases, respectively). Five intrinsic subtypes including 2 new subtypes were identified in the test set, and these were reproducibly found in the validation set. The two new subtypes were very similar to the previously-identified subtypes, D and B. Subtype-D included 26% 5-year survivors with CRT, whereas subtype-B contained 72%, which was clearly higher than the cases treated by neoadjuvant chemotherapy (55%, JCOG9907). Furthermore, we could find certain molecular pathways acting in each subtype that lead to not only elucidation of responsiveness to CRT but also the future treatment.

List of papers published in 2013
Journal

1. Fujita T, Yanagihara K, Takeshita F, Aoyagi K, Nishimura T, Takigahira M, Chiwaki F, Fukagawa T, Katai H, Ochiya T, Sakamoto H, Konno H, Yoshida T, Sasaki H. Intraperitoneal delivery of a small interfering RNA targeting *NEDD*1 prolongs the survival of scirrhous gastric cancer model mice. Cancer Sci, 104:214-222, 2013
2. Aoyagi K, Tamaoki M, Nishumura T, Sasaki H. Technical considerations for analyzing EMT-MET data from surgical samples. Cancer Lett, 341:105-110, 2013
3. Ono H, Chihara D, Chiwaki F, Yanagihara K, Sasaki H, Sakamoto H, Tanaka H, Yoshida T, Saeki N, Matsuo K. Missense allele of a single nucleotide polymorphism rs2294008 attenuated antitumor effects of prostate stem cell antigen in gallbladder cancer cells. J Carcinog, 12:4, 2013
4. Ishii H, Sasaki H, Aoyagi K, Yamazaki T. Classification of gastric cancer subtypes using ICA, MLR and Bayesian network. Stud Health Technol Inform, 192:1014, 2013

Department of Biomarker Evaluation

Takashi Kohno, Yoshinori Ishikawa

Introduction

The Department of Biomarker Evaluation was established in May 2013 to conduct evaluation of candidate biomarkers developed for personalized cancer therapy.

Research activities

By participating in conferences for discussion on translational research (TR, see the report of The Department of Biobank Support Core), TRs that enable us to identify and develop novel biomarkers were considered. Candidates for biomarkers will be obtained both by "seeds push" and "needs pull" TR projects in the near future, therefore, the Department will support the development of biomarkers applicable in cancer clinics through immunohistochemical and other analyses.

Department of Bioinformatics

Mamoru Kato

Introduction

Department of Bioinformatics launches officially on November of this year. Missions of our department are 1) bioinformatics analysis support for experimental departments in Group for Translational Research Support Core, 2) bioinformatics analysis support for other groups in the National Cancer Center (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 the NCC. We developed a new software system that processes a large amount of data produced by the next generation sequencer (NGS) to detect SNVs/indels/fusion genes and to check data quality. The sensitivity and the specificity of the SNV detection system were nearly 100% even for a simulated tumor purity of 20% when we compared with SNP array data. When we used NGS data to compare our SNV detection tool with other computational tools, we confirmed that ours showed a much higher performance than the other tools, in particular, for data from the Ion sequencer. Also, when we made a comparison in the detection of fusion genes, ours was far superior to another commonly-used tool.

- We setup a database that stores clinical sequencing data to be made use of for new findings.

- We provided bioinformatics analysis support for studies on liver cancer as a part of ICGC, metastasis of breast cancer, bile duct cancer in the Division of Cancer Genomics, for studies on DNA adductomics, 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 started a project on single-cell sequencing to reveal intra-tumor heterogeneity and related cancer-cell evolution, collaborating with the Division of Caner Genomics and the Division of Cancer Development System. We succeeded in sequencing with the new technology for some single cells.

List of papers published in 2013
Journal

1. Rajaram M, Zhang J, Wang T, Li J, Kuscu C, Qi H, Kato M, Grubor V, Weil RJ, Helland A, Borrenson-Dale AL, Cho KR, Levine DA, Houghton AN, Wolchok JD, Myeroff L, Markowitz SD, Lowe SW, Zhang M, Krasnitz A, Lucito R, Mu D, Powers RS. Two Distinct Categories of Focal Deletions in Cancer Genomes. PLoS One, 8:e66264, 2013

Exploratory Oncology Research & Clinical Trial Center

Preface

In 2011, our National Cancer Center (NCC) was selected as one of the five designated centers for early/exploratory clinical trials. With budget support from the Japanese Ministry of Health, Labour and Welfare (MHLW), we organized "the Exploratory Oncology Research and Clinical Trial Center" (NCC-EPOC) through the Kashiwa and Tsukiji campuses in 2012, which focused on early/exploratory clinical trials and translational research (TR). The NCC-EPOC was actually activated in April 2013, consisting of a phase I unit in each campus, central/data center function unit for clinical trials, and a translational research (TR) unit. The immunotherapy division was additionally included in the TR unit in July 2013. For innovative oncology drug developments from Japan, the NCC-EPOC has three major missions: 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. A regular weekly teleconference is held to allow the two groups in each hospital to collaborate. In 2013, 8 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 in any academic center in Asia. There were several international phase I studies including an FIH study in 2013.

2) IIT support unit: The central support/data center for IIT has been established with a total of 37 members including a project manager, monitor, data manager, biostatistician, medical writer, and auditors. Since its launch in 2012, the NCC-EPOC has initiated nine registrational IITs in accordance with ICH-GCP (so-called "ishi-syudo chiken") with an unapproved agent. Three of the nine studies have already completed accrual in collaboration with 6 major cancer centers. An additional 4 IITs, including those with new endoscopic instruments, have also been initiated. We have started a nation-wide genome screening program for the RET fusion gene, which was newly discovered in the Research Institute of our center, in patients with non-small cell lung cancer (NSCLC), for accrual to a phase II IIT with a RET inhibitor. This study is the first trial worldwide for RET positive NSCLCs with a large screening program and can be indicated for a similar very small population with driver gene alteration. The registrational IIT for GIST in accordance with a global expanded access program was conducted to improve accessibility for orphan disease. As for the academic seeds development, 10 seeds are being designated for clinical implications including three seeds already under clinical trial. An alliance contract between the NCC and the National Institute of Biomedical Innovation has been formally established for launching a nation-wide oncology seeds collection network. Intellectual property in the NCC is being integrated for efficient new seeds/drugs development.

3) TR unit: In the TR division, several projects with whole exon sequencing in lung, colorectal, and gastric cancers have been conducted to establish molecular epidemiologic data in Japanese patients. A new procedure of companion diagnosis for the RET fusion gene 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 a very small population with driver gene alterations, joined this network under contract with the NCC. A similar screening system for some other driver genes has also started in colorectal and biliary tract cancers, followed by a plan for organizing a nation-wide genome screening academia-industry consortium. This consortium will facilitate new molecular targeting agent development in Japan. A genome-guided individualized therapy system in collaboration with both hospitals named the ABC and TOP-GEAR study has also been started. These studies were conducted with the aim of a better selection of on-going phase I studies for patients who are willing to enter the study. An original sequence panel is also being developed for this study. Another study named the DEF study is now under investigation to make a "cancer encyclopedia" in gastric cancer. Samples from surgically resected specimens are used for establishing human xenograft and primary culture cell lines, followed by genome sequencing analyses. This study will contribute to actual individualized therapy in the future. In the immunotherapy division, a new immune-modulating agent is being developed in collaboration with investigators in Tokyo University. Another project of new immune cell therapy with FITC-CART is also under preclinical investigations. Under the consultation with regulatory authorities, we are planning to incorporate these innovative therapies into clinical studies.

In 2013, the NCC-EPOC conducted various studies for new agent development. For the next step, we are organizing committees to launch organ-specific IIT groups and a nation-wide genome screening network. The goal of the NCC-EPOC is to establish the top innovative academic research organization in the world based on close alliances between academia, industry and 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): Toshihiko Doi
      Chief(Tsukiji): Noboru Yamamoto
- IIT Support Group
  - Clinical Trial Section
    Chief: Akihiro Sato
- Translational Research Group
  - Division of Translational Research
    Chief(Kashiwa): Katsuya Tsuchihara
    Chief(Tsukiji): Takashi Kohno
    - Translational Medicine and Development Section
      Head(Kashiwa): Takeharu Yamanaka
      Head(Tsukiji): Ken Kato
  - Division of Cancer Immunotherapy
    Chief: Tetsuya Nakatsura

Activities of the Divisions

Department of Experimental Therapeutics (Phase I Group)

Toshihiko Doi, Noboru Yamamoto

Overview of the Department of Experimental Therapeutics

The National Cancer Center (NCC)-EPOC Phase I Group has been organized to promote the early drug development especially the first in human (FIH) trial, and in 2012. The phase I group consists 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 an 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 was launched to strongly promote the EPOC missions as previously described. The members of the Department of Experimental Therapeutics comprise specialists in their particular oncology fields (Table 1).

Table 1. Staff members in the Department of Experimental Therapeutics (NCC-EPOC)

Kashiwa		Tsukiji	
Name	Area of expertise	Name	Area of expertise
Tosihiko Doi	Gastrointestinal Oncol.	Noboru Yamamoto	Thoracic Oncol.
Kouhei Shitara	Gastrointestinal Oncol.	Kenji Tamura	Breast & Medical Oncol.
Hideaki Takahashi	Hepato-biliary and pancreatic oncol	Yutaka Fujiwara	Thoracic Oncol.
Yoichi Naito	Breast & Medical Oncol.	Shigehisa Kitano	EPOC-TR group
Kiyotaka Yoh	Thoracic Oncol.	Syunsuke Kondo	Hepato-biliary and pancreatic oncol
		Satoru Iwasa	Gastrointestinal Oncol.
		Yuko Tanabe	Breast & Medical Oncol.

Routine activities

This department plays an important role in the development of new anti-cancer drugs in our center as well as all over 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 joined the global phase I trial to accelerate new drug development in Japan. Web- or tel.-conferences are held with the EU and US sites, and we are discussing patient enrollment as well as the further developmental strategy. Routine web-conference are also held between the Kashiwa and Tsukiji campus every Friday morning, and we are sharing information about adverse events, patient enrollment and are referring candidates to each other to accelerate enrollment.

Research activities

The elucidation of the proof of concept is essential in the development of new anti-cancer drugs, and especially in the early phase we conduct several translational studies in collaboration with the adjoining research institute. In each campus, comprehensive genomic analyses, known as the 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 2013, 33 phase I trials have been conducted in both campus (Table 2).

