Hospital East

Preface

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

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

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

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

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

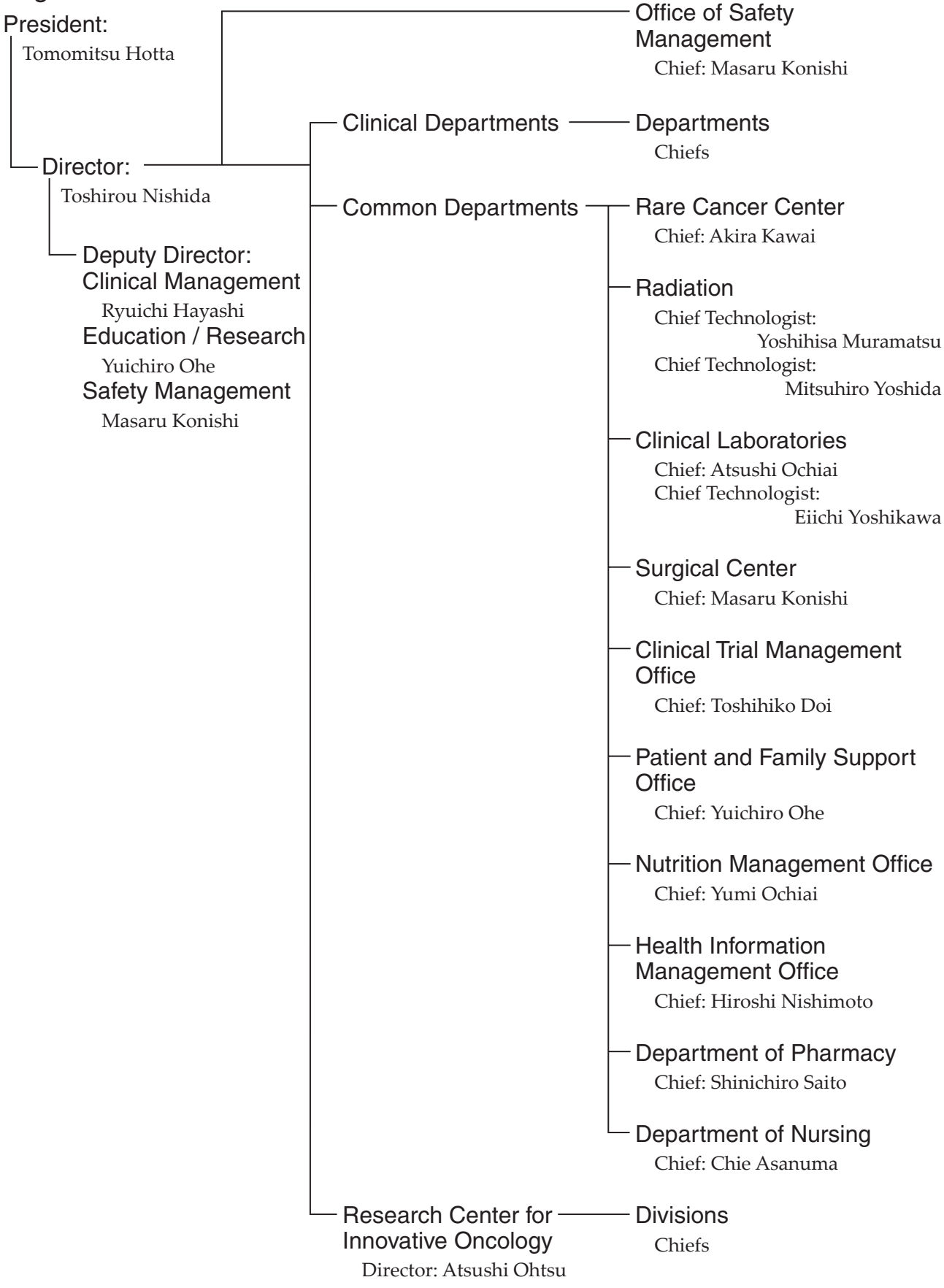
The second feature is minimally invasive therapy (MIT) for cancer patients. In this context, we have provided the highest quality of radiotherapy represented by the indication of proton beam therapy and endoluminal therapy as well as endoscopic surgery in Japan. Twenty years after our foundation, we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

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

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

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

Organization



Clinical Departments

Director:
Toshirou Nishida

Deputy Director:
Clinical Management
Ryuichi Hayashi
Education / Research
Yuichiro Ohe
Safety Management
Masaru Konishi

- Department of Head and Neck Surgery
  Chief: Ryuichi Hayashi
- Department of Head and Neck Medical Oncology
  Chief: Makoto Tahara
- Department of Plastic and Reconstructive Surgery
  Chief: Minoru Sakuraba
- Department of Breast Surgery
  Chief: Noriaki Wada
- Department of Breast and Medical Oncology
  Chief: Yuichiro Ohe
- Department of Thoracic Surgery
  Chief: Kanji Nagai
- Department of Thoracic Oncology
  Chief: Yuichiro Ohe
  Deputy Chief: Hironobu Ohmatsu
- Department of Esophageal Surgery
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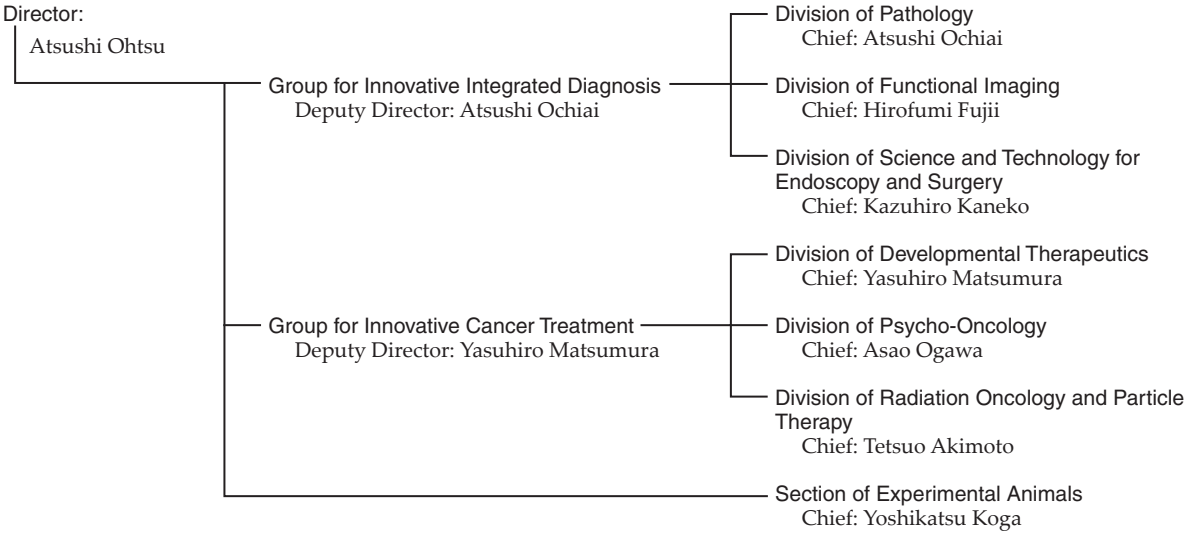
  Chief: Takahiro Kinoshita
- Department of Colorectal Surgery
  Chief: Norio Saito
- Department of Gastrointestinal Oncology
  Chief: Toshihiko Doi
- Department of Digestive Endoscopy
  Chief: Kazuhiro Kaneko
- Department of Hepatobiliary and Pancreatic Surgery
  Chief: Masaru Konishi
- Department of Hepatobiliary and Pancreatic Oncology
  Chief: Masafumi Ikeda
- Department of Urology
  Chief: Norio Saito
- Department of Gynecology
  Chief: Ryuichi Hayashi
- Department of Musculoskeletal Oncology and Rehabilitation
  Chief: Ryuichi Hayashi
- Department of Hematology
  Chief: Kunihiro Tsukasaki
- Departments of General Internal Medicine, Dentistry, Cardiovascular Medicine, Pediatric Oncology
  Chief: Yuichiro Ohe

- Department of Anesthesiology and Intensive Care Unit
  Chief: Vacant
- Department of Palliative Medicine, Palliative Care Service
  Chief: Hiroya Kinoshita
- Department of Psycho-Oncology Service
  Chief: Asao Ogawa
- Department of Diagnostic Radiology
  Chief: Mitsuo Satake
- Department of Radiation Oncology
  Chief: Tetsuo Akimoto
- Department of Pathology and Clinical Laboratories
  Chief: Atsushi Ochiai

Research Center for Innovative Oncology



Activities of the Departments

Department of Head and Neck Surgery

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

Introduction

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

Routine activities

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

Research activities

1. Mucosal Defect Repair with a Polyglycolic Acid Sheet

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

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

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

Clinical trials

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

A prospective observation study was conducting and 68 cases were enrolled to this study from 9 hospitals. Neck dissection at Level IIb and V areas influence the rate of postoperative accessory nerve palsy but the necessity of dissection of these areas is still controversial because of the low prevalence rate of lymph node metastasis. A randomized clinical trial will be run after evaluating the results of this study.

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

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

Table 1. Type of surgical procedures

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

Table 2. Survival rates

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

n.v. : not verified

List of papers published in 2013
Journal

1. Shinozaki T, Hayashi R, Ebihara M, Miyazaki M, Tomioka T. Mucosal defect repair with a polyglycolic acid sheet. Jpn J Clin Oncol, 43:33-36, 2013
2. Kaneko K, Yano T, Minashi K, Kojima T, Ito M, Satake H, Yajima Y, Yoda Y, Ikematsu H, Oono Y, Hayashi R, Onozawa M, Ohtsu A. Treatment strategy for superficial pharyngeal squamous cell carcinoma synchronously combined with esophageal cancer. Oncology, 84:57-64, 2013
3. Fujii S, Uryu H, Akashi K, Suzuki K, Yamazaki M, Tahara M, Hayashi R, Ochiai A. Clinical significance of KRAS gene mutation and epidermal growth factor receptor expression in Japanese patients with squamous cell carcinoma of the larynx, oropharynx and hypopharynx. Int J Clin Oncol, 18:454-463, 2013
4. Tomioka T, Hayashi R, Ebihara M, Miyazaki M, Shinozaki T, Fujii S. Observation as an option for epithelial positive margin after partial glossectomy in stage I and II squamous cell carcinoma: analysis of 365 cases. Jpn J Clin Oncol, 43:520-523, 2013
5. Asai M, Akizuki N, Fujimori M, Shimizu K, Ogawa A, Matsui Y, Akechi T, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Impaired mental health among the bereaved spouses of cancer patients. Psychooncology, 22:995-1001, 2013
6. Yamazaki N, Koga Y, Yamamoto S, Kakugawa Y, Otake Y, Hayashi R, Saito N, Matsumura Y. Application of the fecal microRNA test to the residuum from the fecal occult blood test. Jpn J Clin Oncol, 43:726-733, 2013

Department of Head and Neck Medical Oncology

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

Introduction

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

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

Routine activities

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

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

Research activities

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

1) Development of new treatments

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

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

2) Biomarker analysis

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

has raised the possibility that miRNAs may serve as a novel diagnostic marker. A prospective study to compare the miRNA expression patterns before and after completion of surgery in head and neck cancer patients revealed that a total of 24 miRNAs was significantly changed.

Clinical trials

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

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

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

Table 1. Number of patients

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

Table 2. Type of procedure

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

Table 3. Survival rates

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

n.v. : not verified

List of papers published in 2013
Journal

1. Zenda S, Ishi S, Kawashima M, Arahira S, Tahara M, Hayashi R, Kishimoto S, Ichihashi T. A Dermatitis Control Program (DeCoP) for head and neck cancer patients receiving radiotherapy: a prospective phase II study. Int J Clin Oncol, 18:350-355, 2013
2. Yoshino T, Hasegawa Y, Takahashi S, Monden N, Homma A, Okami K, Onozawa Y, Fujii M, Taguchi T, de Blas B, Beier F, Tahara M. Platinum-based chemotherapy plus cetuximab for the first-line treatment of Japanese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: results of a phase II trial. Jpn J Clin Oncol, 43:524-531, 2013
3. Okano S, Yoshino T, Fujii M, Onozawa Y, Kodaira T, Fujii H, Akimoto T, Ishikura S, Oguchi M, Zenda S, de Blas B, Tahara M, Beier F. Phase II study of cetuximab plus concomitant boost radiotherapy in Japanese patients with locally advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol, 43:476-482, 2013
4. Doi T, Ohtsu A, Fuse N, Yoshino T, Tahara M, Shibayama K, Takubo T, Weinreich DM. Phase 1 study of trebananib (AMG 386), an angiogenesis targeting angiopoietin-1/2 antagonist, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 71:227-235, 2013
5. Fuse N, Nagahisa-Oku E, Doi T, Sasaki T, Nomura S, Kojima T, Yano T, Tahara M, Yoshino T, Ohtsu A. Effect of RECIST revision on classification of target lesions and overall response in advanced gastric cancer patients. Gastric Cancer, 16:324-328, 2013
6. Vermorken JB, Stohlmacher-Williams J, Davidenko I, Licitra L, Winquist E, Villanueva C, Foa P, Rottey S, Skladowski K, Tahara M, Pai VR, Faivre S, Blajman CR, Forastiere AA, Stein BN, Oliner KS, Pan Z, Bach BA. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. Lancet Oncol, 14:697-710, 2013
7. Kawashima M, Ariji T, Kameoka S, Ueda T, Kohno R, Nishio T, Arahira S, Motegi A, Zenda S, Akimoto T, Tahara M, Hayashi R. Locoregional control after intensity-modulated radiotherapy for nasopharyngeal carcinoma with an anatomy-based target definition. Jpn J Clin Oncol, 43:1218-1225, 2013
8. Fujii S, Uryu H, Akashi K, Suzuki K, Yamazaki M, Tahara M, Hayashi R, Ochiai A. Clinical significance of KRAS gene mutation and epidermal growth factor receptor expression in Japanese patients with squamous cell carcinoma of the larynx, oropharynx and hypopharynx. Int J Clin Oncol, 18:454-463, 2013
9. Suzuki K, Hayashi R, Ebihara M, Miyazaki M, Shinozaki T, Daiko H, Sakuraba M, Zenda S, Tahara M, Fujii S. The effectiveness of chemoradiation therapy and salvage surgery for hypopharyngeal squamous cell carcinoma. Jpn J Clin Oncol, 43:1210-1217, 2013

Department of Plastic and Reconstructive Surgery

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

Introduction

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

Routine activities

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

Research activities

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

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

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

Clinical trials

No clinical trial is currently under way.

Table 1. Cooperation with other divisions

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

Table 2. Operative Procedures

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

List of papers published in 2013

Journal

1. Tsuchiya S, Nakatsuka T, Sakuraba M, Kimata Y, Sakurai H, Nakagawa M, Takushima A. Clinical factors associated with postoperative complications and the functional outcome in mandibular reconstruction. Microsurgery, 33:337-341, 2013
2. Umezawa H, Sakuraba M, Miyamoto S, Nagamatsu S, Kayano S, Taji M. Analysis of immediate vascular reconstruction for lower-limb salvage in patients with lower-limb bone and soft-tissue sarcoma. J Plast Reconstr Aesthet Surg, 66:608-616, 2013
3. Sakuraba M, Miyamoto S, Kimata Y, Nakatsuka T, Harii K, Ebihara S, Hayashi R. Recent advances in reconstructive surgery: head and neck reconstruction. Int J Clin Oncol, 18:561-565, 2013

Department of Breast Surgery

Noriaki Wada, Kimiyasu Yoneyama, Chisako Yamauchi

Introduction

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

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

Routine activities

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

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

Research activities

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

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

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

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

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

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

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

Clinical trials

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 3. Overall survival (OS) rate
OP year: Jan 1993- Dec 2007

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

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

List of papers published in 2013
Journal

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

Department of Breast and Medical Oncology

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

Introduction

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

Routine activities

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

Research activities and clinical trials

Phase I studies of the following anticancer agents were conducted: K912 (epirubicin-incorporating micellar nanoparticle formulation) for patients with solid tumors for which standard chemotherapy was unavailable; cabazitaxel (a new taxane derivative) for patients with hormone refractory prostate cancer [JNJ212082 (abiraterone acetate, a CYP17 inhibitor for androgen antagonist) for patients with castration-resistant prostate cancer who have not received chemotherapeutic agents] and NK105 (paclitaxel-incorporating micellar nanoparticle formulation) for patients with advanced or metastatic cancer for which standard chemotherapy was unavailable. Phase I/II studies of new anticancer agents for specific disease targets are conducted in collaboration with pharmaceutical companies. A phase II study of E7389 for treated patients with soft tissue sarcomas is also ongoing.

