

Hospital East

Preface

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

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

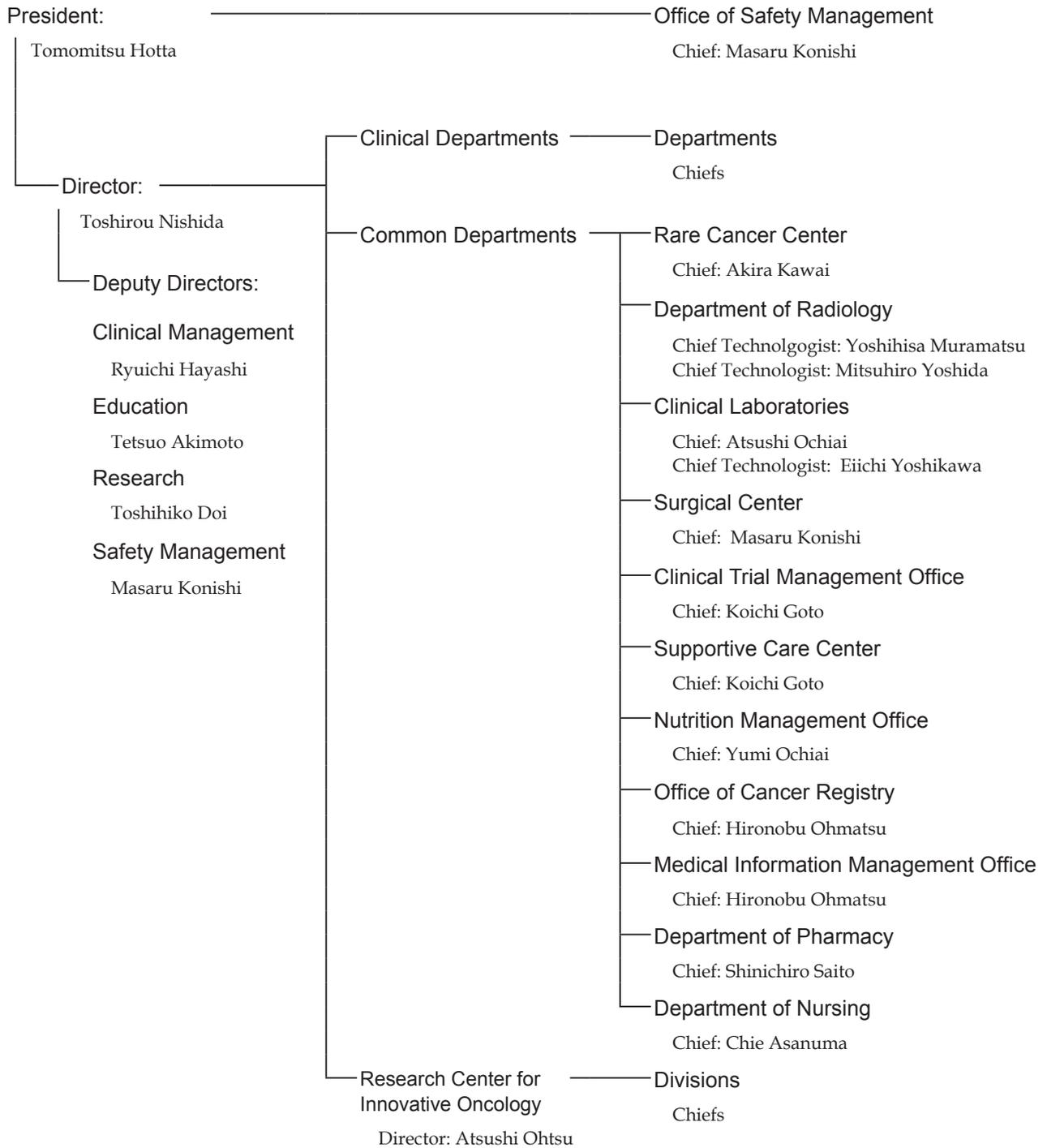
After increasing in the number of cancer patients visiting the NCCHE, there are significant limitations in hospital facilities, especially, of endoscopic examination and treatment as well as operating rooms. We have drawn the exciting and realistic future plan of the Kashiwa campus and, based on the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

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

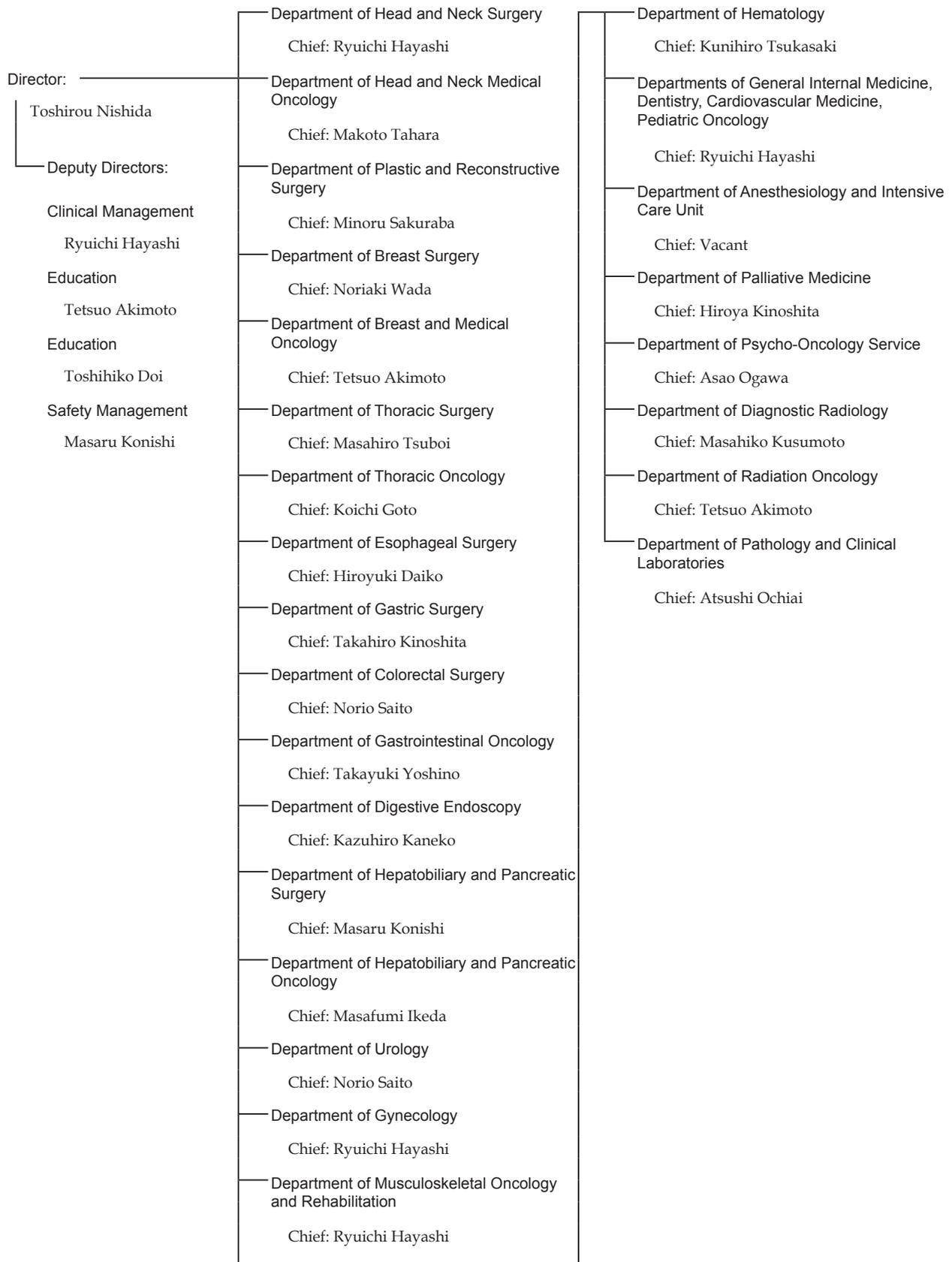
Lastly, we, the NCC, are re-organizing to maximize research outcomes, and the research center for innovative oncology is going to be incorporated into the Exploratory Oncology Research and Clinical Trial Center” (NCC-EPOC). In the Kashiwa campus, the NCCHE and EPOC are mutually collaborating in the clinical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

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

Organization



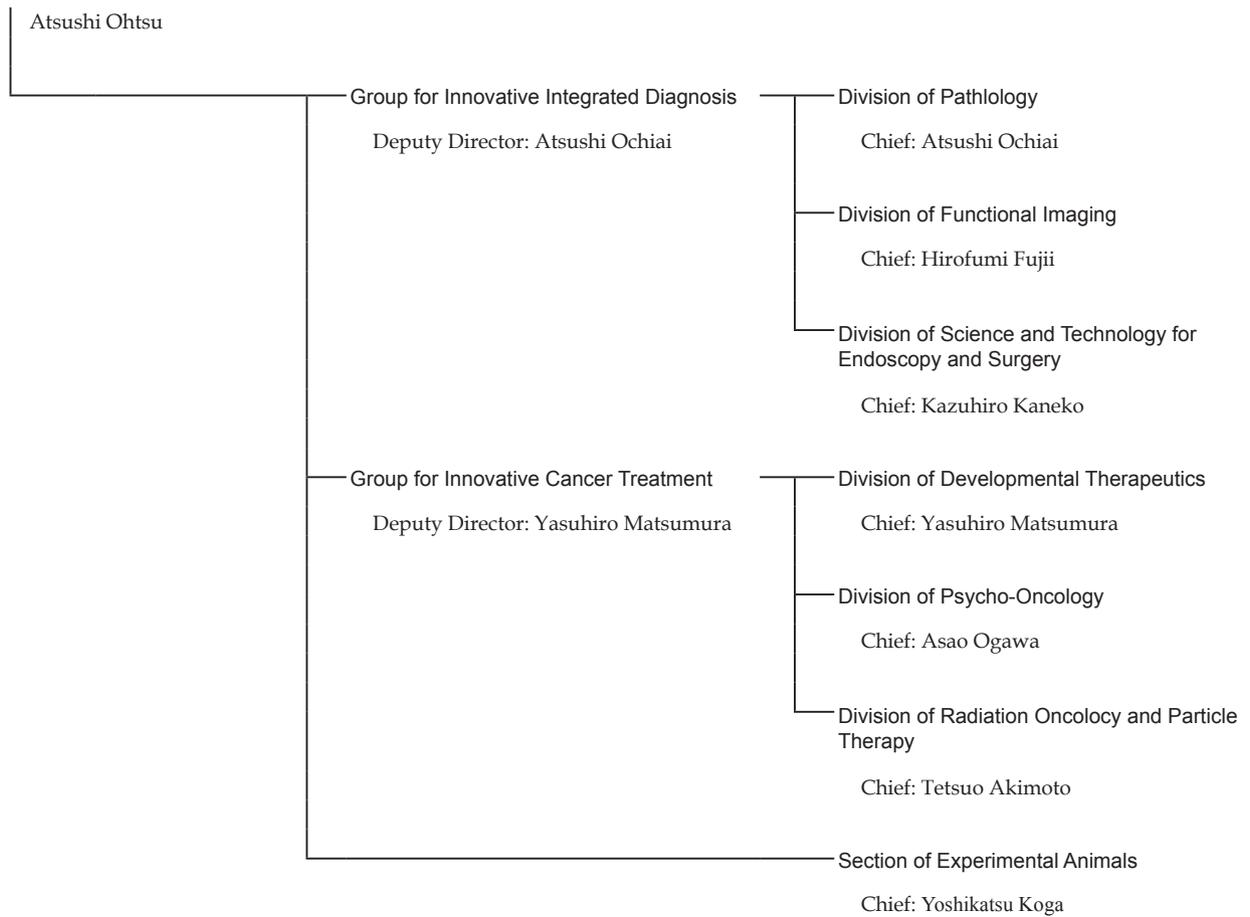
Clinical Departments



Research Center for Innovative Oncology

Director:

Atsushi Ohtsu



Activities of the Departments

DEPARTMENT OF HEAD AND NECK SURGERY

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

Introduction

The Surgical treatment of head and neck cancer must meet two contradictory requirements: (1) the resection volume must be sufficiently large to remove all cancer cells, and (2) the resection volume should be sufficiently small to preserve important functions such as swallowing, speech, vision, and cosmetic appearance. The Head 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, 5 staff surgeons at the Division work closely with plastic surgeons, radiotherapists, medical oncologists,

pathologists, dentists, psycho-oncologists, nurses, and other hospital staff. To facilitate regular communication among the members of this large team, several weekly conferences are conducted. The number of new cases who were treated in the hospital was 567 and the number operation was 472 cases. 111 cases of all underwent free flap reconstruction.

Research activities

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

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

Clinical trials

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

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

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

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

Education

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

observation centers of IFHNOS fellowship program from 2014.

Future prospects

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

Table 1. Number of patients

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

Table 2. Type of surgical procedures

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

List of papers published in 2014

Journal

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

DEPARTMENT OF HEAD AND NECK MEDICAL ONCOLOGY

Makoto Tahara, Tomoko Yamazaki, Tetsuro Wakasugi, Tomohiro Enokida

Introduction

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

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

Routine activities

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

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

service.

Research activities

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

1) Development of new treatments

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

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

2) Biomarker analysis

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

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

Clinical trials

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

To facilitate the timely approval of new drugs and eliminate the drug lag, we have also participated in the global phase trials. Our institution was ranked number one in the world for patient enrollment of SELECT study that is a randomized Phase III study of lenvatinib (E7080) compared to placebo in patients with locally advanced/metastatic RAI-refractory differentiated thyroid cancer. Lenvatinib demonstrated significantly improvement of progression-free survival compared with placebo (HR: 0.21, $p < 0.001$), leading that FDA approved lenvatinib for RAI-refractory differentiated thyroid cancer. In Japan,

a phase 2 study of lenvatinib for all histologic subtypes of advanced thyroid cancer is conducting for approval of all histologic subtypes of advanced thyroid cancer. The preliminary results was presented in last ESMO annual meeting and lenvatinib demonstrated promising activity in all histologic subtypes including anaplastic thyroid cancer with response rate of 27.3%.

Education

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

Future prospects

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

Table 1. Number of patients according to sites

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

Table 2. Number of patients according to procedure

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

List of papers published in 2014

Journal

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

DEPARTMENT OF PLASTIC AND RECONSTRUCTIVE SURGERY

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

Introduction

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

Routine activities

The Department5 plastic surgeons cover reconstructive operations both in the NCCH East in Kashiwa and the NCCH in Tokyo, and train the residents in the 2 hospitals. These reconstructive surgeries are performed in cooperation with the surgeons of another department of the hospital, such as the Head and Neck Surgery, Breast Surgery, Orthopedic Surgery, Esophageal Surgery, Colorectal and Urological Surgery etc. In the NCCH East, Head and Neck reconstruction is the most frequently performed operation accounting for 65% of the reconstructive surgery. In head and neck region, a free jejunal graft and a rectus abdominis musculocutaneous flap are the most frequently used procedures. A weekly conference is held with doctors of the Department of Head and Neck Surgery, Radiation Oncology and Head and Neck Oncology. Breast reconstruction using autologous tissue transfer was employed

in 2005, since then, patients' needs for breast reconstruction is increasing. And also, lymphatico-venulo anastomosis as a surgical treatment for lymphedema of the extremities was introduced since June 2013.

Research activities

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

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

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

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

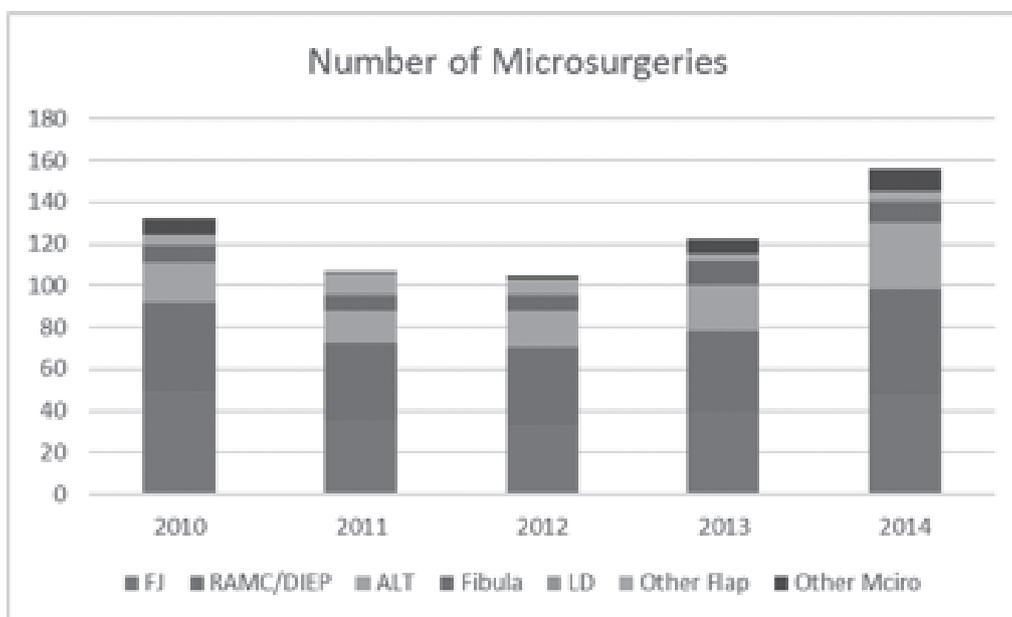


Table 1. Cooperation with other divisions

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

Table 2. Operative procedures

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

List of papers published in 2014

Journal

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

DEPARTMENT OF BREAST SURGERY

Noriaki Wada, Kimiyasu Yoneyama, Chisako Yamauchi

Introduction

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

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

Routine activities

For the regular activities of the Division, a daily morning routine round is scheduled for inpatients by all staff and residents. Moreover, our weekly preoperative diagnostic imaging conference on breast cancer is conducted on Monday evenings to discuss the surgical treatment planning for each patient. A clinical conference to

decide on courses of treatment by multidisciplinary breast care team members is held twice a month. A monthly pathological conference on breast cancer is also conducted on the last Friday of each month. At those conferences, individual cases are presented to a team of highly trained cancer specialists, including radiologists, breast surgeons, pathologists, radiation oncologists, and medical oncologists. Our multidisciplinary team approach to breast cancer treatment sets the superior quality of care we provide for our patients.

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

Research activities

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

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

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

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

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

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

Clinical trials

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

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

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

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

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

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

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

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

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

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

Education

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

Future prospects

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

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

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

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

Table 2. Types of operative procedures

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

Total mastectomy with immediate autologous breast reconstruction was performed in fourteen patients.

BP, partial mastectomy; BT, total mastectomy; SNB, sentinel node biopsy; ALND, axillary lymph node dissection; RFA, radio-frequency ablation

Table 3. Overall survival (OS) rate

OP year: Jan 1993- Dec 2008

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

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

List of papers published in 2014

Journal

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

DEPARTMENT OF BREAST AND MEDICAL ONCOLOGY

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

Introduction

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

Routine activities

The major and specific target disease of the Division comprised breast cancer. Eligible patients were invited to participate in large Phase II/III studies. The Division also treated cancers of the genitourinary tract, cancer of unknown primary origin, soft tissue sarcomas and gynecological cancers including uterine and ovarian cancers. For patients with diseases treated with established standard chemotherapeutic regimens, standard chemotherapy was administered in routine medical practice. Patients for whom standard chemotherapy had failed and those with cancers for which standard chemotherapy was unavailable were invited to participate in clinical studies on experimental drugs and regimens. In 2014, 604 patients with different types of cancer visited the Division for consultation. Approximately 400 patients per month received routine chemotherapy as an outpatient service by the Division. The overall

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

Research activities

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

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

label, phase III study on adjuvant lapatinib versus trastuzumab versus both lapatinib and trastuzumab treatment in patients with HER-2 overexpressed primary breast cancer (ALTO: Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation); a randomised multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive

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

Table 1. Number of new patients

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

List of papers published in 2014

Journal

- Matsubara N, Mukai H, Masumoto M, Sasaki M, Naito Y, Fujii S, Wada N. Survival outcome and reduction rate of Ki-67 between pre- and post-neoadjuvant chemotherapy in breast cancer patients with non-pCR. *Breast Cancer Res Treat*, 147:95-102, 2014
- Ohsumi S, Mukai H, Ohashi Y. Factors affecting enrollment in a randomized controlled trial for Japanese metastatic breast cancer patients (SELECT BC-FEEL)--a prospective study. *Jpn J Clin Oncol*, 44:696-701, 2014
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DEPARTMENT OF THORACIC SURGERY

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

Introduction

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

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

Routine activities

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

The Department has adopted a team approach for patient treatments and resident trainings. Potential surgical intervention candidate cases are presented every Tuesday evening at a multidisciplinary team conference of thoracic surgeons, oncology physicians, radiologists and residents. Each case is thoroughly and vigorously reviewed and discussed. To improve the English fluency of staff members and residents in

preparation for international presentations, and to promote better involvement of visiting physicians from other countries, treatment modality discussions are conducted in English. Moreover, selected patients' records are radiologically and cytopathologically reviewed every Friday morning. These reviews aim to improve the interpretation of radiologic indications to pathology findings, accurately evaluate surgical indications, and upgrade knowledge on rare histologies. The Department believes that these activities improve the knowledge base, treatment indications, and surgical treatment.

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

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

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

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

Research activities

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

Clinical trials

1. Surgical margin lavage cytology examination in limited resection for primary and metastatic lung cancer patients [observational].
2. 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]

Education

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

Future prospects

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

Table 1. Number of patients

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

Table 2. Type of procedure – primary lung cancer

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

Table 3. Survival rates of lung cancer

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

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

List of papers published in 2014

Journal

- Eba J, Kenmotsu H, Tsuboi M, Niho S, Katayama H, Shibata T, Watanabe S, Yamamoto N, Tamura T, Asamura H. A Phase III trial comparing irinotecan and cisplatin with etoposide and cisplatin in adjuvant chemotherapy for completely resected pulmonary high-grade neuroendocrine carcinoma (JCOG1205/1206). *Jpn J Clin Oncol*, 44:379-382, 2014
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Book

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DEPARTMENT OF THORACIC ONCOLOGY

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

Introduction

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

Routine activities

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

Case conferences on thoracic surgery and medical oncology are scheduled on Tuesday evenings and Wednesday evenings, respectively. The staff members and residents of the Division participate in a journal club on Monday and Wednesday mornings. At monthly meetings with physicians in private practice, the staff members and residents are teaching methods of reading for

chest X-ray and CT scan films.