Table 2. Phase I trials in the Dept. of Experimental Therapeutics in 2013

No.	Site	Target	FIH	Target	Enrollment in 2013	Status
1	Kashiwa+Tsukiji	CDK4/6		Solid tumors	10	Closed
2	Kashiwa+Tsukiji	CDDP micelles		Solid tumors	1	Ongoing
3	Kashiwa+Tsukiji	CDK4/6		Solid tumors	12	Ongoing
4	Kashiwa+Tsukiji	PD-L1		Solid tumors	5	Ongoing
5	Kashiwa+Tsukiji	FGFR	○	Solid tumors	3	Ongoing
6	Kashiwa+Tsukiji	FGFR	○	Solid tumors	12	Ongoing
7	Tsukiji	PIM	○	Solid tumors	7	Ongoing
8	Tsukiji	PI3K		Solid tumors	4	Ongoing
9	Tsukiji	Anti PRL		Breast & Prostate cancers	3	Closed
10	Tsukiji	PARP		Solid tumors	9	Closed
11	Tsukiji	PI3K		Solid tumors	10	Ongoing
12	Tsukiji	PD-L1		Solid tumors	4	Closed
13	Tsukiji	Hedgehog		Solid tumors	5	Ongoing
14	Tsukiji	PD-L1		Solid tumors	6	Ongoing
15	Tsukiji	CDK4/6		Solid tumors	3	Ongoing
16	Tsukiji	HSP90	○	Solid tumors	0	Ongoing
17	Kashiwa	c-Met		Solid tumors	7	Ongoing
18	Kashiwa	targeting hypoxia		Solid tumors	14	Ongoing
19	Kashiwa	anti-cancer-stem cell		Solid tumors	7	Ongoing
20	Kashiwa	PTK2		Solid tumors	6	Ongoing
21	Kashiwa	FGFR		Solid tumors	1	Ongoing
22	Kashiwa	epirubicin micelles		Solid tumors	2	Ongoing
23	Kashiwa	EGFR		Solid tumors	3	Ongoing
24	Kashiwa	c-Met		Solid tumors	1	Ongoing
25	Kashiwa	*****		Solid tumors	1	Ongoing
26	Kashiwa	TEM-1		Solid tumors	18	Ongoing
27	Kashiwa	PI3K		Solid tumors	5	Ongoing
28	Kashiwa	MEK		Solid tumors	3	Ongoing
29	Kashiwa	c-Met		Solid tumors	7	Ongoing
30	Kashiwa	c-Met		Solid tumors	7	Ongoing
31	Kashiwa	MEK		Solid tumors	4	Ongoing
32	Kashiwa	EGFL7		Solid tumors	1	Closed
33	Kashiwa	MET		Solid tumors	7	Ongoing

FIH: first in human trial

Publications in 2013
Journal

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58. Hashimoto H, Iwasa S, Yanai T, Honma Y, Kato K, Hamaguchi T, Yamada Y, Shimada Y, Namikawa K, Tsutsumida A, Yamazaki N, Yamamoto H. A double-blind, placebo-controlled study of the safety and efficacy of vitamin K1 ointment for the treatment of patients with cetuximab-induced acneiform eruption. Jpn J Clin Oncol, 43:92-94, 2013

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60. Hori N, Iwasa S, Hashimoto H, Yanai T, Kato K, Hamaguchi T, Yamada Y, Murakoshi K, Yokote N, Yamamoto H, Shimada Y. Reasons for avoidance of bevacizumab with first-line FOLFOX for advanced colorectal cancer. Int J Clin Oncol, 18:435-438, 2013

Clinical Trial Section

Akihiro Sato, Yasutaka Watanabe, Kazushi Endo, Yasuko Nishikubo, Minako Honda, Harumi Nakazima, Rie Ehara, Seiko Kondo, Hiromi Hasegawa, Yoshihiro Aoyagi, Kaori Tobayama, Kyoko furuya, Ayako Sugama, Yuko Tagami, Yushi Nagai, Chika Asami, Miwa Kihara, Sakiko Fushimi, Kaoru Koike, Kashiwa office: Miki Fukutani, Kayo Toyosaki, Noriko Suzuki, Kayoko Ohsumi, Takako Tomisawa, Rieka Yamanaka, Noriko Yamashita, Tamie Sukigara, Ritsuko Nagasaka, Midori Tanaka, Shogo Nomura, Takako Kuwaki, Toshinobu Ishibashi

Introduction

Established in 2008, the Clinical Trial Section supports the Investigator Initiated Clinical Trials (IITs) Program at National Cancer Center Hospital East (NCCHE) through the Clinical Data / Coordinating Center. Our section consults on the development strategy, supports project management and protocol development. The Section consists of 5 groups (CRC for IITs, Data Management, Clinical Trial Management, Audit, and Statistics).

Routine activities

Data management group
- Data base and CRF form design
- Data management
- Central monitoring
- System administration

Clinical Trial management group
- Project management
- Study management
- Site visit monitoring
- Medical writing

Statistical group
- Study design
- Statistical analysis
- Consultation

CRC Group
- Support IITs that are conducted in NCCHE

Audit Group
- Audit
- GCP training

Research activities

CRC Office for IITs
- CRCs, in 2012 supported 32 IITs including a Sponsor Investigator IND trial. A total of 213 patients enrolled in the IITs.

Data Management, Clinical Trial Management, Audit, Statistical Groups
- In 2013 18 IITs were conducted including 9 research IND trials. A total of 187 patients enrolled.

We focused research activities on the clinical trial methodology. We are developing a new EDC system, a sampling source document verification (SDV) method and a comprehensive information sharing infrastructure for early clinical trials.

Division of Translational Research (Kashiwa)

Katsuya Tsuchihara, Sachiyo Mimaki, Hideki Makinoshima, Shingo Matsumoto, Wataru Okamoto, 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 unit also closely collaborates with intramural and extramural clinical research teams to develop companion diagnostic systems and identify biomarkers contributing to individualized cancer therapy. The group is carrying out clinical sequencing programs and establishing new cancer cell line panels with multi-omics information to establish a "cancer encyclopedia".

Routine activities

Weekly conferences for the whole division and individual research groups are held with staff scientists and doctors, technical staffs, visiting scientists, and graduate students from the University of Tokyo, Tokyo Medical and Dental University, Keio University and Juntendo University. A monthly tele-conference is held with the Division of Translational Research at Tsukiji campus.

Research activities

Development of Anti-austeric Drugs

Cancer cells in solid tumors frequently encounter a hypoxic and nutrient-deficient microenvironment. Austerity, which is resistance to nutrient starvation, is a characteristic feature of various cancer cells. Since most non-cancerous tissues seldom encounter such nutrient-deficient circumstance, targeting austerity is a promising new strategy for selective cancer treatment. Arctigenin, a major component of *Arctium lappa* (the greater burdock) is one of the anti-austerity compounds identified in this division. Preclinical studies revealed that a crude extract of *Arctium lappa* exhibited anti-austeric abilities. Accompanying with a phase II clinical trial recruiting advanced pancreatic cancer patients, the mechanism of action of arctigenin has been analyzed.

Implication of biomarkers for cancer therapy

To explore more effective genomic biomarkers in anti-EGFR antibody treatment for advanced colorectal cancer, a multi-centered retrospective study combined with whole exon sequencing and copy number variation analyses (BREAC study) is being conducted. Whole exon sequencing of these characteristic anti-EGFR antibody-sensitive and –resistant cases was completed and exploration of potential new biomarkers has been conducted. To clarify the effectiveness and feasibility of multiplex trans-organ pan-cancer genomic biomarker testing, an intramural expert panel has been organized and an ABC study (Analyses of Biopsy samples for Cancer genomics) has been started. More than 180 cases were enrolled by the end of 2013 and the success rate of genetic tests was more than 90%.

Molecular epidemiology of solid tumors

Whole exon sequencing was adopted to clarify the mutation profiles of Japanese lung cancer. Somatic mutations of 55 cases of small cell lung cancer specimens were identified. Largely diverse mutation patterns of individual tumors were exhibited and potential therapeutic targets were identified. Preclinical study models that represent the wide diversity of genetic and epigenetic alterations of solid tumors have been long waited. A DEF (Discovery and Establishment of new biomarkers For gastric cancer) study, which establishes xenograft models and cell lines from primary gastric cancer specimens surgically resected in National Cancer Center Hospital East, was started. More than 90 cases were enrolled in the first 6 months.

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Journal

1. Tsuchihara K. RET-targeting molecular stratified non-small-cell lung cancers. Translational Lung Cancer Res, 2:463-465, 2013
2. Ichinokawa H, Ishii G, Nagai K, Kawase A, Yoshida J, Nishimura M, Hishida T, Ogasawara N, Tsuchihara K, Ochiai A. Distinct clinicopathologic characteristics of lung mucinous adenocarcinoma with KRAS mutation. Hum Pathol, 44:2636-2642, 2013
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Division of Translational Research (Tsukiji)

Takashi Kohno, Hitoshi Ichikawa, Akinobu Hamada, Shuichi Shinma, Natsuko Hama, Tatsuhiro Shibata, Hiroki Sasaki, Ken Kato, Suga Yamagami, Atsuko Kawami, Kazumi Kanazawa, Nagako Yasuda, Kahori Takeuchi, Yukako Izoe, Sayaka Akimoto, Ayako Iwata, Izumi Kobayashi, Mari Tomoda

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. The Section of Translational Medicine and Development was established to support TR studies and the National Cancer Center Biobank (NCCBB).

Routine activities

The Section of Translational Medicine and Development has routinely obtained the informed consent to participate as an NCCBB donor from patients who consult the National Cancer Center Hospital (NCCH) for the first time. Clinical research coordinators in this section coordinate the translational research in several ways, such as assistance of registration for clinical trial, logistics of pathological specimen, data collection for case report form and coordination between sections.

Research activities

Clinical sequencing for early phase clinical trials

Through a collaborative work with the Department of Clinical Genomics (Group for Translational Research Support Core), a next generation sequencer-based clinical sequencing system was developed, which enables us to identify genetic alterations, including gene fusions, using FFPE tissue DNAs (Figure 1).

Establishment of molecular diagnosis for FGFR fusion genes in pathological archives

FGFR2 fusion genes identified as a driver and druggable alteration in cholangiocarcinomas by the Division of Cancer Genomics, Research Institute, are a promising new molecular target therapy against this rare and intractable tumor. To facilitate the FGFR-targeted clinical trials including First-In-Human ones in EPOC, we have established a molecular diagnosis procedure to enrich FGFR-fusion positive patients using routine formalin-fixed tissues (Figure 2).

Novel Pharmacokinetic (PK)/Pharmacodynamic analysis for the development of new anticancer agents

Drug exposure and distribution in several tissues impact the pharmacology, toxicology, and efficacy in drug development. However, conventional PK analyses, using HPLC, LC-MS/MS and ELISA, have limitations in providing a comprehensive assessment of exact intra-tumor distribution. A newly developed 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 (Figure 3).

Preclinical Studies Using Newly Established Gastric Cancer Cell Lines

Genome-wide genetic information in 770 cancer cell lines is available in the COSMIC database (Sanger Center, UK); however, among them, only 21 cell lines are derived from gastric cancer (GC). We possess 71 GC cell lines including 65 diffuse-type, including 43 newly established by us, and 6 intestinal-type. We have also established a peritoneal metastasis model in mice. In vitro and in vivo preclinical studies of 4 molecular-targeted drugs are being conducted through collaborative studies with two pharmaceutical companies to deriver new therapeutic agents to early phase clinical trial projects in EPOC (Figure 4).

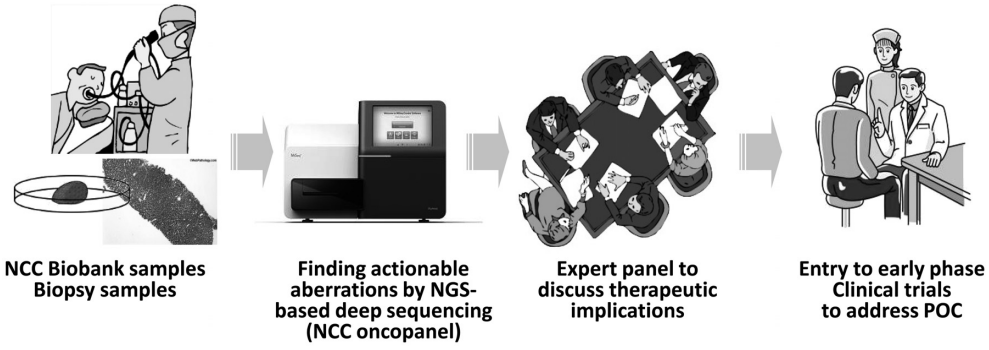
Biobank Support

We explained the purpose and aim NCCBB to 7040 patients from January to December 2013, and received consent on blood collection for research from 6095 patients (86.6% consent rate). We received consent from 6197 patients for research use of their surplus samples (88.0% of consent rate). The patient load with our assistance in filling in the preliminary-diagnosis card and so on was 8,501 (Table 1).