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

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

Table 1. Number of patients

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

List of papers published in 2013
Journal

1. Mukai H. The current status and future perspectives of clinical trial groups in Japan. Breast Cancer, 20:285-286, 2013
2. Matsubara N, Mukai H, Naito Y, Itoh K, Komai Y, Sakai Y. First experience of active surveillance before systemic target therapy in patients with metastatic renal cell carcinoma. Urology, 82:118-123, 2013
3. Kurahashi I, Fujita Y, Arao T, Kurata T, Koh Y, Sakai K, Matsumoto K, Tanioka M, Takeda K, Takiguchi Y, Yamamoto N, Tsuya A, Matsubara N, Mukai H, Minami H, Chayahara N, Yamanaka Y, Miwa K, Takahashi S, Takahashi S, Nakagawa K, Nishio K. A microarray-based gene expression analysis to identify diagnostic biomarkers for unknown primary cancer. PLoS One, 8:e63249, 2013
4. Gnant M, Baselga J, Rugo HS, Noguchi S, Burris HA, Piccart M, Hortobagyi GN, Eakle J, Mukai H, Iwata H, Geberth M, Hart LL, Hadji P, El-Hashimy M, Rao S, Taran T, Sahmoud T, Lebwohl D, Campone M, Pritchard KI. Effect of everolimus on bone marker levels and progressive disease in bone in BOLERO-2. J Natl Cancer Inst, 105:654-663, 2013
5. Ishihara M, Mukai H, Nagai S, Onozawa M, Nihei K, Shimada T, Wada N. Retrospective analysis of risk factors for central nervous system metastases in operable breast cancer: effects of biologic subtype and Ki67 overexpression on survival. Oncology, 84:135-140, 2013
6. Matsubara N, Mukai H, Fujii S, Wada N. Different prognostic significance of Ki-67 change between pre- and post-neoadjuvant chemotherapy in various subtypes of breast cancer. Breast Cancer Res Treat, 137:203-212, 2013
7. Aihara T, Mukai H. The current status and future perspectives of CSPOR-BC. Breast Cancer, 20:287-290, 2013
8. Miura Y, Theriault RL, Naito Y, Suyama K, Shimomura A, Iwatani T, Miura D, Kawabata H, Kumada H, Takano T. The safety of chemotherapy for breast cancer patients with hepatitis C virus infection. J Cancer, 4:519-523, 2013
9. Shitara K, Yuki S, Yamazaki K, Naito Y, Fukushima H, Komatsu Y, Yasui H, Takano T, Muro K. Validation study of a prognostic classification in patients with metastatic colorectal cancer who received irinotecan-based second-line chemotherapy. J Cancer Res Clin Oncol, 139:595-603, 2013
10. Matsubara N, Mukai H, Naito Y, Nezu M, Itoh K. Comparison between neoadjuvant and adjuvant gemcitabine plus cisplatin chemotherapy for muscle-invasive bladder cancer. Asia Pac J Clin Oncol, 9:310-317, 2013

Department of Thoracic Surgery

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

Introduction

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

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

Routine activities

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

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

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

The surgical procedures of the Division have generally remained similar for the past decade, but we have employed port-access thoracoscopic surgery more often for the past several years. Approximately 20% of the surgeries are completed via a 3-port access, and 70% of the surgeries are video-thoracoscopically assisted. To date, the average postoperative hospital stays of patients in the Division have improved and have become shorter, 3 days being the shortest with a median of 7 days for cases of primary lung cancer. These shorter hospital stays are achieved with a slightly better complication rate than the normal rate. This year, no 30-day operative mortality occurred in any patient undergoing surgery for primary lung cancer.

Research activities and Clinical trials

1. Surgical margin lavage cytology examination in limited resection for primary and metastatic lung cancer patients [observational].
2. Member of an organized trial of TS-1 vs. UFT adjuvant chemotherapy for completely resected pathologic stage I (> 2 cm) non-small cell lung cancer [phase III, patient accrual completed].
3. Member of an organized trial of sublobar resection

for peripheral GGO dominant cT1aN0M0 lung adenocarcinomas [phase II, patient accrual completed].
4. Member of an organized trial of segmental resection vs. lobectomy for peripheral T1aN0M0 non-small cell lung cancers [phase III].
5. Member of an organized trial of pleurectomy for malignant pleural mesothelioma [feasibility study, patient accrual completed]
6. Member of an organized trial of recMAGE-A3 + AS15 antigen-specific cancer immunotherapeutic as adjuvant therapy in patients with completely resected MAGE-A3 positive stage IB-IIIA non-small cell lung cancer [phase III, patient accrual completed].
7. Member of an organized trial of WT1 peptide vaccination as adjuvant therapy in patients with completely resected WT1/HLA-A*2402 positive stage IB-II non-small cell lung cancer [randomized phase II, inauguration awaited].

Table 1. Number of patients

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

Table 2. Type of procedure – primary lung cancer

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

Table 3. Overall survival rates

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

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

List of papers published in 2013
Journal

1. Aokage K, Yoshida J, Ishii G, Matsumura Y, Haruki T, Hishida T, Nagai K. Identification of early t1b lung adenocarcinoma based on thin-section computed tomography findings. J Thorac Oncol, 8:1289-1294, 2013
2. Zenke Y, Ishii G, Ohe Y, Kaseda K, Yoshida T, Matsumoto S, Umemura S, Yoh K, Niho S, Goto K, Ohmatsu H, Kuwata T, Nagai K, Ochiai A. Aldehyde dehydrogenase 1 expression in cancer cells could have prognostic value for patients with non-small cell lung cancer who are treated with neoadjuvant therapy: identification of prognostic microenvironmental factors after chemoradiation. Pathol Int, 63:599-606, 2013
3. Kirita K, Ishii G, Matsuwaki R, Matsumura Y, Umemura S, Matsumoto S, Yoh K, Niho S, Goto K, Ohmatsu H, Ohe Y, Nagai K, Ochiai A. Identification of biological properties of intralymphatic tumor related to the development of lymph node metastasis in lung adenocarcinoma. PLoS One, 8:e83537, 2013
4. Ichinokawa H, Ishii G, Nagai K, Kawase A, Yoshida J, Nishimura M, Hishida T, Ogasawara N, Tsuchihara K, Ochiai A. Distinct clinicopathologic characteristics of lung mucinous adenocarcinoma with KRAS mutation. Hum Pathol, 44:2636-2642, 2013
5. Takahashi A, Ishii G, Kinoshita T, Yoshida T, Umemura S, Hishida T, Yoh K, Niho S, Goto K, Ohmatsu H, Ohe Y, Nagai K, Ochiai A. Identification of prognostic immunophenotypic features in cancer stromal cells of high-grade neuroendocrine carcinomas of the lung. J Cancer Res Clin Oncol, 139:1869-1878, 2013
6. Yoshida T, Ishii G, Goto K, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Nagai K, Ohe Y, Ochiai A. Solid predominant histology predicts EGFR tyrosine kinase inhibitor response in patients with EGFR mutation-positive lung adenocarcinoma. J Cancer Res Clin Oncol, 139:1691-1700, 2013
7. Kinoshita T, Yoshida J, Ishii G, Aokage K, Hishida T, Nagai K. The differences of biological behavior based on the clinicopathological data between resectable large-cell neuroendocrine carcinoma and small-cell lung carcinoma. Clin Lung Cancer, 14:535-540, 2013
8. Kaseda K, Ishii G, Aokage K, Takahashi A, Kuwata T, Hishida T, Yoshida J, Kohno M, Nagai K, Ochiai A. Identification of intravascular tumor microenvironment features predicting the recurrence of pathological stage I lung adenocarcinoma. Cancer Sci, 104:1262-1269, 2013
9. Niho S, Kenmotsu H, Sekine I, Ishii G, Ishikawa Y, Noguchi M, Oshita F, Watanabe S, Nakajima R, Tada H, Nagai K. Combination chemotherapy with irinotecan and cisplatin for large-cell neuroendocrine carcinoma of the lung: a multicenter phase II study. J Thorac Oncol, 8:980-984, 2013
10. Takuwa T, Yoshida J, Ono S, Hishida T, Nishimura M, Aokage K, Nagai K. Low-fat diet management strategy for chylothorax after pulmonary resection and lymph node dissection for primary lung cancer. J Thorac Cardiovasc Surg, 146:571-574, 2013
11. Nishijima N, Ishii G, Nagai K, Atsumi N, Aokage K, Tokunaga Y, Ichinokawa H, Ohe Y, Ochiai A. Cancer-initiating cell marker-positive cells generate metastatic tumors that recapitulate the histology of the primary tumors. Pathol Int, 63:94-101, 2013
12. Shiozawa T, Ishii G, Goto K, Nagai K, Mimaki S, Ono S, Niho S, Fujii S, Ohe Y, Tsuchihara K, Ochiai A. Clinicopathological characteristics of EGFR mutated adenosquamous carcinoma of the lung. Pathol Int, 63:77-84, 2013
13. Asamura H, Hishida T, Suzuki K, Koike T, Nakamura K, Kusumoto M, Nagai K, Tada H, Mitsudomi T, Tsuboi M, Shibata T, Fukuda H. Radiographically determined noninvasive adenocarcinoma of the lung: survival outcomes of Japan Clinical Oncology Group 0201. J Thorac Cardiovasc Surg, 146:24-30, 2013
14. Kinoshita T, Ishii G, Hiraoka N, Hirayama S, Yamauchi C, Aokage K, Hishida T, Yoshida J, Nagai K, Ochiai A. Forkhead box P3 regulatory T cells coexisting with cancer associated fibroblasts are correlated with a poor outcome in lung adenocarcinoma. Cancer Sci, 104:409-415, 2013
15. Hishida T, Yoshida J, Ishii G, Nagai K. Reply to Wang et al. Eur J Cardiothorac Surg, 43:1270, 2013
16. Takahashi Y, Ishii G, Aokage K, Hishida T, Yoshida J, Nagai K. Distinctive histopathological features of lepidic growth predominant node-negative adenocarcinomas 3-5 cm in size. Lung Cancer, 79:118-124, 2013
17. Ono S, Ishii G, Nagai K, Takuwa T, Yoshida J, Nishimura M, Hishida T, Aokage K, Fujii S, Ikeda N, Ochiai A. Podoplanin-positive cancer-associated fibroblasts could have prognostic value independent of cancer cell phenotype in stage I lung squamous cell carcinoma: usefulness of combining analysis of both cancer cell phenotype and cancer-associated fibroblast phenotype. Chest, 143:963-970, 2013
18. Hishida T, Yoshida J, Maeda R, Ishii G, Aokage K, Nishimura M, Nagai K. Prognostic impact of intratumoural microvascular invasion and microlymphatic permeation on node-negative non-small-cell lung cancer: which indicator is the stronger prognostic factor? Eur J Cardiothorac Surg, 43:772-777, 2013
19. Ohtaki Y, Hishida T, Yoshida J, Ishii G, Kawase A, Aokage K, Nishimura M, Nagai K. The clinical outcome of non-small cell lung cancer patients with adjacent lobe invasion: the optimal classification according to the status of the interlobar pleura at the invasion point. Eur J Cardiothorac Surg, 43:302-309, 2013
20. Asai M, Akizuki N, Fujimori M, Shimizu K, Ogawa A, Matsui Y, Akechi T, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Impaired mental health among the bereaved spouses of cancer patients. Psychooncology, 22:995-1001, 2013
21. Kawase A, Yoshida J, Miyaoka E, Asamura H, Fujii Y, Nakanishi Y, Eguchi K, Mori M, Sawabata N, Okumura M, Yokoi K. Visceral pleural invasion classification in non-small-cell lung cancer in the 7th edition of the tumor, node, metastasis classification for lung cancer: validation analysis based on a large-scale nationwide database. J Thorac Oncol, 8:606-611, 2013

Department of Thoracic Oncology

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

Introduction

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

Routine activities

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

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

Research activities

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

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

Clinical trials

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

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

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

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

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

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

Table 1. Number of patients in 2013

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

Table 2. Initial treatment of lung cancer in 2013

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

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

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

List of papers published in 2013
Journal

1. Zenke Y, Ishii G, Ohe Y, Kaseda K, Yoshida T, Matsumoto S, Umemura S, Yoh K, Niho S, Goto K, Ohmatsu H, Kuwata T, Nagai K, Ochiai A. Aldehyde dehydrogenase 1 expression in cancer cells could have prognostic value for patients with non-small cell lung cancer who are treated with neoadjuvant therapy: identification of prognostic microenvironmental factors after chemoradiation. Pathol Int, 63:599-606, 2013
2. Kirita K, Ishii G, Matsuwaki R, Matsumura Y, Umemura S, Matsumoto S, Yoh K, Niho S, Goto K, Ohmatsu H, Ohe Y, Nagai K, Ochiai A. Identification of biological properties of intralymphatic tumor related to the development of lymph node metastasis in lung adenocarcinoma. PLoS One, 8:e83537, 2013
3. Ogawa T, Niho S, Nagai S, Kojima T, Nishimura Y, Ohe Y, Kondo N, Yamaguchi T, Endo K, Izumi K, Minami H. Moderate renal dysfunction may not require a cisplatin dose reduction: a retrospective study of cancer patients with renal impairment. Int J Clin Oncol, 18:977-982, 2013
4. Umemura S. Management of leptomeningeal metastasis in patients with lung cancer. Lung Cancer Manag, 6:445-447, 2013
5. Takahashi A, Ishii G, Kinoshita T, Yoshida T, Umemura S, Hishida T, Yoh K, Niho S, Goto K, Ohmatsu H, Ohe Y, Nagai K, Ochiai A. Identification of prognostic immunophenotypic features in cancer stromal cells of high-grade neuroendocrine carcinomas of the lung. J Cancer Res Clin Oncol, 139:1869-1878, 2013

6. Yoshida T, Ishii G, Goto K, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Nagai K, Ohe Y, Ochiai A. Solid predominant histology predicts EGFR tyrosine kinase inhibitor response in patients with EGFR mutation-positive lung adenocarcinoma. J Cancer Res Clin Oncol, 139:1691-1700, 2013

7. Goto K, Nishio M, Yamamoto N, Chikamori K, Hida T, Maemondo M, Katakami N, Kozuki T, Yoshioka H, Seto T, Fukuyama T, Tamura T. A prospective, phase II, open-label study (JO22903) of first-line erlotinib in Japanese patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC). Lung Cancer, 82:109-114, 2013

8. Katakami N, Atagi S, Goto K, Hida T, Horai T, Inoue A, Ichinose Y, Koboyashi K, Takeda K, Kiura K, Nishio K, Seki Y, Ebisawa R, Shahidi M, Yamamoto N. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol, 31:3335-3341, 2013

9. Suzuki A, Mimaki S, Yamane Y, Kawase A, Matsushima K, Suzuki M, Goto K, Sugano S, Esumi H, Suzuki Y, Tsuchihara K. Identification and characterization of cancer mutations in Japanese lung adenocarcinoma without sequencing of normal tissue counterparts. PLoS One, 8:e73484, 2013

10. Nakayama Y, Ikeda M, Kojima M, Goto K, Hara M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Okusaka T. Successful everolimus treatment in a patient with advanced pancreatic neuroendocrine tumor who developed everolimus-induced interstitial lung disease on two occasions: a case report. Chemotherapy, 59:74-78, 2013

11. Suzuki M, Makinoshima H, Matsumoto S, Suzuki A, Mimaki S, Matsushima K, Yoh K, Goto K, Suzuki Y, Ishii G, Ochiai A, Tsuta K, Shibata T, Kohno T, Esumi H, Tsuchihara K. Identification of a lung adenocarcinoma cell line with CCDC6-RET fusion gene and the effect of RET inhibitors in vitro and in vivo. Cancer Sci, 104:896-903, 2013