Research activities

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

Especially, 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 ROS1 fusion gene and BRAF mutation are under investigation as a collaboration with the Research Center for Innovative Oncology.

Clinical trials

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

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

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

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

PD-L1 immune checkpoint inhibitors showed remarkable clinical response against advanced NSCLC including squamous cell lung cancer.

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

Table 1. Number of patients in 2014

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

Table 2. Initial treatment of lung cancer in 2014

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

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

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

List of papers published in 2014

Journal

1. Kenmotsu H, Niho S, Ito T, Ishikawa Y, Noguchi M, Tada H, Sekine I, Watanabe S, Yoshimura M, Yamamoto N, Oshita F, Kubota K, Nagai K. A pilot study of adjuvant chemotherapy with irinotecan and cisplatin for completely resected high-grade pulmonary neuroendocrine carcinoma (large cell neuroendocrine carcinoma and small cell lung cancer). *Lung Cancer*, 84:254-258, 2014
2. Eba J, Kenmotsu H, Tsuboi M, Niho S, Katayama H, Shibata T, Watanabe S, Yamamoto N, Tamura T, Asamura H. A Phase III trial comparing irinotecan and cisplatin with etoposide and cisplatin in adjuvant chemotherapy for completely resected pulmonary high-grade neuroendocrine carcinoma (JCOG1205/1206). *Jpn J Clin Oncol*, 44:379-382, 2014
3. Gemma A, Kudoh S, Ando M, Ohe Y, Nakagawa K, Johkoh T, Yamazaki N, Arakawa H, Inoue Y, Ebina M, Kusumoto M, Kuwano K, Sakai F, Taniguchi H, Fukuda Y, Seki A, Ishii T, Fukuoka M. Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer. *Cancer Sci*, 105:1584-1590, 2014
4. Kawano Y, Okamoto I, Fukuda H, Ohe Y, Nakamura S, Nakagawa K, Hotta K, Kiura K, Takiguchi Y, Saka H, Okamoto H, Takayama K, Semba H, Kobayashi K, Kenmotsu H, Tsuboi M, Yamamoto N, Nukiwa T, Nakanishi Y. Current status and future perspectives of cooperative study groups for lung cancer in Japan. *Respir Investig*, 52:339-347, 2014
5. Seto T, Kato T, Nishio M, Goto K, Atagi S, Hosomi Y, Yamamoto N, Hida T, Maemondo M, Nakagawa K, Nagase S, Okamoto I, Yamanaka T, Tajima K, Harada R, Fukuoka M, Yamamoto N. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol*, 15:1236-1244, 2014
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7. Umemura S, Mimaki S, Makinoshima H, Tada S, Ishii G, Ohmatsu H, Niho S, Yoh K, Matsumoto S, Takahashi A, Morise M, Nakamura Y, Ochiai A, Nagai K, Iwakawa R, Kohno T, Yokota J, Ohe Y, Esumi H, Tsuchihara K, Goto K. Therapeutic priority of the PI3K/AKT/mTOR pathway in small cell lung cancers as revealed by a comprehensive genomic analysis. *J Thorac Oncol*, 9:1324-1331, 2014
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9. Murakami H, Yamamoto N, Shibata T, Takeda K, Ichinose Y, Ohe Y, Yamamoto N, Takeda Y, Kudoh S, Atagi S, Satouchi M, Kiura K, Nogami N, Endo M, Watanabe H, Tamura T. A single-arm confirmatory study of amrubicin therapy in patients with refractory small-cell lung cancer: Japan Clinical Oncology Group Study (JCOG0901). *Lung Cancer*, 84:67-72, 2014
10. Satouchi M, Kotani Y, Shibata T, Ando M, Nakagawa K, Yamamoto N, Ichinose Y, Ohe Y, Nishio M, Hida T, Takeda K, Kimura T, Minato K, Yokoyama A, Atagi S, Fukuda H, Tamura T, Saijo N. Phase III study comparing amrubicin plus cisplatin with irinotecan plus cisplatin in the treatment of extensive-disease small-cell lung cancer: JCOG 0509. *J Clin Oncol*, 32:1262-1268, 2014
11. Yoshida T, Niho S, Toda M, Goto K, Yoh K, Umemura S, Matsumoto S, Ohmatsu H, Ohe Y. Protective effect of magnesium preloading on cisplatin-induced nephrotoxicity: a retrospective study. *Jpn J Clin Oncol*, 44:346-354, 2014
12. Hishida T, Yoshida J, Ohe Y, Aokage K, Ishii G, Nagai K. Surgical outcomes after initial surgery for clinical single-station N2 non-small-cell lung cancer. *Jpn J Clin Oncol*, 44:85-92, 2014
13. Matsuwaki R, Ishii G, Zenke Y, Neri S, Aokage K, Hishida T, Yoshida J, Fujii S, Kondo H, Goya T, Nagai K, Ochiai A. Immunophenotypic features of metastatic lymph node tumors to predict recurrence in N2 lung squamous cell carcinoma. *Cancer Sci*, 105:905-911, 2014
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DEPARTMENT OF ESOPHAGEAL SURGERY

Hiroyuki Daiko, Takeo Fujita

Introduction

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

Routine activities

The Department of Esophageal Surgery consists of 2 staff surgeons and 4 residents. An Esophageal Conference is held every Tuesday evening to discuss the diagnosis, staging, and treatment strategy for each patient and is attended by surgeons, medical oncologists, endoscopists, radiologists, radiation oncologists, and head & neck surgeons. Approximately 4 patients are operated upon every week. In 2014, 156 patients underwent esophagectomy. Transthoracic esophagectomy with extended lymph node dissection was performed on 48 nontreated cases. Thoracoscopic esophagectomy in the prone position with radical lymph node dissection was undertaken in 108 cases. Two-stage surgical procedure divided into resection and reconstruction for more than 80 years old or multiple complicated patients was undertaken in 19 cases. Postoperatively, within 30 days, 1 patient died due to complications after a salvage operation.

Clinical trials

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

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

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

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

Table 1. Type of procedure

1 stage operation	137
2 stage operation	19
Total number of esophagectomy	156
Rt-transthoracic esophagectomy	48
Thoracoscopic esophagectomy	108
Emergency operation	15
Others	32
Total	203

List of papers published in 2014

Journal

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

DEPARTMENT OF GASTRIC SURGERY

Takahiro Kinoshita, Hidehito Shibasaki, Naoki Enomoto, Toshirou Nishida

Introduction

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

Routine activities

Usually 16-18 patients are hospitalized and 5-7 patients undergo operations per week. A weekly film conference is held every Monday from 17:00 with doctors of Department of Diagnostic Radiology and Department of Gastrointestinal Oncology, discussing diagnosis of the patients

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

We place importance on education of the gastric surgeons, including those from other institutions as well as hands-on training for resident surgeons in our hospital. Surgeons from domestic or foreign hospitals visited our Department to learn surgical techniques.

Research activities & clinical trials

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

1. JCOG 1001 Phase III randomized study to evaluate clinical benefits of bursectomy for patients with SS/SE gastric cancer
2. JCOG 1104 A phase II trial to define optimal period of adjuvant S-1 chemotherapy for pathological stage II gastric cancer patients who underwent D2 gastrectomy
3. JCOG1302-A Validity Study to Confirm the Accuracy of Preoperative Imaging Diagnosis for Stage III Gastric Cancer
4. A prospective cohort study to evaluate proper extent of lymph node dissection for esophagogastric junction cancer

List of papers published in 2014

Journal

1. Takahari D, Hamaguchi T, Yoshimura K, Katai H, Ito S, Fuse N, Konishi M, Yasui H, Terashima M, Goto M, Tanigawa N, Shirao K, Sano T, Sasako M. Survival analysis of adjuvant chemotherapy with S-1 plus cisplatin for stage III gastric cancer. *Gastric Cancer*, 17:383-386, 2014
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Table 1. Number of patients

Gastric cancer	243
Others (GIST etc.)	28

Table 2. Type of procedure

Open gastrectomy	45
Distal Gastrectomy	19
Pylorus-preserving Gastrectomy	0
Proximal Gastrectomy	0
Total Gastrectomy	15
Pancreaticoduodenectomy	0
Partial Gastrectomy	2
Others (bypass, exploration, etc.)	9
Laparoscopic Surgery (robot assisted surgery)	226
Distal Gastrectomy	127
Pylorus-preserving Gastrectomy	2
Proximal Gastrectomy	16(1)
Total Gastrectomy	33(4)
Partial Gastrectomy	10
Others (bypass, exploration, etc.)	40

Table 3. Survival rates of gastric cancer

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

Op.year: 1995.1-2004.12

Stage: Japanese Classification (13th Ed.)

DEPARTMENT OF COLORECTAL SURGERY

Norio Saito, Masaaki Ito, Akihiro Kobayashi, Yusuke Nishizawa, Yuji Nishizawa, Mitsuru Yokota, Yuichiro Tsukada, Kenichi Koushi

Introduction

The Department of Colorectal Surgery was established 16 years ago. Its main purpose is to bring together the Divisions that are composed of colorectal surgeons and urologists. Cooperation between these Divisions contributes not only to the establishment of effective operative techniques but also to an oncological consensus including consensus on the quality of life (QOL) and the various functions of patients with pelvic malignancies. New surgical procedures, such as nerve-sparing surgery, sphincter-saving surgery, bladder-sparing surgery, pouch surgery and minimally invasive surgery are being developed to prevent postoperative dysfunctions. These new approaches will contribute to better curability and QOL among patients with pelvic malignancies.

Routine activities

The Department of Colorectal Surgery comprises 7 consultants (5 colorectal surgeons and 2 urologists) and 11 residents. The outpatient clinic is open 5 days a week. More than 360 new patients with colorectal carcinomas and more than 150 new patients with other pelvic malignancies visited this Department during the last year. Treatment plans are discussed at a weekly conference on GI malignancies and at another weekly conference on pelvic malignancies. Many treatment modalities, such as local excision with or without adjuvant chemo- or radiotherapy and other minimally invasive forms of surgery using laparoscopy, have been introduced for the treatment of patients in the early stages of cancer. Laparoscopy-assisted operations (Lap-Ops) with wider lymphadenectomy of up to more than D2 are also increasingly being performed in patients with advanced colorectal carcinomas. Abdominoperineal resection (APR) has, in the past, been the standard

surgery in patients with very low rectal cancer; however, partial anal sphincter preserving surgery such as intersphincteric resection (ISR) and direct CAA have been performed in more than 500 patients with very low rectal tumors and has resulted in cure, preservation of anal function, and better QOL.

Research activities

- 1) A prospective randomized trial for extending the indications for Lap-Op (JCOG0404 CRC Surg-LAP vs. Open). A total of 77 patients have been registered in this Department. This study has been completed.
- 2) Intersphincteric resection with or without neoadjuvant mFOLFOX6 study (NAIR Study)-A prospective multi-center trial -A Phase II/III randomized multicenter trial of intersphincteric resection (ISR) with or without preoperative chemotherapy for very low-lying rectal cancer. APR has been the standard surgery for very low rectal cancer located within 5 cm of the anal verge. However, a permanent colostomy causes severe impairment of QOL. This study was designed to evaluate the feasibility and the oncological and functional outcomes of ISR for treatment of very low rectal cancer. Curability with ISR was verified histologically, and acceptable oncological and functional outcomes were obtained in many patients. However, patients need to be informed preoperatively regarding the potential functional adverse effects after ISR. This study is in progress, and 50 patients have been registered.
- 3) Bladder-sparing surgery for locally advanced rectal cancer involving the prostate. Total pelvic exenteration (TPE) is the standard procedure in such patients. This study aims to evaluate the feasibility of bladder-sparing surgery as an alternative to TPE. This procedure has

been performed in 39 patients with primary or recurrent tumors and permits conservative surgery in selected patients with advanced rectal cancer involving the prostate without compromising local control. The QOL of these patients appears to be better. Evaluation on usefulness and safety of cysto-urethral anastomosis with additional ileal flap in patients with rectal cancer involving the prostate (Ileal flap study) is also in progress.

- 4) A prospective randomized trial for the feasibility and effect of lateral node dissection in low rectal cancer – (Total) Mesorectal Excision (ME) vs. Lateral Node Dissection with preservation of autonomic nerves (D3 with nerve-sparing) [JCOG0212 CRC Surg.]. In this study, 76 patients have been registered. The final results will be seen soon.
- 5) Local excision with postoperative chemoradiotherapy for T1 • T2 rectal cancer. This study aims to evaluate preoperatively the feasibility and the oncologic outcome of local therapy for T1 and a part of T2 rectal cancer without lymph node metastases. In this study, 82 patients have been registered. The final results will be made clear soon.
- 6) A prospective cohort study of Reduced Port Surgery for colorectal cancer. This study is currently in progress, 66 patients have been registered.
- 7) Study on Robotic surgery for rectal cancer. This study is currently in progress, 12 patients have been registered.

Clinical trials

Other clinical trials are also in progress as follows.

- A Phase I/II trial of chemoradiotherapy concurrent with S-1 plus MMC in patients with clinical stage II/III squamous cell carcinoma of the anal canal (JCOG0903)
- A randomized study of conventional technique vs. no-touch isolation technique (JCOG1006)

- A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer (JCOG1007)
- A randomized Phase III study of mFOLFOX7 or CAPOX plus bevacizumab versus 5-fluorouracil/leucovorin or capecitabine plus bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer (JCOG1018)
- A randomized controlled trial comparing laparoscopic surgery with open surgery in palliative resection of primary tumor in incurable Stage IV colorectal cancer (JCOG1107)
- A Prospective Phase II Trial of Laparoscopic Surgery for Ultra-low Rectal Cancers within Five Centimeters from the Anus or Three Centimeters from the Dentate Line. Under the Japanese Society for Cancer of the Colon and Rectum (JSCCR)
- A prospective study of urinary and sexual dysfunction after surgery for rectal cancer
- A Phase II study of neoadjuvant mFOLFOX6 (+ cetuximab) in patients with resectable pelvic recurrences after rectal cancer surgery
- T-REX Study; the International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer (JSCCR)
- Development of LAP-instruments for colorectal surgery

Education

- Guiding university students in their studies
- Guiding colorectal surgeons for obtaining medical specialist

Future prospects

Establishment of less-invasive surgery for cure and function-preserving in cancer patients with colorectal malignances.

Table 1. Number of patients

Primary colorectal cancer			Other cases
Colon	Rectum	Sub-total	
160	216	376	123

Table 2. Type of procedure

Operative Procedures (2014.1-2014.12)

Colon N=160			Rectum N=216		
Laparoscopic(LAP) : 121 Open : 39			Laparoscopic (LAP) : 141 Robot : 10 Open : 65		
Sigmoidectomy	59	(LAP:54)	Low anterior resection	89	(LAP:75) (Robot:8)
Right (hemi) colectomy	31	(LAP:27)	Abdomino Anal resection(AAR)*	68	(LAP:51)
Ileocecal resection	19	(LAP:18)	High anterior resection	11	(LAP:7) (Robot:2)
Limited colectomy	23	(LAP:18)	Abdominoperineal resection (APR)	8	(LAP:8)
Hartmann procedure	2		Hartmann procedure	2	
High anterior resection	2	(LAP:1)	Local excision	2	
Low anterior resection	1	(LAP:1)	Total pelvic exenteration	4	
Left (hemi) colectomy	3	(LAP:2)	Stoma	25	
Total pelvic exenteration	2		Others	7	
Stoma	13		*Conventional coloanal anastomosis : 21		
Other	5		Partial intersphincteric resection (ISR) : 22		
			Subtotal ISR : 18		
			Total ISR : 5		
			Partial external sphincter resection (ESR) : 2		

Table 3. Survival rates

Stage	No. of pts	Colon		No. of pts	Rectum	
		5-yr survival (%)			5-yr survival (%)	
		overall	cancer specific		overall	cancer specific
Stage0	10	100	100	14	100	100
Stage I	210	95.2	100	171	93.6	97.6
Stage II	286	90.3	84.8	215	84.5	89.4
Stage IIIa	194	82.1	86.5	179	79.3	82.0
Stage IIIb	63	71.9	74.5	123	60.5	64.1
Stage IV	167	22.0	23.2	102	23.8	24.0

OP: 2000.1.1-2007.12

List of papers published in 2014

Journal

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DEPARTMENT OF GASTROINTESTINAL ONCOLOGY

Takayuki Yoshino, Atsushi Ohtsu, Toshihiko Doi, Takashi Kojima, Wataru Okamoto, Kohei Shitara, Hideaki Bando, Nozomu Fuse, Yusuke Hashimoto, Ken Hatogai, Sawako Miyoshi

Introduction

In 2014, approximately 630 gastrointestinal (GI) cancer patients were treated by staff oncologists and skilled residents in the Department of GI Oncology, which focuses on the optimal chemotherapy W/ or W/O radiation for the treatment of GI cancers.

Routine activities

Inter-Divisional tumor board conferences with the Surgical/Radiation Oncology Divisions are held regularly to review the current treatment for each patient and to discuss the further treatment strategies. Basically, routine chemotherapy is done on an outpatient basis, and there are approximately 1,900 selected patients who need the hospitalization for the purpose of planned therapy with chemotherapy or palliation. Our activities for each type of GI cancer in 2014 are shown in Table 1 (Number), Table 2 (Treatment), and Table 3 (Efficacy). There are 77 ongoing clinical trials which consisted of 42 Phase I trials including globally first-in-class (FIC), first-in-human (FIH), investigational new drugs (INDs) and 35 Phase II/III clinical trials to approve the INDs.

Research activities

Phase I

Our Department has focused more on early stage clinical development of INDs. The number for patient enrolled for Phase I trials have been increasing recently. During April to December 2014, 149 patients were enrolled for Phase I trials. Importantly, the number of FIH trials and trials around the same time as Western countries is increasing. Several results of Phase I trials, such as a HSP90 inhibitor (AUY922), IgG1

monoclonal antibody of PDGFR α (Olaratumab, IMC-3G3), PI3K inhibitor (buparlisib, BKM120), anti-HGF monoclonal antibody (Rilotumumab) as monotherapy or combination with capecitabine+cisplatin, were published or presented at international meetings. Notably, international Phase 1 study of a potent and selective inhibitor of focal adhesion kinase (BI 853520) was selected for oral presentation in 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics 2014.

Esophageal Cancer (EC)

A non-randomized confirmatory study of definitive chemoradiotherapy including salvage treatment in patients with clinical stage II/III esophageal carcinoma (JCOG 0909) was completed. Surgical safety results from JCOG0502 to compare thoracoscopic esophagectomy versus traditional thoracotomy were reported. And the result of JCOG0604: Phase I/II trial of chemoradiotherapy concurrent with S-1 and cisplatin in patients with clinical stage II/III esophageal carcinoma was presented in ASCO-GI 2014. And sub-analysis of the study of JCOG9907 were published or presented at international meeting.

Gastric Cancer (GC)

The results of a global randomized Phase III trial comparing lapatinib with paclitaxel to placebo with paclitaxel alone (TyTAN) and a multicenter Phase III trial (G-SOX) comparing S-1 plus oxaliplatin to S-1 plus cisplatin were published. We have investigated if each HER2, EGFR and c-Met status is an independent prognostic factor for advanced GC patients who received standard chemotherapy, which indicated poor prognosis of MET positive gastric cancer. Results of other study of comprehensive molecular profiling of advanced gastric cancer using NGS (Next Generation Sequencing) and immunohistochemistry was presented in Poster Highlights Session in ASCO

2014, which identified several possible candidate genes that could be targets for precision medicine. Results of Phase 1 trial of sulfasalazine (SSZ) for 11 patients with gastric cancer were also presented in ASCO 2014. Retrospective analysis of clinical outcomes in 66 patients with advanced gastric cancer treated in Phase I trials was also presented in GI cancer symposium in 2015.

Colorectal Cancer (CRC)

Based on the result of prospective multicenter clinical validation study of a multiplex kit for all RAS mutations (RASKET), the Japanese authority approved all RAS testing for the use of anti-EGFR monoclonal antibodies. We have established the nationwide cancer genome screening project (GI-SCREEN 2013-01) to detect the upfront identification of NRAS, BRAF, and PIK3CA mutations, and have moved forward to the SCRUM-Japan GI-screen (UMIN000016343). As the part of BREAC trial, we reported in GI cancer symposium in 2015, the association between the expanded RAS and BRAF non-V600E mutations and lack of the efficacy on anti-EGFR antibody. Based on the results, we are planning the new clinical trial which targets patients with BRAF non-V600E mutations. We also have conducted a confirmatory study called SUNRISE trial of Oncotype DX Colon Cancer assay to assess the relationship between continuous recurrence score and the likelihood of recurrence in patients with resected stage II and stage III colon cancer. The results of SUNRISE will be presented in upcoming international meeting in 2015. Notably, international Phase III study of TAS-102 over placebo (RECOURSE) was selected for oral presentation in ESMO World Congress on GI Cancer 2014.

Clinical trials

Esophageal Cancer (EC)

Three-arm randomized phase III study comparing preoperative CDDP+5-FU (CF) versus docetaxel+CF versus CF-radiation followed by esophagectomy with D2-3 lymphadenectomy for locally advanced esophageal squamous cell cancer (JCOG1109) is going. And a multicenter

phase II trial of BKM120 in patients with advanced esophagus cancer is going. As in the single institutional clinical study, Phase II trial of definitive chemoprotentherapy in patients with clinical stage I/II/III esophageal carcinoma is going.

Gastric Cancer (GC)

The enrollment for multicenter global trial (JACOB, GATSGY) was completed. A multicenter global phase III trial (ENRICH, ABSOLUTE, BRIGHTER) is ongoing. Several phase 1 or 2 studies of newer agents including c-MET tyrosine kinase inhibitor of MET high GC, FGFR-inhibitor for FGFR high GC as well as immune check point inhibitor are ongoing. The enrollment for a phase II trial of adjuvant chemotherapy with capecitabine plus oxaliplatin and with S-1 plus oxaliplatin has been completed. Several investigator initiated trials of a multicenter phase III trial comparing DCS to cisplatin plus S-1 (JCOG 1013), a multicenter phase II trial comparing 12 months of S-1 to 6 months of S-1 as an adjuvant chemotherapy (JCOG 1104) are ongoing. After confirmation of mode of action of SSZ as cancer stem cell inhibitor, we began phase I trial of SSZ in combination of cisplatin for cisplatin refractory GC patients.