Clinical trials

The TOPICS-1 (Trial of Onco-Panel for Introduction into Clinical Study-Phase 1) study was launched to investigate the feasibility and utility of

this clinical sequencing system to enrich patients for early phase clinical trials based on actionable gene aberrations. We have finished analyses of > 40 patients and found gene aberrations with therapeutic implications in about 50% of the patients. The actionable gene aberrations were discussed in four 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. Data and samples for this study were managed by the Section of Translational Medicine and Development.



TOPICS-1 (Trial of Onco-Panel for Introduction into Clinical Study-Phase 1)

Figure 1. Clinical sequencing for early phase clinical trials

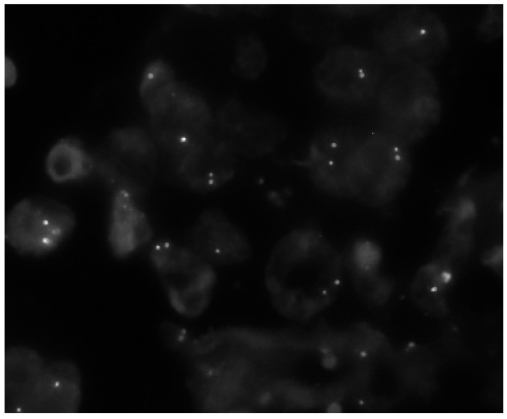
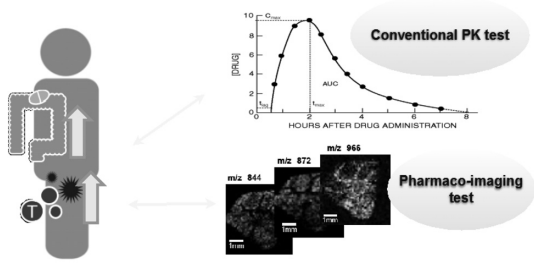


Figure 2. Diagnosis of FGFR gene fusion by FISH



- **Plasma concentration does not represent real drug exposure level.**
- **Imaging Mass spectrometry may provide complementary information to judge an optimal dose and evaluate the proof of concept in the drug development.**

Figure 3. Newly developed Mass Imaging system for PK examination

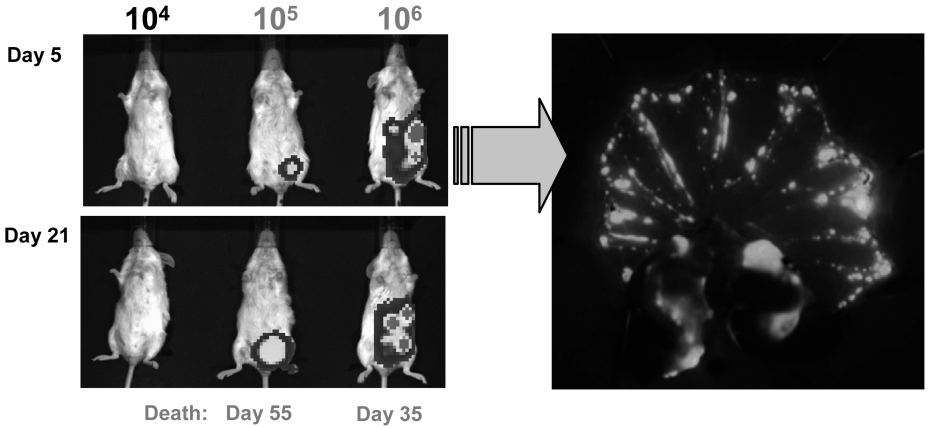


Figure 4. *In vivo* imaging of Peritoneal Metastasis

Table 1. JAN-DEC/2013

Number of patients who were informed about NCCBB	Consent for NCBB for blood collection for research (%)	Consent for NCCBB on research use of the surplus samples (%)	Patient load with our assistance
7,040	6,095 (86.6%)	6,197 (88.0%)	8,501

List of papers published in 2013
Journal

1. Kohno T, Tsuta K, Tsuchihara K, Nakaoku T, Yoh K, Goto K. *RET* fusion gene: translation to personalized lung cancer therapy. Cancer Sci, 104:1396-1400, 2013
2 Shimma S, Takashima Y, Hashimoto J, Yonemori K, Tamura K, Hamada A. Alternative two-step matrix application method for imaging mass spectrometry to avoid tissue shrinkage and improve ionization efficiency. J Mass Spectrom, 48:1285-1290, 2013
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7 Ishii H, Sasaki H, Aoyagi K, Yamazaki T. Classification of gastric cancer subtypes using ICA, MLR and Bayesian network. Stud Health Technol Inform, 192:1014, 2013

Division of Cancer Immunotherapy

Tetsuya Nakatsura, Yuji Heike, Yasushi Uemura, Shigehisa Kitano, Toshiaki Yoshikawa, Keigo Saito, Manami Shimomura, Shoichi Mizuno, Yumi Tokumitsu, Kayoko Shoda, Yukiko Kozaki, Yu Sawada, Kohei Tada, Kaori Kobayashi, Megumi Ozaki, Miki Okazaki, Hikaru Kondou

Introduction

Our Division aims to investigate evidenced-based cancer immunotherapy, repeating basic research and translational research. This Division is focused on developing not only more effective immunotherapeutic strategies but also immunological methods for suppression of recurrence or for cancer prevention.

Research activities

Glypican-3 (GPC3) is overexpressed in human hepatocellular carcinoma (HCC) but not expressed in normal tissues except for the placenta and fetal liver and therefore is an ideal target for cancer immunotherapy. We identified an H2-K^b or H2-D^b restricted and murine GPC3 (mGPC3)-derived cytotoxic T-lymphocyte (CTL) epitope peptide in C57BL/6 (B6) mice, which can be used in the design of preclinical studies of various therapies with GPC3-target immunotherapy *in vivo*. First, 11 types of 9- to 10-mer peptides predicted to bind with H2-K^b or H2-D^b were selected from the mGPC3 amino acid sequence based on the binding score as calculated by the BIMAS software. We evaluated the peptide-binding affinity and confirmed that all peptides were able to bind to H2-K^b or H2-D^b with an *in vitro* cellular binding assay. Subsequently, a mixed peptide vaccine and single peptide vaccine were given to B6 mice to evaluate the immunogenic potential of the 11 selected peptides. Using the splenocytes from peptide-vaccinated mice, interferon (IFN)-γ enzyme-linked immunospot (ELISPOT) assays showed that the mGPC3-$1_{127\text{-}136}$ (AMFKNNYPSL) peptide was the most efficient for inducing CTLs among the 11 peptides. Next, we demonstrated that the mGPC3-1 peptide-specific CTL line could recognize mGPC3-expressing cancer cells, suggesting that the mGPC3-1 peptide was an endogenously presented peptide. In conclusion, we identified mGPC3-1 as an H2-K^b or H2-D^b restricted, mGPC3-derived CTL epitope peptide (1).

Previously, we performed a phase I clinical trial of GPC3 derived peptide vaccination in patients with advanced HCC, and reported that GPC3 peptide vaccination was safe and had clinical efficacy. Moreover, we proposed that a peptide specific CTL response was a predictive marker of overall survival in patients with HCC who were receiving peptide vaccination. We established GPC3 derived peptide-specific CTL clones from the PBMCs of an HLA-A*02:07-positive patient with HCC who was vaccinated with an HLA-A2-restricted GPC3 peptide vaccine and showed a clinical response in the phase I clinical trial. Established CTL clones were analyzed using the IFN-γ ELISPOT assay and a cytotoxicity assay. GPC3 peptide-specific CTL clones were established successfully from the PBMCs of the patient. One CTL clone showed cytotoxicity against cancer cell lines that expressed endogenously the GPC3 peptide. The results suggest that CTLs have high avidity, and that natural antigen-specific killing activity against tumor cells can be induced in a patient with HCC who shows a clinical response to vaccination with the $GPC3_{144\text{-}152}$ peptide (2).

We conducted a subsequent trial in advanced HCC to assess the histopathological findings before and after vaccination with the GPC3 peptide. We present herein on the clinical course and the pathological study including the autopsy of a patient with advanced HCC in the ongoing clinical trial. A 62-year old patient suffering from HCC refractory to sorafenib therapy received the GPC3 peptide vaccine. The patient had fever and remarkably impaired liver function twice after vaccination. Contrast-enhanced CT after the second vaccination showed multiple low-density areas in the liver tumor, indicating tumor necrosis. In contrast, the tumor thrombus in the right atrium increased. The patient discontinued protocol treatment due to disease progression and died 30 days after the second vaccination. An autopsy was performed to determine the main cause of death and to evaluate the antitumor effect of the vaccination. A histological examination showed central necrosis in most of the intrahepatic tumor. The main cause of death was circulatory failure due to a tumor thrombus, which occupied most of the right atrium. An immunohistochemical analysis revealed infiltration of CD8-positive T cells in the residual carcinoma, but not within the cirrhotic area. An *ex*

vivo IFN-γ enzyme-linked immunospot analysis revealed vaccine-induced immune-reactivity against the GPC3 peptide. A histopathological examination at the estimated time of a strong immunological response demonstrated a GPC3 peptide vaccination-induced cytotoxic T-lymphocyte response with an anti-tumor effect (3).

Antigen-specific cancer immunotherapy is a promising strategy for improving cancer treatment. Recently, many tumor-associated antigens and their epitopes recognized by CTLs have been identified. However, the density of endogenously presented antigen-derived peptides on tumor cells is generally sparse, resulting in the inability of antigen-specific CTLs to work effectively. We hypothesized that increasing the density of an antigen-derived peptide would enhance antigen-specific cancer immunotherapy. We successfully demonstrated that intratumoral peptide injection leads to additional peptide loading onto major histocompatibility complex class I molecules of tumor cells, enhancing tumor cell recognition by antigen-specific CTLs. In *in vitro* studies, human leukocyte antigen (HLA)-A*02:01-restricted glypican-$3_{144-152}$ (FVGEFFTDV) and cytomegalovirus$_{495-503}$ (NLVPMVATV) peptide-specific CTLs showed strong activity against all peptide-pulsed cell lines, regardless of whether the tumor cells expressed the antigen. In *in vivo* studies using immunodeficient mice, glypican-$3_{144-152}$ and cytomegalovirus$_{495-503}$ peptides injected into a solid mass were loaded onto HLA class I molecules of tumor cells. In a peptide vaccine model and an adoptive cell transfer model using C57BL/6 mice, intratumoral injection of ovalbumin$_{257-264}$ peptide (SIINFEKL) was effective for tumor growth inhibition and survival against ovalbumin-negative tumors without adverse reactions. Moreover, we demonstrated an antigen-spreading effect that occurred after intratumoral peptide injection. Intratumoral peptide injection enhances tumor cell antigenicity and may be a useful option for improvement in antigen-specific cancer immunotherapy against solid tumors (4).

Clinical trials

We are performing a Phase II study of GPC3 peptide vaccine as adjuvant treatment for HCC after surgical resection or RFA, 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. We are also performing a Phase I study of a peptide cocktail vaccine for patients with refractory pediatric sarcoma.