12. Satouchi M, Okamoto I, Sakai H, Yamamoto N, Ichinose Y, Ohmatsu H, Nogami N, Takeda K, Mitsudomi T, Kasahara K, Negoro S. Efficacy and safety of weekly nab-paclitaxel plus carboplatin in patients with advanced non-small cell lung cancer. Lung Cancer, 81:97-101, 2013

13. Niho S, Kenmotsu H, Sekine I, Ishii G, Ishikawa Y, Noguchi M, Oshita F, Watanabe S, Nakajima R, Tada H, Nagai K. Combination chemotherapy with irinotecan and cisplatin for large-cell neuroendocrine carcinoma of the lung: a multicenter phase II study. J Thorac Oncol, 8:980-984, 2013

14. Suzuki T, Shibata T, Takaya K, Shiraishi K, Kohno T, Kunitoh H, Tsuta K, Furuta K, Goto K, Hosoda F, Sakamoto H, Motohashi H, Yamamoto M. Regulatory nexus of synthesis and degradation deciphers cellular Nrf2 expression levels. Mol Cell Biol, 33:2402-2412, 2013

15. Seto T, Kiura K, Nishio M, Nakagawa K, Maemondo M, Inoue A, Hida T, Yamamoto N, Yoshioka H, Harada M, Ohe Y, Nogami N, Takeuchi K, Shimada T, Tanaka T, Tamura T. CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. Lancet Oncol, 14:590-598, 2013

16. Niho S, Yamanaka T, Umemura S, Matsumoto S, Yoh K, Goto K, Ohmatsu H, Ohe Y. Renal toxicity caused by brand-name versus generic cisplatin: a comparative analysis. Jpn J Clin Oncol, 43:390-395, 2013

17. Niho S, Ikeda N, Michimae H, Suzuki K, Sakai H, Kaburagi T, Minato K, Kato T, Okamoto H, Seto T, Hosomi Y, Shimizu K, Oshita F, Kunitoh H, Tsuboi M, Takeuchi M, Watanabe K. Feasibility trial for adjuvant chemotherapy with docetaxel plus cisplatin followed by single agent long-term administration of S-1 chemotherapy in patients with completely resected non-small cell lung cancer: Thoracic Oncology Research Group Study 0809. Br J Cancer, 109:545-551, 2013

18. Ohashi Y, Uemura Y, Fujisaka Y, Sugiyama T, Ohmatsu H, Katsumata N, Okamoto R, Saijo N, Hotta T. Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: Individual patient data from Japanese randomized, placebo-controlled trials. Cancer Sci, 104:481-485, 2013

19. Yoshida T, Yoh K, Goto K, Niho S, Umemura S, Ohmatsu H, Ohe Y. Safety and efficacy of platinum agents plus etoposide for patients with small cell lung cancer with interstitial lung disease. Anticancer Res, 33:1175-1179, 2013

20. Shiozawa T, Ishii G, Goto K, Nagai K, Mimaki S, Ono S, Niho S, Fujii S, Ohe Y, Tsuchihara K, Ochiai A. Clinicopathological characteristics of EGFR mutated adenosquamous carcinoma of the lung. Pathol Int, 63:77-84, 2013

21. Nishijima N, Ishii G, Nagai K, Atsumi N, Aokage K, Tokunaga Y, Ichinokawa H, Ohe Y, Ochiai A. Cancer-initiating cell marker-positive cells generate metastatic tumors that recapitulate the histology of the primary tumors. Pathol Int, 63:94-101, 2013

22. Niho S, Kubota K, Nihei K, Sekine I, Sumi M, Sekiguchi R, Funai J, Enatsu S, Ohe Y, Tamura T. Dose-escalation study of thoracic radiotherapy in combination with pemetrexed plus Cisplatin followed by pemetrexed consolidation therapy in Japanese patients with locally advanced nonsquamous non-small-cell lung cancer. Clin Lung Cancer, 14:62-69, 2013

23. Horinouchi H, Sekine I, Sumi M, Noda K, Goto K, Mori K, Tamura T. Long-term results of concurrent chemoradiotherapy using cisplatin and vinorelbine for stage III non-small-cell lung cancer. Cancer Sci, 104:93-97, 2013

Department of Esophageal Surgery

Hiroyuki Daiko, Takeo Fujita

Introduction

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

Routine Activities

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

Clinical Activities

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

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

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

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

Table 1. Type of Procedure

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

List of papers published in 2013
Journal

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

Department of Gastric Surgery

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

Introduction

Patients with gastric tumors are treated by the Gastric Surgery Division in the Upper Abdominal Surgical Oncology Group. Our group consists of six staff surgeons, two senior residents and ten resident surgeons. The gastric tumors managed by the Division include not only common gastric adenocarcinomas but also adenocarcinomas of the esophagogastric junction (AEG), the incidence of which is increasing recently, probably due to reduction of *Helicobacter pylori* (HP)-infection rates, and gastric submucosal tumors (GIST etc.). Annually 260-300 patients are operated on either by means of conventional laparotomy or laparoscopic surgery. Laparoscopic gastrectomy with radical LNs dissection was introduced in 2010 to pursue minimal invasiveness and better quality of life (QOL) for the patients. The recent availability of the high-definition laparoscope has enabled more meticulous and accurate maneuvers. In 2013, about 70% of gastrectomies were performed under laparoscopy. The basis of our surgery is radical extirpation of cancer lesions, but at the same time organ functions and better QOL should be maintained. In addition, we attempt to obtain better clinical outcomes for patients with disease with dismal prognoses (scirrhous gastric cancer or with progressive lymph nodes metastasis) by surgery combined with recent advanced chemotherapy regimens, including molecular-targeting drugs (Trastuzumab).

Routine activities

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

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

Research activities & Clinical trials

We aggressively publish our clinical research data in domestic or international congresses. In addition, we participate in multi-institutional clinical trials conducted by the Japan Clinical Oncology Group (JCOG)-Gastric Surgery Study Group. Patients with

gastric cancer are, if eligible to each study, invited to take part in one of the ongoing clinical trials. Current ongoing multi-institutional clinical trials, in which we participate, are as follows:

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

Table 1. Number of patients

Gastric cancer	281
Others (GIST etc.)	6

Table 2. Type of procedure

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

Table 3. Survival rates of gastric cancer

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

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

List of papers published in 2013

Journal

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

Department of Colorectal Surgery

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

Introduction

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

Routine activities

The Colorectal and Pelvic Surgery Division comprises 7 consultants (5 colorectal surgeons and 2 urologists) and 11 residents. The outpatient clinic is open 5 days a week. More than 350 new patients with colorectal carcinomas and more than 150 new patients with other pelvic malignancies visited this Division during the last year. Treatment plans are discussed at a weekly conference on GI malignancies and at another weekly conference on pelvic malignancies. Many treatment modalities, such as local excision with or without adjuvant chemo- or radiotherapy and other minimally invasive forms of surgery using laparoscopy, have been introduced for the treatment of patients in the early stages of cancer. Laparoscopy-assisted operations (Lap-Ops) with wider lymphadenectomy of up to more than D2 are also increasingly being performed in patients with advanced colorectal carcinomas. Abdominoperineal resection (APR) has, in the past, been the standard surgery in patients with very low rectal cancer; however, partial anal sphincter preserving surgery such as intersphincteric resection (ISR) has been performed in about 400 patients with very low rectal tumors and has resulted in cure, preservation of anal function, and better QOL.

Research activities

1) A prospective randomized trial for extending the indications for Lap-Op (JCOG0404 CRC Surg-LAP vs. Open). The criteria for inclusion into this trial include (1) T3 and T4 tumors located at C, A, and S in the colon and Rs in the rectum; (2) stage N0-2; (3) stage M0; and (4) a maximum tumor size ≤8 cm. A total of 77 patients has been registered in this Division. This study is currently in progress.
2) Intersphincteric resection study (ISR Study). APR has been the standard surgery for very low rectal cancer located within 5 cm of the anal verge. However, a permanent colostomy causes severe impairment of QOL. This study was designed to evaluate the feasibility and the oncological and functional outcomes of ISR for treatment of very low rectal cancer. Curability with ISR was verified histologically, and acceptable oncological and functional outcomes were obtained by performing ISR in patients with very low rectal cancer. However, patients need to be informed preoperatively regarding the potential functional adverse effects after ISR. This study is in progress, and 43 patients have been registered. The final results will be obtained soon.
3) Bladder-sparing surgery for locally advanced rectal cancer involving the prostate and/or seminal vesicles. Total pelvic exenteration (TPE) is the standard procedure in patients with locally advanced rectal cancer involving the prostate and seminal vesicles. This study aims to evaluate the feasibility of bladder-sparing surgery as an alternative to TPE. This procedure has been performed in 34 patients with primary or recurrent tumors and permits conservative surgery in selected patients with advanced rectal cancer involving the prostate and/or seminal vesicles without compromising local control. The QOL of these patients appears to be better. This study is also in progress.
4) A prospective randomized trial for the feasibility and effect of lateral node dissection in low rectal cancer–(Total) Mesorectal Excision (ME) vs. Lateral Node Dissection with preservation of autonomic nerves (D3 with nerve-sparing) [JCOG0212 CRC Surg.]. This study aims to evaluate the feasibility and effects of lateral node dissection in patients

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

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

Clinical trials

Other clinical trials are also in progress as follows.

- The role of diverting stoma in low anterior resection for rectal cancer – A prospective multi-center study under the Japanese Society for Cancer of the Colon and Rectum (JSCCR)
- Comparing surgical site infection rates in colorectal surgery following closure of abdominal wounds with metallic skin staples or subcuticular absorbing-monofilament suture; A prospective randomized trial
- A phase I study of preoperative chemoradiotherapy with S-1+L-OHP for locally advanced rectal cancer
- A phase I/II trial of chemoradiotherapy concurrent with S-1 plus MMC in patients with clinical stage II/III squamous cell carcinoma of the anal canal. (JCOG0903)
- A randomized study of conventional technique vs. no-touch isolation technique. (JCOG1006)
- A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer (JCOG1007)
- A randomized Phase III study of mFOLFOX7 or CAPOX plus bevacizumab versus 5-fluorouracil/leucovorin or capecitabine plus bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer (JCOG1018)
- A randomized controlled trial comparing laparoscopic surgery with open surgery in palliative resection of primary tumor in incurable Stage IV colorectal cancer (JCOG1107)
- A Phase II/III randomized multicenter trial of intersphincteric resection (ISR) with or without preoperative chemotherapy for very low-lying rectal cancer.
- A prospective cohort study of Reduced Port Surgery for colorectal cancer
- A prospective study of urinary and sexual dysfunction after surgery for rectal cancer
- A phase II study of neoadjuvant mFOLFOX6 (+ cetuximab) in patients with resectable pelvic recurrences after rectal cancer surgery

Table 1. Number of patients (2013.1-2013.12)

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

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

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

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

Table 3. Survival rates

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

OP:1991.1-2006.12

List of papers published in 2013
Journal

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

Department of Gastrointestinal Oncology

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

Introduction

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

Routine activities

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

Research activities

Phase I

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

Esophageal Cancer (EC)

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

Gastric Cancer (GC)

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

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

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

Colorectal Cancer (CRC)

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

Clinical trials

Esophageal Cancer (EC)

A non-randomized confirmatory study of definitive chemoradiotherapy including salvage treatment in patients with clinical stage II/III esophageal carcinoma (JCOG 0909) and a three-arm randomized phase III study comparing preoperative CDDP+5-FU versus docetaxel+CF versus CF-radiation followed by esophagectomy with D2-3 lymphadenectomy for locally advanced esophageal squamous cell cancer (JCOG1109) is ongoing. In addition, a multicenter phase II trial of BKM120 in patients with advanced esophagus cancer has been opened.

Gastric Cancer (GC)

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

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

The enrollment for a multicenter global phase II/III trial comparing trastuzumab emtansine to taxane in HER2-positive GC patients (GATSBY) and a multicenter phase III trial comparing DCS to cisplatin plus S-1 (JCOG 1013), a multicenter phase II trial comparing 12 months of S-1 to 6 months of S-1 as an adjuvant chemotherapy (JCOG 1104) are ongoing.

Colorectal Cancer (CRC)

An international phase III trial called the

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

Table 1. Number of new patients

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

Table 2. Treatment

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

Table 3. Survival rates

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

List of papers published in 2013
Journal

1. Andre T, Iveson T, Labianca R, Meyerhardt JA, Souglakos I, Yoshino T, Paul J, Sobrero A, Taieb J, Shields AF, Ohtsu A, Grothey A, Sargent DJ. The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration: Prospective Combined Analysis of Phase III Trials Investigating Duration of Adjuvant Therapy with the FOLFOX (FOLFOX4 or Modified FOLFOX6) or XELOX (3 versus 6 months) Regimen for Patients with Stage III Colon Cancer: Trial Design and Current Status. Curr Colorectal Cancer Rep, 9:261-269, 2013
2. Bando H, Yoshino T, Shinozaki E, Nishina T, Yamazaki K, Yamaguchi K, Yuki S, Kajiura S, Fujii S, Yamanaka T, Tsuchihara K, Ohtsu A. Simultaneous identification of 36 mutations in KRAS codons 61 and 146, BRAF, NRAS, and PIK3CA in a single reaction by multiplex assay kit. BMC Cancer, 13:405, 2013
3. Doi T, Hamaguchi T, Shirao K, Chin K, Hatake K, Noguchi K, Otsuki T, Mehta A, Ohtsu A. Evaluation of safety, pharmacokinetics, and efficacy of vorinostat, a histone deacetylase inhibitor, in the treatment of gastrointestinal (GI) cancer in a phase I clinical trial. Int J Clin Oncol, 18:87-95, 2013
4. Doi T, Muro K, Yoshino T, Fuse N, Ura T, Takahari D, Feng HP, Shimamoto T, Noguchi K, Ohtsu A. Phase 1 pharmacokinetic study of MK-0646 (dalotuzumab), an anti-insulin-like growth factor-1 receptor monoclonal antibody, in combination with cetuximab and irinotecan in Japanese patients with advanced colorectal cancer. Cancer Chemother Pharmacol, 72:643-652, 2013
5. Doi T, Ohtsu A, Fuse N, Yoshino T, Tahara M, Shibayama K, Takubo T, Weinreich DM. Phase 1 study of trebananib (AMG 386), an angiogenesis targeting angiopoietin-1/2 antagonist, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 71:227-235, 2013
6. Fuse N, Nagahisa-Oku E, Doi T, Sasaki T, Nomura S, Kojima T, Yano T, Tahara M, Yoshino T, Ohtsu A. Effect of RECIST revision on classification of target lesions and overall response in advanced gastric cancer patients. Gastric Cancer, 16:324-328, 2013
7. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouche O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet, 381:303-312, 2013
8. Kanda T, Nishida T, Wada N, Kobayashi O, Yamamoto M, Sawaki A, Boku N, Koseki M, Doi T, Toh Y, Kakeji Y, Sugiyama T, Komatsu Y, Kikuchi S, Ogoshi K, Katai H, Miyachi K, Hirota S, Ohtsu A. Adjuvant therapy with imatinib mesylate after resection of primary high-risk gastrointestinal stromal tumors in Japanese patients. Int J Clin Oncol, 18:38-45, 2013

9. Kobayashi Y, Fukui T, Ito S, Shitara K, Ito S, Hatooka S, Mitsudomi T. Pulmonary metastasectomy for gastric cancer: a 13-year single-institution experience. Surg Today, 43:1382-1389, 2013

10. Makuuchi Y, Honda K, Osaka Y, Kato K, Kojima T, Daiko H, Igaki H, Ito Y, Hoshino S, Tachibana S, Watanabe T, Furuta K, Sekine S, Umaki T, Watabe Y, Miura N, Ono M, Tsuchida A, Yamada T. Soluble interleukin-6 receptor is a serum biomarker for the response of esophageal carcinoma to neoadjuvant chemoradiotherapy. Cancer Sci, 104:1045-1051, 2013

11. Nishida T, Doi T. Rechallenge of drugs in the era of targeted therapy. Lancet Oncol, 14:1143-1145, 2013

12. Oba K, Paoletti X, Alberts S, Bang YJ, Benedetti J, Bleiberg H, Catalano P, Lordick F, Michiels S, Morita S, Ohashi Y, Pignon JP, Rougier P, Sasako M, Sakamoto J, Sargent D, Shitara K, Cutsem EV, Buyse M, Burzykowski T. Disease-free survival as a surrogate for overall survival in adjuvant trials of gastric cancer: a meta-analysis. J Natl Cancer Inst, 105:1600-1607, 2013