Colorectal Cancer (CRC)

The results of an international phase III trial comparing TAS-102 with BSC (best supportive care) (RECOURSE) were presented in ESMO World Congress on GI Cancer 2014. We have completed the phase 1b/2 trial of the novel combination of TAS-102 plus bevacizumab as an investigator-initiated trial (IIT). An international phase III trial which investigate the survival benefits of oral multi-target kinase inhibitor, nintedanib with placebo in a salvage setting (LUME-COLON 1) is ongoing. We are participating two different international phase 1b/2 trials which target the patients with BRAF V600E mutated CRC, whose results of phase 1b part were reported in Poster Highlights Session of ASCO 2014. We have conducted two randomized, multicenter, phase III studies called ACHIEVE and ACHIEVE-2 trial, together with other nations' collaborative groups in US, UK/Australia, Italy, Greece and France.

Education

Our residents learn the latest evidence-based medicine and apply this knowledge pragmatically to enhance care for patients with GI cancers, and eventually have qualifications as a comprehensive GI oncologist through the daily practice and the direct training from our staffs. Accordingly, our staffs actively provide a pile of valuable opportunities to polish the skill of various chemotherapies, especially in collaboration with Department of Experimental Therapeutics as well as diagnostic & therapeutic endoscopies collaborated with Department of Digestive Endoscopy. We regularly held tumor board meetings and frequently do numerous face-to-face opportunities with experts in different specialties. We instruct them how to conduct valuable clinical trials, the chance to attend international academic conferences, and the best way to present the academic meeting and work on many high-impact articles in scholarly journals. To date, our

Table 1. Number of new patients

Esophageal	295
Gastric	217
Colorectal	215
Other type of tumors	54
Total	746

department has led many residents to become 'true' skilled GI oncologists who play major roles at leading cancer centers across the country

Future prospects

We continue to provide the best treatment for cancer patients, the best education for residents, and aim to perform the following activities:

- 1) To provide more the latest, cutting-edged medicine to cancer patients and to foster more the next generation of skilled GI oncologists.
- 2) To achieve medical innovation from Japan, we aim to play leading roles in the clinical developments of INDs by contributing to various types of clinical trials including FIC, FIH early trials, IITs with proof-of-concept, and international clinical trials.
- 3) To enhance our research activity, we will establish the research networks with cutting-edged researchers in Japan as well as globally.

Table 2. Treatment

Esophageal Cancer	Chemotherapy (include CRT*)	248
Gastric Cancer	Chemotherapy	180
Colorectal Cancer	Chemotherapy	194

List of papers published in 2014

Journal

1. Yasui H, Terashima M, Goto M, Tanigawa N, Shirao K, Sano T, Sasako M. Survival analysis of adjuvant chemotherapy with S-1 plus cisplatin for stage III gastric cancer. *Gastric Cancer*, 17:383-386, 2014
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DEPARTMENT OF DIGESTIVE ENDOSCOPY

Kazuhiro Kaneko, Tomonori Yano, Hiroaki Ikematsu, Yasuhiro Oono

Introduction

The Department of Digestive Endoscopy covers the fields of the gastrointestinal (GI) tract and head and neck regions. In 2014, over 10,000 examinations were performed. A narrow band imaging (NBI) system using the LUCERA spectrum (Olympus Optical Co., Ltd.) has been included for routine examination in 6 endoscopy rooms since September 2009. In addition, Blue LASER imaging (BLI) system was equipped in 2013. Furthermore, endoscopic treatments such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), percutaneous endoscopic gastrostomy (PEG), endoscopic balloon dilation (EBD), radial incision and cutting (RIC), and photodynamic therapy (PDT) have been performed.

In addition, research studies have been conducted in various fields: endoscopic diagnosis and treatment, or prevention for cancer patients in the GI tract and head and neck. Many of the research projects are conducted as prospective clinical studies either in a single institution or in collaboration with other institutions. The present research activities mainly focus on the development of new instruments for endoscopic diagnosis and new endoscopic treatment modalities. In addition, molecular biology research is also performed using blood and tissues samples of patients in order to examine strategies to enable the early detection, prevention, or prediction of prognosis for treatment. These projects are conducted in collaboration with not only commercial companies but also the faculties of Technology and Science of the university.

Routine activities

Routine endoscopic examinations including magnifying NBI and endoscopic ultrasound are presently used for head and neck, esophageal,

gastric, and colorectal cancers, and the NBI or BLI systems have become essential in detecting very early cancer in these areas. With the NBI or BLI systems, a differential diagnosis between neoplasia and non-neoplasia can be performed without the need for any dye solution. Single-balloon enteroscopy and capsule endoscopy are performed for examinations of the small intestine. Follow-up examinations after endoscopic treatment and chemotherapy are also performed in many cases, in addition to routine examinations.

With the recent progress in instruments and techniques, the number of endoscopic treatments has been increasing. EMR is indicated routinely for early GI tract cancers, and ESD is basically used not only for gastric cancers but also for esophageal or colorectal cancers. For the colon and rectum, colonoscopic day surgeries such as polypectomy and EMR are currently performed in one-third of all examinations. Furthermore, EMR and PDT are sometimes indicated as salvage treatments for local residual/recurrent tumors after chemoradiotherapy for esophageal cancer. PEG and EBD are valuable supporting techniques during the treatments of patients with head and neck, and esophageal cancers.

Research activities

Furthermore, molecular biological analysis of cancers of the esophagus, head and neck, stomach, and colorectum is underway. Importantly, analysis of the genetic polymorphism in the genes coding for alcohol dehydrogenase (ADH 1B) and aldehyde dehydrogenase (ALDH 2) regarding alcohol metabolism is performed as a useful novel strategic approach in the prevention of upper aerodigestive tract cancers. In addition, the relationships between the production of acetaldehyde and oral microflora after consumption of alcohol are being investigated in our study group.

In contrast, developing research into novel endoscopy systems is being performed. Hypoxia imaging is detected for neoplastic lesions of the head and neck and alimentary tracts, with blue visualized images. First in-human clinical trial of hypoxia imaging was finished. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and nanoparticles of the rare earth, doped yttrium oxide. This system is capable of penetrating through the intestinal wall and obtaining images. Furthermore, molecular imaging endoscopy for the use of this system with InGaAs CCD has been developed, since nanoparticles of rare earth act as fluorescent agents. With a low-temperature atmospheric pressure plasmas system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnosis system using photosensitizing agents, such as hypericin and 5ALA, has been constructed. Moreover, a new clinical trial of biodegradable (BD) stent has been performed for patients with benign esophageal stricture after curative treatment, such as ESD, surgery, and chemoradiotherapy.

Clinical trials

A wide range of many prospective clinical trials is ongoing into the endoscopic treatment of cancers of the esophagus, stomach, and colorectum, as follows: first in-human clinical trial of hypoxia imaging for neoplasia of alimentary tract in a single unit; phase II clinical trial for BD stent implantation for benign esophageal stricture; clinical trial for photodynamic diagnosis using 5ALA; multicenter clinical trials of a follow-up study after EMR of m1-3 esophageal cancers; a phase I/II study of PDT using Laserphyrin in residual/recurrent cases followed by chemoradiation for esophageal cancers; a phase II trial of combined treatment of endoscopic mucosal resection and chemoradiotherapy for clinical stage I esophageal carcinoma (JCOG0508); a multicenter clinical study for enrollment of early

gastric cancer following endoscopic treatment for enrollment system using the Web; a multicenter clinical trial of ESD for undifferentiated gastric cancer (JCOG1009); a multicenter clinical study regarding residual/recurrent rates and observation periods of endoscopic piecemeal mucosal resection (EPMR) for colorectal neoplastic lesions; and the Japan Polyp Study (JPS) for determination of observation periods after endoscopic treatment for colorectal polyps.

Education

The aim is to cultivate human resources specializing in endoscopic diagnosis and treatment for alimentary tract cancer. Staff supervises individual residents. Positiveness is made importance in a periodic case conference and joint conferences among internal medicine, surgery and radiology. Staff supervises in congress presentation and writing manuscripts after decision of individual themes, and much discussion is made in the department conference. For residents interested in development research, their opportunity to study is supported after graduation.

Future prospects

Existing endoscopic diagnosis for neoplasia of alimentary tract is performed on the basis of morphological feature of tumor. A molecular imaging endoscopy is a novel system to visualize cancer using specific laser sources under phosphor combined with cancer specific agents. We can obtain a new imaging, since function or metabolic state in cancer cells is visualized. In additional modalities, there are photodynamic diagnosis, endomicroscopy, and hypoxia imaging endoscopy. These modalities will be expected as a next generation endoscopy, and we try innovative development to produce all new endoscopy.

DEPARTMENT OF HEPATOBILIARY AND PANCREATIC SURGERY

Masaru Konishi, Shinichiro Takahashi, Naoto Gotohda, Yuichiro Kato, Kazuhiko Kitaguchi

Introduction

The recent development of various diagnostic techniques has led to the detection of an increasing number of early-stage and borderline malignancies, and for such patients, limited resection preserving organ function is indicated. However, some diseases, such as invasive ductal pancreatic cancer, advanced gallbladder cancer, and hilar cholangiocarcinoma, remain a difficult challenge for surgeons and are still associated with dismal long-term prognoses. Recently, chemotherapy for hepatobiliary and pancreatic malignancies has been developed. In line with this development, several studies on adjuvant chemotherapy for malignancies with dismal prognoses have been conducted.

With the refinements in laparoscopic instruments and advances in surgical experience, laparoscopic surgery is a safe alternative for selected patients with hepatobiliary pancreatic neoplasms, and has fulfilled its indications. In our division, laparoscopic hepatectomy has been performed since 2002, and laparoscopic distal pancreatectomy since 2011.

Routine activities

Our group is composed of 4 attending surgeons, 1 chief resident, and 5 residents. The outpatient clinic is open 5 days a week. Staff meetings are held 3 times a week during which treatment strategies from the medical and surgical points of view are discussed. A case conference on imaging diagnosis is conducted every Tuesday in cooperation with radiologists and medical oncologists, and a pathology conference is held every month with pathologists. In 2014, 250 patients with hepatobiliary and pancreatic diseases underwent surgical treatment including 56 laparoscopic hepatectomies and 5 laparoscopic distal pancreatectomies.

Research activities

We studied the safety margin afforded by the use of stroke volume variation (SVV), in place of central venous pressure (CVP), in the circulatory management during liver resection. The purpose of this study is to conduct a new circulatory management using the Flo Trac™ system in liver resection and evaluate specific fluctuations of SVV.

Clinical trials

- JASPAC04 is a randomized Phase II study on neoadjuvant chemotherapy using combination therapy with gemcitabine and S-1 vs. S-1 and concurrent radiotherapy in patients with resected pancreatic cancer. Recruitment started in 2014.
- JASPAC05 is a Phase II study on neoadjuvant S-1 and concurrent radiotherapy for patients with borderline resectable pancreatic cancer. Recruitment started in 2012.
- JCOG1202 (ASCOT) is a Phase III study to compare S-1 with surgery alone as adjuvant chemotherapy for patients with curatively resected extrahepatic bile duct cancer. Recruitment started in 2013.
- JCOG0605 is a randomized Phase III trial to compare FOLFOX with surgery alone as adjuvant chemotherapy for patients with curatively resected liver metastasis from colorectal cancer. Recruitment is on-going.
- EXPERT trial is a randomized Phase III trial of surgery followed by mFOLFOX6 as adjuvant chemotherapy versus peri-operative mFOLFOX6 plus cetuximab for KRAS wild type resectable liver metastases of colorectal cancer.
- COAST 15983 is a global Phase III trial studying adjuvant Regorafenib in patients with colorectal cancer after surgical removal of liver metastases and completion of all planned chemotherapy.

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

Education

'Board certified expert surgeons' is a high level of skill in the field of hepatobiliary-pancreatic surgery. To be qualified as a board certified surgeon, surgeons are required to perform a prescribed number of operations under the guidance of a board certified instructor. The residents of our department are training to get the certifications until the end of the chief resident course.

Table 1. Number of new patients

Invasive pancreatic cancer	46
Other pancreatic neoplasms	11
Hepatocellular carcinoma	42
Hepatic metastases	53
Intrahepatic cholangiocarcinoma	11
Perihilar cholangiocarcinoma	11
Distal bile duct cancer	24
Ampullary cancer	3
Gallbladder cancer	6

List of papers published in 2014

Journal

1. Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Gotohda N, Konishi M. Surgical procedure depending on the depth of tumor invasion in duodenal cancer. *Jpn J Clin Oncol*, 44:224-231, 2014
2. Komai Y, Sakai Y, Gotohda N, Kobayashi T, Kawakami S, Saito N. A novel 3-dimensional image analysis system for case-specific kidney anatomy and surgical simulation to facilitate clampless partial nephrectomy. *Urology*, 83:500-506, 2014
3. Sugimoto M, Takahashi S, Kojima M, Gotohda N, Kato Y, Kawano S, Ochiai A, Konishi M. What is the nature of pancreatic consistency? Assessment of the elastic modulus of the pancreas and comparison with tactile sensation, histology, and occurrence of postoperative pancreatic fistula after pancreaticoduodenectomy. *Surgery*, 156:1204-1211, 2014
4. Sugimoto M, Mitsunaga S, Yoshikawa K, Kato Y, Gotohda N, Takahashi S, Konishi M, Ikeda M, Kojima M, Ochiai A, Kaneko H. Prognostic impact of M2 macrophages at neural invasion in patients with invasive ductal carcinoma of the pancreas. *Eur J Cancer*, 50:1900-1908, 2014
5. Oba A, Takahashi S, Kato Y, Gotohda N, Kinoshita T, Shibasaki H, Ikeda M, Konishi M. Usefulness of resection for hepatocellular carcinoma with macroscopic bile duct tumor thrombus. *Anticancer Res*, 34:4367-4372, 2014

Table 2. Type of procedure

Hepatectomy and pancreaticoduodenectomy	2
Pancreaticoduodenectomy	59
Distal pancreatectomy	14
Total pancreatectomy	7
Laparoscopic distal pancreatectomy	5
Hapatectomy with biliary reconstruction	11
Hapatectomy without biliary reconstruction	54
Laparoscopic hepatectomy	56
Others	42
Total	250

Table 3. Survival rates

Diagnosis	No. of pts	5-yr survival(%)
Invasive pancreatic cancer	367	17.7
Hepatocellular carcinoma	350	48.5
Hepatic metastases	575	51.7
Intrahepatic cholangiocarcinoma	60	39.0
Perihilar cholangiocarcinoma	121	42.0
Distal bile duct cancer	97	45.6
Ampullary cancer	68	52.1
Gallbladder cancer	82	47.1

DEPARTMENT OF HEPATOBILIARY AND PANCREATIC ONCOLOGY

Masafumi Ikeda, Shuichi Mitsunaga, Satoshi Shimizu, Izumi Ohno, Hideaki Takahashi, Hiroyuki Okuyama

Introduction

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

Routine activities

Our Department is composed of 5 staff oncologists, 1 senior resident and 2 residents, with 35-50 beds in the hospital and conduct clinical rounds for admitted patients every morning and evening. Most new patients with unresectable hepatobiliary and pancreatic tumors are hospitalized for the diagnosis and treatment of tumors. The treatment strategies on individual patient are discussed in weekly tumor board conferences attended by medical oncologists, surgeons, radiologists, radiation oncologists, and pharmacists. Furthermore, we are also responsible for external or endoscopic abdominal ultrasonographic examinations, percutaneous or endoscopic ultrasound-guided biopsies of abdominal masses, percutaneous local ablative therapy for liver tumors, percutaneous or endoscopic biliary drainage and stenting for obstructive jaundice.

Research activities

Hepatocellular carcinoma (HCC)

The following clinical studies have been investigated for advanced HCC patients: the efficacy and adverse events of sorafenib as a first line chemotherapy in patients with advanced HCC, the prognostic factors in patients with HCC

refractory or intolerant to sorafenib and the efficacy and safety of hepatic arterial infusion chemotherapy with cisplatin after sorafenib treatments, etc.

Pancreatic cancer (PC)

FOLFIRINOX has been established as a standard chemotherapy for advanced PC, but the myelosuppression and gastrointestinal toxicities have been reportedly high frequencies. In our hospital, modified regimen of FOLFIRINOX has been adapted and it became easy to manage the toxicities. The number of patients who treated with this regimen was No.1 in Japan. The treatment efficacy and adverse events of modified FOLFIRINOX on clinical practice have been reported, and the efficacies have been clarified to be comparable on each subgroup of patient characteristics to those of original FOLFIRINOX.

Hepatitis B viral (HBV) reactivation following chemotherapy

In a multicenter retrospective cooperative study of patients who developed HBV reactivation following chemotherapy, the clinical features of HBV reactivation and the patient outcomes after HBV reactivation have been clarified. A prospective study has been also conducted to investigate the incidence and outcome of the patients in whom the HBV reactivation developed among the patients with solid tumors receiving first line chemotherapy, and no clinically significant HBV reactivation has been reported to be developed by periodical measurement of HBV DNA and proper management at the reactivation.

Clinical trials

42 clinical trials (sponsored: 28 trials, investigator-initiated: 21 trials) are ongoing, and 8 clinical trials (sponsored: 4 trials, investigator-initiated: 4 trials) are being planned for the upcoming year.

HCC

A randomized Phase II trial comparing sorafenib vs. observation in combination with TACE is ongoing. Some sponsored trials of lenvatinib, sorafenib plus resmetinostat, and sorafenib plus TGF- β inhibitor (LY2157299) are ongoing as the first line chemotherapy. As the second line setting, the enrollment of some clinical trials of ALK-1 inhibitor (PF-03446962), rafametinib, nintedanib, pimasertib, a stat 3 inhibitor (AZD9150), etc. have been finished, but some clinical trials of tivantinib, regorafenib, a peptide vaccine including glypican-3 (ONO-7268MX1), etc. are ongoing. As the adjuvant setting after resection or ablation, phase III trials of peretinoin vs. a placebo is also underway.

Biliary tract cancer (BTC)

A randomized Phase III trial comparing adjuvant S-1 with observation in patients with resected BTC (JCOG1202) is ongoing. And a randomized Phase III trial comparing Gemcitabine (Gem) plus S-1 with Gem plus cisplatin (JCOG1113) and a Phase I trial of Gem, cisplatin plus MEK inhibitor (AZD6244) for first line chemotherapy and some sponsored trials of trametinib, and PD-L1 inhibitor for advanced BTCs refractory to Gem are underway.

PC

A multicenter Phase II trial of neoadjuvant S-1 and concurrent radiotherapy for borderline resectable PC (JASPAC05) is ongoing. A Phase III trial of Gem plus TH-302 vs. Gem+Placebo in chemo-naive PC patients has been finished on the enrollments. A randomized Phase II trial of mixed agents of S-1 plus leucovorin (TAS-118) vs. S-1 in Gem refractory PC patients is underway. A multicenter investigators-initiated Phase II trial of GBS-01, which is an orally administered drug rich in arctigenin and has been reported to exert antitumor activity by attenuating the tolerance of cancer cells to glucose deprivation has been conducted in PC patients who are refractory to Gem and fluoropyrimidine therapy.

Education

For our resident and senior residents, one-to-one training is provided on the daily practice of management of inpatients and outpatients. And they can learn all cancer treatments from local treatments

to systemic chemotherapy for hepatic, biliary, and pancreatic cancer patients and the accompanied procedures to make a diagnosis, drainage for obstructive jaundice and management of the adverse events. In addition, they can make a presentation of their research in the domestic and overseas meetings and make a paper in English under the instruction of staff physicians.

Future prospects

The prognosis of patients with hepatic, biliary, and pancreatic cancers remains dismal and standard treatments for these cancers are limited. In Japan, the incidences of these cancers, especially HCC and BTC, are higher than those in western countries. Therefore, we must conduct a lot of novel and promising clinical trials and researches which take a lead worldwide. And it is necessary to develop the biomarker research as accompanied with cancer treatment in cooperated with our cancer research center and pharmaceutical companies to identify the more effective and less toxic patients subgroups.

Table 1. Number of new patients

Hepatocellular carcinoma	82
Biliary tract cancer	
Intrahepatic cholangiocarcinoma	28
Extrahepatic cholangiocarcinoma	24
Gallbladder cancer	35
Papilla of Vater carcinoma	5
Pancreatic cancer	
Locally advanced disease	42
Metastatic disease	154
Other	15
Total	385

Table 2. Type of procedure

Hepatocellular carcinoma	
Radiofrequency ablation	82
Transarterial chemoembolization	196
Intra-arterial chemotherapy	47
Systemic chemotherapy	47
Proton beam radiotherapy	30
Biliary tract cancer	
Systemic chemotherapy	118
Radiotherapy	7
Pancreatic cancer	
Systemic chemotherapy	264
Chemoradiotherapy	8
Total	799

List of papers published in 2014

Journal

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7. Okusaka T, Ikeda M, Fukutomi A, Kobayashi Y, Shibayama K, Takubo T, Gansert J. Safety, Tolerability, Pharmacokinetics and Antitumor Activity of Ganitumab, an Investigational Fully Human Monoclonal Antibody to Insulin-like Growth Factor Type 1 Receptor, Combined with Gemcitabine as First-line Therapy in Patients with Metastatic Pancreatic Cancer: A Phase 1b Study. *Jpn J Clin Oncol*, 44:442-7, 2014
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9. Sugimoto M, Mitsunaga S, Yoshikawa K, Kato Y, Gotohda N, Takahashi S, Konishi M, Ikeda M, Kojima M, Ochiai A, Kaneko H. Prognostic impact of M2 macrophages at neural invasion in patients with invasive ductal carcinoma of the pancreas. *Eur J Cancer*, 50:1900-8, 2014
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12. Ikeda M, Shiina S, Nakachi K, Mitsunaga S, Shimizu S, Kojima Y, Ueno H, Morizane C, Kondo S, Sakamoto Y, Asaoka Y, Tateishi R, Koike K, Arioka H, Okusaka T. Phase I study on the safety, pharmacokinetic profile, and efficacy of the combination of TSU-68, an oral antiangiogenic agent, and S-1 in patients with advanced hepatocellular carcinoma. *Invest New Drugs*, 32:928-36, 2014
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14. Shiba S, Okusaka T, Ikeda M, Saito H, Ichida T. Characteristics of 18 patients with hepatocellular carcinoma who obtained a complete response after treatment with sorafenib. *Hepatol Res*, 44:1268-76, 2014
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DEPARTMENT OF UROLOGY

Yasuyuki Sakai, Yoshinobu Komai

Introduction

The Department of Urological Surgery has existed as part of the Department of Pelvic Surgery at the National Cancer Center Hospital East from 2003. This Department mainly treats diseases of the pelvic organs, including urogenital cancer, with the aim of preserving the sexual and/or voiding functions under minimally invasive surgery.