List of papers published in 2013
Journal

1. Iwama T, Horie K, Yoshikawa T, Nobuoka D, Shimomura M, Sawada Y, Nakatsura T. Identification of an H2-K^b or H2-D^b restricted and glypican-3-derived cytotoxic T-lymphocyte epitope peptide. Int J Oncol, 42:831-838, 2013
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9. Fuji S, Ueno N, Hiramoto N, Asakura Y, Yakushijin K, Kamiyama Y, Kurosawa S, Kim SW, Heike Y, Yamashita T, Fukuda T. Reduced-intensity conditioning regimen with low-dose ATG-F for unrelated bone marrow transplant is associated with lower non-relapse mortality than a regimen with low-dose TBI: a single-center retrospective analysis of 103 cases. Int J Hematol, 98:608-614, 2013
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12. Nishimura T, Kaneko S, Kawana-Tachikawa A, Tajima Y, Goto H, Zhu D, Nakayama-Hosoya K, Iriguchi S, Uemura Y, Shimizu T, Takayama N, Yamada D, Nishimura K, Ohtaka M, Watanabe N, Takahashi S, Iwamoto A, Koseki H, Nakanishi M, Eto K, Nakauchi H. Generation of rejuvenated antigen-specific T cells by reprogramming to pluripotency and redifferentiation. Cell Stem Cell, 12:114-126, 2013

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Book

14. Nakatsura T, Nakamura Y. Chapter21. Immunotherapies for Liver Tumors. In: Yuman F, Jia-Hong D (eds), Hepatobiliary Cancer, People's Medical Publishing House-USA, Ashland Ohio, pp 607-638, 2013

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Research Center for Cancer Prevention and Screening

Preface

The Research Center for Cancer Prevention and Screening (RCCPS) was established in October, 2003. The organization at the present time consists of three groups and a division: Epidemiology and Prevention Group, Screening Research Group, Research Infrastructure Group, and the Division of Cancer Screening that is responsible for cancer screening services. Our mission is advancing research projects and activities for cancer prevention and screening to provide correct information and the optimal methods in order to keep the largest possible number of people from developing and dying from cancer.

The Epidemiology and Prevention Group worked as one division till May, 2013, and was then reorganized as the Division of Epidemiology and the Division of Prevention. The former conducts research activities to build evidence to understand etiology of cancer while the latter to evaluate evidence and to provide correct information on cancer prevention proposing guidelines. Research activities are reported as one group here. Various scales of epidemiologic studies have been promoted including the Japan Public Health Center-based prospective study (JPHC Study) started in 1990 and the JPHC-NEXT started in 2011. The results contribute to build evidence steadily in Japan and also on a global scale with international collaborative projects. The accumulated experience was used to deal with a project presenting a vision of all molecular epidemiology cohort studies united nationwide. To develop an evidence-based cancer prevention strategy in terms of lifestyle intervention suitable for the Japanese population, some systematic literature reviews and pooled analyses were conducted to update current evidence-based cancer prevention recommendations.

The Screening Research group was organized in June. The Division of Screening Assessment and Management and the Division of Screening Technology and System Development belong to the group. Research activities are reported as the Screening Assessment and Management Division here. The division has conducted studies on the assessment and management of screening programs, particularly nationwide programs, and on other issues relevant to cancer screening. Guidelines on screening for breast cancer and gastric cancer were developed, being revised by comments, and to be open. Quality Assurance (QA) in cancer screening at municipalities was performed using a checklist and was also used to eliminate cancer-screening disparities. A study to calculate a standardized screening rate was undertaken. Furthermore, the survey was conducted in order to grope for the effective countermeasure against low cancer screening rates. A workshop on cancer screening management was held for the members of prefectural committees. A randomized controlled trial (RCT) of colonoscopic screening has been carried out. The Division also participated in other RCTs and conducted a case-control study for gastric cancer screening using endoscopy.

The Research Infrastructure Group to which the Division of Public Health Policy Research belongs was newly installed in June. The division investigates the methods of distribution and dissemination of scientific evidence concerning cancer prevention, screening, and survivorship. To establish a research infrastructure, the Division conducts methodological research and education concerning behavioral science, epidemiology and biostatistics and supports large scale interventional studies. Several leaflets to remind the general population about cancer screening were developed. Workshops were conducted to support local governments. Comics on cancer education for children were produced and distributed.

A large cohort is being established for breast cancer patients. Novel contents were created to enrich the education on the ICR web, an e-learning site for those who are involved in any clinical research.

The Division of Cancer Screening changed its name from the Division of Screening and Development in April and came to be run under the management of vice director of the RCCPS. The Division is in charge of multiphasic cancer screening using several imaging modalities. With informed consent, the data and samples are stored for future research. Malignant tumors were detected in 44 out of 819 new participants and in 43 out of 1745 repeaters who underwent multi-phasic clinical programs in 2012. Detection rates were 5.37% and 2.46%, respectively.

Research results are returned to the public through paper publications, conference presentations, lectures, and information on the *Ganjoho* (Cancer Information) service by the Center for Cancer Control and Information Services and other websites, leaflets and pamphlets, and so on. To achieve our mission, all the members in 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 Group
  Chief: Shoichiro Tsugane
  - Epidemiology Division
    Chief: Motoki Iwasaki
  - Prevention Division
    Chief: Shizuka Sasazuki
- Screening Assessment and Management Group
  Chief: Hiroshi Saito
  - Screening Assessment and Management Division
    Chief: Hiroshi Saito
  - Division of Screening Technology and Development
    Chief: Hiroshi Saito
- Research Infrastructure Group
  Chief: Shoichiro Tsugane
  - Division of Public Health Policy Research
    Chief: Seiichiro Yamamoto
- Dupty Director:
  Yasuaki Arai
  - Division of Screening Practice
    Chief: Yukio Muramatsu

Activities of the Divisions

Epidemiology and Prevention Division (until May 31, 2013)
Epidemiology and Prevention Group: Epidemiology Division, Prevention Division (since June 1, 2013)

Shoichiro Tsugane, Shizuka Sasazuki, Motoki Iwasaki, Norie Sawada, Taichi Shimazu, Taiki Yamaji, Ai Noda, Izumi Suenaga, Hadrien Charvat, Sanjeev Budhathoki, Azusa Hara, Akihisa Hidaka, Manami Inoue, Thomas Svensson, Eiko Saito, Yuri Ishii, Yingyan Gong, Jun Umesawa, Tomomi Mukai, Hiroko Ogata, Kayo Ohashi, Koichi Kawamura, Izumi Matsumoto, Yurie Shinozawa, Noriko Wada, Miho Onishi, Yuko Kato, Yasuko Iba, Michiko Okajima, Ayako Toyama

Introduction

The Epidemiology and Prevention Division has conducted research activities as one division until May, 2013, and was then recognized as two divisions, the Epidemiology and Prevention Divisions. The activities of the divisions are thus described together as The Epidemiology and Prevention Group in this annual report. The group has planned and conducted independent and collaborative studies on cancer etiology and prevention, with a special focus on dietary, environmental and genetic factors. Several epidemiological projects are currently in progress.

Research activities

Population-based Prospective Study (the JPHC Study and the JPHC-NEXT Study)

Diet has been implicated in the etiology of cancer and in the unique patterns of cancer incidence in Japan. However, the epidemiological evidence for this contention has been limited. The group therefore initiated a cohort study, the Japan Public Health Center-based Prospective Study (JPHC Study), in 1990, in collaboration with 11 public health centers and other institutes, in which approximately 140,000 individuals from 11 areas were scheduled to be followed up for at least 30 years. A total of 23,629 deaths, 19,708 cases of cancers, 6,225 cases of strokes and 1,224 cases of myocardial infarctions, had been documented as of December, 2013.

In the cohort, lifestyle factors that were assessed in the baseline and/or 5 and/or 10 year follow up questionnaire, examination data from health checkups or stored blood samples were investigated in relation to the subsequent risk of total death, total or specific cancer and other lifestyle-related diseases.

Death: Although dietary patterns have been linked to depression, no study had yet examined the association between dietary patterns and suicide risk. Among both men and women, a 'prudent' dietary pattern with a high intake of vegetables, fruits, potatoes, soy products, mushrooms, seaweed and fish was associated with a decreased risk of suicide. Total Cancer: Being a known human carcinogen, total arsenic and inorganic arsenic showed no association with the risk of total cancer in both men and women but their intake tended to be associated with an increased risk of lung cancer especially in currently smoking men (1). The association between social support and risk of cancer incidence and mortality was examined. Low social support was not associated with the risk of total cancer in men and women but was associated with a higher risk of colorectal cancer in men (2). Ten year estimates of the probability of cancer occurrence based on age, sex, and the pattern of adherence to five healthy lifestyle habits (never smoking, moderate or no alcohol consumption, adequate physical activity, moderate salt intake, and appropriate body mass index) was provided. Adherence to all five habits was estimated to reduce the 10-year probability of cancer occurrence by 1/2 in men and 1/3 in women, suggesting the importance of lifestyle improvement (3). Stomach Cancer: No association of plasma isoflavone concentrations with gastric cancer risk was found in a nested case-control study, which supported the previously observed null association between isoflavone intake and gastric cancer risk (4). Liver Cancer: Higher plasma adiponectin levels were associated with an increased risk of primary liver cancer with hepatitis virus infection in a nested case-control study (5). Breast Cancer: For total fruit and vegetable consumption, our results did not provide any substantial association with a decreased risk of breast cancer. Intake of cruciferous vegetable showed a statistically significant association with a decreased risk of breast cancer among premenopausal women (6). The others: Not only cancer but also other non-communicable diseases (NCDs) are designed to be endpoints of the cohort study. Associations between lifestyle factors and suicide (7), stroke (8-11), coronary heart disease (10 and 11), cardiovascular disease (CVD) (12), myocardial infraction (13), dentition status (14) and diabetes (15-19) were investigated.

Recruitment for the JPHC-NEXT study and the collaborative studies set for 100,000 participants started in 2011 and is in progress in several areas

in order to update evidence with the current generation. Men and women of 40-74 years old of age at the baseline survey are to be followed up for 20 years. Overall survival and NCDs such as cancer, CVD, diabetes and mental illness are listed as the main endpoints. The collected data and samples are to be analyzed with up-to-date technology including genomics. A standard protocol for a molecular epidemiology cohort study in Japan is projected to be developed based on the JPHC-NEXT protocol. To conduct verification of a feasibility and validation study to consolidate data together with the other cohort study with its original protocol, a new cohort study by Strategic Funds for the Promotion of Science and Technology was launched and about 7000 men and women were recruited in 2 areas by 2013. The eventual goal of the project is to promote the Japanese Consortium for Cohort Studies of Molecule and Lifestyle presenting a vision of all molecular epidemiology cohort studies united nationwide.

Epidemiological Study of Japanese Brazilians (Sao Paulo-Japan Cancer Study)

Studies on migrants offer some clues as to the relative importance of genetic and environmental factors in the etiology of cancer. Several epidemiologic studies in Brazil, a multi-ethnic nation with 1.2 million people of Japanese ancestry, are in progress. A case-control study was conducted with subjects in Nagano, Japan, and São Paulo, Brazil to clarify whether particular genetic markers of immunoglobulin G (IgG) contributed to the magnitude of natural antibody responsiveness to tumor-associated antigen human epidermal growth factor receptor 2 (HER2) in patients with breast cancer and racially restricted contributions were observed (20). A colorectal adenoma case-control study in Japanese Brazilians in São Paulo is in progress. The validity of the quantitative FFQ used in the study was assessed (21).

Cancer Prevention Study

To develop an evidence-based cancer prevention strategy in terms of lifestyle intervention suitable for the Japanese population, a systematic literature review project (22) and a pooled analysis (23) were conducted. Evidence on smoking, alcohol, anthropometry, fruit and vegetables intake, other foods and lifestyles and infectious diseases as risk factors of the main cancers in Japan was reviewed to make final or updated judgments, each of which has been made public on the WEB (http://epi.ncc.go.jp/can_prev/) and distribution of booklets. Based on the judgments, current evidence-based cancer prevention recommendations for Japanese provided by the study group were also updated. The evidence-based materials to build up the recommendations were used to develop measures and policies in national health promotions. A population-based double-blind randomised controlled trial in a Japanese population with atrophic gastritis in an area of high stomach cancer incidence was conducted between 1995 and 2000 (Hiraka Study), and suggested that vitamin C supplementation may not have a strong effect on reducing infections in individuals with atrophic gastritis (24). Prediction model applications that calculate changes in risk through lifestyle modification are to put on the internet based on results from JPHC study. Data on the probability of 10-year survival free from cancer and cardiovascular incidence, and, for men, of the 10-year risk of colorectal cancer development are now available (http://epi.ncc.go.jp/riskcheck/), and others are under construction.