13. Okamoto W, Yoshino T, Takahashi T, Okamoto I, Ueda S, Tsuya A, Boku N, Nishio K, Fukuoka M, Yamamoto N, Nakagawa K. A phase I, pharmacokinetic and pharmacodynamic study of nimotuzumab in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 72:1063-1071, 2013

14. Okano S, Yoshino T, Fujii M, Onozawa Y, Kodaira T, Fujii H, Akimoto T, Ishikura S, Oguchi M, Zenda S, de Blas B, Tahara M, Beier F. Phase II study of cetuximab plus concomitant boost radiotherapy in Japanese patients with locally advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol, 43:476-482, 2013

15. Paoletti X, Oba K, Bang YJ, Bleiberg H, Boku N, Bouche O, Catalano P, Fuse N, Michiels S, Moehler M, Morita S, Ohashi Y, Ohtsu A, Roth A, Rougier P, Sakamoto J, Sargent D, Sasako M, Shitara K, Thuss-Patience P, Van Cutsem E, Burzykowski T, Buyse M. Progression-free survival as a surrogate for overall survival in advanced/recurrent gastric cancer trials: a meta-analysis. J Natl Cancer Inst, 105:1667-1670, 2013

16. Shirao K, Boku N, Yamada Y, Yamaguchi K, Doi T, Goto M, Nasu J, Denda T, Hamamoto Y, Takashima A, Fukuda H, Ohtsu A. Randomized Phase III study of 5-fluorouracil continuous infusion vs. sequential methotrexate and 5-fluorouracil therapy in far advanced gastric cancer with peritoneal metastasis (JCOG0106). Jpn J Clin Oncol, 43:972-980, 2013

17. Shitara K, Matsuo K, Muro K, Doi T, Ohtsu A. Progression-free survival and post-progression survival in patients with advanced gastric cancer treated with first-line chemotherapy. J Cancer Res Clin Oncol, 139:1383-1389, 2013

18. Shitara K, Yuki S, Yamazaki K, Naito Y, Fukushima H, Komatsu Y, Yasui H, Takano T, Muro K. Validation study of a prognostic classification in patients with metastatic colorectal cancer who received irinotecan-based second-line chemotherapy. J Cancer Res Clin Oncol, 139:595-603, 2013

19. Takahashi H, Kaniwa N, Saito Y, Sai K, Hamaguchi T, Shirao K, Shimada Y, Matsumura Y, Ohtsu A, Yoshino T, Takahashi A, Odaka Y, Okuyama M, Sawada J, Sakamoto H, Yoshida T. Identification of a candidate single-nucleotide polymorphism related to chemotherapeutic response through a combination of knowledge-based algorithm and hypothesis-free genomic data. J Biosci Bioeng, 116:768-773, 2013

20. Takahashi S, Konishi M, Kinoshita T, Gotohda N, Kato Y, Saito N, Sugito M, Yoshino T. Predictors for early recurrence after hepatectomy for initially unresectable colorectal liver metastasis. J Gastrointest Surg, 17:939-948, 2013

21. Watanabe T, Yoshino T, Uetake H, Yamazaki K, Ishiguro M, Kurokawa T, Saijo N, Ohashi Y, Sugihara K. KRAS mutational status in Japanese patients with colorectal cancer: results from a nationwide, multicenter, cross-sectional study. Jpn J Clin Oncol, 43:706-712, 2013

22. Yoshino T, Hasegawa Y, Takahashi S, Monden N, Homma A, Okami K, Onozawa Y, Fujii M, Taguchi T, de Blas B, Beier F, Tahara M. Platinum-based chemotherapy plus cetuximab for the first-line treatment of Japanese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: results of a phase II trial. Jpn J Clin Oncol, 43:524-531, 2013

23. Yoshino T, Yamazaki K, Yamaguchi K, Doi T, Boku N, Machida N, Onozawa Y, Asayama M, Fujino T, Ohtsu A. A phase I study of intravenous aflibercept with FOLFIRI in Japanese patients with previously treated metastatic colorectal cancer. Invest New Drugs, 31:910-917, 2013

24. Koizumi W, Yamaguchi K, Hosaka H, Takinishi Y, Nakayama N, Hara T, Muro K, Baba H, Sasaki Y, Nishina T, Fuse N, Esaki T, Takagi M, Gotoh M, Sasaki T. Randomised phase II study of S-1/cisplatin plus TSU-68 vs S-1/cisplatin in patients with advanced gastric cancer. Br J Cancer, 109:2079-2086, 2013

25. Oba K, Paoletti X, Bang YJ, Bleiberg H, Burzykowski T, Fuse N, Michiels S, Morita S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, Sasako M, Shitara K, Tsuburaya A, Van Cutsem E, Buyse M. Role of chemotherapy for advanced/recurrent gastric cancer: an individual-patient-data meta-analysis. Eur J Cancer, 49:1565-1577, 2013

Department of Digestive Endoscopy

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Introduction

The Digestive Endoscopy Division covers the fields of the gastrointestinal (GI) tract and head and neck regions. In 2013, a total of 11,696 examinations were performed. A narrow band imaging (NBI) system using the LUCERA spectrum (Olympus Optical Co., Ltd.) has been included for routine examination in 6 endoscopy rooms since September 2009. In addition, A Blue LASER imaging (BLI) system was installed in 2013. Furthermore, endoscopic treatments such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), percutaneous endoscopic gastrostomy (PEG), endoscopic balloon dilation (EBD), radial incision and cutting (RIC), and photodynamic therapy (PDT) have been performed.

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

Routine activities

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

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

Research activities

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

In contrast, developing research into novel endoscopy systems is being performed. Hypoxia imaging is used for the detection of neoplastic lesions of the head and neck and alimentary tracts, with blue visualized images. A first in-human clinical trail of hypoxia imaging was finished. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and nanoparticles of the rare earth, doped yttrium oxide. This system is capable of penetrating through the intestinal wall and obtaining images. Furthermore, molecular imaging endoscopy using this system with an InGaAs CCD has been developed, since nanoparticles of rare earth act as fluorescent agents. With a low-

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

Clinical trials

A wide range of many prospective clinical trials is ongoing into the endoscopic treatment of cancers of the esophagus, stomach, and colorectum, as follows: a first in-human clinical trial of hypoxia imaging for neoplasia of alimentary tract in a single unit; a phase II clinical trial for BD stent implantation for benign esophageal stricture; a clinical trial for photodynamic diagnosis using 5-ALA; a multicenter clinical trials of a follow-up study after EMR of m1-3 esophageal cancers; a phase I/II study of PDT using Laserphyrin in residual/recurrent cases followed by chemoradiation for esophageal cancers; a phase II trial of combined treatment with endoscopic mucosal resection and chemoradiotherapy for clinical stage I esophageal carcinoma (JCOG0508); a multicenter clinical study on enrollment of early gastric cancer following endoscopic treatment with an enrollment system using the Web; a multicenter clinical trial of ESD for undifferentiated gastric cancer (JCOG1009); a multicenter clinical study regarding residual/recurrent rates and observation periods of endoscopic piecemeal mucosal resection (EPMR) for colorectal neoplastic lesions; and the Japan Polyp Study (JPS) for determination of observation periods after endoscopic treatment for colorectal polyps.

Table 1. Number of Patients Examined in 2009-2013

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

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

Table 2. Endoscopic procedures in 2013

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

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

List of papers published in 2013
Journal

1. Hatogai K, Oono Y, Fu KI, Odagaki T, Ikematsu H, Kojima T, Yano T, Kaneko K. Unexpected endoscopic full-thickness resection of a duodenal neuroendocrine tumor. World J Gastroenterol, 19:4267-4270, 2013
2. Ikematsu H, Singh R, Yoda Y, Matsuda T, Saito Y. Follow up after endoscopic resection in submucosal invasive colorectal cancers. Dig Endosc, 25 Suppl 2:6-10, 2013
3. Ikematsu H, Yoda Y, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, Fujii T, Oono Y, Sakamoto T, Nakajima T, Takao M, Shinohara T, Murakami Y, Fujimori T, Kaneko K, Saito Y. Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology, 144:551-559; quiz e514, 2013
4. Kaneko K, Yano T, Minashi K, Kojima T, Ito M, Satake H, Yajima Y, Yoda Y, Ikematsu H, Oono Y, Hayashi R, Onozawa M, Ohtsu A. Treatment strategy for superficial pharyngeal squamous cell carcinoma synchronously combined with esophageal cancer. Oncology, 84:57-64, 2013
5. Miyamoto H, Oono Y, Fu KL, Ikematsu H, Fujii S, Kojima T, Yano T, Ochiai A, Sasaki Y, Kaneko K. Morphological change of a laterally spreading rectal tumor over a short period. BMC Gastroenterol, 13:129, 2013
6. Nakajima T, Saito Y, Tanaka S, Iishi H, Kudo S, Ikematsu H, Igarashi M, Saitoh Y, Inoue Y, Kobayashi K, Hisasbe T, Matsuda T, Ishikawa H, Sugihara K. Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surg Endosc, 27:3262-3270, 2013
7. Yano T, Yoda Y, Satake H, Kojima T, Yagishita A, Oono Y, Ikematsu H, Kaneko K. Radial incision and cutting method for refractory stricture after nonsurgical treatment of esophageal cancer. Endoscopy, 45:316-319, 2013
8. Yoda Y, Ikematsu H, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, Fujii T, Oono Y, Sakamoto T, Nakajima T, Takao M, Shinohara T, Fujimori T, Kaneko K, Saito Y. A large-scale multicenter study of long-term outcomes after endoscopic resection for submucosal invasive colorectal cancer. Endoscopy, 45:718-724, 2013

Department of Hepatobiliary and Pancreatic Surgery

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

Introduction

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

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

Routine activities

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

Research activities

1) Pancreatic cancer

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

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

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

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

2) Biliary tract cancer

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

JCOG1202 (ASCOT) is a phase III study to compare S-1 with surgery alone as adjuvant chemotherapy for patients with curatively resected extrahepatic bile duct cancer. Recruitment started in 2013.

3) Hepatocellular carcinoma

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

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

4) Liver metastasis from colorectal cancer

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

5) Immune-enhancing enteral diet (IED)

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

6) Surgical device efficacy

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

Table 1. Number of patients

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

Table 2. Type of procedure

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

Table 3. Survival rates

Diagnosis	No. of pts	5-yr survival(%)
Invasive pancreatic cancer	367	17.7
Hepatocellular carcinoma	350	48.5
Hepatic metastases	575	51.7
Intrahepatic cholangiocarcinoma	89	37.3
Extrahepatic bile duct cancer	254	47.2
Papilla Vater cancer	96	54.2
Gallbladder cancer	116	44.8

List of papers published in 2013
Journal

1. Kinoshita T, Gotohda N, Kato Y, Takahashi S, Konishi M, Kinoshita T. Laparoscopic proximal gastrectomy with jejunal interposition for gastric cancer in the proximal third of the stomach: a retrospective comparison with open surgery. Surg Endosc, 27:146-153, 2013
2. Sugimoto M, Gotohda N, Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Kojima M, Ochiai A, Zenda S, Akimoto T, Konishi M. Pancreatic resection for metastatic melanoma originating from the nasal cavity: a case report and literature review. Anticancer Res, 33:567-573, 2013
3. Nakajima K, Takahashi S, Saito N, Sugito M, Konishi M, Kinoshita T, Gotohda N, Kato Y. Efficacy of the predicted operation time (POT) strategy for synchronous colorectal liver metastasis (SCLM): feasibility study for staged resection in patients with a long POT. J Gastrointest Surg, 17:688-695, 2013
4. Takahashi S, Konishi M, Kinoshita T, Gotohda N, Kato Y, Saito N, Sugito M, Yoshino T. Predictors for early recurrence after hepatectomy for initially unresectable colorectal liver metastasis. J Gastrointest Surg, 17:939-948, 2013
5. Kobayashi S, Gotohda N, Kato Y, Takahashi S, Konishi M, Kinoshita T. Infection control for prevention of pancreatic fistula after pancreaticoduodenectomy. Hepatogastroenterology, 60:876-882, 2013
6. Sugimoto M, Gotohda N, Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Nomura S, Konishi M, Kaneko H. Risk factor analysis and prevention of postoperative pancreatic fistula after distal pancreatectomy with stapler use. J Hepatobiliary Pancreat Sci, 20:538-544, 2013
7. Sugimoto M, Kinoshita T, Shibasaki H, Kato Y, Gotohda N, Takahashi S, Konishi M. Short-term outcome of total laparoscopic distal gastrectomy for overweight and obese patients with gastric cancer. Surg Endosc, 27:4291-4296, 2013
8. Sugimoto M, Takahashi S, Gotohda N, Kato Y, Kinoshita T, Shibasaki H, Konishi M. Schematic pancreatic configuration: a risk assessment for postoperative pancreatic fistula after pancreaticoduodenectomy. J Gastrointest Surg, 17:1744-1751, 2013

Department of Hepatobiliary and Pancreatic Oncology

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Introduction

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

Routine activities

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

Research activities

Hepatocellular carcinoma (HCC)

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

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

Pancreatic cancer (PC)

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

Biliary tract cancer (BTC)

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

Hepatitis B viral (HBV) reactivation following chemotherapy

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

Clinical trials

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

HCC

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

BTC

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

PC

The enrollment for a randomized phase II trial of S-1 and concurrent radiotherapy with versus without induction chemotherapy for locally advanced pancreatic cancer (JCOG1106) has been completed. As sponsored trials, the enrollments for a phase II trial of Gem plus nab-paclitaxel for untreated metastatic PC and a phase III trial of a peptide vaccine (OCV-C01) for Gem refractory PC have been completed. A multicenter phase II trial of neoadjuvant S-1 and concurrent radiotherapy for borderline resectable pancreatic cancer (JASPAC05) is ongoing. A randomized phase II trial of mixed agents of S-1 plus leucovorin, TAS-118 vs. S-1 in Gem refractory PC patients is underway.