Routine activities

Outpatient activities: An outpatient clinic is open 2 days a week as a Urology Department. Flexible cystoscopy, abdominal ultrasonography, retrograde pyelography and some prostate biopsies are performed in the outpatient clinic. Superficial bladder cancer (G3, cis, or recurrent tumor) after

TUR-Bt is treated by instillation of BCG into the bladder. Advanced urogenital cancers including stage D2 prostate cancer are referred to the Medical Oncology Division for chemotherapy or hormonal therapy. Extrinsic obstructions of the upper urinary tract that directly result from invasion of an adjacent malignancy or peritoneal metastasis are also treated. In most cases, internal stenting is better tolerated than percutaneous nephrostomy. 67 patients newly received ureteral stents and 25 underwent nephrostomy for obstructive uropathy.

Inpatient activities: A daily conference is held with doctors of the Department of Pelvic Surgery on diagnosis and treatment of the patients with colorectal and urological cancer. We performed about 28 combination surgeries with colorectal surgeons. In the Department of Urology, 102 general anaesthesia surgeries, 77 spinal anaesthesia surgeries and 39 prostate biopsies were performed.

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

muscle invasive bladder cancer, combination therapy of hormone and radiation for prostate cancer, treatment strategies for metastatic renal cell carcinoma and testicular cancer, and so on, are determined in the meeting.

Research activities

In recent years, partial nephrectomy has become the standard treatment of T1 renal cell carcinoma instead of radical nephrectomy. We reported on the Synapse Vincent 3D image analysis system for kidney surgery. Its 3D images and surgical simulation helped not only surgeons in their performance of clampless partial nephrectomy but also patients in their understanding of the operation. Total pelvic exenteration (TPE) is the standard procedure for locally advanced rectal cancer involving the prostate and seminal vesicles. We evaluated the feasibility of bladder-sparing surgery as an alternative to TPE. We performed concomitant prostatectomy and cysto-urethral anastomosis.

Clinical trials

1. A retrospective study of perioperative results in partial nephrectomy for renal cell carcinoma
2. An estimate of the prevalence of Lynch syndrome in upper urinary tract urothelial cancer
3. Development and validation of a nomogram to predict recurrences of upper urinary tract urothelial cancer in Japanese patients
4. A Phase II clinical study of robotic assisted radical prostatectomy by da Vinci S/Si Surgical System
5. A Phase III study: BCG instillation for high grade T1 bladder cancer (JCOG1019)

Table 1. Number of new patients

Renal cell carcinoma	20
Upper urinary tract urothelial carcinoma	18
Bladder cancer	45
Prostate cancer	51
Testicular cancer	3

Table 2. Type of procedure

Radical nephrectomy	4
Partial nephrectomy	16
Nephroureterectomy	18
Radical cystectomy	15
TURBT	69
Radical prostatectomy (RARP)	34 (31)

List of papers published in 2014**Journal**

1. Komai Y, Sakai Y, Gotohda N, Kobayashi T, Kawakami S, Saito N. A novel 3-dimensional image analysis system for case-specific kidney anatomy and surgical simulation to facilitate clampless partial nephrectomy. *Urology*, 83:500-506, 2014
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DEPARTMENT OF MUSCULOSKELETAL ONCOLOGY AND REHABILITATION

Fumihiko Nakatani

Introduction

The Department of Musculoskeletal Oncology and Rehabilitation of the National Cancer Center Hospital East is a team consisting of a panel of orthopedic surgeons and rehabilitation professionals starting from 2012. We strive to provide expert interdisciplinary care for a variety of benign and malignant bone and soft tissue tumors and tumor-like conditions, and we also provide comprehensive rehabilitation services. Currently, we have a chief orthopedic surgeon and 2 rehabilitation staff engaging in the treatment of a variety of patients with the aid of other orthopedic staff from the National Cancer Center Hospital (NCCH).

Routine activities

Our outpatient service is open 3 days a week (Mondays, Wednesdays and Fridays) for patients with a variety of musculoskeletal tumors or cancer patients who need rehabilitation care. We also manage the patients who suffer bone metastases, other orthopedic diseases, consulted from other cancer specialists on a daily basis. To provide the prosthetic and orthotic care for our patients, a special outpatient service is open every Friday. In cases patients who need multidisciplinary approaches to the treatments, we offer appropriate referral to the NCCH for further treatments.

In 2014, we have conducted 43 operations in total, consisted of twenty resections of soft tissue tumors, 17 osteosyntheses of pathological fractures from bone metastases and 5 operations for bone tumors.

On September 2014, we have opened the spacious rehabilitation unit with adequate equipment for the aim to reduce the common side effects of cancer treatment, including fatigue, weakness, poor endurance, pain, nausea, anxiety,

depression and loss of confidence. As a result, we have conducted rehabilitation of 493 patients in 2014 (Table 1).

Research activities

We have been focusing on regional cooperation with the local physiotherapists of the Kashiwa-city for the aim to provide cancer patients of the community with seamless rehabilitation care after the invasive cancer operations. Until now, we have established the standard methods of physiotherapy and functional evaluations in common.

Clinical trials

We have been focusing on the standardization of multidisciplinary treatment for bone and soft tissue sarcomas cooperated with the Musculoskeletal Oncology Department of the NCCH. Two multi-institutional clinical trials are active as follows:

1. A multi-institutional Phase III clinical trial of multidrug adjuvant chemotherapy for osteosarcoma (JCOG 0905) has been ongoing since 2010.
2. A multi-institutional Phase III clinical trial of adjuvant chemotherapy for high-grade soft part sarcoma (JCOG 1306) has started in February 2014.

Education

We have been engaging in several educational lectures for the medical staff to prevail the importance of rehabilitation for cancer treatment. We also provide some instructive lectures for the medical staff of the community.

Future prospects

Recent evolution of the cancer treatment increases the demands for the orthopedic care and rehabilitation of cancer survivors. We must consistently focus on the standardization for the methodology of rehabilitation for all the cancer patients, which will be beneficial for the augmentation of quality of life for the cancer patients.

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

Department	2012	2013	2014
Hematology	39	24	11
Thoracic oncology	35	44	54
Thoracic surgery	29	13	30
Head and neck oncology	21	10	5
Gastrointestinal oncology	21	23	59
Esophageal surgery	19	34	60
Musculoskeletal oncology	17	52	23
Palliative medicine	15	18	2
Colorectal surgery	13	2	42
Hepatobiliary and pancreatic oncology	12	15	24
Breast and medical oncology	-	27	34
Head and neck surgery	-	13	97
Others	24	19	52
Total	146	245	493

List of papers published in 2014

Journal

1. Miyamoto S, Kayano S, Kamizono K, Fukunaga Y, Nakao J, Nakatani F, Kobayashi E, Sakuraba M. Pedicled superficial femoral artery perforator flaps for reconstruction of large groin defects. *Microsurgery*, 34:470-474, 2014
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DEPARTMENT OF HEMATOLOGY

Kunihiro Tsukasaki, Masahiko Nezu, Sachiko Seo, Kuniaki Ito

Introduction

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

Routine activities

The number of patients with newly diagnosed hematologic malignancies in our Department is increasing, and approximately 250 patients with newly diagnosed hematological malignancies including non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, macroglobulinemia, acute leukemia, myelodysplastic syndrome and chronic leukemia were cared this year (Table 1). The Department is currently providing routine chemotherapy as an outpatient service to an increasing number of relatively aged patients with hematological malignancies. All patients undergoing intensive chemotherapy and autologous peripheral blood hematopoietic stem cell transplantation (APBSCT) (Table 2) are managed in laminar airflow rooms in the designated ward on the eighth floor. Besides managing patients, the Department also provides consultation on hematological abnormalities detected in the Department of Clinical Laboratories. Morning case conference on inpatient care of our Department is held from Mondays to Friday, and a weekly case conference on new patients visiting our clinic is held on Thursday evenings. On Wednesday evenings, a weekly joint conference on lymphoid

malignancies with expert pathologists and an educational cytology conference on bone marrow specimens are held. Joint morning journal club of Departments of ours and Breast and Medical Oncology is held on Mondays and Fridays.

Research activities

Ancillary studies associated with retrospective case series and clinical trials at this Department have been continuously conducted focusing on several kinds on hematological malignancies and their complications. Recently, nation-wide survey of human T-lymphotropic virus type I (HTLV-1) associated adult T-cell leukemia-lymphoma (ATL) is ongoing by us under a grant for Cancer Research from the Ministry of Health to elucidate the pathophysiology including geographical findings as compared to those surveys in 1980' to 1990'.

Clinical trials

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

cytarabine, dexamethasone, etoposide and rituximab (CHASER) followed by high dose melpharan, cyclophosphamide, etoposide and dexamethasone (LEED) with APBSCT in patients with newly diagnosed poor risk CD20+ DLBCL (JCOG0908); a randomized Phase II study of two induction treatments of melphalan, prednisolone, plus bortezomib, JCOG-MPB versus modified PETHEMA-MPB, in elderly patients or non-elderly patients refusing transplant with untreated symptomatic myeloma (JCOG1105); and a Phase II study of mLSG15 chemotherapy followed by allo-

HSCT, comparing the results with historical control in JCOG9801 to evaluate the promising efficacy of allo-HSCT, possibly associated with a graft-versus-ATL effect, especially in view of a comparison with intensive chemotherapy (JCOG0907). A Phase III study evaluating the efficacy of combination of interferon-alpha (IFN) and zidovudine (AZT) as compared to watchful-waiting for indolent ATL (JCOG1111) is ongoing under the highly advanced medical technology assessment system because IFN and AZT are not covered for ATL by the National Health Insurance in Japan.

Table 1. Number of new patients

Non-Hodgkin's lymphoma	155
Hodgkin's lymphoma	7
Multiple myeloma	25
Acute leukemia	2
Chronic leukemia	10
Others	48
Total	247

Table 2. Type of procedure

PBSCT for non-Hodgkin's lymphoma in relapse	2
PBSCT for myeloma in remission	5
Total	7

List of papers published in 2014

Journal

1. Yamaguchi M, Takata K, Yoshino T, Ishizuka N, Oguchi M, Kobayashi Y, Isobe Y, Ishizawa K, Kubota N, Itoh K, Usui N, Miyazaki K, Wasada I, Nakamura S, Matsuno Y, Oshimi K, Kinoshita T, Tsukasaki K, Tobinai K. Prognostic biomarkers in patients with localized natural killer/T-cell lymphoma treated with concurrent chemoradiotherapy. *Cancer Sci*, 105:1435-1441, 2014
2. Fukushima T, Nomura S, Shimoyama M, Shibata T, Imaizumi Y, Moriuchi Y, Tomoyose T, Uozumi K, Kobayashi Y, Fukushima N, Utsunomiya A, Tara M, Nosaka K, Hidaka M, Uike N, Yoshida S, Tamura K, Ishitsuka K, Kurosawa M, Nakata M, Fukuda H, Hotta T, Tobinai K, Tsukasaki K. Japan Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A). *Br J Haematol*, 66:739-748, 2014
3. Ogura M, Ishida T, Hatake K, Taniwaki M, Ando K, Tobinai K, Fujimoto K, Yamamoto K, Miyamoto T, Uike N, Tanimoto M, Tsukasaki K, Ishizawa K, Suzumiya J, Inagaki H, Tamura K, Akinaga S, Tomonaga M, Ueda R. Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-CC chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. *J Clin Oncol*, 32:1157-1163, 2014
4. Tsukasaki K, Tobinai K. Human T-cell lymphotropic virus type I-associated adult T-cell leukemia-lymphoma: new directions in clinical research. *Clin Cancer Res*, 20:5217-5225, 2014
5. Makiyama J, Imaizumi Y, Tsushima H, Taniguchi H, Moriwaki Y, Sawayama Y, Imanishi D, Taguchi J, Hata T, Tsukasaki K, Miyazaki Y. Treatment outcome of elderly patients with aggressive adult T cell leukemia-lymphoma: Nagasaki University Hospital experience. *Int J Hematol*, 100:464-472, 2014
6. Yoshida N, Karube K, Utsunomiya A, Tsukasaki K, Imaizumi Y, Taira N, Uike N, Umino A, Arita K, Suguro M, Tsuzuki S, Kinoshita T, Ohshima K, Seto M. Molecular characterization of chronic-type adult T-cell leukemia/lymphoma. *Cancer Res*, 74:6129-6138, 2014
7. Taniguchi H, Hasegawa H, Sasaki D, Ando K, Sawayama Y, Imanishi D, Taguchi J, Imaizumi Y, Hata T, Tsukasaki K, Uno N, Morinaga Y, Yanagihara K, Miyazaki Y. Heat shock protein 90 inhibitor NVP-AUY922 exerts potent activity against adult T-cell leukemia-lymphoma cells. *Cancer Sci*, 105:1601-1608, 2014
8. Tsukasaki K, Imaizumi Y, Tokura Y, Ohshima K, Kawai K, Utsunomiya A, Amano M, Watanabe T, Nakamura S, Iwatsuki K, Kamihira S, Yamaguchi K, Shimoyama M. Meeting report on the possible proposal of an extranodal primary cutaneous variant in the lymphoma type of adult T-cell leukemia-lymphoma. *J Dermatol*, 41:26-28, 2014
9. Seo S, Xie H, Campbell AP, Kuypers JM, Leisenring WM, Englund JA, Boeckh M. Parainfluenza virus lower respiratory tract disease after hematopoietic cell transplant: viral detection in the lung predicts outcome. *Clin Infect Dis*, 58:1357-1368, 2014
10. Seo S, Xie H, Karron RA, Thumar B, Englund JA, Leisenring WM, Stevens-Ayers T, Boeckh M, Campbell AP. Parainfluenza virus type 3 Ab in allogeneic hematopoietic cell transplant recipients: factors influencing post-transplant Ab titers and associated outcomes. *Bone Marrow Transplant*, 49:1205-1211, 2014
11. Kobayashi T, Seo S, Morita S, Goto A, Masuda A, Shimizu N, Nishida M, Nunobe S, Ichikawa M, Takazawa Y, Seto Y, Fukayama M, Kurokawa M. Esophageal intramucosal hematoma after peripheral blood stem cell transplantation: case report and review of literature. *Int J Clin Exp Pathol*, 7:2690-2694, 2014
12. Little JL, Serzhanova V, Izumchenko E, Egleston BL, Parise E, Klein-Szanto AJ, Loudon G, Shubina M, Seo S, Kurokawa M, Ochs MF, Golemis EA. A requirement for Nedd9 in luminal progenitor cells prior to mammary tumorigenesis in MMTV-HER2/ErbB2 mice. *Oncogene*, 33:411-420, 2014
13. Riccomagno MM, Sun LO, Brady CM, Alexandropoulos K, Seo S, Kurokawa M, Kolodkin AL. Cas adaptor proteins organize the retinal ganglion cell layer downstream of integrin signaling. *Neuron*, 81:779-786, 2014

Book

1. Tsukasaki K, Watanabe T, Tobinai K. Adult T-cell Leukemia-Lymphoma. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE (eds), *Abeloff's Clinical Oncology*, 5th Edition, USA, Churchill Livingstone, an imprint of Elsevier, pp 2076-2091, 2014
2. Tsukasaki K, Tobinai K. Adult T-cell Leukemia- Lymphoma. In: Dreyling M, Williams ME (eds), *Rare Lymphomas*, Germany, Springer-Verlag Berlin Heidelberg, pp 99-110, 2014

DEPARTMENT OF DENTISTRY

Tetsuhito Konishi, Toshiro Miyata, Tomoko Kaneda

Introduction

We are attempting to cope with the diverse intraoral complications associated with cancer treatment and to maintain and improve the patients' quality of life (QOL) in the field of dentistry.

Cancer treatment is frequently associated with a variety of intraoral complications, such as mucositis, taste disorder, dry mouth, pain, and infection. In particular, in patients undergoing treatment for head and neck cancer (chemoradiotherapy, surgery) and hematopoietic stem cell transplantation, severe intraoral symptoms may occur, and strict infection control measures are needed.

When such measures are inadequate, composite complications may result in secondary complications such as eating disorders and undernutrition, and the oral cavity may serve as a source of systemic infections; these may lead to the need for deferring or discontinuing treatment, making continuation and completion of cancer treatment difficult.

To manage and prevent intraoral complications, we evaluate and stabilize the oral status before the initiation of cancer treatment. Proactive intervention by dentists or dental hygienists to educate the patients, their families, and the attending medical staff is extremely important.

Routine activities

We undertake efforts to prevent infection of wounds and aspiration pneumonia and to reduce other complications by oral hygiene management before and after surgery. To maintain postoperative functions of jaw defects, we are attempting to correct speech-language and eating functions by preparing appropriate artificial dentition and prostheses at an early stage, thereby improving the QOL of patients after treatment. For patients receiving chemotherapy and radiotherapy, we are supporting continuation and completion of treatment by taking

measures to prevent infections arising from the dentistry realm and mucositis and by reducing pain. In regard to delayed complications, we are undertaking preventive and treatment activities for multiple dental caries, osteomyelitis of the jaw, and necrosis of the jaw bone. Patients treated over the long-term with zoledronic acid or denosumab may develop Medication-Related Osteonecrosis of the Jaw (MRONJ) as a result of contamination of the oral cavity and tooth extraction; thus, we are undertaking measures to prevent/ treat this complication.

By participating in multidisciplinary conferences, we apply prevailing practices and information updates to future medical care support. In 2014, the numbers of new and revisiting patients were 874 and 7,491, respectively, and the total number of patients was 8,365. These numbers represent an approximately 1.5-fold increase as compared to those in the first year when dentists at the National Cancer Center Hospital East began to hold full-time positions. We believe that the importance of supportive care in cancer has been recognized.

Research activities

We are participating in a multicenter study being conducted to evaluate the effectiveness of proactive use of supportive care for preventing serious oral mucositis in patients with head and neck cancer undergoing chemoradiotherapy.

We are carrying out a study on multiple dental caries and radiation-induced osteomyelitis developing after radiotherapy for head and neck cancers. In addition, we are a part of the nutrition support team.

We cooperate with other facilities for the establishment of oral care programs for patients with head and neck cancers receiving chemoradiotherapy.

DEPARTMENT OF PEDIATRIC ONCOLOGY

Ako Hosono

Introduction

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

Routine activities

The pediatric outpatients service is open for three days a week, Monday, Wednesday and Friday, to treat newly diagnosed patients, patients who received chemotherapy in the outpatient setting and to provide follow-up treatment to patients who have completed

an intensive treatment course. Also, the care of children receiving palliative treatment is carried out with the Palliative care and Psycho-Oncology group. Daily rounds and a conference are held every morning with the Medical Oncology group, where we hold discussions about patients among various experts. We also join the conference with the Orthopedic Surgery, Thoracic Surgery and Urology Divisions at any time.

Research activities and Clinical trials

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

One clinical trial described below is currently active.

A Phase I trial of immunotherapy using HLA-A2 and A24-restricted glypican-3 peptide vaccine for pediatric tumors.

Table 1. Number of new patients

Benign bone tumors	12
Soft tissue sarcoma	3
Rhabdomyosarcoma	1
Ewing sarcoma	2
Leiomyosarcoma	2
Synovial sarcoma	1
Hepatoblastoma	1

DEPARTMENT OF ANESTHESIOLOGY AND INTENSIVE CARE UNIT

Hiroyuki Yamamoto, Aiko Ooshita, Kazuaki Hiraga, Kei Torigoe

Introduction

The Department of Anesthesiology and Intensive Care Unit (ICU) consists of 4 staff members (3 Japan Society of Anesthesiologists Board Certified Anesthesiologists and a JSA Qualified Anesthesiologist) and 2 or 3 rotating residents. Each year, we provide more than 2,500 anesthesia services in 8 operating rooms and over 1,200 patients are admitted to the ICU. A large number of operations in the Head and Neck Surgery Division and procedures involving a thoracotomy for lung and esophageal cancer are one of the features of this hospital. Accordingly a special anesthesia induction method for difficult airway and use of the one-lung ventilation technique are often necessary for anesthesiologists. Currently, our ICU admits mainly postsurgical patients that have undergone major abdominal, thoracic and complex surgical procedures, as well as patients who have suffered from serious preoperative complications. Increasingly complex procedures are being performed on more seriously ill patients with coronary disease, chronic obstructive pulmonary disease (COPD), neurological disorders and so on. The ICU needs to play a more and more important role in postsurgical care for such patients. The goals of the Department of Anesthesiology and Intensive Care Unit are to provide anesthetic and perioperative care to patients, with their safety being the highest priority.

Routine activities

4 staff members (2 full-time and 2 visiting anesthesiologists), 3 rotating residents and 12 part-time anesthesiologists cover 8 operating rooms. A

preanesthesia case presentation is held every morning to examine the case of the day and discuss the anesthesia problem and strategy for patients with various complications. In 2014 we provided 2,697 anesthesia services (Table 1). Annual number of patients admitted to the ICU was 1,458, and more than 95% of them were postsurgical patients (Table 2).

Education

The Department of Anesthesiology and Intensive Care Unit has no resident. For rotating residents we provide opportunities of epidural anesthesia, one lung ventilation technique for thoracotomy, and difficult airway management including fiberoptic intubation. A Journal club is also held once a week other than everyday morning conference. We support residents who hope to obtain the qualification of anesthesiologist or JSA Qualified Anesthesiologist during rotation periods.