International Collaborative Projects

International collaborative projects to contribute on to the global scale with a focus on Asian cancer prevention strategies (Japan-China cooperative research work, Asia Cohort Consortium (ACC) (25-27), Asia Breast Cancer Consortium (28 and 29), Pooling project of Prospective Studies of Diet and Cancer, Collaborative Group on Hormonal Factors in Breast Cancer, and a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide (30).

Reviews and others

Analysis of the clinical data was carried out (31 and 32) as well as some contribution to a systematic review and meta-analysis on definition of incident type 2 diabetes (33) and a report of the Japan Diabetes Society/Japanese Cancer Association Joint Committee on Diabetes and Cancer (34).

List of papers published in 2013
Journal

1. Sawada N, Iwasaki M, Inoue M, Takachi R, Sasazuki S, Yamaji T, Shimazu T, Tsugane S. Dietary arsenic intake and subsequent risk of cancer: the Japan Public Health Center-based (JPHC) Prospective Study. Cancer Causes Control, 24:1403-1415, 2013
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3. Charvat H, Sasazuki S, Inoue M, Iwasaki M, Sawada N, Shimazu T, Yamaji T, Tsugane S. Impact of five modifiable lifestyle habits on the probability of cancer occurrence in a Japanese population-based cohort: results from the JPHC study. Prev Med, 57:685-689, 2013
4. Hara A, Sasazuki S, Inoue M, Miura T, Iwasaki M, Sawada N, Shimazu T, Yamaji T, Tsugane S. Plasma isoflavone concentrations are not associated with gastric cancer risk among Japanese men and women. J Nutr, 143:1293-1298, 2013
5. Michikawa T, Inoue M, Sawada N, Sasazuki S, Tanaka Y, Iwasaki M, Shimazu T, Yamaji T, Mizokami M, Tsugane S. Plasma levels of adiponectin and primary liver cancer risk in middle-aged Japanese adults with hepatitis virus infection: a nested case-control study. Cancer Epidemiol Biomarkers Prev, 22:2250-2257, 2013
6. Suzuki R, Iwasaki M, Hara A, Inoue M, Sasazuki S, Sawada N, Yamaji T, Shimazu T, Tsugane S. Fruit and vegetable intake and breast cancer risk defined by estrogen and progesterone receptor status: the Japan Public Health Center-based Prospective Study. Cancer Causes Control, 24:2117-2128, 2013
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9. Kokubo Y, Iso H, Saito I, Yamagishi K, Yatsuya H, Ishihara J, Inoue M, Tsugane S. The impact of green tea and coffee consumption on the reduced risk of stroke incidence in Japanese population: the Japan public health center-based study cohort. Stroke, 44:1369-1374, 2013
10. Yamagishi K, Iso H, Kokubo Y, Saito I, Yatsuya H, Ishihara J, Inoue M, Tsugane S. Dietary intake of saturated fatty acids and incident stroke and coronary heart disease in Japanese communities: the JPHC Study. Eur Heart J, 34:1225-1232, 2013
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12. Nishiwaki Y, Michikawa T, Takebayashi T, Nitta H, Iso H, Inoue M, Tsugane S. Long-term exposure to particulate matter in relation to mortality and incidence of cardiovascular disease: the JPHC Study. J Atheroscler Thromb, 20:296-309, 2013
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24. Ma E, Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Tsugane S. Vitamin C supplementation in relation to inflammation in individuals with atrophic gastritis: a randomised controlled trial in Japan. Br J Nutr, 109:1089-1095, 2013
25. Lin Y, Fu R, Grant E, Chen Y, Lee JE, Gupta PC, Ramadas K, Inoue M, Tsugane S, Gao YT, Tamakoshi A, Shu XO, Ozasa K, Tsuji I, Kakizaki M, Tanaka H, Chen CJ, Yoo KY, Ahn YO, Ahsan H, Pednekar MS, Sauvaget C, Sasazuki S, Yang G, Xiang YB, Ohishi W, Watanabe T, Nishino Y, Matsuo K, You SL, Park SK, Kim DH, Parvez F, Rolland B, McLerran D, Sinha R, Boffetta P, Zheng W, Thornquist M, Feng Z, Kang D, Potter JD. Association of body mass index and risk of death from pancreatic cancer in Asians: findings from the Asia Cohort Consortium. Eur J Cancer Prev, 22:244-250, 2013
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30. Powles J, Fahimi S, Micha R, Khatibzadeh S, Shi P, Ezzati M, Engell RE, Lim SS, Danaei G, Mozaffarian D. Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. BMJ Open, 3:e003733, 2013

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34. Kasuga M, Ueki K, Tajima N, Noda M, Ohashi K, Noto H, Goto A, Ogawa W, Sakai R, Tsugane S, Hamajima N, Nakagama H, Tajima K, Miyazono K, Imai K. Report of the Japan Diabetes Society/Japanese Cancer Association Joint Committee on Diabetes and Cancer. Cancer Sci, 104:965-976, 2013

Screening Assessment and Management Division

Hiroshi Saito, Chisato Hamashima, Kumiko Saika, Ryoko Machii

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 breast cancer have been developed and will be published in 2014. Gastric cancer screening guidelines have been revised and will also be published in 2014.

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 quality assurance at municipalities. The division also evaluated process indicators such as rate of work-up, and ranked those indicators in all cities by prefecture in order of excellence so that each city compares its indicator with those of other cities. The overall CL score in 2013 collected this year was improved by 5-9 % for five cancer screening programs as compared to those in 2007. Based on such improvement, we prepared a revised version of the CLs, which was submitted to the Cancer Screening Expert Committee of the Ministry of Health, Labour and Welfare.

The division set up the website which allows mutual communication and support toward municipalities such as provision of their QA data archives and information relevant to cancer screening. In 2013, CL data were collected from municipalities and evaluation results were fed back to participants on the website. One thousand three hundred and ninety municipalities (82%) utilized the website by registering as members of the site.

Calculation of standardized screening rate

The division calculated the standardized screening rate using an equation to estimate target population size in municipalities. The calculated data were released on the website of the Center for Cancer Control and Information Services. This activity will be continued on an annual basis.

Workshop on cancer screening management

The Division held a one-day educational workshops for the members of prefectural committees of cancer screening management, aiming at activating quality assurance activities in each of the 47 prefectures. The themes this year were breast and cervix. The main contents of the workshops were the methods of quality assurance of the screening programs within each prefecture. Other basic issues required conducting organized cancer screening programs and issues of such as those of screening assessment were also included in the contents.

There were 86 participants in the workshops from 44 prefectures, who consisted of administrative officers (45%) and members of the committee (55%). This activity was performed as a 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, 34 prefectures held meetings to discuss cancer screening management and 22 (8 in the previous year) released the evaluation results of municipalities using CLs for lung cancer. This result suggests 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 (CS) for colorectal

cancer was started in 2009. The division has been responsible for designing and managing the study as the head office of the study. The cumulative number of subjects who gave informed consent, and who were thus enrolled in the study, was 6512 at December 2013, corresponding to 65% of the planned number. Data monitoring results showed randomization had been performed successfully. No serious adverse effect was reported associated with screening colonoscopy. Eleven cases of minor complications were reported in the therapeutic procedure. The division have 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, case-control study was conducted to evaluate the efficacy of endoscopic screening in Tottori and Niigata prefectures. Compared with those who had never been screened, the ORs for those having been screened within the past 36 months were 0.695 (95% CI: 0.489-0.986) for endoscopic screening and 0.865 (95% CI : 0.631-1.185) for radiographic screening.

The sensitivities of endoscopic and radiographic screening were calculated by the detection method and the incidence method. Endoscopic screening for gastric cancer had a higher sensitivity than radiographic screening for both methods in prevalence and incidence screening rounds.

List of papers published in 2013
Journal

1. Hirai K, Harada K, Seki A, Nagatsuka M, Arai H, Hazama A, Ishikawa Y, Hamashima C, Saito H, Shibuya D. Structural equation modeling for implementation intentions, cancer worry, and stages of mammography adoption. Psychooncology, 22:2339-2346, 2013
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Division of Public Health Policy Research

Seiichiro Yamamoto, Yuri Mizota, Ayumi Nakagawa, Mika Takai

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 our studies is to fill the gap between the scientific evidence and the behavior of the people towards cancer prevention and screening by supporting local government and directly approaching the public. In addition, because of the lack of evidence, we try to establish scientific evidence for cancer survivorship.

As for the activity for establishing a research infrastructure, we conduct methodological research and education concerning behavioral science, epidemiology and biostatistics and support large scale interventional studies.

Research concerning promotion of cancer prevention and screening using social marketing method

The examples of the Division's achievements during 2013 for promoting cancer screening are as follows: development of leaflets for individual reminders regarding for several cancer types such as "5 cancers", "breast cancer", "colorectal cancer", and "cervical cancer" (Figure 1), support of local governments by conducting workshops and developing a website, and intervention for the promotion of cancer screening in several local municipalities as a model. To educate elementary school students about cancer, we developed the comic style book "Gan no Himitsu (Secret of Cancer)", which is a series of long sellers by Gakken Publishing Co., Ltd (Figure 2). The book was distributed to 23,500 elementary schools and 3,000 public libraries. In addition, 4,005 books were purchased by the local municipalities using their own budgets. We are planning to conduct research for the promotion of 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 December 2013, we had recruited more than 700 breast cancer patients last year and 3,000 patients in total. The cohort became one of the largest patient cohorts in the world. We are planning to extend the cohorts for other cancers such as colon and rectum.

Education of staffs involved in clinical research

We develop an e-learning site for the education of staff involved in clinical research such as researchers, data managers, clinical research coordinators, and members of institutional review boards. ICRweb (http://icrweb.jp) provides more than 120 subject headings. As of December 2013, more than 4,000 users had registered on the site in last year and more than 26,000 users have registered in total.

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Figure 1

Figure 2

Division of Screening Practice

Yukio Muramatsu, Ryutaro Kakinuma, Takashi Terauchi, Gen Iinuma,Nachiko Uchiyama, Yasuo Kakugawa, Minoru Machida, Seiko Kuroki, Minori Matsumoto, Yosuke Otake, Takehiro Izumo, Chihiro Tsunoda, Takahiro Kasamatsu, Tomoyasu Kato, Mitsuya Ishikawa, Syunichi Ikeda, Satoshi Okada, Yasuaki Arai

Introduction

In April 2013, a change in the Research Center for Cancer Prevention and Screening (RCCPS) organization was made to clarify the function of each of its divisions. As a result, what was originally the Screening and Development Division became the Division of Screening Practice. Cancer screening is performed by medical staff from the new division. There are 8 radiologists, 3 gastroenterologists, 4 gynecologists, 1 pharmacist, 7 radiologic technologists, 2 ultrasonographic technologists, 2 medical laboratory technologists, and 6 nurses. The division is in charge of multiphasic cancer screening using several imaging modalities to develop new cancer screening systems and to evaluate new screening tests. Our Division now has one multi-detector computed tomography (MD-CT) system, two magnetic resonance imaging (MRI) systems (1.5 T and 3.0 T), two positron emission tomography/computed tomography (PET/CT) systems, one cyclotron system, one digital radiography (DR) system with a newly developed flat panel detector, two mammography (MMG) systems, three ultrasonography (US) systems, and three endoscopy systems. All medical images are digitalized and all imaging diagnosis can be made from the cathode ray tube (CRT) monitors.