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

Table 1. Number of patients

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

Table 2. Type of procedure

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

Table 3. Survival rates

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

List of papers published in 2013
Journal

1. Suyama K, Ikeda M, Suzuki E, Kojima M, Mitsunaga S, Shimizu S, Ohno I, Takahashi H, Okuyama H, Kuwahara A, Okusaka T, Furuse J. Early relapse of unresectable gallbladder cancer after discontinuation of gemcitabine monotherapy administered for 5 years in a patient who had complete response to the treatment. Case Rep Oncol, 6:531-537, 2013
2. Nakayama Y, Ikeda M, Kojima M, Goto K, Hara M, Okuyama H, Takahashi H, Ohno I, Shimizu S, Mitsunaga S, Okusaka T. Successful everolimus treatment in a patient with advanced pancreatic neuroendocrine tumor who developed everolimus-induced interstitial lung disease on two occasions: a case report. Chemotherapy, 59:74-78, 2013
3. Ikeda M, Okusaka T, Furuse J, Mitsunaga S, Ueno H, Yamaura H, Inaba Y, Takeuchi Y, Satake M, Arai Y. A multi-institutional phase II trial of hepatic arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Cancer Chemother Pharmacol, 72:463-470, 2013
4. Morizane C, Okusaka T, Mizusawa J, Takashima A, Ueno M, Ikeda M, Hamamoto Y, Ishii H, Boku N, Furuse J. Randomized phase II study of gemcitabine plus S-1 versus S-1 in advanced biliary tract cancer: a Japan Clinical Oncology Group trial (JCOG 0805). Cancer Sci, 104:1211-1216, 2013
5. Inagaki M, Akechi T, Okuyama T, Sugawara Y, Kinoshita H, Shima Y, Terao K, Mitsunaga S, Ochiai A, Uchitomi Y. Associations of interleukin-6 with vegetative but not affective depressive symptoms in terminally ill cancer patients. Support Care Cancer, 21:2097-2106, 2013
6. Asai M, Akizuki N, Fujimori M, Shimizu K, Ogawa A, Matsui Y, Akechi T, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Impaired mental health among the bereaved spouses of cancer patients. Psychooncology, 22:995-1001, 2013
7. Otsuka T, Morizane C, Nara S, Ueno H, Kondo S, Shimada K, Kosuge T, Ikeda M, Hiraoka N, Okusaka T. Gemcitabine in patients with intraductal papillary mucinous neoplasm with an associated invasive carcinoma of the pancreas. Pancreas, 42:889-892, 2013
8. Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Furuse J, Inagaki M, Higashi S, Kato H, Terao K, Ochiai A. Serum levels of IL-6 and IL-1beta can predict the efficacy of gemcitabine in patients with advanced pancreatic cancer. Br J Cancer, 108:2063-2069, 2013
9. Sawada Y, Yoshikawa T, Fujii S, Mitsunaga S, Nobuoka D, Mizuno S, Takahashi M, Yamauchi C, Endo I, Nakatsura T. Remarkable tumor lysis in a hepatocellular carcinoma patient immediately following glypican-3-derived peptide vaccination: an autopsy case. Hum Vaccin Immunother, 9:1228-1233, 2013
10. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, Fukutomi A, Sugimori K, Baba H, Yamao K, Shimamura T, Sho M, Kitano M, Cheng AL, Mizumoto K, Chen JS, Furuse J, Funakoshi A, Hatori T, Yamaguchi T, Egawa S, Sato A, Ohashi Y, Okusaka T, Tanaka M. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol, 31:1640-1648, 2013
11. Kondo S, Ojima H, Tsuda H, Hashimoto J, Morizane C, Ikeda M, Ueno H, Tamura K, Shimada K, Kanai Y, Okusaka T. Clinical impact of c-Met expression and its gene amplification in hepatocellular carcinoma. Int J Clin Oncol, 18:207-213, 2013
12. Suzuki E, Ikeda M, Okusaka T, Nakamori S, Ohkawa S, Nagakawa T, Boku N, Yanagimoto H, Sato T, Furuse J. A multicenter phase II study of S-1 for gemcitabine-refractory biliary tract cancer. Cancer Chemother Pharmacol, 71:1141-1146, 2013
13. Ikeda M, Arai Y, Park SJ, Takeuchi Y, Anai H, Kim JK, Inaba Y, Aramaki T, Kwon SH, Yamamoto S, Okusaka T. Prospective study of transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: an Asian cooperative study between Japan and Korea. J Vasc Interv Radiol, 24:490-500, 2013
14. Ikeda M. Reactivation of hepatitis B virus in patients receiving chemotherapy. Jpn J Clin Oncol, 43:8-16, 2013
15. Ikeda M, Ioka T, Ito Y, Yonemoto N, Nagase M, Yamao K, Miyakawa H, Ishii H, Furuse J, Sato K, Sato T, Okusaka T. A multicenter phase II trial of S-1 with concurrent radiation therapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys, 85:163-169, 2013

Department of Urology

Yasuyuki Sakai, Yoshinobu Komai

Introduction

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

Routine activities

Outpatient activities: An outpatient clinic is open 2 days a week as a Urology Department. Flexible cystoscopy, abdominal ultrasonography, retrograde pyelography and some prostate biopsies are performed in the outpatient clinic. Superficial bladder cancer (G3, cis, or recurrent tumor) after TUR-Bt is treated by instillation of the BCG vaccine into the bladder. Advanced urogenital cancers including stage D2 prostate cancer are referred to the Medical Oncology Division for chemotherapy or hormone therapy. Extrinsic obstructions of the upper urinary tract that directly result from invasion of an adjacent malignancy or peritoneal metastasis are also treated. In most cases, internal stenting is better tolerated than percutaneous nephrostomy. Fifty-three patients newly received ureteral stents and 23 underwent nephrostomy for obstructive uropathy.

Inpatient activities: A daily conference is held with doctors of the Department of Pelvic Surgery on diagnosis and treatment of the patients with colorectal and urological cancer. We performed about 31 combination surgeries with colorectal surgeons. In the Department of Urology, 102 general anaesthesia surgeries, 76 spinal anesthesia surgeries and 42 prostate biopsies were performed.

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

Research activities

Minimum incision endoscopic surgery was introduced from 2011, which comprises a gasless, single-port access, cost-effective, and minimally invasive surgery. We intend to make this operation more sophisticated in coordination with the Department of Urology, Tokyo Medical and Dental University. In recent years, partial nephrectomy has become the standard treatment of T1 renal cell carcinoma instead of radical nephrectomy. We reported on the Synapse Vincent 3D image analysis system for kidney surgery. Its 3D images and surgical simulation helped not only surgeons in their performance of clampless partial nephrectomy but also assisted patients in their understanding of the operation. Total pelvic exenteration (TPE) is the standard procedure for locally advanced rectal cancer involving the prostate and seminal vesicles. We evaluated the feasibility of bladder-sparing surgery as an alternative to TPE. We performed concomitant prostatectomy and cysto-urethral anastomosis .

Clinical trials

1. A retrospective study of perioperative results in partial nephrectomy for renal cell carcinoma
2. An estimate of the prevalence of Lynch syndrome in upper urinary tract urothelial cancer
3. Development and validation of a nomogram to predict recurrences of upper urinary tract urothelial cancer in Japanese patients
4. A phase II clinical study of robotic assisted radical prostatectomy with the da Vinci S/Si Surgical System

Table 1. Number of patients

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

Table 2. Type of procedure

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

Table 3. Survival rates

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

List of papers published in 2013
Journal

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

Department of Musculoskeletal Oncology and Rehabilitation

Umio Yamaguchi

Introduction

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

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

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

Routine activities

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

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

List of papers published in 2013
Journal

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

Department of Hematology

Kunihiro Tsukasaki, Masahiko Nezu, Kuniaki Itoh, Hiromi Yuasa

Introduction

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

Routine Activities

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

Research activities

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

Clinical trials

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

induction treatments of melpharan, prednisolone, plus bortezomib, JCOG-MPB versus modified PETHEMA-MPB, in elderly patients or non-elderly patients refusing transplant with untreated symptomatic myeloma (JCOG1105); and a phase II study of mLSG15 chemotherapy followed by allo-HSCT, comparing the results with historical controls in JCOG9801 to evaluate the promising efficacy of allo-HSCT, possibly associated with a graft-versus-ATL effect, especially in view of a comparison with intensive chemotherapy (JCOG0907). A phase III study evaluating the efficacy of the combination of interferon-alpha (IFN) and zidovudine (AZT) as compared to watchful-waiting for indolent ATL (JCOG1111) has been initiated at our Department and the Department of Hematology at the National Cancer Center Hospital at Tsukiji under the highly advanced medical technology assessment system because IFN and AZT are not covered for ATL by the National Health Insurance system in Japan.

Table 1. Number of patients

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

Table 2. Type of procedure

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

List of papers published in 2013

Journal

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

Book

4. Tsukasaki K, Tobinai K. T-cell Lymphomas: 8. HTLV-1-Assorted T-cell Diseases. In: Francine Foss (ed), Spring Science/Business Media New York, USA, 2013

Department of Dentistry

Tetsuhito Konishi, Toshiro Miyata, Tomoko Kaneda

Introduction

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

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

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

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

Routine activities

We undertake efforts to prevent infection of wounds and aspiration pneumonia and to reduce other complications by oral hygiene management before and after surgery. To maintain postoperative functions of jaw defects, we are attempting to correct speech-language and eating functions by preparing appropriate artificial dentition and prostheses at an early stage, thereby improving the QOL of patients after treatment. For patients receiving chemotherapy and radiotherapy, we are supporting the continuation and completion of treatment by taking measures to prevent infections arising from the dentistry realm and mucositis and by reducing pain. In regard to delayed complications, we are undertaking preventive and treatment activities for multiple dental caries, osteomyelitis of the jaw, and necrosis of the jaw bone. Patients treated over the long-term with zoledronic acid or denosumab may develop osteoclast-modifying agent-related osteonecrosis of the jaw (OMAONJ) as a result of contamination of the oral cavity and tooth extraction; we are therefore undertaking measures to prevent/treat this complication.

By participating in multidisciplinary conferences, we apply prevailing practices and information updates to future medical care support. In 2013, the numbers of new and revisiting patients were 841 and 7108, respectively, and the total number of patients was 7949. These numbers represent an approximately 1.5-fold increase as compared to those in the first year when dentists at the National Cancer Center Hospital East began to hold full-time positions. We believe that the importance of supportive dental care in cancer has been recognized.

Research activities

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

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

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

Department of Pediatric Oncology

Ako Hosono

Introduction

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

Routine activities

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

Research activities

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

Clinical trials

Three clinical trials described below are currently active.

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

Table 1. Number of patients

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

Department of Anesthesiology and Intensive Care Unit

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

Introduction

The Department of Anesthesiology and Intensive Care Unit (ICU) consists of 5 staff members, including 4 JSA (Japan Society of Anesthesiologists) board certified anesthesiologists and two or three rotating residents. Each year, we provide more than 2,500 anesthesia services in 8 operating rooms and over 1200 patients are admitted to the ICU. A large number of operations in the Head and Neck Surgery Division and procedures involving a thoracotomy for lung and esophageal cancer are one of the features of this hospital. Accordingly a special anesthesia induction method for a difficult airway and use of the one-lung ventilation technique are often necessary for anesthesiologists. Currently, our ICU admits mainly postsurgical patients that have undergone major abdominal, thoracic and complex surgical procedures, as well as patients who have suffered from serious preoperative complications. Increasingly complex procedures are being performed on more seriously ill patients with coronary disease, chronic obstructive pulmonary disease (COPD), neurological disorders and so on. The ICU needs to play a more and more important role in postsurgical care for such patients. The goals of The Department of Anesthesiology and Intensive Care Unit are to provide anesthetic and perioperative care to patients, with their safety being the highest priority.

Routine activities

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

Research activities

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

Table 1. Number of Anesthesia Cases

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

Table 2. Number of Patients Admitted to the ICU

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

Department of Palliative Medicine

Hiroya Kinoshita, Yoshihisa Matsumoto, Kazuaki Hiraga, Yoichiro Higashi

Introduction

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

Routine activities

1. Palliative care unit

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

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

2. Outpatient clinic

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

3. Supportive care team

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

Research activities

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

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

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

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

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

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

List of papers published in 2013
Journal

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

Department of Psycho-Oncology Service

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

Introduction

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

Routine activities

The Psycho-Oncology Division is composed of 2 attending psychiatrists, 3 clinical psychologists, and 1 psychiatry resident. The clinical activities include psychiatric consultation, involving comprehensive assessment and addressing of psychiatric problems of cancer patients. The patients are either self-referred or referred by their oncologists in charge. The consultation data are shown in the Table. Psychiatric diagnosis is based on the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria. Consultation data also imclude individuals who are family members of cancer patients.

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

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

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

List of papers published in 2013
Journal

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

Supportive Care Team

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

Introduction

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

Routine activities

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

Research activities and Clinical trials

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

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

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

List of papers published in 2013
Journal

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

Department of Diagnostic Radiology

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

Introduction

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

Routine activities

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

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

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

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

Table 1. Number of Cases Examined

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

Research activities and Clinical trials

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

(1) Development of new Nuclear Medicine tracers

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

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

(2) Development of new CT technology

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

(3) Construction of a cancer image reference database

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

List of papers published in 2013

Journal

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

Department of Radiation Oncology

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

Introduction

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

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

Routine activities

At present, the staff of the Radiation Oncology Division consists of 7 consultant physicians (radiation oncologists), 15 radiation technologists, 3 medical physicists, 1 nurse, and 1 clerk. We have more than 1000 new cases for conventional RT and 2000 new patients for proton beam therapy every year, and the quality assurances of both conventional RT and PBT is performed by medical physicists and radiation technologists, and the conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. RT and PBT are routinely based on three-dimensional radiation therapy planning and PBT using RT-dedicated multi-detector-row helical computed tomography (CT) scanning in order to confirm the precise radiation dose to the targeted tumors. Respiratory-gating has been applied especially in radiotherapeutic management for patients with lung, esophagus and liver cancers.

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

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

Research activities

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

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

8) Exploration of biomarkers for head and neck cancer.

Clinical trials

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

1) JCOG0701: Accelerated fractionation vs. conventional fractionation radiation therapy for glottic cancer of T1-2N0M0 Phase III study.
2) JCOG0701-A1: Evaluation of single-nucleotide polymorphisms (SNPs) in the development of acute and late complications after accelerated fractionation and/or conventional fractionation radiation therapy for glottic cancer of T1-2N0M0.
3) JCOG1015: A phase II study of intensity modulated radiation therapy (IMRT) with chemotherapy for loco-regionally advanced nasopharyngeal cancer (NPC).
4) A phase II study of PBT for malignant melanoma of the nasal cavity.
5) A phase II trial of concurrent chemoradiotherapy with 5-FU plus cisplatin for resectable squamous cell carcinoma of the cervical esophagus.
6) A JROSG phase II trial of IMRT with concurrent chemoradiotherapy for resectable squamous cell carcinoma of the cervical esophagus.

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

Number of patients treated with radiotherapy during 2008-2012

	2008	2009	2010	2011	2012
New patients	1084	1230	1248	1305	1470
Head and neck cancers	211	281	220	223	183
Lung and mediastinal cancers	220	230	280	329	413
Breast cancers	264	281	283	325	362
Gastrointestinal cancers	203	202	219	176	188
Hepatobiliary tract cancers	47	46	54	38	69
Urological cancers	89	120	151	174	151
Bone and soft tissue cancers	8	6	15	2	10
Hematological cancers	33	27	6	19	24
Others	9	35	20	19	70

List of papers published in 2013
Journal

1. Kawashima M, Ariji T, Kameoka S, Ueda T, Kohno R, Nishio T, Arahira S, Motegi A, Zenda S, Akimoto T, Tahara M, Hayashi R. Locoregional control after intensity-modulated radiotherapy for nasopharyngeal carcinoma with an anatomy-based target definition. Jpn J Clin Oncol, 43:1218-1225, 2013
2. Matsubara K, Kohno R, Nishioka S, Shibuya T, Ariji T, Akimoto T, Saitoh H. Experimental evaluation of actual delivered dose using mega-voltage cone-beam CT and direct point dose measurement. Med Dosim, 38:153-159, 2013
3. Kiyozuka M, Akimoto T, Fukutome M, Motegi A, Mitsuhashi N. Radiation-induced dimer formation of EGFR: implications for the radiosensitizing effect of cetuximab. Anticancer Res, 33:4337-4346, 2013
4. Okano S, Yoshino T, Fujii M, Onozawa Y, Kodaira T, Fujii H, Akimoto T, Ishikura S, Oguchi M, Zenda S, de Blas B, Tahara M, Beier F. Phase II study of cetuximab plus concomitant boost radiotherapy in Japanese patients with locally advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol, 43:476-482, 2013
5. Sugimoto M, Gotohda N, Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Kojima M, Ochiai A, Zenda S, Akimoto T, Konishi M. Pancreatic resection for metastatic melanoma originating from the nasal cavity: a case report and literature review. Anticancer Res, 33:567-573, 2013

Department of Pathology and Clinical Laboratories

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

Introduction

The Department of Pathology and Clinical Laboratories (DPCL) is composed of two divisions; the Pathology Division (PD) and the Clinical Laboratory Division (CLD). Both divisions play a fundamental role in routine hospital service and support research activities at National Cancer Center Hospital East (NCCHE). In 2013, the CLD received ISO15189 accreditation ensuring the quality control of the laboratory tests performed in the department.

Seven pathologists, including 6 pathologists board-certified by the Japanese Society of Pathology are assigned to the PD. Also working in the Division are 6 clinical laboratory technicians. Two doctors and 3 technicians are cytology experts and cytoscreeners, respectively, board-certified by The Japanese Society of Clinical Cytology.

The CLD consists of 6 subsections for i) general laboratory medicine, ii) hematology, iii) biochemistry/serology, iv) Physiology, v) Bacteriology and vi) blood transfusion. A total of 13 full-time clinical laboratory technicians and 1 secretary are working at the CLD. From April in 2013, under the contract between the NCCHE and SRL, the role of three subsections (general laboratory medicine, hematology and biochemistry/serology) has been undertaken by an intramural referee laboratory, where 8 clinical technicians are working.