Future prospects

In 2015 one staff anesthesiologist increases and a senior resident belonging to a surgical division is to be assigned to our Department for the study of hemodynamic change during liver resection. With these additional members the increase of 100-150 operations are expected next year. Under the NEXT project a construction plan of new surgical and endoscopic center which has 12 operating rooms has been launched. We are going to be involved in the design of operating rooms.

Table 1. Number of anesthesia cases

Type of Surgery	2010	2011	2012	2013	2014
Head and Neck	515	424	454	423	409
Thoracic	488	466	473	501	520
Esophageal	137	126	182	201	215
Gastric, Hepatobiliary, Pancreatic	542	-	-	-	-
Hepatobiliary and Pancreatic	-	269	231	282	253
Gastric	-	286	308	292	268
Colorectal	491	426	453	479	550
Urology	88	78	107	114	111
Orthopedic	-	-	22	43	34
Breast	297	291	309	325	315
Plastic and Reconstructive	-	-	3	8	20
Others	-	-	-	-	2
Total	2,558	2,366	2,542	2,668	2,697

Table 2. Number of patients admitted to the ICU

	2010	2011	2012	2013	2014
Number of Patients	1,435	1,228	1,412	1,458	1,348

DEPARTMENT OF PALLIATIVE MEDICINE

Hiroya Kinoshita, Yoshihisa Matsumoto, Hideaki Hasuo, Tomofumi Miura, Kazuaki Hiraga, Keita Tagami, Hanako Iwamoto, Yoriko Herai

Introduction

The purpose of our Department is to improve the quality of life in the cancer patients and their family caregivers by management of irritable symptom burden and establishment of a regional palliative care system. Therefore, we provide 3 palliative care services; 1) outpatient clinic, 2) supportive care team and 3) palliative care unit.

Routine activities

1) Outpatient clinic

Patients with or without anti-cancer therapy consult our outpatient clinic for management of their devastating symptoms or support to decide where and how spend their lives. The concept of early palliative care gradually spread, the consultations of patient undergoing anti-cancer therapy have been increasing.

2) Supportive care team

This team consist of physician, psycho-oncologist, nurse, dietician, physiotherapist speech-language-hearing therapist. Our supportive care team performs a multidisciplinary approach for inpatients with various sufferings in the oncology floor.

3) Palliative care unit

Our palliative care unit is Japanese version of acute palliative care unit (APCU). The features of APCU are multidimensional assessment, rapid symptom control and intensive psychosocial care with shorter length of stay and lower death rate than in traditional PCU. Medical social worker greatly contributes to a transition to palliative home care and a transfer to other hospital.

Research activities

The aim of research in our Division is to establish the regional palliative care system and to integrate the early palliative care with oncology. Following researches are conducted;

1. A system construction of counseling-and-support centers and regional palliative care in a disaster stricken area.
2. An application of "Information and Communication Technology" for regional palliative care system.
3. A feasibility study of the integration of early palliative care in metastatic lung cancer.
4. A prospective cohort study about end of life care discussions and informal caregiver's burdens.
5. A registration for Japanese multicenter cohort studies and international multicenter project.

Education

The purpose is to promote understanding about palliative care in cancer patients and their families for residents. Residents can train in home palliative care on request. To spread the knowledge of primary palliative care, we held several workshops for medical staff in the NCCHE and for regional palliative care staff.

Future prospects

Our Department will continue above activities and develop new researches to improve QOL in cancer patients and their family caregivers.

List of papers published in 2014

Journal

1. Morita T, Sato K, Miyashita M, Yamagishi A, Kizawa Y, Shima Y, Kinoshita H, Suzuki S, Shirahige Y, Yamaguchi T, Eguchi K. Does a regional comprehensive palliative care program improve pain in outpatient cancer patients? *Support Care Cancer*, 22:2445-2455, 2014
2. Yamagishi A, Sato K, Miyashita M, Shima Y, Kizawa Y, Umeda M, Kinoshita H, Shirahige Y, Akiyama M, Yamaguchi T, Morita T. Changes in quality of care and quality of life of outpatients with advanced cancer after a regional palliative care intervention program. *J Pain Symptom Manage*, 48:602-610, 2014
3. Imura C, Morita T, Kato M, Akizuki N, Kinoshita H, Shirahige Y, Suzuki S, Takebayashi T, Yoshihara R, Eguchi K. How and why did a regional palliative care program lead to changes in a region? A qualitative analysis of the Japan OPTIM study. *J Pain Symptom Manage*, 47:849-859, 2014
4. Sasahara T, Watakabe A, Aruga E, Fujimoto K, Higashi K, Hisahara K, Hori N, Ikenaga M, Izawa T, Kanai Y, Kinoshita H, Kobayakawa M, Kobayashi K, Kohara H, Namba M, Nozaki-Taguchi N, Osaka I, Saito M, Sekine R, Shinjo T, Suga A, Tokuno Y, Yamamoto R, Yomiya K, Morita T. Assessment of reasons for referral and activities of hospital palliative care teams using a standard format: a multicenter 1000 case description. *J Pain Symptom Manage*, 47:579-587 e576, 2014
5. Miura T, Matsumoto Y, Motonaga S, Hasuo H, Abe K, Kinoshita H. Dyspnea, relative youth and low daily doses of opioids predict increased opioid dosage in the last week of a terminal cancer patient's life. *Jpn J Clin Oncol*, 44:1082-1087, 2014

DEPARTMENT OF PSYCHO-ONCOLOGY SERVICE

Asao Ogawa, Yosio Iwata, Daisuke Fujisawa, Hiroyuki Nobata, Kensuke Higa, Lina Orikabe, Daisuke Fujisawa, Junko Ueda, Natsuki Hori, Rina Kakinuma

Introduction

The Department of Psycho-Oncology (Psycho-Oncology Service), established in July 1996, aims to manage and alleviate emotional distress of cancer patients, their families and the caring staff. The Division, adjunctive with the Psycho-oncology Division of the Research Center for Innovative Oncology, also aims to study the influence of psychosocial issues upon quality of life and survival of cancer patients. Management of elderly patients with cancer, who are frequently comorbid with cognitive impairment or dementia, is another focus of interest.

Routine activities

The Psycho-Oncology Division is composed of 2 attending psychiatrists, 3 clinical psychologists, and 2 psychiatry residents. The clinical activities

include psychiatric consultation, involving comprehensive assessment and addressing of psychiatric problems of cancer patients. The patients are either self-referred or referred by their oncologists in charge. The consultation data are shown in the Table. Psychiatric diagnosis is based on the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria. Consultation data also includes individuals who are family members of cancer patients.

A conference with the Supportive Care Team is held on Wednesdays, and a multicenter joint clinical teleconference involving 6 cancer center hospitals and 3 university hospitals is held on Thursdays. In 2014, the Supportive Care Center was developed. This center is the multi professional attention to the individual's overall physical, psychosocial, and social needs, cooperate with the Department of Psycho-Oncology.

Table 1. Psychiatric consultation data (n=973; January-December, 2014)

Section		N (%)
Age	Mean ± SD (median, range) (yr)	64.4±12.6 (67,15 ~ 92)
Gender	(male/female)	599 (61.6%) / 374 (38.4%)
Inpatient / Outpatient		685 (70.4%)/288 (29.6%)
Cancer patient / Family member		939 (96.5%) / 34 (3.5%)
Cancer site	Head and Neck	192 (19.7%)
	Lung	178 (18.3%)
	esophagus	99 (10.2%)
Stage	I/II/III/IV/Recurrent	82 (8.4%) / 70 (7.7%) / 120 (12.3%) / 410 (42.1%) / 143 (14.7%) /
PS	0/1, 2/3, 4	288 (29.6%) / 516 (53.0%) / 16 (17.4%)
Psychiatric diagnosis	Delirium	247 (25.4%)
	Adjustment disorders	169 (17.4%)
	Major depression	26 (2.7%)
	Dementia	90 (9.2%)
	No diagnosis	139 (14.3%)

List of papers published in 2014

Journal

1. Shibayama O, Yoshiuchi K, Inagaki M, Matsuoka Y, Yoshikawa E, Sugawara Y, Akechi T, Wada N, Imoto S, Murakami K, Ogawa A, Akabayashi A, Uchitomi Y. Association between adjuvant regional radiotherapy and cognitive function in breast cancer patients treated with conservation therapy. *Cancer Med*, 3:702-709, 2014
2. Nakanotani T, Akechi T, Takayama T, Karato A, Kikuuchi Y, Okamoto N, Katayama K, Yokoo M, Ogawa A. Characteristics of elderly cancer patients' concerns and their quality of life in Japan: a Web-based survey. *Jpn J Clin Oncol*, 44:448-455, 2014
3. Yokoo M, Akechi T, Takayama T, Karato A, Kikuuchi Y, Okamoto N, Katayama K, Nakanotani T, Ogawa A. Comprehensive assessment of cancer patients' concerns and the association with quality of life. *Jpn J Clin Oncol*, 44:670-676, 2014

SUPPORTIVE CARE TEAM

Hiroya Kinoshita, Yoshihisa Matsumoto, Hideaki Hasuo, Tomofumi Miura, Asao Ogawa, Yoshio Iwata, Naoko Kobayashi, Chiyuki Sasaki, Shinya Motonaga, Jyunya Ueno, Yoshie Iino, Kazuaki Hiraga, Daisuke Fujisawa, Hiroyuki Nobata, Keita Tagami, Hanako Iwamoto, Kensuke Higa, Lina Oriabe, Kentaro Abe, Junko Ueda, Natsuki Hori, Rina Kakinuma, Hideo Uesugi, Kumi Nakamura, Kentaro Abe, Taichi Watanabe, Hatoe Sakamoto

Introduction

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

Routine activities

The SCT is an interdisciplinary team composed of palliative care physicians, psychiatrists,

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

Clinical trials

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

Table 1. Supportive Care Team consultation data (n =929; January-December, 2014)

		N (%)
Age	Mean ± SD (range) (yr) (male/female)	64.3±12.4 599 (61.6%) / 374 (38.4%)
Gender	(male/female)	612 (66%) / 317 (34%)
Service	Palliative care/ Psycho-oncology	244 / 685
Performance status	0/ 1/ 2/ 3/ 4	127 (14%) / 246 (27%) / 247 (27%) / 214 (23%) / 95 (10%)
Physical symptoms (moderate - severe)	Pain	452 (49%)
	Appetite loss	411 (44%)
	Fatigue	518 (58%)
	Respiratory distress	238 (26%)
Psychiatric diagnosis (primary diagnosis)	Delirium	234 (25%)
	Adjustment disorders	81 (9%)
	Dementia	61 (7%)
	Major Depressive Disorder	9(1%)
Outcome	Discharge/ Hospital transfer	812 (87%) / 114 (12%)

List of papers published in 2014

Journal

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

DEPARTMENT OF DIAGNOSTIC RADIOLOGY

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

Introduction

The Department of Diagnostic Radiology is committed to improving health through excellence in image-oriented patient care and research. Our Division performs more than 94,000 inpatient and outpatient procedures annually. The Division also conducts clinical scientific research as well as basic scientific studies, with the results translated directly into better patient care.

Routine activities

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

This Department has 7 consulting radiologists and 22 technologists. As part of our routine activities, every effort is made to produce an integrated report covering almost all examinations, such as MMG, contrast radiological procedures, CT, MRI, RI, PET, angiography and IVR, mainly transarterial chemoembolization (TACE).

The number of cases examined in 2014 is shown in the Table below. Several conferences are routinely held at our division, including pre-and

postoperative conferences.

Research activities

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

(1) Development of new Nuclear Medicine tracers

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

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

(2) Development of new CT/MRI technology

For evaluation of head and neck cancer, dual-energy CT images have revealed tumor invasion within the cartilage as red color-coded areas of the iodine distribution, resulting in contrast enhancement between the tumor and non-

calcified cartilage. Preliminary evidence suggests that dual-energy CT can improve interobserver reproducibility and diagnostic performance for the evaluation of laryngeal cartilage invasion and deserve the assessment of extralaryngeal spread in laryngeal and hypopharyngeal cancer patients.

In 320-row area-detector CT, newly-developed single-energy metal artifact reduction (SEMAR) algorithm applied to images acquired on a 320-MDCT volume scanner reduces image artifacts from dental metal without increasing the radiation dose. Metal artifacts due to dental restorations considerably deteriorate the quality of computed tomography (CT) images of the head and neck region. Our study has been performed to clarify this influence. A novel phantom comprising the jaws, gingiva, and replaceable teeth with and without amalgam restorations were used. Twelve models with single to multiple restorations based on the tooth decay rate were scanned using a 320 detector row CT scanner. The results of this preliminary study have suggested that the location of dental amalgam restorations has a greater influence on

the SEMAR effect compared with the number of restorations, with the presence of multiple restorations in the same axial plane being the most important factor.

In 3-Tesla MR images, mandibular cross-sectional multiplanar reconstruction (CS-MPR) using 3D sequences are applied for the preoperative evaluation of mandibular bone marrow invasion in patients with oral carcinomas. Diagnosis on Mandibular CS-MPR images showed significantly higher specificities with no compromise to the sensitivity for bone marrow invasion. High diagnostic performance could be achieved because Mandibular CS-MPR images taken with 3T-MRI visualized the longitudinal section of the mandible, delineating the relationship between the tumor lesion, cortical bone and mandibular marrow, thus enabling verification of the presence/absence of mandibular invasion and detailed assessment of the continuity with the main tumor. This is of the utmost importance for the selection of appropriate surgical techniques.

Table 1. Number of cases examined

	2010	2011	2012	2013	2014
Plain X-ray examination	34,330	35,032	39,128	38,722	39,802
Mammography (MMG)	2,595	2,434	2,380	2,354	2,664
Fluoroscopic Imaging (GI-series, etc.)	3,478	3,903	4,029	4,628	5,358
CT	21,128	21,967	24,101	28,963	34,918
MRI	5,830	5,708	5,619	5,657	6,546
RI	1,676	1,582	1,586	1,363	1,623
PET	2,048	2,239	2,284	2,208	2,695
Angiography	728	656	742	511	800
Total	71,813	73,521	79,869	84,406	94,406

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Journal

1. Yanagawa M, Tanaka Y, Leung AN, Morii E, Kusumoto M, Watanabe S, Watanabe H, Inoue M, Okumura M, Gyobu T, Ueda K, Honda O, Sumikawa H, Johkoh T, Tomiyama N. Prognostic importance of volumetric measurements in stage I lung adenocarcinoma. *Radiology*, 272:557-567, 2014
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12. Kuno H, Onaya H. A case of oropharyngeal squamous cell carcinoma with nasopharyngeal extension via the levator veli palatini muscle. *Jpn J Clin Oncol*, 44:195, 2014

DEPARTMENT OF RADIATION ONCOLOGY

Tetsuo Akimoto, Naoki Nakamura, Sadatomo Zenda, Masakatsu Onozawa, Satoko Arahira, Masamichi Toshima, Atsushi Motegi, Yasuhiro Hirano

Introduction

Radiotherapy (RT) plays an essential role in the management of cancer patients. It is used as (1) a curative treatment for many patients with loco-regional localized malignant disease, (2) integrated therapy combined with chemotherapy and/or surgery, and (3) palliative treatment for patients in whom curative treatment is not a treatment option. In radiotherapeutic approaches, the radiation dose to the loco-regional tumor must be as high as possible, while dose to the surrounding normal tissues should be kept as low as possible in order to maintain severity of radiation-related complications within acceptable level.

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

Routine activities

At present, the staff of the Radiation Oncology Division is consisted from 7 consultant physicians (radiation oncologist), 19 radiation technologists, 4 medical physicists, 1 nurse, and 1 clerk. We have more than 1,000 new cases for conventional RT and 300 or more new patients for proton beam therapy in every year, and quality assurances of both conventional RT and PBT are performed by medical physicists and radiation technologists, and the conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. RT and PBT are routinely based on three-dimensional radiation therapy planning and PBT using RT-dedicated multi-

detector-row helical computed tomography (CT) scanning in order to confirm precise radiation dose to the targeted tumors. Respiratory-gating has been applied especially in radiotherapeutic management for patients with lung, esophagus and liver cancers.

Selection of treatment approaches is determined through clinical conferences between radiation oncologist, surgical oncologists and medical oncologists. More than 20 clinical trials involving RT as the sole or a combined treatment modalities for various cancers are in progress.

The Section is responsible for conventional (photon-electron) RT that is consisted from 4 linear accelerators, a CT simulator, 4 treatment planning computer workstations, and other important devices. IMRT and IGRT have been routinely applied for head and neck cancer and prostate cancer. The Section is also responsible for PBT that is composed of 7 operating staff members and 1 technician for fabricating the compensator and aperture; they are sent from manufacturing companies and work in collaboration with the other staff members of the Division. PBT is consisted from 2 treatment rooms and both rooms are routinely used for rotational gantry treatment. The Division ensures quality assurance and regular maintenance of the PBT machines for precise dose delivery and safe treatment.

Research activities

In the Radiation Oncology Division, the following research activities are under progress.

- 1) Establishment of optimal combined approaches including RT and chemotherapy for locally advanced head and neck cancer, non-small cell lung cancer and esophageal cancer, and so on.
- 2) Establishment of clinical usefulness of IMRT for head and neck cancer, localized prostate cancer and cervical esophageal cancer.
- 3) Hypofractionated IMRT for localized prostate cancer.

- 4) Hypofractionated PBT for localized prostate cancer.
- 5) Evaluation of feasibility of PBT combined with chemotherapy for inoperable locally advanced non-small cell lung cancer and locally advanced esophageal cancer.
- 6) Evaluation of long-term complications after PBT for pediatric malignancies.
- 7) The role of gene polymorphism in development of acute and late radiation-related complications.
- 8) Exploration of biomarker for head and neck cancer.
- 9) Radiobiological investigation of cellular response to radiation and proton beam.

Clinical trials

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

- 1) JCOG0701: Accelerated fractionation vs. conventional fractionation radiation therapy for glottic cancer of T1-2N0M0 Phase III study.
- 2) JCOG0701-A1: Evaluation of single-nucleotide polymorphisms (SNPs) in development of acute and late complications after accelerated fractionation and/or conventional fractionation radiation therapy for glottic cancer of T1-2N0M0.
- 3) JCOG1015: A phase II study of intensity modulated radiation therapy (IMRT) with chemotherapy for loco-regionally advanced nasopharyngeal cancer (NPC).
- 4) Phase II study of PBT for malignant melanoma of nasal cavity.
- 5) Phase II trial of concurrent chemoradiotherapy with 5-FU plus cisplatin for resectable squamous cell carcinoma of cervical esophagus.
- 6) JROSG Phase II trial of IMRT with concurrent chemoradiotherapy for resectable squamous cell carcinoma of cervical esophagus.
- 7) JCOG1208: A non-randomized confirmatory study of intensity modulated radiation therapy (IMRT) for T1-2N0-1M0 oropharyngeal cancer.
- 8) JCOG1008: Phase II/III Trial of Postoperative Chemoradiotherapy Comparing 3-Weekly Cisplatin with Weekly Cisplatin in High-risk Patients with Squamous Cell Carcinoma of Head and Neck

Table 1. The changes in the number of patients treated with RT

Number of patients treated with radiation therapy during 2010-2014

	2010	2011	2012	2013	2014
New patients	1,039	1,074	1,058	1,148	1,082
IMRT	98	122	218	243	258

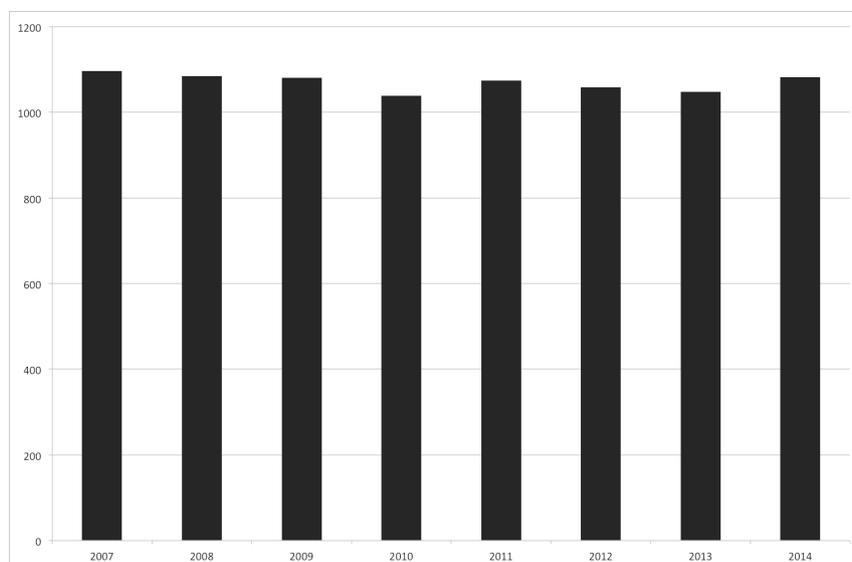


Figure 1.

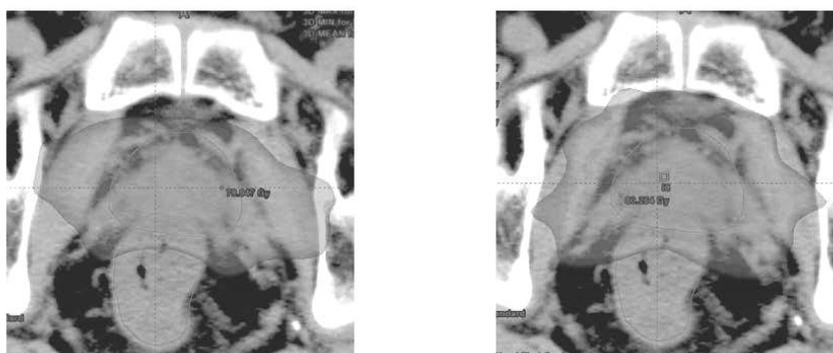


Figure 2.