Routine activities

1. Course of cancer screening

The basic plan for males consists of screening for cancer of the lung, esophagus, stomach, colon, liver, gall bladder, pancreas, kidney, and prostate. In the basic plan for females, the screening for cancer of the breast, uterus, and ovary are added to the plan for males, excluding the prostate. In addition, for both men and women who undergo a complete set of screening, whole body scanning using PET is provided as an option. Other than multi-phasic programs, a screening program has been prepared for lung and female genital cancers, including cancer of the uterus and ovary, breast cancer and gastrointestinal cancer. Blood samples are also obtained for biochemistry and tumor markers such as CA19-9, CEA, CA125, PSA, and genetic analysis.

2. Eligibility criteria for participants

The cancer screening program at the Research Center for Cancer Prevention and Screening has been planned for applicants 40 years or older who give written informed consent for the screening, including blood samples for genetic analysis, and who take the questionnaire survey concerning lifestyles. These study protocols have been approved by The Institutional Review Board (IRB). Applicants who have been diagnosed as having cancer, and/or have a history of cancer treatment, such as surgery or endoscopic mucosal resection or chemotherapy within the previous one year, are excluded.

3. Cancer screening methods

In the multiphasic cancer screening programs, CT for lung cancer, abdominal US for cancer of the liver, gall bladder, pancreas, and kidney, MRI for cancer of the uterus and ovary, gynecological examinations with Pap-smear, and MMG and US for breast cancer are performed on the first day. On the following day, gastroscopy for cancer of the esophagus and stomach, and total colonoscopy for cancer of the colon and rectum are conducted. If a barium enema is chosen, the examination is carried out on the third day. Moreover, from the beginning of December 2010, CT-colonography (CTC) has been provided as an optional method for cancer screening. FDG-PET is offered on the first day as an option, if the participants wish to undergo the examination.

4. Results of cancer screening

Recent accurate data on cancers have not been obtained due to lack of adequately long follow-up data from our 2013 patients. We have therefore presented confirmed data from the previous year. Two thousand four hundred and sixty six participants underwent multi-phasic programs (new, 753; repeater, 1713). Malignant tumors were detected in 44 out of 753 new participants and in 43 out of 1713 repeaters who underwent multi-phasic clinical programs in 2012 (Tables 1 and 2). Detection rates were 5.84% and 2.51%, respectively.

5. Imaging system

All medical images in our center are digitized. Original or compressed computed radiography (CR), DR, CT, MRI, PET, US, and endoscopy images can be easily and rapidly referenced on the medical information system for research, administration, and clinical expertise (MIRACLE). A reporting system has been established. MIRACLE for cancer screening is used for all routine work.

Research activities

(1) The first breast tomosynthesis system in Japan was installed at RCCPS in September 2009. Since October 2010, a breast tomosynthesis study has started in cooperation with breast surgeons at the National Cancer Center Hospital (NCCH). Regarding the study, NCC IRB approval was granted in December 2008. The sensitivity and specificity of tomosynthesis in comparison with conventional MMG, US, other modalities, and pathological findings are in the process of evaluation. The usefulness of the adjunction of digital breast tomosynthesis to full-field digital mammography in evaluation of the pathological response after neoadjuvant chemotherapy for breast cancer detected at the NCCH has been assessed.

(2) The clinical usefulness of CT-colonography has been assessed.

(3) In order to establish guidelines for the management of pulmonary nodules detected with low-dose chest CT screening, patients with pulmonary nodules between 5 mm and 10 mm in size are being examined in the follow-up clinic.

(4) A computer-aided system for detection of pulmonary nodules on low- dose CT images is being developed and the clinical usefulness of a super high-resolution CT scanner has been assessed.

(5) The clinical usefulness of C11-methionine-PET in several kinds of brain tumors detected at the NCCH has been assessed.

Clinical trials

Cancer re-screening for those subjects who have finished a follow-up of five years began in February, 2009 in our center. As a result, a new study based on the follow-up data has been started.

Table 1. Cancerous detection rate in new participants (2012.4.1-2013.3.31)

	No. of cancerous cases	No. of new participants	Detection rate (%)
colo-rectum	16	753	2.12
stomach	8	753	1.06
esophagus	4	753	0.53
prostate	4	494	0.81
lung	4	753	0.53
breast	4	259	1.54
thyroid	2	753	0.27
uterus	2	259	0.77
Total	44	753	5.84

Table 2. Cancerous detection rate in repeat participants (2012.4.1-2013.3.31)

	No. of cancerous cases	No. of repeat participants	Detection rate (%)
colo-rectum	12	1713	0.70
stomach	9	1713	0.53
esophagus	8	1713	0.47
breast	6	571	1.05
prostate	3	1142	0.26
lung	3	1713	0.18
uterus	1	571	0.18
others	1	1713	0.06
Total	43	1713	2.51

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Center for Cancer Control and Information Services

Preface

The Center for Cancer Control and Information Services (CIS) is a nationally funded program established in 2006, as an essential part of the National Cancer Center's (NCC) extramural activities. The Division of Health Services Research and the Division of Cancer Survivorship were newly established in April 2013. The former aims to establish an evaluation system for health systems and health policy performance in cancer care in Japan and the latter aims to enhance the quality of life of people with cancer and their caregivers, and to promote social awareness in Japan about cancer survivorship issues. Then the CIS consisted of six Divisions.

The mission statement of the CIS is as follows: "The Center for Cancer Control and Information Services provides information needed to promote comprehensive and systematic cancer control program in Japan." In collaboration with designated cancer care hospitals, the Japanese Ministry of Health Labour and Welfare and other relevant Ministries, the Center plays a central role to plan, manage and evaluate nation-wide cancer control programs, through promotion of specialized, multidisciplinary and comprehensive cancer research, coordination of training and information dissemination, and support of prevention, diagnosis, treatment of cancer, rehabilitation from cancer and the continuing care of cancer patients and their families.

One of our key mandates is to provide all patients and their dear ones, the means to access comprehensive cancer-related information at the point of need, and with appropriate context including websites such as "ganjoho.jp-www.ganjoho.jp". Followed by publications for patients with cancer diagnosis, the revision of a cancer information handbook for patients with cancer named "Guidebook for Cancer Patients", and publication for workers named "Prescription for Cancer Survivors" represented an important step in this direction.

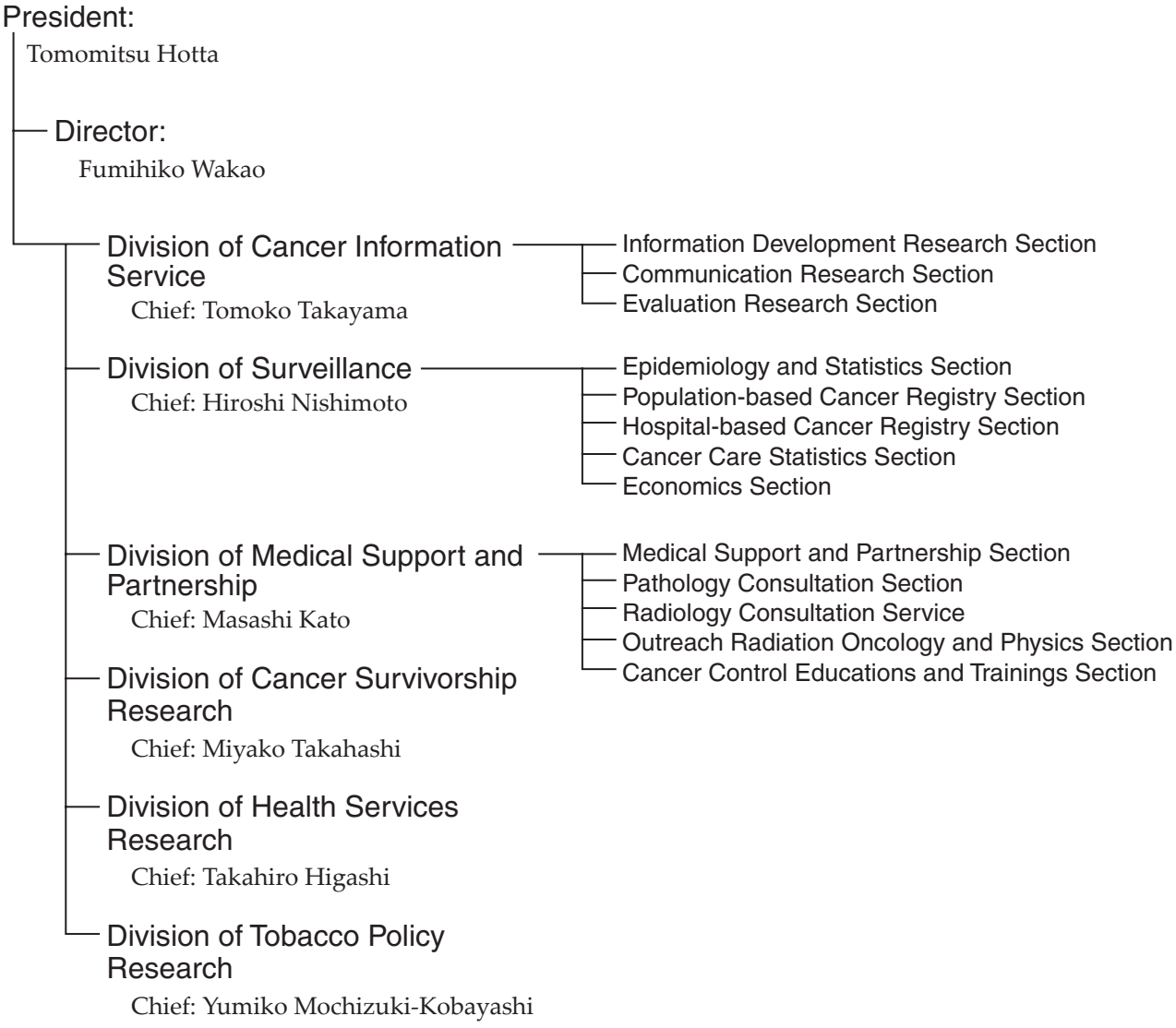
The CIS promotes the standardization of hospital-based cancer registries in designated cancer care hospitals and population-based cancer registries in prefectures. The data are collected from both hospital-based and population-based cancer registries, analyzed to calculate accurate cancer statistics and disseminated throughout Japan. Furthermore, The CIS has continuously made strong efforts to develop a reliable cancer surveillance system in Japan, which is stated as a key element in the Cancer Control Act. In the year 2013, the Act on Promotion of Cancer Registries was enacted as well.

The CIS also builds partnership with Designated Cancer Care Hospitals to support all health-allied professionals concerned with cancer control in Japan with the pathology consultation service, radiology consultation service, cancer image reference database, radiotherapy case service and promotion of medical education programs for cancer control

The CIS aims to research activities and advocacies based on the following four pillars: Monitoring and Evaluation, Development and Research of Practical Programs, Public Education and Information Services, and Promoting Policy and Networking.