Routine activities

Primarily, the routine activities of the PD comprise surgical pathology. In 2013, 9168 biopsy specimens, including 852 frozen sections, and 2358 surgical specimens, were examined and pathologically diagnosed (see Table 1 for details). Three thousand nine hundred and thirty eight (3938) cytology specimens were evaluated (Table 2). Four autopsies were performed, and all cases were presented and discussed in clinicopathological conferences. Conference-style training sessions are open every Thursday morning for the residents.

The CLD provides accurate and reliable data to understand the patients' conditions and support prompt decision making for all clinicians working at the NCCHE (see Table 3 for details). The most of essential laboratory test services are available on a round-the-clock basis. Most of the general laboratory tests for hematology, biochemistry, serology and urinalysis were automatically performed by an automated analyzer, which enable the division to provide the results within one hour after samples submission. A special computer-based ordering system is equipped for ensuring sample-processing and data-transfer to and from outside commercial laboratories.

Research activities

All of the pathologists were involved in research activities at RCIO. All the technicians working in the Department are also highly motivated to develop advanced diagnostic technology and some results have been presented in several meetings including the one organized by the Japanese Society of Laboratory Medicine.

Clinical trials

The CLD participated practically in almost all of the clinical trials carried out at the NCCHE through the provision of laboratory data.

Table 1. Number of pathology samples examined at Pathology Division in 2013

Department	Biopsy	Surgical	Autopsy
Digestive Endoscopy	3828	0	0
Gastrointestinal Oncology	1083	2	0
Breast Surgery	652	330	0
Head and Neck Surgery	595	365	0
Thoracic Surgery	547	472	0
Thoracic Oncology	490	3	1
Hematology and medical oncology	481	4	1
Hepatobiliary and Pancreatic Oncology	372	1	2
Urology	241	82	0
Upper Abdominal Surgery	221	493	0
Radiation Oncology	204	0	0
Lower Abdominal Surgery	168	358	0
Orthopedics	90	36	0
Ambulant Treatment Center	80	9	0
Esophageal Surgery	39	186	0
Head and Neck Oncology	32	0	0
Obstetrics and Gynecology	16	0	0
Dental division	10	0	0
Anesthesiology	8	0	0
Dermatology	6	0	0
Plastic Surgery	3	16	0
Others	2	1	0
Total	9,168	2,358	4

Table 2. Number of cytology samples examined at the Pathology Division in 2013

Department	
Urology	835
Thoracic Oncology	793
Thoracic Surgery	706
Head and Neck Surgery	395
Hepatobiliary and Pancreatic Oncology	338
Upper Abdominal Surgery	247
Obstetrics and Gynecology	216
Hematology and medical oncology	131
Breast Surgery	115
Lower Abdominal Surgery	71
Gastrointestinal Oncology	41
Orthopedics	10
Head and Neck Oncology	10
Esophageal Surgery	8
Digestive Endoscopy	4
Ambulant Treatment Center	3
Radiation Oncology	2
Dermatology	1
Plastic Surgery	1
Others	11
Total	3,938

Table 3. Number of laboratory tests examined at the Clinical Laboratory Division in 2009-2013

Section	2009	2010	2011	2012	2013
General laboratory medicine	230,610	265,517	264,452	282,716	306,136
Hematology	560,110	589,144	622,666	676,889	712,962
Biochemistry	1,493,858	1,569,963	1,648,755	1,811,244	1,834,169
Serology	136,127	139,759	146,104	141,224	175,102
Bacteriology	22,466	21,978	21,657	25,112	26,870
Blood transfusion	24,181	22,441	21,895	20,550	19,853
Physiology	39,232	43,215	43,275	45,408	45,555
Total	2,506,584	2,652,017	2,768,804	3,003,143	3,120,647

Clinical Trial Coordination (& Support) Office

Toshihiko Doi, Miyuki Hara, Yumiko Uchiyama

Introduction

The Clinical Trial Coordination (& Support) Office aims to promote clinical trials on unapproved drugs and medical devices, with the goal of allowing patients to receive the benefits arising from life science research as quickly as possible. The mission of the Clinical trials management office (CTMO) is to facilitate the conduct of quality clinical trials at the National Cancer Center Hospital-East (NCCHE), especially those which are all conducted as a sponsored initiated trial, to achieve registration. The CTMO will also assist investigators with infrastructure support, including Institutional Review Board (IRB) and initial regulatory guidance. A total of 40 staff members support the CTMO:12 Clinical Research Coordinators(CRCs) (9 nurses and 3 pharmacists), 7 data managers, 6 medical technologists, and 15 secretaries.

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

Routine activities

The CTMO function forms the key relationship between the study investigators, sponsor/contract research organization (CRO), subjects and institutional organizations including the IRB, and the clinical trials office. Our role is critical in helping to ensure that assigned studies are conducted in accordance with human subjects' federal regulations/ guidelines regarding human subjects, and meet good clinical practice (GCP) standards. The number of the industry-sponsored registration trials is increasing year by year, and the increase in the rate of phase 1 trial is particularly striking. We supported 164 registration-directed clinical trials including 21 phase1 trials in 2013 (Table 1). These early clinical trials need more complicated and specific management rather than conventional trials. With the increasing number of phase1 trials as previously described, the supporting area covered by the CRCs will expand to encompass registration trials. All members of the CTMO will work together to contribute to reinforcing the clinical research capabilities and to making the CTMO a valuable unit for all members of our hospital. An operational committee is formed and meets with other core members including primary investigations from the clinical laboratory division, pharmacy division and nurse division, and the clinical study support office for the purpose of proper management of trials. Furthermore, we will contribute to the worldwide network system for phase 1 trials to establish the acceleration of the pre-clinical and clinical development of investigational anti-cancer agents.

Table 1. Supported Trials in Clinical Trial Coordination (& Support) Office in 2013

Phase	New (since 2013)	Ongoing
I	21	56
I/II	4	8
II	17	38
II/III	0	1
III	19	61
POS	0	3
Total	61	164

POS: post marketing study

Consultation, Counseling and Support Service Center

Yuichiro Ohe, Hatoe Sakamoto, Tokiko Suzuki, Yoko Iida, Erika Sekine, Chiharu Tanaka, Aiko Kotani, Mina Saito, Tomomi Ohsugi, Yukari Nishizaki, Satomi Tanaka, Kazuyuki Sawada

Introduction

Our Center staff members form "Cancer Counseling and Support Specialists". We provide psycho-social and spiritual support for cancer patients, families and caregivers with various anxieties and burdens during their course of illness. In our Division, Cancer counseling and support specialists deliver the various forms of support though the following four services: 1) counseling services; 2) coordination of community resources; 3) managing support group; and 4) information service.

Patients and Families Care Coordination

1. Patients and families counseling
   - Counseling Services face-to-face and telephone counseling
     In 2013, we received 4782 new consultations (Table 1). As for the patient's condition in the case of new consultations, an increasing numbers of patients have either not yet received initial treatment or are in the stage of receiving anti-cancer therapy (Table 2). Our services are available to patients and families throughout all phases of the caner continuum, including prevention, diagnosis, survivorship, terminal care, and bereavement.

2. Support group
   - Pancreatic Cancer Support Group
     This support group focuses on various pancreatic cancer-related topics including education, emotional support and pancreatic cancer treatments. This support group was held 7 times in 2013, with a total of 49 participants.

3. Community healthcare coordination

In the coordination function, cancer counseling and support specialists provide discharge planning and case management, linking patients with a variety of services necessary to meet each person's multiple needs.

During 2013, we had 3156 cases of community resources coordination. Other coordination-related events were as follows:

- Official Publication of *Kokuganhigashi News*
  This publication aims to provide information about our center and to gather new patients from other hospitals. We have published "*Kokuganhigashi News*" 4 times from January 2013 to December 2013. The publications were sent to 1800 hospitals in Japan.

- Meetings for regional collaboration
  The meetings were held twice in the year with a total of 288 participants.

- Medical pathway
  We developed a medical pathway to collaboration with the regional Tujinaka hospital, which resulted in increasing the numbers of patient referrals. As an example of collaboration, the doctors in our hospital worked at Tujinaka Hospital.

Training and Education of Cancer Counseling and Support Specialists

- Training Sessions for Cancer Consultation Worker in Chiba
  With the theme "Support for cancer patient employment", two training sessions were held in 2013 for Cancer counseling and support specialists. Cancer counseling and support specialists from 20 hospitals attended the sessions.

Table 1. Numbers of cases

	2010	2011	2012	2013
Total	8091	8604	9412	11940
New cases	4260	4700	4760	4782
The contents of consultation (New cases)				
Finding community resources	2032	2250	2475	2796
Coping with life changes	857	1046	990	588
Adjustment to diagnosis and treatment	547	570	499	525
Family counseling	148	124	85	57
Spiritual or religious concerns	60	36	38	27
Other	616	674	673	386

Table 2. New consultation data (N=4782, January_December,2013)

		N	%
Age	Mean±SD (median, range)	62.7±12.3(1-94)	
Inpatient/Outpatient	Inpatient	3518	73.6%
	Outpatient	1135	23.7%
	Other	129	2.7%
Cancer Site	Lung	969	20.3%
	Head and Neck	508	10.6%
	Colon	485	10.1%
	Stomach	347	7.3%
	Pancreas	335	7.0%
	Esophagus	329	6.9%
	Brest	287	6.0%
	HCC	210	4.4%
	Other	1312	27.1%
Treatment Profile	No diagnosis	80	1.7%
	Before first time cancer treatment	936	19.6%
	Receiving anti-cancer therapy	1302	27.2%
	Post-treatment/Monitored	814	17.0%
	No anti-cancer therapy (palliative care)	1327	27.8%
	Deaths (Bereaved family)	10	0.2%
	Other	312	6.5%

Health Information Management Office

Hiroshi Nishimoto, Tokiko Inagaki, Chie Ogura, Maiko Miura, Yayoi Otsuka

Introduction

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

Routine Activities

Auditing Discharge Summary (Quantitative inspection)

Data on discharge summaries should be entered by the attending physician. We inspected and checked about 7,000 summaries and, where required, gave some advice regarding correct input.

NCCH Cancer Registry (Hospital-based Cancer Registry)

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

Table 1. NCCHE Cancer Registry

Year of Diagnosis	Numbers of New Cancer Cases		
	Total	Male	Female
2009	4,613	3,029	1,584
2010	4,679	3,053	1,626
2011	4,878	3,145	1,733
2012	5,184	3,435	1,749

Department of Pharmacy

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

Introduction

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

Our residents' training program started in 2006. In 2013, 9 residents joined our department. Presently, we have a total of 19 residents. In addition, our department has accepted 6 trainees from other institutions for our oncology pharmacist training programs. Through 2013, 3 terms of the training courses, we have educated 14 pharmacy students and 3 advanced-training pharmacy students.

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

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

New developments

Over the years, the services of our Department of Pharmacy have been under continuous expansion and development. We used to place pharmacists in 3 wards only. Finally our department has successfully assigned pharmacists as dedicated staff members to all wards (10 wards including the surgical unit) on a full time basis since May 2013. These dedicated pharmacists have evaluated high-risk medications, drug interactions, and drug compatibilities. They also have monitored prescriptions and suggested medications through medical conferences or by attending multi-disciplinary team rounds. At the surgical unit, in addition to the above work, we have perfectly controlled the whole medication inventory that includes narcotic drugs and muscle relaxants.

Table 1. Pharmacy Achievement

	2010	2011	2012	2013
Number of Prescriptions				
Prepared in hospital pharmacy				
Total	84,492	86,643	90,392	97,444
Inpatients	78,327	80,837	84,800	91,549
Outpatients	6,165	5,806	5,592	5,895
Taken to outside pharmacies	50,731	55,826	59,722	64,123
(% of prescription filled outside)	(89.2%)	(90.6%)	(91.4%)	(91.6%)
Injections				
Total	157,958	159,730	160,105	158,557
Inpatients	132,407	132,969	126,428	125,106
Outpatients	25,551	26,761	33,677	33,451
Number of Prescriptions				
(Investigational new Drugs)	4,435	4,676	4,584	5,110
Aseptic Preparation of Injection Mixture				
Anticancer drugs	32,007	35,386	38,663	42,735
Others	4,689	3,320	3,994	4,204
Number of medication counseling (for inpatients)				
Patients	5,063	5,067	6,418	7,248
counselings which earned the counseling fee	6,522	6,645	7,139	5,005
Number of medication counseling (for outpatients)				
in the Outpatient Chemotherapy Center	5,705	6,701	8,965	10,073
in the pharmacy outpatient service	479	738	1,782	2,375
in the ‘Nexavar’ outpatient service	416	583	381	202
Number of calls on the Chemotherapy Hotline	980	1,468	1,665	2,087
Number of checking home medications	5,422	5,364	6,017	6,506
Number of insurance-reimbursement claims for dedicated clinical-pharmacist services				8,094

Department of Nursing

Chie Asanuma

Introduction

The Department of Nursing has been promoting several actions for team healthcare not only through the activities of the Department of Nursing, but also through collaboration with doctors, pharmacists, *etc*., in order to improve and to maintain the quality of medical cares for out-patients and in-patients the number of whom has been increasing on an annual basis.

In a consensus of the hospital, the chief nurse has been authorized to control the bed for hospitalization, which establishes a hospitalization management system in cooperation with the doctor and it contributes to improvement of annual bed occupancy rate. We promoted the effective management of the hospital ward with collaboration between the ward and related sections, and we integrated two nursing units (5A and 5B) into one unit with a chief nurse in order to equalize Nursing services, to correct the gap between quantity and content of work in the ward, and to allow the effective performance of ward activities.

We plan to open the Supportive Care Center, in collaboration with relevant departments, which will provide patients with the continuous services of mental, psychical, and social support through the environmental changes experienced by patients from the out-patient and in-patient settings to home medical care. Additionally, a full-time chief nurse has been allocated in order to collect information, to develop the organization framework, to strengthen of support for patient discharge and partnership with home visit nursing stations.

A Delirium Care program has been started in order to provide early intervention in the development and prevention of delirium in collaboration with the Department of Psycho-Oncology, nurses and relatives, and it provides screening for all hospitalized patients, enables extraction of high-risk patients, and provides unification of treatment orders and appropriate practice for patients with delirium.

We have been authorized as an institution providing educational courses towards nurse certification by the Japan Nursing Association in order to promote palliative care for the development of the quality of life (QOL) of patients and to encourage human resources development for improvement of the quality of nursing, and in June, an educational course for certification of palliative care nurses was opened with 12 participants. In addition, the role of the certified expert nurse course in the hospital for intravenous anticancer drug delivery was described and the training framework was established.

We set these following goals for our activities in 2013 based on the policy of the national Cancer Center (NCC)

1. To secure human resources for safety care services and patient satisfaction.
2. To collaborate with the relevant of outpatient and inpatient sections to offer seamless palliative care.
3. To enhance the study of Nursing for the improvement of the quality of Nursing, ability in Nursing practice.
4. To get accreditation from the JCQHC (Japan Council for Quality Health Care) for improvement of health care.
5. To take part in the hospital's administration in order to implement strategic hospital management.
6. To manage the educational course for certification of the palliative care nurse

Routine Activities

In 2013, of the current 349 nurses, 35 were newly employed. The average number of outpatients per day was 933.5, while that of inpatients was 370.6. The average hospitalization term was 13.8 days. The number of chemotherapy treatments in The Medical Treatment Center per day was 104.4. We provided educational services for patients undergoing chemotherapy on how to deal with the side effects, and also provided telephone-follow-up servicers and hot-line-telephone services to solve patient problems and relieve anxiety once they had returned home. The number of operations conducted was 2,829 and the average of per day was 11.6.The Division aims to improve nurse education to provide proper quality nursing services. Four courses have been initiated (1) an introductory course for new employees; (2) a practical course; (3) a specialized cancer nursing course; and (4) a "power up" course, and we prepared the post of head nurse in charge of nursing education to help nurses to study and to to support their mental health.

There are 6 expert nurses,1 psychiatric mental health nurse and 24 certified expert nurses specializing in wound ostomy care (3), cancer pain (6), cancer chemotherapy (6), palliative care (1), infection control (2), breast care (2), swallowing and eating (2) and

radiation (2). They are in charge of the specialized cancer nursing course education programs. We have subsequently accepted trainees participating in the expert nurse course and certified expert nurse course. As for nursing-related research projects, not only expert nurses and certified nurses, but also registered nurses in our hospital have both participated and attended external training programs. We gave 24 presentations at academic conferences in 2013.