List of papers published in 2014

Journal

1. Maebayashi T, Ishikawa H, Yorozu A, Yoshida D, Katoh H, Nemoto K, Ishihara S, Takemoto S, Ishibashi N, Tokumaru S, Akimoto T; Working Subgroup of Urological Cancers in Japanese Radiation Oncology Study Group. Patterns of Practice in the Radiation Therapy for Bladder Cancer: Survey of the Japanese Radiation Oncology Study Group (JROSG). *Jpn J Clin Oncol* 44(11): 1109-15, 2014.
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DEPARTMENT OF PATHOLOGY AND CLINICAL LABORATORIES

Atsushi Ochiai, Takeshi Kuwata, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Chisako Yamauchi, Eiiichi Yoshikawa, Naoki Maezawa, Masahiro Inoue, Masahiro Karibe, Seiji Iwasaki, Miki Gotou, Masaki Takeda, Satoru Sunohara, Hiromi Kimura, Hiroyuki Shimada, Yasuharu Hashimoto, Yukihiko Okano, Akiko Yamada, Mari Hisano, Shinya Yanagi, Takuya Yamaguchi, Takuya Aiba, Keiko Nakai, Ayumi Setsuta, Mayumi Motohashi, Miwa Kanehira, Aya Koike, Sayuri Shibayama, Yasuko Yoshihara, Kazumi Yamaguchi, Rie Taniguchi, Izumi Suzuki, Eriko Iwamoto, Michiteru Yamagishi, Nagisa Bouno, Kasumi Tamura, Tomomi Sekine, Noriko Motonon, Yuki Soeda, Rie Kuroiwa, Masayuki Ito, Iida Michiko, Chizuru Asanuma, Akiko Matsumoto, Megumi Michikawa, Emiko Yoshikawa, Yoshiko Ohtake, Miwa Yamada, Megumi Yamaguchi, Tomoko Hirasawa

Introduction

The Department of Pathology and Clinical Laboratories (DPCL) has 2 divisions; the Pathology Division (PD) and the Clinical Laboratory Division (CLD). Both Divisions play a fundamental role in routine hospital service and support research activities at the National Cancer Center Hospital East (NCCHE).

The DPCL received ISO15189:2007 accreditation in 2012, and successfully transit to the newest version (ISO15189:2012) in 2014, ensuring quality control and quality assurance of the testing, including the one for clinical trials, performed in the departments.

Routine activities

Primarily of routine activities at the PD is surgical pathology. The number of samples examined at the Department in 2014 is listed in Table1.

The Clinical Laboratory Division consists of 7 sections; i) General laboratory medicine, ii) Hematology, iii) Biochemistry/serology, iv) Physiology, v) Bacteriology ,vi) Blood transfusion and vii) Supporting laboratory testing in clinical studies. Numbers of testing performed in each division are listed in Table 2 and 3. The total number of testing performed in the DPCL in 2014 increased 11.5% from the previous year; including 64.3% and 11.3% increase in the Serology and Bacteriology Sections, respectively.

Research activities

All of the pathologists were involved in research

activities at the RCIO. All the technologists working at the Department were also highly motivated to develop advanced diagnostic technology and some results were presented in several meetings.

Clinical trials

Practically the CLD participated in all of clinical trials operated at the NCCHE by providing laboratory data. The section for supporting laboratory testing in clinical studies has been transferred to the DPCL since Jun, 2014. The section, coordinated with pathology and physiology sections, reinforces quality control and quality assurance for clinical testing performed in clinical trials at the NCCHE.

Education

Clinicopathological conferences were held regularly with each clinical department/section. In the PD, conference-style training sessions were open weekly for the residents.

Future prospects

Pathological diagnosis and laboratory testing play fundamental role not just in routine hospital works but also in medical researches. As an ISO15189-certified clinical laboratory, the DPCL will be continuously involved in investing new diagnostic technologies, developing new drugs and conducting translational /clinical researches in the NCCHE with our slogan “all the activities for cancer patients.”

Table 1. Number of pathology and cytology samples examined at Pathology Division in 2014

Department	Biospy	Surgical	Cytology	Autopsy
Digestive Endoscopy	5,036	1	2	0
Gastrointestinal Oncology	144	4	75	1
Breast Surgery	482	327	117	0
Head and Neck Surgery	604	362	404	0
Thoracic Surgery	453	488	558	1
Thoracic Oncology	651	3	817	0
Hematology and medical oncology	450	3	132	1
Hepatobiliary and Pancreatic Oncology	443	1	407	1
Urology	251	99	817	0
Upper Abdominal Surgery	181	453	190	0
Radiation Oncology	147	0	4	0
Lower Abdominal Surgery	88	352	40	0
Orthopedics	51	24	6	0
Ambulant Treatment Center	0	0	0	0
Esophageal Surgery	7	197	14	0
Head and Neck Oncology	23	0	8	0
Obstetrics and Gynecology	33	0	221	0
Dental division	12	0	0	0
Anesthesiology	0	0	0	0
Dermatology	19	0	0	0
Plastic Surgery	6	4	4	0
Palliative medicine	2	0	5	0
Others	16	0	5	0
Total	9,099	2,318	3,826	4

Table 2. Number of laboratory tests examined at Clinical Laboratory Division in 2013&2014

	2013	2014
General laboratory medicine	47,980	48,199
Hematology	276,610	302,752
Biochemistry	1,834,169	1,970,515
Serology	164,382	270,112
Blood transfusion	10,720	11,438
Bacteriology	26,870	29,917
Physiology	22,730	24,703
total	2,383,461	2,657,636

Table 3. Number of case and samples prepared in Clinical Laboratory Division for clinical trials in 2014

	Cases	Samples
General Laboratory test	3,733	6,336
ECG	867	1,128
Pathology	156	996

RARE CANCER CENTER

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

Introduction

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

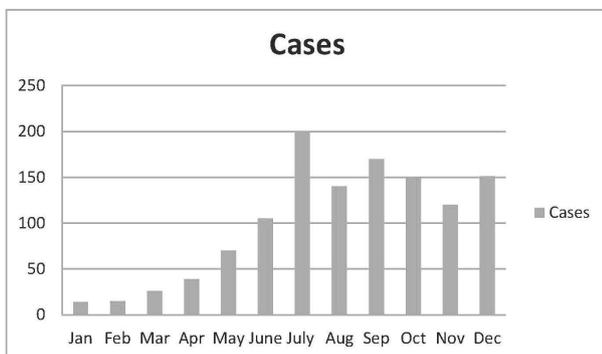


Figure 1. The Number of telephone call to Rare Cancer Hotline in 2014

Routine activities

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

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

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

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

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

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

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Journal

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DEPARTMENT OF RADIOLOGY

Yoshihisa Muramatsu, Mitsuhiro Yoshida, Yutaka Ohnuma, Kazuyoshi Yamano, Kazutoshi Yokoyama, Koichi Nemoto, Takaki Ariji, Kuniiji Naoi, Keisuke Takahashi, Naotaka Yamazawa, Satoe Kito, Hajime Ohyoshi, Kaoru Ikeno, Tsunemichi Akita, Keiichi Nomura, Hiroyuki Shitara, Daiki Kumagai, Shogo Amano, Fuminori Shimizu, Noriko Nishikawa, Asami Tanaka, Ryuzo Uehara, Tatsuya Mogaki, Hiromi Baba, Shota Hosokawa, Kaori Yanagisawa, Syun Aoyagi, Yukihiro Matsukawa, Yuto Iwabuchi, Yuki Ito, Toshiyuki Shibuya, Kazuto Kano, Hikaru Sugahara, Hiroyuki Asai, Fumiya Tanaka, Toshiya Rachi, Daiki Kanke, Taku Tochinai, Yohei Takeda, Makoto Gohdo, Tomohiro Ohishi, Hiroshi Tsuruoka, Hikari Inagawa

Routine activities and research activities

The number of radiographic examination and radiation therapy in 2014 was increasing, as it shown in Table 1.

Related to radiological diagnosis; inquiry, injection and contrast radiography assistance by interventional radiology specialized nurses have been launched, and a regulation of peripheral intravenous injection was stipulated with the cooperation of Department of Nursing. Thus enabled to improve the percentage of radiographic image interpretation by radiologists, providing them more time spending on image reading. Certified radiological technologists participated in primary image reading on low-dose lung cancer CT screening in cooperation with certified radiologists. A sequence which visualizes tumors and blood vessels on plain head and neck MRI examinations without contrast media has been designed and clinically applied. Taking part in clinical trial on a cancer pain palliative using alpha-emitting nuclide which is Phase III study in progress.

Number of intensity-modulated radiation therapy (IMRT), which has lower risk of side effects by irradiation, was applied in photon radiation therapy. IMRT requires complex treatment planning and verification, hence it takes 1 to 2 weeks before launching a treatment in general, although, according to coordination between each staff and reinforcing the educational system for long years, have been achieved less than 3 days for preparation. Furthermore, image guided radiation therapy which compensates millimeter measures of irradiation positions has been applied to the most of the cases. When it comes to proton therapy, patch field irradiation has been applied that

enabled to treat over 20 centimeters size of nidus. Also, scanning irradiation which enables much more complicated dose distribution is heading toward to its final phase of the practical use.

Clinical trials

Participating in Ishigaki section (Rikuta Ishigaki: the Ministry of Education, Culture, Sports, Science and Technology, Japan and Kyoto College of Medical Science.) A software managing dose of radiological examinations is in under development. Related to this, a research on CT radiation dose simulation has been proceeded. These productions have been reported in international conferences, domestic conferences and published in academic journals.

Education

For the purpose of learning National Cancer Center Hospital East's particular radiation technology, technics have been documented by each type of the cancer classification. By discussing with other staffs belong to different modalities, it is expected to develop better understanding between each staff and to improve clinical technique, in the process of documentation.

Owing to the numbers of MRI accidents, such as projectile related or carrying in ferromagnetic objects, were reported recent years, a magnetic field experience program was carried out with new employees to be targets.

4 of the radiological technologists learned in master's course of graduate schools in this year,

and 2 of them received the master's degree. In addition to that, accepted and educated 12 trainees from 3 universities in radiological technology.

Future prospects

Therefore the Department of Radiology consists of multidisciplinary staffs, ensuring

medical safety with close cooperation and effective management are work in progress. Refining clinical trials, research activities and education, the Department of Radiology will continue striving to provide benefit to other clinical departments in the next year.

Table 1. Transition of number of radiological examination and radiation therapy by year.

	2010	2011	2012	2013	2014
Plain X-ray examination	34,330	35,032	39,128	38,722	39,802
Mammography (MMG)	2,595	2,434	2,380	2,354	2,664
"Fluoroscopic Imaging (GI-series, etc.)"	3,478	3,903	4,029	4,628	5,358
CT	21,128	21,967	24,101	28,963	34,918
MRI	5,830	5,708	5,619	5,657	6,546
RI (Scintiscan)	1,676	1,582	1,586	1,363	1,623
PET	2,048	2,239	2,284	2,208	2,695
Angiography	728	656	742	511	800
Radiation therapy	15,120	16,798	19,254	32,453	29,524
Proton therapy	2,888	4,941	5,910	11,460	9,513
Total	71,813	73,521	79,869	84,406	94,406

CLINICAL TRIAL MANAGEMENT OFFICE

Koichi Goto, Yumiko Uchiyama

Introduction

The Clinical Trial Management Office (CTMO) aims to promote clinical trials on unapproved drugs and medical devices, with the goal of allowing patients to receive the benefits arising from life science research as quickly as possible. The mission of the CTMO is to facilitate the conduct of quality clinical trials at the National Cancer Center Hospital East (NCCHE), especially those which are all conducted as a sponsored initiated trial, to achieve registration. The CTMO will also assist investigators with infrastructure support, including Institutional Review Board (IRB) and initial regulatory guidance. A total of 30 staff members support the CTMO.

All staff work with investigators, co-medicals (including out/inpatient divisions, wards for clinical research, the nursing division and pharmacy), they also collaborate with pharmaceutical personnel and regulatory authorities, and they always contribute to “Chicken” based on best practice.

Routine activities

The CTMO function forms the key relationship between the study investigators, sponsor/contract research organization (CRO), subjects and institutional organizations including the IRB, and the clinical trials office. Our role is critical in helping to ensure that assigned studies are conducted in accordance with human subjects’ federal regulations/guidelines regarding human subjects, and meet good clinical practice (GCP)

standards. The number of the industry-sponsored registration trials is increasing year by year, and the increase in the rate of phase 1 trial is particularly striking. We supported 176 registration-directed clinical trials including 11 phase1 trials in 2014 (Table 1). These early clinical trials need more complicated and specific management rather than conventional trials. With the increasing number of phase1 trials as previously described, the supporting area covered by the CRCs will expand to encompass registration trials. All members of the CTMO will work together to contribute to reinforcing the clinical research capabilities and to making the CTMO a valuable unit for all members of our hospital. An operational committee is formed and meets with other core members including primary investigations from the clinical laboratory division, pharmacy division and nurse division, and the clinical study support office for the purpose of proper management of trials. Furthermore, we will contribute to the worldwide network system for phase 1 trials to establish the acceleration of the preclinical and clinical development of investigational anti-cancer agents.

Table 1. Supported trials in clinical trial management office in 2014

Phase	New (since 2014)	Ongoing
I	11	60
I/II	2	7
II	5	37
II/III	1	2
III	15	62
POS	2	8
Total	36	176

POS: post marketing study

SUPPORTIVE CARE CENTER

Koichi Goto, Miho Kurihara, Hiroya Kinoshita, Hatoe Sakamoto

Introduction

Our Department was established as an organization to provide, in addition to conventional consultation support, positive and comprehensive support from a variety of professional occupations for actual or potential, physical, mental, and social problems that cancer patients and their families have to confront. The main activities are establishment of a continuous support system for the patients' families, enhancement of a home care support system, and promotion of community cooperation for establishing early palliative care.

Routine activities

1. Consultation support/community medicine cooperation

In 2014, we received 5,115 new consultations. Among them, 3,849 (75.2%) were from patients who had received medical treatment from our hospital or their families, and 1,266 (24.8%) were from patients who had received medical treatment at other medical institutions or their families, or local medical welfare workers (Table 1).

In the same year, we started new services such as an educational program for patients with esophageal cancer, a cancer patient support group for children, and a program for providing cosmetic camouflage. We provide the new services taking

into account the difficulties faced by the patients.

As part of the activities for acquiring new patients, we have started to collect information and to adjust schedules of the participants in case conferences held in communities in order to build face-to-face relationships between the physicians of our hospital and local physicians.

2. Continuous nursing support

For outpatients, we provide continuous nursing support. In fiscal year 2014, we provided continuous support and consultation services to about 3,300 patients, mainly in the areas of thoracic and gastrointestinal oncology.

In order to promote acquisition of self-care by inpatients and/or their families, as well as to secure appropriate social resources, we provide medical and social supports with a view to home care even from an early timing of hospitalization. We carried out a screening program about 1,700 patients who needed any social support and provided them the appropriate support.

In order to sustain seamless medical and social supports, we strengthen cooperation with home-visit nursing stations to deal with the problems faced by home care patients and/or their families, mainly related to medical management. In fiscal year 2014, we carried out interventions such as approximately 980 phone-calls and face-to-face consultations.

Table 1. Details of the consultation support provided in 2014

	Number	%
New consultation	5,115	
Total number	16,495	
Purpose of new support request		
Support for nursing hospital selection	3,036	59.4
Consultation about treatment and diagnosis	570	11.1
Consultation about social problems	565	11.0
Consultation about physical symptoms	116	2.3
Consultation for the caregiver	65	1.3
Mental problems	42	0.8
Others	721	14.1
Responsible hospital		
Our hospital	3,849	75.2
Other hospitals	1,117	21.8
Others (no treatment, etc.)	149	2.9
Treatment state		
Before the diagnosis	201	3.9
Before the first treatment	1,125	22.0
During chemotherapy	1,356	26.5
After treatment/under follow-up	840	16.4
Only palliative care	1,352	26.4
Dead (Bereaved family)	17	0.3
Others	224	4.4

OFFICE OF CANCER REGISTRY

Hironobu Ohmatsu, Takashi Kojima, Tokiko Inagaki, Yumi Ishii, Chie Ogura, Maiko Miura, Yayoi Ohtsuka

Introduction

In September 2014, the "Health Information Management Office" was separated into the Medical Information Management Office and the Office of Cancer Registry. The Office of Cancer Registry is a department for executing a hospital-based cancer registry.

Routine activities

Diagnostic cases registered in 2013 in the hospital cancer registry (the first visit of cancer

patients diagnosed from January to December in our hospital) were 6,039 (of which, an initial treatment conducted in our hospital: 3,923 cases: in our hospital diagnosis only: 161 cases; after the start of treatment in another hospital: 985 cases; and diagnosis and treatment in another hospital (including a second opinion): 970 cases). The number of new registrations shows that the number of female patients has been consistently less with time than male patients due to uneven situations by department, but the number of diagnosis cases in our hospital has increased steadily since 2010 (see Table 1).

Table 1. The number of cancer registries of the NCCH-East

year	male	female	Total
2000	3,054	1,625	4,679
2011	3,145	1,733	4,878
2012	3,435	1,749	5,184
2013	3,996	2,043	6,039

MEDICAL INFORMATION MANAGEMENT OFFICE

Hironobu Ohmatsu, Tokiko Inagaki, Setsuko Mori

Introduction

In September 2014, the "Health Information Management Office" was separated into the Medical Information Management Office and the Office of Cancer Registry. The Medical Information Management Office is a department for managing the medical records of hospital by professional medical information management officers.

Routine activities

- Auditing Discharge Summary (quantitative inspection)
Data on discharge summaries should be entered by attending physician. We inspected and

checked the summaries and, where required, gave some advice for correct input.

- Maintenance of disease codes based on ICD-10
- Analysis of medical contents on DPC (Diagnostic Procedure Combination) and recommendation for efficiency.

Future prospects

Approved discharge summaries within 2 weeks after patient's discharge should be held over 95%.

Table 1. Submitting rate of discharge summary

2012	2013	2014
79%	81%	97%

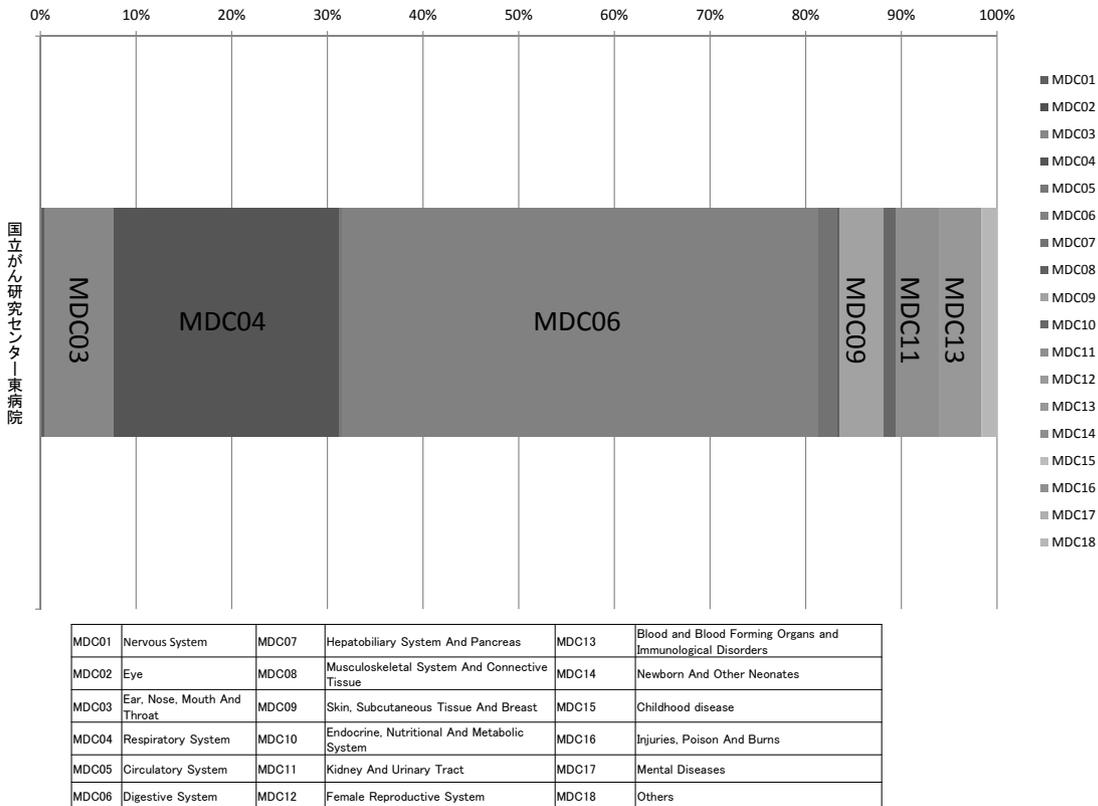


Figure 1. Ratio of Major Diagnostic Category in our Hospital

DEPARTMENT OF PHARMACY

Shinichiro Saito, Kunio Takahashi, Yasuhiko Ichida, Tomoyuki Akimoto, Reiko Matsui, Hisanaga Nomura, Yasuaki Ryushima, Naoko Yoshino, Minako Yoshida, Yoshiki Kojima, Daisuke Kanou, Yosuke Maki, Nobuo Mochizuki, Kenji Kawasumi, Tomoka Okano, Shinya Motonaga, Ryoko Udagawa, Hiroko Ouchi, Tomoko Morita, Mai Itagaki, Shinya Suzuki, Takeshi Koike, Misaki Kobayashi, Motoko Kaneko, Akira Shinohara, Asuka Iwamoto, Akihito Kibune, Sonoko Kobayashi

Introduction

The main objectives of the Department of Pharmacy are: (1) To promote clinical studies to create new evidence-based data; (2) To provide chemotherapy based on the most updated evidence-based data; and (3) To pursue patient-centered pharmaceutical care.

Our residents' training program started in 2006. In 2014, 8 residents joined our department. Presently, we have a total of 21 residents. In addition, our department has accepted 4 trainees from other institutions for our oncology pharmacist training programs. Through 2014, 3 terms of the training courses, we have educated 8 pharmacy students and 2 advanced-training pharmacy students.

The Department of Pharmacy provides various important services: controlling inventory; dispensing medications; preparing i.v. solutions for chemotherapy, which include the aseptic mixing of antineoplastic agents; collecting and providing drug information; managing therapeutic drug monitoring; checking treatment regimens for each patient's chemotherapy; and providing pharmaceutical management and counseling.