Fumihiko Wakao, M.D.
Director, Center for Cancer Control and Information Services

Organization



Activities of the Divisions

Division of Cancer Information Service

Fumihiko Wakao, Tomoko Takayama, Seiichiro Yamamoto, Kiyotaka Watanabe, Teruo Ito, Akiko Urakubo, Nozomu Suzuki, Yoko Setoyama, Ryoko Otsuka, Mika Takai, Chikako Yamaki, Yumiko Yamazaki, Yuri Mizota, Tamaki Kumagai

Introduction

The mission of the Cancer Information Services is to provide credible information about cancer. In the National Cancer Information Network, the Cancer Information Services plays an important role in disseminating cancer-related information directly to our audiences, including patients and their families, the public at large, healthcare professionals, policy makers and researchers. Our dissemination channels also include the 397 designated cancer care hospitals and their respective cancer information and support teams. Currently, multi-channel cancer information services are provided through the internet, brochures, lectures, and public meetings. One of our key mandates, is to provide all patients and their loved ones, with the means to access comprehensive cancer-related information at the point of need, and with appropriate context including websites such as "ganjoho.jp-www.ganjoho.jp". Followed by publications for patients with a cancer diagnosis, the revision of a cancer information handbook for patients with cancer named "Guidebook for Cancer Patients", and a publication for workers entitled "Prescription for Cancer Survivors" represented an important step in this direction. In order to disseminate information effectively to the general public, we concluded agreements for the spread of information with health insurance companies and pharmaceutical companies.

Line of service

Cancer Information Development Section

The Cancer Information Development Section has exerted efforts to provide reliable, evidence-based cancer information to patients, their families, citizens, healthcare professionals, researchers, and policy makers. Evidence databases such as clinical practice guidelines and research findings are continuously sourced, assessed, and edited, ensuring that the information is presented in a manner consistent with how the users digest and process the information. As part of continually providing reliable information in an easily understood format, treatment guidelines are evaluated using the AGREE II (Appraisal of Guidelines for Research & Evaluation II) instrument and are accumulated as evidence repositories. 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. 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 CIS peer reviews, as well as other cancer information sources that are of interest to health care professionals.

Communication Research Section

In order to disseminate and utilize reliable cancer information, the Communication Research Section is in charge of supporting the smooth operation of cancer information services and of encouraging the collaboration among relevant stakeholders, such as the Cancer Information & Support Centers (CISCs) in designated cancer hospitals (397 locations around the nation), support groups, and prefectural government units responsible for planning and managing their respective regional cancer programs. The Section handles broader scale training workshops and region block forums for CISC's staff, in addition to seminars for the public and local health care workers. The section also prepares and manages collaborative work with the "Patient-civil panel" which consists of 100 supporters with a variety of experinces with cancer and different regional backgrounds from throughout Japan, and provides mutual educational forums for media professionals.

Research activities

Cancer Information Development Section

To ensure timely dissemination of accurate and pertinent information on cancer, and to more effectively support decision-making by patients, their families and 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 regional community stakeholders, patients and care providers, to help compile more a regionally pertinent set of information, in the effort to improve our community outreach efforts.

Communication Research Section

To overcome the disparities of cancer related information all over Japan and to contribute to building better cancer information and support systems, this Section conducts a portfolio of research in wide ranging areas such as the identification of underserved populations, building a cross functional network of community care providers, defining the activities of cancer information centers, developing innovative educational programs and training methods that help accelerate best practice adoption among cancer information counselors.

Division of Surveillance

Hiroshi Nishimoto, Kota Katanoda, Tomohiro Matsuda, Akiko Shibata, Koichi B. Ishikawa, Ayako Matsuda, Yoshiko Emori, Kaori Nakano

Introduction

The Division of Surveillance is in charge of providing credible cancer statistics to patients and their families, to the public, to healthcare professionals, to policy makers and to researchers. The Division also collects accurate and useful information on cancer statistics at the national level. We promote the standardization of hospital-based cancer registries in designated cancer care hospitals and population-based cancer registries in prefectures. The data are collected from both hospital-based and population-based cancer registries, analyzed to calculate accurate cancer statistics and disseminated throughout Japan. A newly incorporated economics section will augment the epidemiologic data with economic information crucial for formulation of future policy.

Routine activities

Population-based Cancer Registries

The division has continuously exerted efforts to develop a reliable cancer surveillance system in Japan, which is stated as a key element in the Cancer Control Act. In the year 2013, the Act on Promotion of Cancer Registry was enacted as well. 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 a one day seminar in May for administrative officers in charge of cancer control who were new to their post, a total of 36 participants; and by organizing 2-day educational workshops for cancer registrars and administrative officers, a total of 198 participants attending the one 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 in 2013. Standardization of the population-based cancer registry has steadily advanced: 45 registries out of 47 use the standard registry items. Forty registries had introduced the SDS as of January 2014. Introduction is in progress in one registry and the other one is planning to introduce it in 2014. The self-check software on security control in cancer registration, and security educational materials for new workers were updated and provided by the division.

Hospital-based Cancer Registries

Since a hospital-based cancer registry (HCR) is essential to evaluate cancer care in each hospital and also to achieve high completeness of population-based cancer registries, it should be established urgently for cancer control. The Division plays an important role as a driving force for the standardization and quality improvement of HCRs, which has been performed at 397 designated cancer care hospitals (DCCHs) and over 300 other hospitals in 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 2013, individual records for 584,120 cancer cases diagnosed in 2011 were collected from 395 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 a book titled "Cancer Statistics in Japan".

Research activities

Population-based Cancer Registries

The national cancer incidences in 2009 and 2010 were estimated based on the data from 37 and 31 cancer registries, respectively. The prefectures that have met the data quality standards have increased since last year. The incidence data were then analyzed in detail by cancer site. The study results were published in an international journal. The cancer incidence data have been used in a couple of research analyses; the results are presented at

conferences both in Japan and abroad.

Table 1. Population-based Cancer Registries from Prefectural Registries

Year of Diagnosis	Prefectures	Number of New Cancer Cases
2009	37 (32 for estimation)	775,601
2010	31 (28 for estimation)	805,236

Cancer Patients Data from Hospital-based Cancer Registries at Designated Cancer Care Hospitals

Table 2. Year of Diagnosis Applied Hospitals Number of New Cancer Cases

Year of Diagnosis	Applied Hospitals	Number of New Cancer Cases
2010	387	548,979
2011	395	584,120

Cancer Statistics

International comparisons of cancer burden and survival rate were conducted based on the WHO mortality, GLOBOCAN, and cancer registry databases. An updated trend analysis of cancer incidence and mortality in Japan was conducted. A trend analysis was also conducted for adult T-cell leukemia/lymphoma. Tobacco control situations were analyzed in three East Asian countries: Japan, China and the Republic of Korea.

Economic studies on cancer care

In order to construct a nation-wide database of inpatient and outpatient clinical practice, we started to collect DPC-survey compliant data from over 1,000 hospitals. These data are used to identify cancer care process, accessibility and costs. Initial findings on the use of pharmaceuticals related to chemotherapy will be published in early 2014. Findings from this database and other information related to the utilization of services will be linked with population estimates to form future forecasts of supply and demand in cancer care.

List of papers published in 2013

Journal

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2. Katanoda K, Matsuda T, Matsuda A, Shibata A, Nishino Y, Fujita M, Soda M, Ioka A, Sobue T, Nishimoto H. An updated report of the trends in cancer incidence and mortality in Japan. Jpn J Clin Oncol, 43:492-507, 2013
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8. Machii R, Saika K. Estimated Disability-Adjusted Life Year (DALY) in Asia in GLOBOCAN 2008. Jpn J Clin Oncol, 43:846-847, 2013
9. Matsuda A, Katanoda K. Estimated disability-adjusted life year (DALY) in all cancers in GLOBOCAN 2008, in Asia by the country. Jpn J Clin Oncol, 43:943-944, 2013
10. Matsuda A, Katanoda K. Five-year relative survival rate of lung cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 43:1287-1288, 2013
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13. Matsuda A, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H. Cancer incidence and incidence rates in Japan in 2007: a study of 21 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol, 43:328-336, 2013
14. Matsuda T, Matsuda A. Burden of cancer incidence below the age of 40 in Asia 2002 extrapolated from the Cancer Incidence in Five Continents Vol. IX. Jpn J Clin Oncol, 43:449-450, 2013
15. Matsuda T, Saika K. The 5-year relative survival rate of stomach cancer in the USA, Europe and Japan. Jpn J Clin Oncol, 43:1157-1158, 2013
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21. Shimizu S, Ishikawa KB, Ikeda S, Fushimi K. How does prescription of generic drugs spread out?: data mining and visualization by using prescription data from acute care hospitals nationwide. Value Health, 16:A460-A461, 2013

Division of Medical Support and Partnership

Masashi Kato, Hiroaki Onaya, Jun Itami, Ryoji Kushima, Yoshinori Makino, Miki Hosoya, Toshiyuki Minemura, Yoko Nakazawa, Takashi Hanada, Yuki Aono, Tadakazu Shimoda, Kanako Kono, Yuko Ogo, Saran Yoshida, Satoshi Ishikura, Hiroko Suketomo, Megumi Fukuda, Ritsuko Chinda, Yuri Yamauchi, Hiromi Nakamura, Toshiko Sakaguchi, Shiho Hirai, Hiroyo Ohchi, Chisako Ito, Erina Sasaki

Introduction

The Division builds partnership with 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 suggesting the cancer control policy in Japan. The Pathology Consultation Section (PCS) strives to perform human pathology research based on histology of tumor cells and tumor-stromal cells to improve the diagnostic pathology of tumors. The Diagnostic Radiology Section (DRS) provides a consultation service and a cancer image reference database (NCC-CIR). A radiology consultation service is aimed at the improvement of the quality of diagnosis based on medical images. The NCC-CIR is a web-based reference database system of images of neoplasms for physicians, radiologists, and pathologists, providing medical diagnostic images and information together with the pathology. The Outreach Radiation Oncology and Physics Section (ORPS) provides the following support programs for designated regional cancer centers and institutions participating in clinical trials. The Cancer Control 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 formed a network among the designated cancer care hospitals to build partnership for cancer control in Japan. The designated cancer care hospitals are important partners with the NCC to promote comprehensive cancer control in Japan. The Palliative Care Committee was established as a subsidiary organization of the Designated Cancer Care Hospitals Liaison-Council in this year.

B. Pathology consultation service

The pathology slides of lesions arising in various organs have been submitted from clients. Eighty-four consultant pathologists who are specialists in various fields are registered, and one pathologist who was assigned as consultant examined the slides and rapidly sent back the report and opinion to each client. Most of the clients expressed satisfaction with the contents of the report and this consultation system. We started the selection of typical and educational consultation cases from accumulated archival slides and the construction of a referential database.

C. Radiology consultation service

Ninety-three consultation reports have been put together for requests mainly from the Kanto and Kyushu region. 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 2012, about 100000 per month. Cases with cancers who underwent interventional radiology (n=11), head and neck cancers (n=8), musculoskeletal malignancies (n=7), lung cancers (n=5), and other cancers have been published, resulting in the total provision of 284 cases.

E. Radiotherapy case service

Mailed dosimetry and on-site dosimetry were performed in 45 institutions and 11 institutions, respectively. All data of the institutions were within the permissible limit. In clinical trials, radiotherapy case reviews were performed in 39 institutions.

F. Promotion of medical education programs for cancer control

The CCET provides and evaluates various

oncology professional training programs about up-to-date information on early detection, diagnosis, treatment, 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)

Research activities

Evaluate changes in Palliative Care with the Cancer Control Program

To evaluate the changes of palliative care induced by the Basic Plan to Promote Cancer Control Program in japan, evaluation indicators are developed, and an interview survey is conducted with cancer patients and healthcare professionals.

Cancer Control Program Evaluation Workshop for Government Employees

The MSPS conducted a workshop for government employees on 'How to evaluate your prefecture's cancer control programs.' It was funded by the Japanese Ministry of Health, Labour and Welfare and was used by 33 prefectures in Japan that deal with cancer control programs.

Trend of pathology consultation services

Activity of the section was introduced in "Pathology and Clinical Medicine" which is the most popular journal for Japanese pathologists.

Develop and use of a teleradiology system

The section is investigating methods to improve the way how we can send and receive digital imaging files more easily and more quickly using a teleradiology system.