Table 1. The number of trainee (< 1 week)

	2008	2009	2010	2011	2012	2013
Postgraduate Nurse	8	6	14	6	5	5
Certified Expert	12	13	12	17	25	11
Total	20	19	26	23	28	16
Nursing student	208	172	156	141	139	154

Preface

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

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

In the Pathology Division, the investigators play a central role in various types of TR and standardized a procedure in pathological sample analysis. With many collaboration studies with the EPOC and commercial companies to establish companion diagnosis, they are acting as the central pathology diagnostic function in an international randomized control trial. Various TRs are also on-going in collaboration with the EPOC TR division. Large amounts of molecular epidemiologic data in lung, colorectal, and gastric cancer have already been published, which will become a landmark in the development of molecular targeting agents. With a grant support from Japan Science and Technology Agency (JST), they are investigating new predictive markers for an anti-EGFR antibody using a large number of samples from the collaborative institutions.

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

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

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Division of Pathology

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

Introduction

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

Routine activities

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

Research activities

The research activities of the Division of Pathology currently focus on the application of the morphological study of cancer tissue to the clinical course of the patient. These activities aim I) to elucidate new biological roles for cancer epigenetics and cancer-stromal interaction; II) to develop a new cancer diagnosis and treatment strategy (Preclinical study); and III) to design and perform experimental and clinicopathological studies on cancer. Prognostic factors and clinicopathological characteristics of various cancers have also been investigated in collaboration with the NCCH-E Diagnostic Pathology Section and other institutions. I) To elucidate new biological roles for cancer epigenetics and cancer-stromal interaction: in addition to adenocarcinoma of the lung, podoplanin (PDPN) expressing cancer associated fibroblasts (CAFs) correlated with a poor prognosis of the stage-I squamous cell carcinoma of the lung (14). II) Development of a new cancer diagnosis and treatment strategy (Preclinical study): 1) Pathological diagnosis of blood and lymphatic vessel invasion (BLI) of colon adenocarcinomas was reported to be subjective and inconsistent among pathologists. In order to create an objective pathological diagnostic system for BLI, a framework for pathological diagnostic criteria was developed by reviewing concordance and using the Delphi method. The criteria developed may serve as the basis for creating a standardized procedure for pathological diagnosis (8). 2) To characterize the impact of pro-inflammatory cytokines on the outcomes of gemcitabine monotherapy (GEM) in patients with pancreatic cancer (PC). Treatment-naive patients with advanced PC and no obvious infections were eligible for enrolment. All of the patients were scheduled to undergo systemic chemotherapy. Serum pro-inflammatory cytokines were measured using an electro-chemiluminescence assay method before chemotherapy. High IL-6 and IL-1β levels were poor prognostic factors for overall survival in a multivariate analysis (P=0.011 and P=0.048, respectively). Patients with both a high IL-6 level and a high IL-1β level exhibited shortened overall and progression-free survival, a reduction in the tumor control rate, and a high dose intensity of GEM compared with patients with low levels of both IL-6 and IL-1β (9). III) Experimental and clinicopathological studies on cancer: The histological predictive and prognostic factors for in various cancers including lung cancers (1,5,6,10,11,13,17-19,21-26), colon cancers (12,15,16,29), hepatocellular carcinoma (31), head and neck cancer (3,27,28,30,32,34) and other tumors (7,33) are also being investigated and reported in collaboration with the clinical divisions of the NCCH-E and other institutions. Other basic studies which have elucidated cancer biology have been published (2,4,20)

List of papers published in 2013
Journal

1. Kinoshita T, Ishii G, Hiraoka N, Hirayama S, Yamauchi C, Aokage K, Hishida T, Yoshida J, Nagai K, Ochiai A. Forkhead box P3 regulatory T cells coexisting with cancer associated fibroblasts are correlated with a poor outcome in lung adenocarcinoma. Cancer Sci, 104:409-415, 2013
2. Ishii G, Hashimoto H, Atsumi N, Hoshino A, Ochiai A. Morphophenotype of floating colonies derived from a single cancer cell has a critical impact on tumor-forming activity. Pathol Int, 63:29-36, 2013
3. Sugimoto M, Gotohda N, Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Kojima M, Ochiai A, Zenda S, Akimoto T, Konishi M. Pancreatic resection for metastatic melanoma originating from the nasal cavity: a case report and literature review. Anticancer Res, 33:567-573, 2013
4. Kanomata N, Hasebe T, Moriya T, Ochiai A. Simultaneous demonstration of gelatinolytic activity, morphology, and immunohistochemical reaction using zymography film. Med Mol Morphol, 46:193-197, 2013
5. Nishijima N, Ishii G, Nagai K, Atsumi N, Aokage K, Tokunaga Y, Ichinokawa H, Ohe Y, Ochiai A. Cancer-initiating cell marker-positive cells generate metastatic tumors that recapitulate the histology of the primary tumors. Pathol Int, 63:94-101, 2013
6. Shiozawa T, Ishii G, Goto K, Nagai K, Mimaki S, Ono S, Niho S, Fujii S, Ohe Y, Tsuchihara K, Ochiai A. Clinicopathological characteristics of EGFR mutated adenosquamous carcinoma of the lung. Pathol Int, 63:77-84, 2013
7. Inagaki M, Akechi T, Okuyama T, Sugawara Y, Kinoshita H, Shima Y, Terao K, Mitsunaga S, Ochiai A, Uchitomi Y. Associations of interleukin-6 with vegetative but not affective depressive symptoms in terminally ill cancer patients. Support Care Cancer, 21:2097-2106, 2013
8. Kojima M, Shimazaki H, Iwaya K, Kage M, Akiba J, Ohkura Y, Horiguchi S, Shomori K, Kushima R, Ajioka Y, Nomura S, Ochiai A. Pathological diagnostic criterion of blood and lymphatic vessel invasion in colorectal cancer: a framework for developing an objective pathological diagnostic system using the Delphi method, from the Pathology Working Group of the Japanese Society for Cancer of the Colon and Rectum. J Clin Pathol, 66:551-558, 2013
9. Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Furuse J, Inagaki M, Higashi S, Kato H, Terao K, Ochiai A. Serum levels of IL-6 and IL-1beta can predict the efficacy of gemcitabine in patients with advanced pancreatic cancer. Br J Cancer, 108:2063-2069, 2013
10. Suzuki M, Makinoshima H, Matsumoto S, Suzuki A, Mimaki S, Matsushima K, Yoh K, Goto K, Suzuki Y, Ishii G, Ochiai A, Tsuta K, Shibata T, Kohno T, Esumi H, Tsuchihara K. Identification of a lung adenocarcinoma cell line with CCDC6-RET fusion gene and the effect of RET inhibitors in vitro and in vivo. Cancer Sci, 104:896-903, 2013
11. Noro R, Honda K, Tsuta K, Ishii G, Maeshima AM, Miura N, Furuta K, Shibata T, Tsuda H, Ochiai A, Sakuma T, Nishijima N, Gemma A, Asamura H, Nagai K, Yamada T. Distinct outcome of stage I lung adenocarcinoma with ACTN4 cell motility gene amplification. Ann Oncol, 24:2594-2600, 2013
12. Miyamoto H, Oono Y, Fu KL, Ikematsu H, Fujii S, Kojima T, Yano T, Ochiai A, Sasaki Y, Kaneko K. Morphological change of a laterally spreading rectal tumor over a short period. BMC Gastroenterol, 13:129, 2013
13. Yoshida T, Ishii G, Goto K, Yoh K, Niho S, Umemura S, Matsumoto S, Ohmatsu H, Nagai K, Ohe Y, Ochiai A. Solid predominant histology predicts EGFR tyrosine kinase inhibitor response in patients with EGFR mutation-positive lung adenocarcinoma. J Cancer Res Clin Oncol, 139:1691-1700, 2013
14. Kaseda K, Ishii G, Aokage K, Takahashi A, Kuwata T, Hishida T, Yoshida J, Kohno M, Nagai K, Ochiai A. Identification of intravascular tumor microenvironment features predicting the recurrence of pathological stage I lung adenocarcinoma. Cancer Sci, 104:1262-1269, 2013
15. Ichikawa K, Fujimori T, Moriya T, Ochiai A, Yoshinaga S, Kushima R, Nagahama R, Ohkura Y, Tanaka S, Ajioka Y, Hirata I, Tanaka M, Hoshihara Y, Kinoshita Y, Sasano H, Iwashita A, Tomita S, Hirota S, Yao T, Fujii S, Matsuda T, Ueno H, Ishikawa Y, Takubo K, Fukushima N, Sugai T, Iwafuchi M, Imura J, Manabe T, Fukayama M. Digestive disease management in Japan: a report on The 6th Diagnostic Pathology Summer Fest in 2012. Digestion, 88:153-160, 2013
16. Ueno H, Shirouzu K, Eishi Y, Yamada K, Kusumi T, Kushima R, Ikegami M, Murata A, Okuno K, Sato T, Ajioka Y, Ochiai A, Shimazaki H, Nakamura T, Kawachi H, Kojima M, Akagi Y, Sugihara K. Characterization of perineural invasion as a component of colorectal cancer staging. Am J Surg Pathol, 37:1542-1549, 2013
17. Takahashi A, Ishii G, Kinoshita T, Yoshida T, Umemura S, Hishida T, Yoh K, Niho S, Goto K, Ohmatsu H, Ohe Y, Nagai K, Ochiai A. Identification of prognostic immunophenotypic features in cancer stromal cells of high-grade neuroendocrine carcinomas of the lung. J Cancer Res Clin Oncol, 139:1869-1878, 2013
18. Ichinokawa H, Ishii G, Nagai K, Kawase A, Yoshida J, Nishimura M, Hishida T, Ogasawara N, Tsuchihara K, Ochiai A. Distinct clinicopathologic characteristics of lung mucinous adenocarcinoma with KRAS mutation. Hum Pathol, 44:2636-2642, 2013
19. Kirita K, Ishii G, Matsuwaki R, Matsumura Y, Umemura S, Matsumoto S, Yoh K, Niho S, Goto K, Ohmatsu H, Ohe Y, Nagai K, Ochiai A. Identification of biological properties of intralymphatic tumor related to the development of lymph node metastasis in lung adenocarcinoma. PLoS One, 8:e83537, 2013
20. Kami K, Fujimori T, Sato H, Sato M, Yamamoto H, Ohashi Y, Sugiyama N, Ishihama Y, Onozuka H, Ochiai A, Esumi H, Soga T, Tomita M. Metabolomic profiling of lung and prostate tumor tissues by capillary electrophoresis time-of-flight mass spectrometry. Metabolomics, 9:444-453, 2013
21. Ono S, Ishii G, Nagai K, Takuwa T, Yoshida J, Nishimura M, Hishida T, Aokage K, Fujii S, Ikeda N, Ochiai A. Podoplanin-positive cancer-associated fibroblasts could have prognostic value independent of cancer cell phenotype in stage I lung squamous cell carcinoma: usefulness of combining analysis of both cancer cell phenotype and cancer-associated fibroblast phenotype. Chest, 143:963-970, 2013
22. An J, Enomoto A, Weng L, Kato T, Iwakoshi A, Ushida K, Maeda K, Ishida-Takagishi M, Ishii G, Ming S, Sun T, Takahashi M. Significance of cancer-associated fibroblasts in the regulation of gene expression in the leading cells of invasive lung cancer. J Cancer Res Clin Oncol, 139:379-388, 2013
23. Niho S, Kenmotsu H, Sekine I, Ishii G, Ishikawa Y, Noguchi M, Oshita F, Watanabe S, Nakajima R, Tada H, Nagai K. Combination chemotherapy with irinotecan and cisplatin for large-cell neuroendocrine carcinoma of the lung: a multicenter phase II study. J Thorac Oncol, 8:980-984, 2013
24. Takahashi Y, Ishii G, Aokage K, Hishida T, Yoshida J, Nagai K. Distinctive histopathological features of lepidic growth predominant node-negative adenocarcinomas 3-5 cm in size. Lung Cancer, 79:118-124, 2013
25. Kinoshita T, Yoshida J, Ishii G, Aokage K, Hishida T, Nagai K. The differences of biological behavior based on the clinicopathological data between resectable large-cell neuroendocrine carcinoma and small-cell lung carcinoma. Clin Lung Cancer, 14:535-540, 2013
26. Aokage K, Yoshida J, Ishii G, Matsumura Y, Haruki T, Hishida T, Nagai K. Identification of early t1b lung adenocarcinoma based on thin-section computed tomography findings. J Thorac Oncol, 8:1289-1294, 2013
27. Zenke Y, Ishii G, Ohe Y, Kaseda K, Yoshida T, Matsumoto S, Umemura S, Yoh K, Niho S, Goto K, Ohmatsu H, Kuwata T, Nagai K, Ochiai A. Aldehyde dehydrogenase 1 expression in cancer cells could have prognostic value for patients with non-small cell lung cancer who are treated with neoadjuvant therapy: identification of prognostic microenvironmental factors after chemoradiation. Pathol Int, 63:599-606, 2013
28. Suzuki K, Hayashi R, Ebihara M, Miyazaki M, Shinozaki T, Daiko H, Sakuraba M, Zenda S, Tahara M, Fujii S. The effectiveness of chemoradiation therapy and salvage surgery for hypopharyngeal squamous cell carcinoma. Jpn J Clin Oncol, 43:1210-1217, 2013
29. Bando H, Yoshino T, Shinozaki E, Nishina T, Yamazaki K, Yamaguchi K, Yuki S, Kajiura S, Fujii S, Yamanaka T, Tsuchihara K, Ohtsu A. Simultaneous identification of 36 mutations in KRAS codons 61 and 146, BRAF, NRAS, and PIK3CA in a single reaction by multiplex assay kit. BMC Cancer, 13:405, 2013

30. Kuno H, Fujii S. A case of adenoid cystic carcinoma arising from the nasopharynx. Jpn J Clin Oncol, 43:942, 2013

31. Sawada Y, Yoshikawa T, Fujii S, Mitsunaga S, Nobuoka D, Mizuno S, Takahashi M, Yamauchi C, Endo I, Nakatsura T. Remarkable tumor lysis in a hepatocellular carcinoma patient immediately following glypican-3-derived peptide vaccination: an autopsy case. Hum Vaccin Immunother, 9:1228-1233, 2013

32. Tomioka T, Hayashi R, Ebihara M, Miyazaki M, Shinozaki T, Fujii S. Observation as an option for epithelial positive margin after partial glossectomy in stage I and II squamous cell carcinoma: analysis of 365 cases. Jpn J Clin Oncol, 43:520-523, 2013

33. Matsubara N, Mukai H, Fujii S, Wada N. Different prognostic significance of Ki-67 change between pre- and post-neoadjuvant chemotherapy in various subtypes of breast cancer. Breast Cancer Res Treat, 137:203-212, 2013

34. Fujii S, Uryu H, Akashi K, Suzuki K, Yamazaki M, Tahara M, Hayashi R, Ochiai A. Clinical significance of KRAS gene mutation and epidermal growth factor receptor expression in Japanese patients with squamous cell carcinoma of the larynx, oropharynx and hypopharynx. Int J Clin Oncol, 18:454-463, 2013

Division of Functional Imaging

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

Introduction

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

Research activities

Tumor hypoxia imaging is important for the optimization of cancer therapy because hypoxic lesions in tumors are closely related with their resistance to radiation therapy and chemotherapy. We have been developing several hypoxia imaging probes with capacities for clinical application in nuclear medicine diagnosis. During 2013 we investigated ^{99m}Tc-labeled hypoxia imaging probes with a novel retention mechanism. By modifying their molecular structures, promising probes were synthesized and we determined that they were able to reach the tumor after intravenous injection and specifically accumulated in the tumor hypoxic lesions. We applied for a patent for a series of these compounds.

The liposome project to apply radionuclide-encapsulated liposomes for diagnostic imaging and radionuclide therapy is also ongoing. This year, we developed some new liposomes containing radionuclides and it was revealed that one of them was useful for arteriosclerosis nest imaging. In apolipoprotein E-deficient mice, the aorta was successfully visualized with SPECT imaging using ^{111}In-labeled liposomes.