Our Department reviews the drugs taken by patients before and during their hospitalization. In inpatient care, the Department assigns pharmacists to provide medication counseling and drug information for healthcare providers and patients, to pursue effective pharmaceutical care. In outpatient care, the Department provides a

pharmacy outpatient service in which pharmacists check patients for adverse reactions and doses of antineoplastic agents, especially in the case of oral anticancer medications. We then assess the necessity of supportive-care medications and suggest them to physicians. The pharmacy outpatient service also reviews the drugs taken by all patients to evaluate when patients have to stop their anticoagulants before their operation or when they have to stop to take metformin before examinations with iodinated-contrast material. Pharmacists are on duty at the Outpatient Chemotherapy Center as dedicated staff members. The pharmacists provide the Chemotherapy Hotline Service, which is a direct line for our outpatients who have any problems concerning their chemotherapy treatment. In the Outpatient Chemotherapy Center, pharmacists are always available to provide drug information for healthcare providers and patients. We also manage investigational drugs.

New developments

In the research activities, we launched the Clinical Pharmacokinetics Unit, and the unit has analyzed pharmacokinetics data in clinical studies. In the education, we have started 2-year chief pharmacy resident program. This year, one pharmacist was selected as a chief resident pharmacist in the department.

Table 1. Pharmacy Achievement

	2010	2011	2012	2013	2014
Chemotherapy hotline service	980	1,468	1,665	2,087	2,258
Pharmacy outpatient service	479	738	1,782	2,375	3,493

List of papers published in 2014

Journal

1. Suzuki S, Enokida T, Kobayashi T, Yajima Y, Ishiki H, Izumi K, Endo K, Tahara M. Evaluation of the impact of a flow-chart-type leaflet for cancer inpatients. *SAGE Open Medicine*, 2:2014

DEPARTMENT OF NURSING

Chie Asanuma

Introduction

The Department of Nursing promoted several actions such as taking part in the hospital's administration through collaboration with departments concerned, preparation of providing system of medical and nursing service, improvement of routine activities of staff, Team health care, public health cooperation, and human resource development.

We could prepare a new framework of outpatient system in the new building constructed in 2004 through reorganization of outpatient booth including emergency room and reallocation of staff, and it contributed to operate outpatient services more safely and effectively.

The 13th Open Nursing Seminar "A delirium Care" was took place with 102 participants, and we also managed several training programs such as (1) a delirium Care Assessment course for palliative care nurse team, (2) communication skill training course for leader nurse (3) a delirium care program training for leader nurse of other institutions. In an educational course for certification of palliative care nurses opened in 2013, 12 attendees were completed of the course, and 11 of them were passed in a certification exam authorized by the Japan Nursing Association. The course was opened with 18 new participants in July 2014. In the certified expert nurse course in the hospital for intravenous anticancer drug delivery, 34 nurses were certified, and a framework of new training "intravenous radiological examination" was established.

While the average hospitalization term was shortened from November 2014, the number of outpatients has been increasing, so we need to work on functional development of the supportive care center and strategic collaboration system with regional institutions in order to promote "Regional care" which is provided home care continuously for outpatient after they leave hospital, and we

also promote increase of the number of inpatients and new patients, and it has been planned to be expanded and advanced at the clinical research and medical treatment fields in the National Cancer Center Hospital East, so we try to prepare appropriate staff allocation, to develop of nursing and research skills, and to manage educational training for human resource development.

Stable management of institution is indispensable for realization of our mission, so we also take part in the hospital's administration in order to implement strategic hospital management.

Routine activities

In 2014, the number of nurses newly employed was doubled and the ratio of separated nurse among the current 370 nurses was 8.1 % (13.8% in 2013) through promotion of recruitment and improvement of routine activities and it has been continued to strengthen nursing system.

The number of patients has been increasing on an annual basis. In 2014, the number of outpatients per day was 995.7 while that of impatient was 382.4. The average hospitalization term was 13.4 days and the occupancy rate of bed was 90.0%. The number of operations conducted per day was 12.0. The number of chemotherapy treatments in the Medical Treatment Center per day was 115. The number of consultations for support of decision making of patient has been increasing dramatically.

We gave 43 presentations at academic conferences in 2014 including one at an international conference. Increase in the number of them were contributed by support system by expert nurse and certified expert nurse and financial back up from the hospital and nursing association. The number of contributions to journal was 17 and of 145 expert nurses and certified expert nurses were dispatched as a lecturer.

CERTIFIED NURSE CURRICULUM

Asuko Sekimoto, Yuko Tanaka

The educational program for certified palliative care nurse in the NCCHE

The certified nurse course of palliative care was prepared and organized in the National Cancer Center Hospital East (NCCHE) in July 2012, and it was accredited by the Japanese Nursing Association (JNA) on Dec. 21, 2012. The first-year program was launched with 12 applicant nurses in July 2013. All trainees had successfully completed the required whole program, and 11 applicant nurses passing the credentialing examination have been certified by JNA. In the second year, the course was started with 18 applicant nurses out of 22 passing the admission test of the NCCHE, and all 18 nurses finished the required program in March 2014. They

are going to have the credentialing examination this summer. This year, we welcome 22 nurses out of 26 applicants into our educational program, and it will be started in upcoming May. The surveillance of JNA have recognized and validated our program.

The certified nurse system has been established by JNA to provide high level of nursing practice and to improve nursing expertise in specific nursing areas. We are ready to expand our educational programs for other nursing fields depending on requirement of neighboring hospitals and prefectures.

Preface

The Research Center for Innovative Oncology (RCIO) was originally funded as the branch of the Research Institute in 1994 at Kashiwa campus. For the purpose of more focusing on translational researches (TR) and mutual collaborations between basic and clinical researchers, the National Cancer Center Kashiwa campus was reorganized, which made the RCIO belong to the Hospital East in 2005. With the launch of the Exploratory Oncology Research & Clinical Trial Center (EPOC), some divisions in the RCIO were included into the EPOC. A large number of studies in collaborations with the Hospital East, EPOC, and Research Institute have been conducted for TR and support for hospital services.

In the Pathology Division, the investigators play a central role in bio-bank system, various types of TR and standardization of a procedure in pathological sample analysis. With many collaboration studies with the EPOC and industries for establishing companion diagnosis, they are acting as a central pathology diagnosis in an international IND registration trial. Various TRs are also on-going in collaboration with TR division in the EPOC. Large molecular epidemiologic data in lung, colorectal, and gastric cancer have already been published, which will become a landmark in the development of molecular targeting agents. A project for making patient-derived xenograft in combination with genome profiling is also underway.

Several new drug-delivery system (DDS) agents based on cutting-edge nanotechnology have originally been developed in the Developmental Therapeutics Division and one of them is now under evaluation in an international phase III trial. The division has also yielded some antibody-drug-conjugates for innovative targets including anti-tissue factor antibody, which are now being optimized for preclinical study and will be implicated into clinical study within a few years. They are participating the “Center of Innovation for nanotechnology” at Kanagawa prefecture designated by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) as an antibody yielding laboratory.

In 2012, our hospital was also selected as “a designated center for new endoscopic instrument development” by the Ministry of Health, Labour and Welfare and several exploratory studies with new diagnostic instruments/devices have been initiated. Several studies for new endoscopic/surgical instruments development were conducted in the Division of Science and Technology for Endoscopy and Surgery. A first in human clinical trial of hypoxia imaging they conducted was finished into the endoscopic diagnosis of neoplasia of the esophagus, stomach, and colon/rectum. Preclinical studies, such as a low-temperature atmospheric pressure plasmas system and photodynamic diagnosis of hypericin, are performed using animal model. Furthermore, clinical trial for biodegradable (BD) stent implantation for benign esophageal stricture after curative treatment, and clinical trial for photodynamic diagnosis using 5ALA has been started. A new generation surgical device/technique development (NEXT) project is also being planned for establishing new surgical techniques. The Division of Functional Imaging actively investigates mainly 2 kinds of imaging modalities, namely, radionuclide imaging and magnetic resonance (MR) imaging, to establish therapeutic strategies for minimally invasive and personalized cancer treatments. Clinical trials of hypoxia PET tests are ongoing using Cu-62 labeled diacetyl methyl-thiosemicarbazone (ATSM). Patients with lung cancer or head and neck cancer were tested to investigate the clinical and pathological features of tumors with high avidity to these radiopharmaceuticals. The effects of systemic chemotherapy on the cerebral metabolism and cognitive function in breast cancer patients were evaluated with MR spectroscopy.

We are also pioneers of proton-beam therapy, new imaging instruments such as super-MRI, and psycho-oncology, in which our researchers are leading. In the Particle Therapy Division, the investigator experimentally evaluated the proton beam dose reproducibility, sensitivity, angular dependence and depth-dose relationships for a new Metal Oxide Semiconductor Field Effect Transistor (MOSFET) detector. The detector was fabricated with a thinner oxide layer and was operated at high-bias voltages. In order to accurately measure dose distributions, they developed a practical method for correcting the MOSFET response to proton beams. The number of patients who received proton-beam irradiation has been rapidly increasing in recent years and multi-institutional clinical trials with proton beam radiation has been started. The Psycho-oncology Division has focused on developing effective interventions for depression in cancer patients as well as on determining the mechanism underlying the relationship between cancer and the mind through a combination of neuropsychiatric, psychosocial, and behavioral sciences. Supportive care center with a collaboration of psycho-oncology, palliative care, nursing, pharmacy, and social worker divisions has also been organized for various patient supports. With these activities, we eagerly establish a top innovative cancer center with best amenities for cancer patients in the world.

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National Cancer Center Hospital East

DIVISION OF PATHOLOGY

Atsushi Ochiai, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Takeshi Kuwata, Syuichi Mitsunaga, Akiko Nagatsuma, Chisako Yamauchi, Kazuyoshi Yanagihara, Yuka Nakamura, Shinya Neri, Tomofumi Miura, Eiji Higaki, Akiko Takahashi, Kenji Sakai, Ken Hatogai, Mitsuru Yokota, Masayuki Ishibashi, Kouji Ikeda, Shingo Kawano, Hiroko Hashimoto, Sachiko Fukuda, Tamae Hanai, Ayumi Iwaya, Aya Endo, Natsuko Maruyama, Yuki Iino, Masaaki Sato, Motoko Suzuki, Yoshiko Onuma, Youichi Higuchi, Anna Abe, Kei Natori, Yoshitaka Suda, Tomoyuki Miyashita, Ukyo Inaba, Yusuke Asai

Introduction

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

Routine activities

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

Research activities

The goal of the research at the Division of Pathology is to explore the cause of the cancer and to develop novel diagnostic and therapeutic methods for cancer patients. The research activities of the Division of Pathology start with the detection of cancer specific pathological conditions closely associated with clinical outcomes. The appropriate *in vitro* and *in vivo* models are required to solve

molecular mechanism of the relevant issues. Researches are further confirmed in final validation studies using human samples. Followings are major research results of this year.

- 1) Podoplanin-positive cancer associated fibroblasts play an important role in primary resistance to EGFR-TKIs and may be an ideal therapeutic target in EGFR mutated lung adenocarcinoma patients.
- 2) Basal cell hyperplasia detected in superficial-type esophageal or head and neck squamous cell carcinoma was an independent entity in terms of not only pathological findings, but also endoscopic findings observed using narrow-band imaging (25).
- 3) Peritoneal invasion in colon cancer is an important prognostic factor and cancer microenvironment formed by the peritoneal invasion is involved in the promotion of tumor growth and metastasis (8,20).
- 4) Approximately two-thirds of patients with gastric adenocarcinoma exhibited the expression of at least one tyrosine kinase receptors and would be candidates for targeted therapies (14,16).
- 5) Higher number of CD204(+) macrophage at extrapancreatic nerve plexus invasion of pancreatic ductal carcinoma was associated with shortened OS and DFS and early recurrence in the peritoneal cavity and locoregional space (11).

Prognostic factors and clinicopathological characteristics of various cancers have also been investigated in collaboration with the NCCH-E Diagnostic Pathology Section and other institutions.

These include lung cancers (1,2,4,5,6,7,19), colon cancers (8,9,13,17,20,21,23), gastric cancers (14,15,16,18,22), pancreatic cancers (10,11), breast cancers (3) and head and neck cancers (12,25).

Education

The Division participates in the pathological training of clinical residents in NCCH-E. Moreover staff members give professional guidance for doctoral students of Juntendo University, Keio University, Tokyo Medical and Dental University and Graduate School of Frontier Sciences, The University of Tokyo.

Future prospects

As a research institution, we are strengthening particularly in 1) collecting fundamental pathological information for cancer diagnosis and treatment, 2) promotion of translational research and 3) promotion of basic research of cancer biology.

List of papers published in 2014

Journal

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2. Hishida T, Yoshida J, Ohe Y, Aokage K, Ishii G, Nagai K. Surgical outcomes after initial surgery for clinical single-station N2 non-small-cell lung cancer. *Jpn J Clin Oncol*, 44:85-92, 2014
3. Matsubara N, Mukai H, Masumoto M, Sasaki M, Naito Y, Fujii S, Wada N. Survival outcome and reduction rate of Ki-67 between pre- and post-neoadjuvant chemotherapy in breast cancer patients with non-pCR. *Breast Cancer Res Treat*, 147:95-102, 2014
4. Matsumura Y, Hishida T, Shimada Y, Ishii G, Aokage K, Yoshida J, Nagai K. Impact of extratumoral lymphatic permeation on postoperative survival of non-small-cell lung cancer patients. *J Thorac Oncol*, 9:337-344, 2014
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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. Recently, dual modality probes of radionuclides and optical dyes are also under investigation. For MR imaging, some experimental studies were done using both a 9.4 T scanner dedicated to small animal imaging and a 3.0 T whole-body scanner.

Research activities

In the field of nuclear medicine, imaging probes including multimodality ones were investigated.

Since *in vivo* visualization of tumor hypoxia can greatly contribute to the optimization of cancer therapy, we are developing new hypoxia imaging probes. We proposed ^{99m}Tc -labeled ones that can be used more widely than PET probes in the light of feasibility of tests. These probes also had unique retention mechanism that was different from conventional hypoxia imaging agents. We synthesized many candidates of this kind of hypoxia imaging probes and obtained some promising results. *In vivo* imaging tests using tumor-bearing mice indicated that some candidates of our unique probes accumulated in hypoxic cells well after the successful delivery to tumors.

To improve the detectability of sentinel lymph nodes (SLNs) in head and neck cancer, multimodality imaging probes of radionuclides

and optical dyes are under investigation. The combination of indocyanine green (ICG) and ^{99m}Tc -phytate are attractive because both of them have been already covered by health insurance. We found that ICG-colloid mixture showed good optical signal of near-infrared lights for a longer period than ICG alone, improving the accuracy for the detection of true SLNs. In experimental studies using mice, fusion images of radionuclides and optical ones confirmed that gamma rays and optical signals were emitted from the same node. Multimodal imaging of SLN would contribute to improved sentinel node navigation surgery.

In boron neutron capture therapy (BNCT), 4-borono-L-phenylalanine (BPA) is an important ^{10}B carrier and its concentration of target tumors is a key to successful treatment. ^{18}F -FBPA is an analog of BPA and it can be visualized by PET. We examined ^{18}F -FBPA would be a useful PET tracer to predict the sensitivity to BNCT using BPA. We investigated the transport mechanism of ^{18}F -FBPA using human glioma cell lines and transport inhibitors. 2-aminobicyclo-(2.2.1)-heptane-2-carboxylic acid (BCH) drastically inhibited the uptake of ^{18}F -FBPA, indicating that system L amino acid transporter was dominantly involved in the uptake of ^{18}F -FBPA. In addition, the inhibition study using BPA indicated that 1 mM of BPA reduced the uptake of ^{18}F -FBPA to 2-7% of control. This result suggested that the transport mechanism of ^{18}F -FBPA would be similar to that of BPA and ^{18}F -FBPA PET would be useful to predict the sensitivity to BNCT using BPA.

In the field of magnetic resonance (MR) imaging, ferucarbotran-enhanced MR imaging, which is currently covered by health insurance, was investigated to precisely visualize the margins of treated areas of hepatic tumors after radiofrequency ablation (RFA) as well as radiation therapies. Our experimental studies using rats revealed that iron ions derived from ferucarbotran

remained for a long time in damaged liver tissues due to RFA or radiotherapy and these iron ions successfully delineated the margin of treated areas on MR images. We expect that the sustained signal reduction in ferucarbotran-accumulated liver tissues can be utilized to visualize ablative margins after RFA as well as target volumes in radiation therapy, both of which help clinicians to evaluate the risk of recurrence and enhance the curability of liver tumors.

Clinical trials

The effects of systemic chemotherapy on the cerebral metabolism and cognitive function in breast cancer patients were evaluated with MR spectroscopy.

List of papers published in 2014

Journal

1. Tani H, Kurihara H, Hiroi K, Honda N, Yoshimoto M, Kono Y, Murakami R, Kumita S, Arai Y, Itami J. Correlation of ^{18}F -BPA and ^{18}F -FDG uptake in head and neck cancers. *Radiother Oncol*, 113:193-197, 2014
2. Takeda A, Sanuki N, Fujii H, Yokosuka N, Nishimura S, Aoki Y, Oku Y, Ozawa Y, Kunieda E. Maximum standardized uptake value on FDG-PET is a strong predictor of overall and disease-free survival for non-small-cell lung cancer patients after stereotactic body radiotherapy. *J Thorac Oncol*, 9:65-73, 2014
3. Ogawa M, Umeda IO, Kosugi M, Kawai A, Hamaya Y, Takashima M, Yin H, Kudoh T, Seno M, Magata Y. Development of ^{111}In -labeled liposomes for vulnerable atherosclerotic plaque imaging. *J Nucl Med*, 55:115-120, 2014
4. Yoshii Y, Matsumoto H, Yoshimoto M, Furukawa T, Morokoshi Y, Sogawa C, Zhang M-R, Wakizaka H, Yoshii H, Fujibayashi Y, Saga T. Controlled administration of penicillamine reduces radiation exposure in critical organs during ^{64}Cu -ATSM internal radiotherapy: a novel strategy for liver protection. *PLoS One*, 9:e86996, 2014
5. Yoshimoto M, Hirata M, Kanai Y, Naka S, Nishii R, Kagawa S, Kawai K, Ohmomo Y. Monitoring of gefitinib sensitivity with radioiodinated PHY based on EGFR expression. *Biol Pharm Bull*, 37:355-360, 2014
6. Nakagami R, Yamaguchi M, Ezawa K, Kimura S, Hamamichi S, Sekine N, Furukawa A, Niitsu M, Fujii H. Recovery correction technique for NMR spectroscopy of perchloric acid extracts using DL-valine-2,3-d2: validation and application to 5-fluorouracil-induced brain damage. *Magn Reson Med Sci*, 13:145-153, 2014

Education

Some graduate school students took part in our studies and received degrees of doctor or master in the field of medicine and related sciences.

Future prospects

We will develop our research projects to translate our research products into clinical practice.

Book

1. Iimoto T, Fujii H, Someya S, Iizumi S, Ebisawa T, Hirose S, Furuta E, Kusama K, Nogawa N, Mitani H, Kamiko M, Kutsuna N, Watanabe Y, Suzuki T. Environmental Radiation Status In and Around Tokyo Immediately After the TEPCO Fukushima Dai-ichi Nuclear Power Plant Disaster. In: Takahashi S (ed), *Radiation Monitoring and Dose Estimation of the Fukushima Nuclear Accident, Japan*, Springer Verlag Tokyo, pp 49-57, 2014

DIVISION OF SCIENCE AND TECHNOLOGY FOR ENDOSCOPY AND SURGERY

Kazuhiro Kaneko, Tomonori Yano, Mari Takahashi, Atsushi Yagishita

Introduction

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

One of the characteristic natures of the early cancer is the growth of blood vessels (neovascularity). Using two narrow wave bands of light (blue: 390-445 nm; green: 530-550 nm) that can be absorbed by circulating hemoglobin, narrow band imaging (NBI) endoscopy may provide better images of the capillaries in the mucosal surface.

Another characteristic nature of the tumor is hypoxia. As a tumor grows, it rapidly outgrows its blood supply, leaving portions of the tumor with regions where the oxygen concentration is significantly lower than in healthy tissues. Thus, there have been attempts to visualize spatial distribution of tumor hypoxia, such as fluorescent labeling techniques or hemoglobin absorption-based techniques. However, these methods are limited because of low spatiotemporal resolution. We developed an imaging technology that can derive the oxygen saturation (StO₂) images from small numbers of wavelength measurements. Thus, novel endoscopy of next generation would be required to be visible to specific function in cancerous tissue. To progress the technology, laser light and near-infrared light would be necessary.

Routine activities

The present research activities mainly focus on the development of new instruments for endoscopic diagnosis and new endoscopic treatment modalities. Since posing a problem in the present condition is required in development research regarding endoscopy, our Division collaborates with the Endoscopy Division. Therefore, endoscopic diagnoses are routinely performed for cancer patients, endoscopic treatments, such as EMR or ESD, are performed in patients with early GI tract cancers. We perform lectures to resident doctors regarding individual projects. Furthermore, meeting is constantly conducted with the faculties including students of Technology and Science of the university.

Research activities

Research studies have been conducted in various fields: endoscopic diagnosis and treatment, or prevention for cancer patients in the GI tract and head and neck. In addition, the present researches are to develop new devices or procedures in innovative less invasive laparoscopic surgery for gastrointestinal malignancies. These projects are conducted as prospective clinical studies and preclinical studies in collaboration with not only commercial companies but also the faculties of Technology and Science of the university.

Developing research into novel endoscopy systems is being performed. Hypoxia imaging is detected for neoplastic lesions of the head and neck and alimentary tracts, with two types of visualized images, such as pseudocolour StO₂ image and a StO₂ overlay image. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and nanoparticles of the rare earth, doped yttrium oxide. This system is capable of penetrating through the gastrointestinal

wall and obtaining images. Furthermore, a preclinical study of molecular imaging endoscopy using small molecular was planned in this year. With a low-temperature atmospheric pressure plasmas system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnosis system using photosensitizing agents, such as hypericin, has been constructed. A novel tattooing system under endoscopy has been developed. Now, this system is applied for a patent. Ongoing projects are to develop needle graspers, needle ultrasonic coagulator in surgical field. Clinical trial regarding confocal laser endocytoscopy using fluorescein was planned. This type of endocytoscopy is classified into a new category.