Develop the IMRT quality control support program

The Outreach Radiation Oncology and Physics Section were developing enforcement of the on-site dosimetry regarding the output dose of Intensity Modulated Radiotherapy (IMRT) in 4 institutions (designated regional cancer centers).

Clinical trials

In the Japan Clinical Oncology Group (JCOG1015, JCOG1208) and Japanese Radiation Oncology Study Group (JROSG12-1), the Outreach Radiation Oncology and Physics Section performed the on-site dosimetry regarding the output dose of IMRT in 5 institutions.

Table 1. Training programs conducted during April 2012 - March 2013

Category of Education and Training program	Titles of Education and Training program	Number of participants
Oncology nursing education	Continuing education and development of oncology nursing workshop for trainers	63
	Continuing education and development of oncology nursing workshop for trainers-Follow up	33
	Oncology nursing seminar for trainers	245
	Oncology nursing on the job training for trainers	6
CI specialist education	CI Specialist Education Program -Basic course 1	665
	CI Specialist Education Program -Basic course 2	664
	CI Specialist Education Program -Basic course 3	321
	CI Specialist Education Program for trainers	59
	CI Specialist Education Program for trainers-Follow up	47
Hospital-based cancer registrar training	Training program for instructors of hospital-based cancer registrars	21
	Continuous training program for instructors of hospital-based cancer registrars	2
	Supplementary training program for instructors of hospital-based cancer registrars	78
	Basic training program for hospital-based cancer registrars	1249
	Supplementary training program for hospital-based cancer registrars of basic course completion	715
	Advanced training program for hospital-based cancer registrars	157
	Site Visiting program on hospital-based cancer registries in national cancer center hospital	74
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 in charge of cancer control	76
	Basic training programs on population-based cancer registry for administrative officers in charge of cancer control	211
Technologist education	Trainer training for oncologic radiology technologists	17
	Trainer training for oncologic laboratory medical technologists	5
Pharmacist education	Seminar for pharmacists of dispensing neoplastic agents to be trainers	56
	On the job training for pharmacists of dispensing neoplastic agents to be trainers	23
Palliative care physicians education	Palliative care education meeting for trainers	56
Psycho-oncologistseducation	Psycho-oncology education meeting for trainers	33
Palliative care team education	Palliative care team workshops for consultation-Basic course	70
Chemotherapy Team education	Chemotherapy Team workshops to introduce a new drug safety	64
Total		5010

List of papers published in 2013
Journal

1. Morita T, Sato K, Miyashita M, Akiyama M, Kato M, Kawagoe S, Kinoshita H, Shirahige Y, Yamakawa S, Yamada M, Eguchi K. Exploring the perceived changes and the reasons why expected outcomes were not obtained in individual levels in a successful regional palliative care intervention trial: an analysis for interpretations. Support Care Cancer, 21:3393-3402, 2013
2. Morita T, Miyashita M, Yamagishi A, Akiyama M, Akizuki N, Hirai K, Imura C, Kato M, Kizawa Y, Shirahige Y, Yamaguchi T, Eguchi K. Effects of a programme of interventions on regional comprehensive palliative care for patients with cancer: a mixed-methods study. Lancet Oncol, 14:638-646, 2013
3. Komura K, Yamagishi A, Akizuki N, Kawagoe S, Kato M, Morita T, Eguchi K. Patient-perceived usefulness and practical obstacles of patient-held records for cancer patients in Japan: OPTIM study. Palliat Med, 27:179-184, 2013
4. Yamamoto R, Kizawa Y, Nakazawa Y, Morita T. The palliative care knowledge questionnaire for PEACE: reliability and validity of an instrument to measure palliative care knowledge among physicians. J Palliat Med, 16:1423-1428, 2013
5. Sato Y, Watanabe H, Sone M, Onaya H, Sakamoto N, Osuga K, Takahashi M, Arai Y. Tumor response evaluation criteria for HCC (hepatocellular carcinoma) treated using TACE (transcatheter arterial chemoembolization): RECIST (response evaluation criteria in solid tumors) version 1.1 and mRECIST (modified RECIST): JIVROSG-0602. Ups J Med Sci, 118:16-22, 2013

Division of Cancer Survivorship Research

Miyako Takahashi, Makiko Tomita, Yuko Furuya, Kyoko Onozawa

Introduction

The Division of Cancer Survivorship was newly 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.

As for academic research, we deal with various psychosocial issues associated with the cancer experience 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 beyond cancer, and try to propose countermeasures based on the research findings.

As for activities to promote social awareness toward cancer survivorship, we plan and implement educational programs for the general public as well as healthcare providers.

Routine activities

Education programs to promote social awareness of cancer survivorship

We plan and implement two lecture series, "Community Center Café" and "Gotochi (Local) Café", which are open to the public. These café programs, which are held in a relaxed atmosphere with a cup of tea or coffee, provide participants an opportunity to learn about cancer survivorship issues as well as exchange views among survivors, medical professionals, and the general public. The Community Center Café is held bimonthly in the Tsukishima Community Center in Chuo ward, where the National Cancer Center is located. This program consists of a lecture that takes up various cancer survivorship topics followed by a small group discussion by participants based on the lecture. The Gotochi (Local) Café has the same structure as the Community Center Cafe, but is co-sponsored by our Division and healthcare providers in other prefectures in Japan, and focuses on high priority survivorship issues within the local community. In 2013, we held the Community Center Café three times and 150 people participated. Two Gotochi Cafés are in preparation; both are to be held in January 2014 in Okinawa and Miyagi prefectures in co-sponsorship with local healthcare providers.

Education for healthcare providers

In addition to the café programs, we conduct symposia in academic conferences and deliver lectures for healthcare providers that include oncologists, nurses, social workers, and occupational physicians. In 2013, we participated in six symposia in academic conferences, and conducted 28 invited lectures on cancer survivorship. We also delivered lectures in universities for medical and nursing students.

Research activities

Cancer and work

In order to support working cancer survivors in both the workplace setting and the hospital setting, we developed and evaluated pilot intervention programs targeting occupational health staff and medical social workers (MSW), respectively. Also, we conducted surveys with occupational physicians (OPs) to collect good practices about sharing a patient's medical information between oncologists and OPs.

Sexuality, life-style modification, parental cancer

In preparation for a multi-center survivorship survey with gynecological cancer patients, we conducted literature review and developed a questionnaire that includes items regarding sexual changes, life-style modification after having cancer, and communication with children.

List of papers published in 2013
Journal

1. Takeda Y, Morio K, Snell L, Otaki J, Takahashi M, Kai I. Characteristic profiles among students and junior doctors with specific career preferences. BMC Med Educ, 13:125-135, 2013
2. Inoue M, Takahashi M, Kai I. Impact of communicative and critical health literacy on understanding of diabetes care and self-efficacy in diabetes management: a cross-sectional study of primary care in Japan. BMC Fam Pract, 14:40-48, 2013

Division of Health Services Research

Takahiro Higashi, Momoko Iwamoto, Kota Tanaka, Izumi Kamiya, Ayako Okuyama, Fumiaki Nakamura, Yoichiro Tsukada, Rei Goto, 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 three research projects in 2013.

Research activities

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 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 from over 160 hospitals across the country. The data are currently being cleaned and analyzed to measure cancer quality measures, such as the proportion of stage III colorectal cancer patients that received adjuvant chemotherapy within 8 weeks of surgery.

Defining key terminologies in cancer policy

Some words and phrases often used in cancer policy have never been clearly defined. For example, "cancer board" could imply a small meeting of surgeons, radiologists, and oncologists, or an extensive multidisciplinary conference involving nurses, pharmacists, and social workers. Even routine administrative meetings among heads of departments are sometimes referred to as cancer boards. Specialists and various stakeholders were interviewed regarding their understanding and use of key terminologies often used in cancer policy. Although a detailed consensus was not achieved in most cases, the basic concepts and underlying definitions that were commonly shared were clarified and published into a final report.

Designing performance indicators for cancer 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 programs, the Division gathered a panel of experts including clinical specialists, patient representatives, biomedical and public health researchers, cancer information experts, and policy makers. Using the Delphi method, a list of candidate performance indicators were evaluated by the panel, along with instructions to make suggestions for new indicators. The Division hopes to release these sets of performance indicators by the end of the fiscal year.

Research training and education

The Division has had a continuous flow of physicians and graduate students for research trainings throughout the year. Additionally, the Division accepted fifth year medical students from the University of Tokyo for a clerkship in Public Health.

Future prospects

The Division supports evidence-based policy-making and strives to improve the care of cancer patients in Japan by monitoring the performance of cancer policy and quality of care in cancer treatment centers across the country. In addition to the current activities, the Division is working to provide an information exchange platform for specialists and various stakeholders, designed to foster smooth communication and active exchange of ideas for cancer policy planning at the local government level. The Division will continue to endeavor to make policy recommendations that are clinically relevant and evidence-based, for various cancer control programs in Japan.

List of papers published in 2013
Journal

1. Higashi T, Nakamura F, Shimada Y, Shinkai T, Muranaka T, Kamiike W, Mekata E, Kondo K, Wada Y, Sakai H, Ohtani M, Yamaguchi T, Sugiura N, Higashide S, Haga Y, Kinoshita A, Yamamoto T, Ezaki T, Hanada S, Makita F, Sobue T, Okamura T. Quality of gastric cancer care in designated cancer care hospitals in Japan. Int J Qual Health Care, 25:418-428, 2013
2. Higashi T, Nakamura F, Saruki N, Sobue T. Establishing a quality measurement system for cancer care in Japan. Jpn J Clin Oncol, 43:225-232, 2013
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4. Nakamura F, Higashi T. Pattern of prophylaxis administration for chemotherapy-induced nausea and vomiting: an analysis of city-based health insurance data. Int J Clin Oncol, 18:971-976, 2013

Division of Tobacco Policy Research

Yumiko Mochizuki-Kobayashi, Koji Ishibashi, Seiko Ishiuchi, Minori Yamashita, Ayako Seike

Introduction

The death toll attributable to tobacco use is 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: Monitoring and Evaluation, Development and Research of Practical Programs, Public Education and Information Services, and Promoting Policy and Networking.

Routine and Research activities

- We developed a database for tobacco-related studies supported by government research grants. It enabled us to review intensively researcher, research outcomes and research areas and to demonstrate evidence to allow the appropriate allocation of resource and research gaps. In order to conduct rigorous monitoring of the implementation of tobacco policies, we developed a tobacco information repository which contains public information and data such as statistics, policies, studies, and activities so that experts such as administrators and researchers could have efficient access to the necessary and accurate information. By using this repository, we could analyze intensively the current trend of the tobacco epidemic in Japan.
- We conducted participatory workshops with elementary to junior high school children on tobacco with respect to cancer education. We also examined cancer patients-oriented cessation programs and quitline service programs in Japan based on expert panel discussion.
- We organized educational events at the WHO-backed World No Tobacco Day (marked on May 31) and Science Agora of Japan Science and Technology Agency (JST) to educate people on tobacco and cancer issues and also contributed to policy and program development by governments, schools and NGO/NPOs. We marked February 27 to celebrate the WHO Framework Convention on Tobacco Control (FCTC) and broadcast a Ustream program. Essential documents which are internationally available were intensively translated into Japanese.
- We organized a research and policy network with other National Centers to develop research areas comparable with US NIH research activities as well as policy recommendations to the government. As a part of the Tobacco Free Committee of Japan Science Council, we made an urgent policy recommendation to stop the epidemic of smokeless tobacco use. As a part of the Tobacco Risk Assessment Committee of Ministry of Health, Labour and Welfare, we submitted a thorough review on tobacco products from the viewpoint of regulatory science. Policy advocacy for research and regulatory framework was needed.

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