Clinical trials

A first in-human clinical trial of hypoxia imaging was finished into the endoscopic diagnosis of neoplasia of the esophagus, stomach, and colorectum. We conducted a proof-of-the-concept trial for 40 patients with neoplastic lesions in the esophagus including the pharynx, stomach and colorectum. In this first in-human trial (UMIN 00004983), two types of StO₂ images were used. One was a pseudocolour StO₂ image that showed StO₂ levels as different hues, and the other was a StO₂ overlay image that overlapped StO₂ levels in blue on a white light illumination image to detect background mucosa. In a system of near-infrared light with nanoparticles, nanoparticles of rare earth act as fluorescent agents. Nanoparticles attached probe excite due to emission of near-infrared light, when probe attaches surface of cancer cells. Now, molecular imaging endoscopy for the use of this system with InGaAs CCD has been developed in collaboration with Technology of University. Preclinical studies,

such as a low-temperature atmospheric pressure plasmas system and photodynamic diagnosis of hypericin, are performed using animal model. Furthermore, clinical trial for biodegradable (BD) stent implantation for benign esophageal stricture after curative treatment, and clinical trial for photodynamic diagnosis using 5ALA are on going.

Education

The aim is to cultivate of human resources specializing in endoscopic diagnosis and treatment for alimentary tract cancer. Staff supervises individual residents. Positiveness is made importance in a periodic case conference and joint conferences among internal medicine, surgery and radiology. Staff supervises in congress presentation and writing manuscripts after decision of individual themes, and much discussion is made in the department conference. For residents interested in development research, their opportunity to study is supported after graduation.

Future prospects

Existing endoscopic diagnosis for neoplasia of alimentary tract is performed on the basis of morphological feature of tumor. A molecular imaging endoscopy is a novel system to visualize cancer using specific laser source under phosphor combined with cancer specific agents. We can obtain a new imaging, since function or metabolic state in cancer cells is visualized. In additional modalities, there are photodynamic diagnosis, endomicroscopy, and hypoxia imaging endoscopy. These modalities will be expected as a next generation endoscopy, and we try innovative development to produce all new endoscopy.

DIVISION OF DEVELOPMENTAL THERAPEUTICS

Yasuhiro Matsumura, Masahiro Yasunaga, Yoshikatsu Koga

Introduction

Our Division has been involved in basic research on drug delivery systems (DDS) and antibody therapeutics including anticancer agent incorporating micelle system, monoclonal antibody development (mAb), and antibody drug conjugate. We also investigate a mechanism of cancer induced blood coagulation and are developing a new cancer diagnosis based on the cancer specific mAb. In addition to the research works, we are operating the Japan Clinical Oncology Group Tumor Repository.

Routine activities

Examination of clinical trials as an IRB member
Operation of the JCOG Tumor Repository
Management of personal information protection in the NCC East Hospital

Research activities

(DDS in Cancer Chemotherapy)

Tumor-targeted delivery of therapeutic agents is a longstanding pharmacological goal to improve the treatment selectivity and therapeutic index. Most scientists have sought to use 'active' receptor-mediated tumor-targeting systems. However, the 'passive' targeting afforded by the "Enhanced Permeability and Retention (EPR) effect" provides a versatile and non-saturable approach for tumor-selective delivery. Polymeric micelles are ideally suited to exploit the EPR effect, and have been used for the delivery of a range of anticancer drugs in preclinical and clinical studies.

We showed the stronger antitumor effect and lower toxicity of the combination of the epirubicin-incorporating polymeric micelle and

DACHP (oxaliplatin parent complex)-incorporating polymeric micelle in a human gastric cancer model than that of epirubicin and oxaliplatin.

(Cancer Stromal Targeting Therapy)

In spite of recent success of antibody drug conjugate (ADC) therapy in patients with hypervascular and special tumors recognized by a particular mAb, there are several issues to be solved for ADC counted as universal therapy for any types of cancer. Especially most human solid tumors possess abundant stroma that hinders the distribution of ADC. To overcome these drawbacks, we developed a unique strategy that the cancer-stromal targeting (CAST) therapy by cytotoxic immunoconjugate bound to the collagen 4, tissue factor (TF), or fibrin network in the tumor stroma from which the payload released gradually and distributed throughout the tumor, resulting in the arrest of tumor growth due to induced damage to tumor cells and tumor vessels. During this study, we found that anti-TF scFv may be suitable as an imaging probe for the diagnosis of solid tumors.

(Infrastructure for the mAb development)

We have established an infrastructure for antibody development including antigen production, animal immunization, hybridoma production, antibody expansion and purification, SPR characterization, and ELISA development. Simultaneously, we have found various cell surface molecules specific to colorectal cancer and succeeded in developing the one of those molecules.

(Noninvasive Diagnostic Test for Colorectal Cancer)

Regarding colorectal cancer (CRC), we investigated the applicability of the fecal miRNA test (FmiRT) to fecal samples used for previous fecal occult blood test (FOBT) stored under various conditions.

Education

(Doctoral student)

Graduate School of Frontier Science, The University of Tokyo: 5 students

Juntendo University Graduate School of Medicine: 2 students

Department of Gastroenterology and Hepatology, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba: 1 student

Department of Neurosurgery, Kumamoto University Graduate School of Medical Science: 1 student

(Master course student)

Graduate School of Frontier Science, The University of Tokyo: 5 students

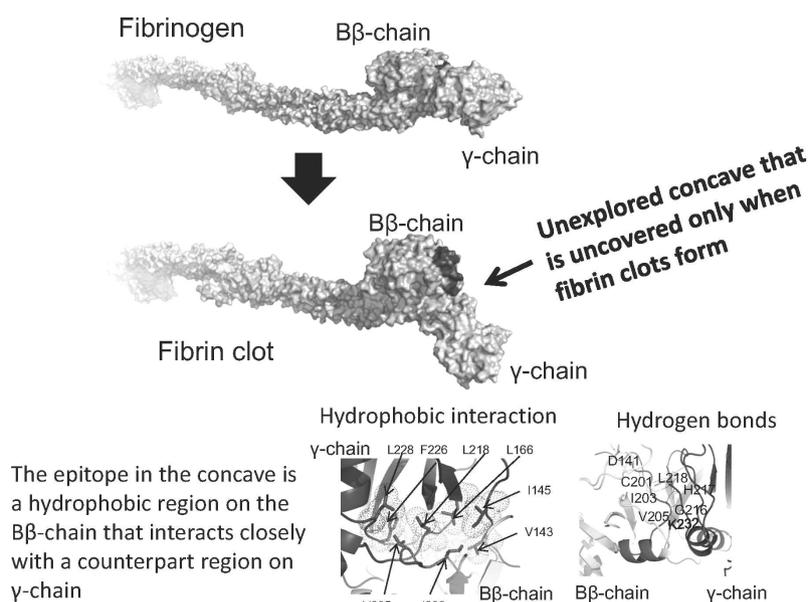


Figure 1. Image of structural change from fibrinogen to fibrin clot and discovery of unique concave in fibrin clot

List of papers published in 2014

Journal

1. Yanagihara K, Takigahira M, Kubo T, Ochiya T, Hamaguchi T, Matsumura Y. Marked antitumor effect of NK012, a SN-38-incorporating micelle formulation, in a newly developed mouse model of liver metastasis resulting from gastric cancer. *Ther Deliv*, 5:129-138, 2014
2. Koga Y, Yamazaki N, Takizawa S, Kawauchi J, Nomura O, Yamamoto S, Saito N, Kakugawa Y, Otake Y, Matsumoto M, Matsumura Y. Gene expression analysis using a highly sensitive DNA microarray for colorectal cancer screening. *Anticancer Res*, 34:169-176, 2014
3. Koga Y, Yamazaki N, Matsumura Y. New molecular diagnosis and screening methods for colorectal cancer using fecal protein, DNA and RNA. *Expert Rev Mol Diagn*, 14:107-120, 2014
4. Yamamoto Y, Hyodo I, Takigahira M, Koga Y, Yasunaga M, Harada M, Hayashi T, Kato Y, Matsumura Y. Effect of combined treatment with the epirubicin-incorporating micelles (NC-6300) and 1,2-diaminocyclohexane platinum (II)-incorporating micelles (NC-4016) on a human gastric cancer model. *Int J Cancer*, 135:214-223, 2014
5. Matsumura Y. The drug discovery by nanomedicine and its clinical experience. *Jpn J Clin Oncol*, 44:515-525, 2014
6. Yasunaga M, Matsumura Y. Role of SLC6A6 in promoting the survival and multidrug resistance of colorectal cancer. *Sci Rep*, 4:4852, 2014
7. Sato R, Obonai T, Tsumura R, Tsumoto K, Koga Y, Yasunaga M, Matsumura Y. Preparation and characterization of anti-tissue factor singlechain variable fragment antibody for cancer diagnosis. *Cancer Sci*, 105:1631-1637, 2014

DIVISION OF PSYCHO-ONCOLOGY

Asao Ogawa, Hiroya Kinoshita, Ken Shimizu

Introduction

The aim of the Division is to develop mind-centered interventions to restore, maintain, and improve the quality of life of patients and their families who face a life-threatening illness, cancer. The Division has focused on developing effective interventions for depression in cancer patients as well as on determining the mechanism underlying the relationship between cancer and the mind through a combination of neuropsychiatric, psychosocial, and behavioral sciences.

Research activities

Consent capacity and associated risk factors in patients with lung cancer

Little is known regarding consent capacity in patients newly diagnosed with as having lung cancer and clinical factors associated with incapacity. Over an 11-month period, we recruited 135 newly diagnosed patients newly diagnosed as having with lung cancer. All patients were receiving a combination of treatments (e.g., chemotherapy, chemoradiotherapy, or targeted therapy). Participants were administered the MacArthur Competence Tool for Treatment was administered to participants, in addition to a neurocognitive test battery, to help us identify clinical factors associated with incapacity in lung cancer patients. 27 (24%, 95% CI, 16–31%) patients were judged to not to have consent capacity. Logistic regression identified vulnerability (odds ratio, 3.51; 95% CI, 1.13 to 10.8) and cognitive impairment (odds ratio, 5.45; 95% CI, 1.26 to 23.6) as the factors associated with mental incapacity.

Place of death and the differences in patient quality of death

Little is known regarding the associations between place of death and quality of death and dying and caregiver burden in terminally ill patients with cancer and their families. Two bereavement surveys were conducted in October 2008 and October 2011. A total of 2,247 family caregivers of patients with cancer who were deceased responded to the mail surveys (response rate, 67%). Family members reported patient quality of death and dying and caregiver burden by using the Good Death Inventory and Caregiving Consequences Inventory. Patient quality of death and dying was significantly higher at home relative to other places of dying after adjustment for patient and/or family characteristics (adjusted means): 5.0 (95% CI, 4.9 to 5.2) for home, 4.6 (95% CI, 4.5 to 4.7) for palliative care units, and 4.3 (95% CI, 4.2 to 4.4) for hospitals. Home was superior to palliative care units or hospitals with respect to "dying in a favorite place," "good relationships with medical staff," "good relationships with family," and "maintaining hope and pleasure" ($P < .001$ for all combinations of home v palliative care units and home v hospitals). Home death was significantly associated with a lower overall ($P = .03$) and financial caregiver burden ($P = .004$) relative to hospital death. Dying at home may contribute to achieving good death in terminally ill patients with cancer without causing remarkably increased caregiver burden. Place of death should be regarded as an essential goal in end-of-life care.

List of papers published in 2014

Journal

1. Shibayama O, Yoshiuchi K, Inagaki M, Matsuoka Y, Yoshikawa E, Sugawara Y, Akechi T, Wada N, Imoto S, Murakami K, Ogawa A, Akabayashi A, Uchitomi Y. Association between adjuvant regional radiotherapy and cognitive function in breast cancer patients treated with conservation therapy. *Cancer Med*, 3:702-709, 2014
2. Morita T, Sato K, Miyashita M, Yamagishi A, Kizawa Y, Shima Y, Kinoshita H, Suzuki S, Shirahige Y, Yamaguchi T, Eguchi K. Does a regional comprehensive palliative care program improve pain in outpatient cancer patients? *Support Care Cancer*, 22:2445-2455, 2014
3. Yamagishi A, Sato K, Miyashita M, Shima Y, Kizawa Y, Umeda M, Kinoshita H, Shirahige Y, Akiyama M, Yamaguchi T, Morita T. Changes in quality of care and quality of life of outpatients with advanced cancer after a regional palliative care intervention program. *J Pain Symptom Manage*, 48:602-610, 2014
4. Imura C, Morita T, Kato M, Akizuki N, Kinoshita H, Shirahige Y, Suzuki S, Takebayashi T, Yoshihara R, Eguchi K. How and why did a regional palliative care program lead to changes in a region? A qualitative analysis of the Japan OPTIM study. *J Pain Symptom Manage*, 47:849-859, 2014
5. Sasahara T, Watakabe A, Aruga E, Fujimoto K, Higashi K, Hisahara K, Hori N, Ikenaga M, Izawa T, Kanai Y, Kinoshita H, Kobayakawa M, Kobayashi K, Kohara H, Namba M, Nozaki-Taguchi N, Osaka I, Saito M, Sekine R, Shinjo T, Suga A, Tokuno Y, Yamamoto R, Yomiya K, Morita T. Assessment of reasons for referral and activities of hospital palliative care teams using a standard format: a multicenter 1000 case description. *J Pain Symptom Manage*, 47:579-587 e576, 2014
6. Miura T, Matsumoto Y, Motonaga S, Hasuo H, Abe K, Kinoshita H. Dyspnea, relative youth and low daily doses of opioids predict increased opioid dosage in the last week of a terminal cancer patient's life. *Jpn J Clin Oncol*, 44:1082-1087, 2014
7. Nakanotani T, Akechi T, Takayama T, Karato A, Kikuuchi Y, Okamoto N, Katayama K, Yokoo M, Ogawa A. Characteristics of elderly cancer patients' concerns and their quality of life in Japan: a Web-based survey. *Jpn J Clin Oncol*, 44:448-455, 2014
8. Yokoo M, Akechi T, Takayama T, Karato A, Kikuuchi Y, Okamoto N, Katayama K, Nakanotani T, Ogawa A. Comprehensive assessment of cancer patients' concerns and the association with quality of life. *Jpn J Clin Oncol*, 44:670-676, 2014

Book

1. Shimizu K, Yoshiuchi K, Onishi H. Treatment of Anxiety and Stress-Related Disorders. In: Grassi L, Riba M (eds), *Psychopharmacology in Oncology and Palliative Care: A Practical Manual*, Germany, Springer-Verlag Berlin Heidelberg, pp 129-144, 2014

DIVISION OF RADIATION ONCOLOGY AND PARTICLE THERAPY

Tetsuo Akimoto, Sadatomo Zenda, Teiji Nishio, Hidenobu Tachibana, Ryosuke Kohno, Tomoko Miyagishi, Kenji Hotta

Introduction

The aim of research in the Radiation Oncology and Particle Therapy Division at the National Cancer Hospital East is to study and develop innovative treatment techniques and pilot clinical trial for proton beam therapy (PBT). Medical physicists mainly perform development and verification of the systems for beam irradiation, dose calculation system, dose measurement and imaging of PBT. Radiation oncologists mainly perform studies on the clinical trials, efficacy and side effects of PBT.

Routine activities

At present, the staff of the Radiation Oncology and Particle Therapy Division is consisted from 7 consultant physicians (radiation oncologist), 6 radiation technologists, 4 medical physicists, 1 nurse, and 1 clerk. We have more than 300 or more new patients for PBT in every year, and quality assurances of PBT are performed by medical physicists and radiation technologists, and the conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. PBT are routinely based on three-dimensional radiation therapy planning and PBT using RT-dedicated multi-detector-row helical computed tomography (CT) scanning in order to confirm precise radiation dose to the targeted tumors. Respiratory-gating has been applied especially in radiotherapeutic management for patients with lung, esophagus and liver cancers. The Section is responsible for PBT that is composed of 7 operating staff members and 1 technician for fabricating the compensator and aperture; they are sent from manufacturing companies and work in collaboration with the other staff members of the Division. PBT is consisted from 2 treatment rooms and both rooms

are routinely used for rotational gantry treatment. The Division ensures quality assurance and regular maintenance of the PBT machines for precise dose delivery and safe treatment.

Research activities

- 1) PBT as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study.
- 2) Phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.
- 3) Phase I/II study of dose escalated PBT combined with chemotherapy for esophageal cancer.
- 4) Establishment of feasibility and effectiveness of line scanning for localized prostate cancer.
- 5) Proton dose distribution measurements using a MOSFET detector with a simple dose-weighted correction method for LET effects.
- 6) Radiobiological evaluation of cellular response to PBT.
- 7) Radiobiological evaluation of combined effect of chemotherapeutic agents on enhancement of PBT.
- 8) Standardization of methods of PBT and quality assurance of PBT among Japanese proton beam facilities.
- 9) Establishment of infrastructure for multi-institutional study of PBT for various cancers.
- 10) Technical development of intensity modulated proton beam therapy (IMPT).

Clinical trials

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

- 1) Phase II study of PBT for malignant melanoma of nasal cavity.
- 2) Phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.

3) Phase I/II study of dose escalated study of PBT combined with chemotherapy for esophageal cancer.

4) Phase I/II study of line scanning for localized prostate cancer.

Table 1. The changes in the number of patients treated with PBT

Number of patients treated with PBT during 2010-2014

	2010	2011	2012	2013	2014
New patients	107	200	245	378	331
Head and neck cancers	39	49	45	35	33
Lung and mediastinal cancers	12	24	76	101	82
Hepatocellular carcinoma	12	27	35	38	21
Prostate cancer	42	93	79	143	111
Others	2	7	17	45	54

List of papers published in 2014

Journal

- Hatanaka S, Miyabe Y, Tohyama N, Kumazaki Y, Kurooka M, Okamoto H, Tachibana H, Kito S, Wakita A, Ohotomo Y, Iikagawa H, Ishikura S, Nozaki M, Kagami Y, Hiraoka M, Nishio T. Dose calculation accuracies in whole breast radiotherapy treatment planning: a multi-institutional study. *Radiol Phys Technol.* 2015.
- Matsumoto Y, Matsuura T, Wada M, Egashira Y, Nishio T, Furusawa Y. Enhanced radiobiological effects at the distal end of a clinical proton beam: in vitro study. *J Radiat Res.* 55(4): 816-22, 2014.
- Nishio T, Shirato H, Ishikawa M, Miyabe Y, Kito S, Narita Y, Onimaru R, Ishikura S, Ito Y, Hiraoka M. Design, development of water tank-type lung phantom and dosimetric verification in institutions participating in a phase I study of stereotactic body radiation therapy in patients with T2N0M0 non-small cell lung cancer: Japan Clinical Oncology Group trial (JCOG0702). *J Radiat Res.* 55(3): 600-7, 2014.
- Motegi K, Kohno R, Ueda T, Shibuya T, Arijii T, Kawashima M, Akimoto T. Evaluating positional accuracy using megavoltage conebeam computed tomography for IMRT with head-and-neck cancer. *J Radiat Res.* 55:568-574, 2014
- Aoki-Nakano M, Furusawa Y, Uzawa A, Matsumoto Y, Hirayama R, Tsuruoka C, Ogino T, Nishio T, Kagawa K, Murakami M, Kagiya G, Kume K, Hatashita M, Fukuda S, Yamamoto K, Fuji H, Murayama S, Hata M, Sakae T, Matsumoto H. Relative biological effectiveness of therapeutic proton beams for HSG cells at Japanese proton therapy facilities. *J Radiat Res.* 55:812-815, 2014
- Zenda S, Nakagami Y, Toshima M, Arahira S, Kawashima M, Matsumoto Y, Kinoshita H, Satake M, Akimoto T. Strontium-89 (Sr-89) chloride in the treatment of various cancer patients with multiple bone metastases. *Int J Clin Oncol.* 19:739-743, 2014

SECTION OF EXPERIMENTAL ANIMALS

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Introduction

The basic and translational researches investigated in the Research Center for Innovative Oncology (RCIO) and the Exploratory Oncology Research & Clinical Trial Center (EPOC) are aimed toward a future clinical use. To develop anti-cancer drugs based on a novel concept or a novel imaging technology, the animal experiments are necessary. The Section of Experimental Animals supports the animal experiments conducted in RCIO and EPOC.

Routine activities

- Health management of the experimental animals and maintenance of the animal laboratories.
 - Animal-breeding rooms: specific pathogen-free (SPF) rooms (8 rooms for mice and 1 room for rats), conventional rooms (1 room for mice, 1 room for rats, hamsters, and rabbits, and 1 room for pigs), and P2 animal laboratory.
- Approval of animal experiments and gene recombinant experiments in accordance with the regulations.
 - In 2014, 62 studies involving animal experiments and 25 studies with gene recombinant experiments were approved by the Committee of Experimental Animals and Gene Recombination.

List of papers published in 2014

Journal

1. Koga Y, Yamazaki N, Takizawa S, Kawauchi J, Nomura O, Yamamoto S, Saito N, Kakugawa Y, Otake Y, Matsumoto M, Matsumura Y. Gene expression analysis using a highly sensitive DNA microarray for colorectal cancer screening. *Anticancer Res*, 34:169-176, 2014
2. Koga Y, Yamazaki N, Matsumura Y. New molecular diagnosis and screening methods for colorectal cancer using fecal protein, DNA and RNA. *Expert Rev Mol Diagn*, 14:107-120, 2014
3. Yamamoto Y, Hyodo I, Takigahira M, Koga Y, Yasunaga M, Harada M, Hayashi T, Kato Y, Matsumura Y. Effect of combined treatment with the epirubicin-incorporating micelles (NC-6300) and 1,2-diaminocyclohexane platinum (II)-incorporating micelles (NC-4016) on a human gastric cancer model. *Int J Cancer*, 135:214-223, 2014
4. Sato R, Obonai T, Tsumura R, Tsumoto K, Koga Y, Yasunaga M, Matsumura Y. Preparation and characterization of anti-tissue factor singlechain variable fragment antibody for cancer diagnosis. *Cancer Sci*, 105:1631-1637, 2014