Lung cancer is one of the leading causes of cancer-related deaths worldwide. Although computed tomography (CT) can detect small lung lesions such as ground glass opacity (GGO), it cannot differentiate between malignant and non-malignant lesions. ^{111}In-DOTA-c(RGDfK) could clearly visualize lung nodules, though we failed to detect small lung nodules like adenomas and hyperplasias (adenocarcinomas: 66.7%, adenoma:s 33.6%, hyperplasias: 0.0%). Histopathological examination using human lung tissue samples revealed clear up-regulation of $\alpha_v\beta_3$ integrin in well-differentiated adenocarcinomas rather than atypical adenomatous hyperplasia. SPECT with ^{111}In-DOTA-c(RGDfK) might be a useful non-invasive imaging approach for evaluating the characteristics of lung tumors.

Magnetic resonance (MR) imaging can provide anatomical images of experimental animals with high spatial resolution and high tissue contrast, however its long examination time (typically 1hr per animal) affects the efficiency of experiments when a large number of animals need to be examined. To increase the throughput, we have developed multiple-animal MR imaging techniques, constructing a dedicated radiofrequency coil to receive signals from several animals, applying a data acquisition method which is less susceptible to motion artifacts, and programming new post-processing software to promote precise interpretation of multi-animal MR images. At present, we can complete MR imaging of the liver for a group of hepatoma-bearing rats in under 10 min per rat, and can measure two important markers to determine tumor response to therapy; the tumor volume and the apparent diffusion co-efficient (ADC) levels. The latter reflects diffusion of water molecules and provides information regarding tumor cell density and membrane stability.

Delayed hepatic signal recovery on ferucarbotran-enhanced MR images is another topic. Ferucarbotran is carboxydextran-coated iron oxide and has a superparamagnetic property. After intravenous administration, ferucarbotran particles are trapped by Kupffer cells (KCs) and reduce the signal intensity of the liver. While hepatic signals are normally restored within one week as the particles are degraded to ferric iron by KCs, the recovery was delayed when we administered a compound that impaired this KC function. It is thought that hepatic signal recovery is a potential MRI marker to monitor KC function *in vivo*.

Clinical trials

Clinical trials of hypoxia PET tests are ongoing using Cu-62 labeled diacetyl methyl-thiosemicarbazone (ATSM). Patients with lung cancer or head and neck cancer were tested to investigate the clinical and pathological features of tumors with high avidity to these radiopharmaceuticals. The effects of systemic chemotherapy on the cerebral metabolism and cognitive function in breast cancer patients were evaluated with MR spectroscopy.

List of papers published in 2013
Journal

1. Fujii H, Umeda IO, Iimoto T, Oda S, Someya S, Iiizumi S. Increased Radiation Dose Issues in Tokatsu Area in Chiba Prefecture, Japan – How the Situation and Measures were Explained to the Local Residents. Radiat Emerg Med, 2:76-81, 2013
2. Furuta T, Yamaguchi M, Nakagami R, Akahane M, Minami M, Ohtomo K, Moriyama N, Fujii H. Delayed hepatic signal recovery on ferucarbotran-enhanced magnetic resonance images: an experimental study in rat livers with gadolinium chloride-induced Kupffer cell damage. MAGMA, 26:313-324, 2013
3. Hayakawa T, Mutoh M, Imai T, Tsuta K, Yanaka A, Fujii H, Yoshimoto M. SPECT/CT of lung nodules using ^{111}In-DOTA-c(RGDfK) in a mouse lung carcinogenesis model. Ann Nucl Med, 27:640-647, 2013
4. Hirata M, Kanai Y, Naka S, Yoshimoto M, Kagawa S, Matsumuro K, Katsuma H, Yamaguchi H, Magata Y, Ohmomo Y. A useful EGFR-TK ligand for tumor diagnosis with SPECT: development of radioiodinated 6-(3-morpholinopropoxy)-7-ethoxy-4-(3′-iodophenoxy)quinazoline. Ann Nucl Med, 27:431-443, 2013
5. Mitsuda M, Yamaguchi M, Nakagami R, Furuta T, Sekine N, Niitsu M, Moriyama N, Fujii H. Intensity correction method customized for multi-animal abdominal MR imaging with 3T clinical scanner and multi-array coil. Magn Reson Med Sci, 12:95-103, 2013
6. Suzuki C, Blomqvist L, Hatschek T, Carlsson L, Einbeigi Z, Linderholm B, Lindh B, Loman N, Malmberg M, Rotstein S, Soderberg M, Sundqvist M, Walz TM, Astrom G, Fujii H, Jacobsson H, Glimelius B. Impact of the first tumor response at eight weeks on overall survival in metastatic breast cancer patients treated with first-line combination chemotherapy. Med Oncol, 30:415, 2013
7. Takeda A, Kunieda E, Fujii H, Yokosuka N, Aoki Y, Oooka Y, Oku Y, Ohashi T, Sanuki N, Mizuno T, Ozawa Y. Evaluation for local failure by ^{18}F-FDG PET/CT in comparison with CT findings after stereotactic body radiotherapy (SBRT) for localized non-small-cell lung cancer. Lung Cancer, 79:248-253, 2013
8. Yamaguchi M, Mitsuda M, Ezawa K, Nakagami R, Furuta T, Sekine N, Niitsu M, Fujii H. Artifact-reduced simultaneous MRI of multiple rats with liver cancer using PROPELLER. J Magn Reson Imaging, 38:225-230, 2013
9. Yoshimoto M, Kurihara H, Honda N, Kawai K, Ohe K, Fujii H, Itami J, Arai Y. Predominant contribution of L-type amino acid transporter to 4-borono-2-^{18}F-fluoro-phenylalanine uptake in human glioblastoma cells. Nucl Med Biol, 40:625-629, 2013

Division of Science and Technology for Endoscopy and Surgery

Kazuhiro Kaneko, Masaaki Ito, Takahiro Kinoshita, Tomonori Yano, Mari Takahashi, Atsushi Yagishita

Introduction

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

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

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

Routine activities

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

Research activities

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

Research into developing novel endoscopy systems is being performed. Hypoxia imaging is being used to detect neoplastic lesions of the head and neck and alimentary tracts, with two types of visualized images, such as a pseudocolor StO_2 image overlaid with an StO_2 image. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and nanoparticles of the rare earth, doped yttrium oxide. This system is capable of penetrating through the gastrointestinal wall and obtaining images. Furthermore, a preclinical study of molecular imaging endoscopy using small molecular has been planned for this year. With a low-temperature atmospheric pressure plasmas system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnostic system using photosensitizing agents, such as hypericin, has been constructed. A novel tattooing system under endoscopy has been developed, and a patent is currently being applied for. Ongoing projects are to develop needle graspers, and a needle ultrasonic coagulator in the surgical field. A clinical trial regarding confocal laser endocytoscopy using fluorescein has been planned and has been classified into a new category.

Clinical trials

A first in human clinical trial of hypoxia imaging was finished on the endoscopic diagnosis of neoplasia of the esophagus, stomach, and colorectum. We conducted a proof-of-the-concept trial for 40 patients with neoplastic lesions in the esophagus including the pharynx, stomach and colorectum. In this first in human trial (UMIN 000004983), two types of StO_2 images were used. One was a pseudocolor StO_2 image that showed StO_2 levels as different hues, and the other was a StO_2 overlay image that overlapped StO_2 levels in blue on a white light illumination image to detect background mucosa. A system has been developed using near-infrared light with nanoparticles which act as fluorescent agents. Nanoparticles in a probe attach themselves to the surface of cancer cells and fluoresce when activated with near-infrared light, which can penetrate through target organ walls. Molecular imaging endoscopy for the use of this system with an InGaAs CCD is currently in development in collaboration with a university Faculty of Technology. Preclinical animal model studies are under way, such as a low-temperature atmospheric pressure plasma system and photodynamic diagnosis with hypericin. Furthermore, clinical trials are ongoing on biodegradable (BD) stent implantation for benign esophageal stricture after curative treatment, and on photodynamic diagnosis (PDD) using aminolevulinic acid (5-ALA).

List of papers published in 2013
Journal

1. Hatogai K, Oono Y, Fu KI, Odagaki T, Ikematsu H, Kojima T, Yano T, Kaneko K. Unexpected endoscopic full-thickness resection of a duodenal neuroendocrine tumor. World J Gastroenterol, 19:4267-4270, 2013
2. Ikematsu H, Yoda Y, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, Fujii T, Oono Y, Sakamoto T, Nakajima T, Takao M, Shinohara T, Murakami Y, Fujimori T, Kaneko K, Saito Y. Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology, 144:551-559; quiz e514, 2013
3. Kaneko K, Yano T, Minashi K, Kojima T, Ito M, Satake H, Yajima Y, Yoda Y, Ikematsu H, Oono Y, Hayashi R, Onozawa M, Ohtsu A. Treatment strategy for superficial pharyngeal squamous cell carcinoma synchronously combined with esophageal cancer. Oncology, 84:57-64, 2013
4. Miyamoto H, Oono Y, Fu KL, Ikematsu H, Fujii S, Kojima T, Yano T, Ochiai A, Sasaki Y, Kaneko K. Morphological change of a laterally spreading rectal tumor over a short period. BMC Gastroenterol, 13:129, 2013
5. Yano T, Yoda Y, Satake H, Kojima T, Yagishita A, Oono Y, Ikematsu H, Kaneko K. Radial incision and cutting method for refractory stricture after nonsurgical treatment of esophageal cancer. Endoscopy, 45:316-319, 2013
6. Yoda Y, Ikematsu H, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, Fujii T, Oono Y, Sakamoto T, Nakajima T, Takao M, Shinohara T, Fujimori T, Kaneko K, Saito Y. A large-scale multicenter study of long-term outcomes after endoscopic resection for submucosal invasive colorectal cancer. Endoscopy, 45:718-724, 2013

Division of Developmental Therapeutics

Yasuhiro Matsumura, Masahiro Yasunaga, Yoshikatu Koga

Introduction

Our Division has been involved in basic research on drug delivery systems (DDS) including anticancer agent incorporating micelle systems and antibody drug conjugates and in the clinical development of drugs used in DDS. We also investigated a mechanism of cancer induced blood coagulation and are developing a new cancer diagnosis based on cancer specific monoclonal antibodies (mAbs). In addition to the research work, we are operating the Japan Clinical Oncology Group Tumor Repository.

Routine activities

Examination of clinical trials as an IRB member

Operation of the JCOG Tumor Repository

Management of personal information protection in the NCC East Hospital

Research activities

(Drug Delivery System in Cancer Chemotherapy)

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

A phase 3 study of NK-105, a paclitaxel incorporating micelle, is now underway in Japan, Taiwan, and Korea in patients with metastatic breast cancer. Phase 2 trials of NC-6004, a cisplatin incorporating micelle, A Phase 1 study of K-912, an epirubicin incorporating micelle has begun (1). We also reported for the first time, the precise distribution of a non-radiolabelled DDS drug using the imaging mass spectrometry (IMS) technique (2). In addition to clinical trials, we have published a reflection paper on the development of micelle medical products in collaboration with the European Medicines Agency (EMA) (Reflection paper 1)

(Cancer Stromal Targeting (CAST) Therapy)

In spite of the recent success of mAb drug conjugate (ADC) therapy in patients with hypervascular and special tumors recognized by a particular mAb, there are several issues to be solved before ADC can be recognized as a universal therapy for any type of cancer. A particular problem is that most human solid tumors possess abundant stroma that hinders the distribution of any ADC. To overcome these drawbacks, we developed a unique strategy, known as cancer-stromal targeting (CAST) therapy through the application of cytotoxic immunoconjugate bound to the collagen 4 or fibrin network in the tumor stroma, from which the payload is released gradually and distributed throughout the tumor, resulting in the arrest of tumor growth due to induced damage of tumor cells and tumor vessels. During this study, we discovered an unexplored hole in fibrin clots occurring only when insoluble fibrin clots formed, and we also found that our monoclonal antibodies developed against structures inside the hole recognized only insoluble fibrin and not fibrinogen, soluble fibrin, or D-dimer (fibrin degradation products). Finally, we assessed the clinical significance of these mAbs (3, 7).

(Noninvasive Diagnostic Test for Colorectal or Uterus Cancer)

In our laboratory, simple and non-invasive methods for detecting colorectal and endometrial cancers have been investigated for the last decade. Regarding colorectal cancer (CRC), we investigated the applicability of the fecal miRNA test (FmiRT) to fecal samples used for previous fecal occult blood tests (FOBTs) stored under various conditions (4). We subsequently investigated a new colorectal cancer screening method combining FOBT and FmiRT to improve the sensitivity compared with FOBT alone (5). For endometrial cancer diagnosis, we prepared immuno-magnetic beads conjugated with anti-human EpCAM rat mAb to isolate exfoliated endometrial cells including endometrial cancer cells in the vaginal discharge (6).

List of papers published in 2013

Journal

1. Takahashi A, Yamamoto Y, Yasunaga M, Koga Y, Kuroda J, Takigahira M, Harada M, Saito H, Hayashi T, Kato Y, Kinoshita T, Ohkohchi N, Hyodo I, Matsumura Y. NC-6300, an epirubicin-incorporating micelle, extends the antitumor effect and reduces the cardiotoxicity of epirubicin. Cancer Sci, 104:920-925, 2013
2. Yasunaga M, Furuta M, Ogata K, Koga Y, Yamamoto Y, Takigahira M, Matsumura Y. The significance of microscopic mass spectrometry with high resolution in the visualisation of drug distribution. Sci Rep, 3:3050, 2013
3. Hisada Y, Yasunaga M, Hanaoka S, Saijou S, Sugino T, Tsuji A, Saga T, Tsumoto K, Manabe S, Kuroda J, Kuratsu J, Matsumura Y. Discovery of an uncovered region in fibrin clots and its clinical significance. Sci Rep, 3:2604, 2013
4. Yamazaki N, Koga Y, Yamamoto S, Kakugawa Y, Otake Y, Hayashi R, Saito N, Matsumura Y. Application of the fecal microRNA test to the residuum from the fecal occult blood test. Jpn J Clin Oncol, 43:726-733, 2013
5. Koga Y, Yamazaki N, Yamamoto Y, Yamamoto S, Saito N, Kakugawa Y, Otake Y, Matsumoto M, Matsumura Y. Fecal miR-106a is a useful marker for colorectal cancer patients with false-negative results in immunochemical fecal occult blood test. Cancer Epidemiol Biomarkers Prev, 22:1844-1852, 2013
6. Koga Y, Katayose S, Onoda N, Kasamatsu T, Kato T, Ikeda S, Ishikawa M, Ishitani K, Hirai Y, Matsui H, Matsumura Y. Usefulness of immunomagnetic beads conjugated with anti-EpCAM antibody for detecting endometrial cancer cells. J Cancer Ther, 4:1273-1282, 2013

Book

7. Matsumura Y, Yasunaga M, Manabe S. Cancer stromal targeting (CAST) therapy and tailored antibody drug conjugate therapy depending on the nature of tumor stroma. In Cancer Targeted Drug Delivery, An Elusive Dream, In: Bae YH, Mrsny RJ, and Park K (eds) Springer New York Heidelberg Dordrecht London, pp161-181, 2013

Reflection paper

8. Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products. 19 December 2013 EMA/CHMP/13099/2013. Committee for medicinal Products for Human Use (CHMP)

Division of Psycho-Oncology

Asao Ogawa, Hiroya Kinoshita, Ken Shimizu

Introduction

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

Research activities

Consent capacity and associated risk factors in patients with lung cancer

Little is known regarding consent capacity in patients newly diagnosed as having lung cancer and clinical factors associated with incapacity. Over an 11-month period, we recruited 135 patients newly diagnosed as having lung cancer. All patients were receiving a combination of treatments (e.g., chemotherapy, chemoradiotherapy, or targeted therapy). The MacArthur Competence Tool for Treatment was administered to participants, in addition to a neurocognitive test battery and the Vulnerable Elders Survey-13 (VES-13) to help us identify clinical factors associated with incapacity in lung cancer patients. Twenty-seven (24%, 95% CI, 16–31%) patients were judged not to have consent capacity. In contrast, clinical teams only identified 6 (22.2%) patients who did not have consent capacity. Logistic regression identified vulnerability (odds ratio, 3.51; 95% CI, 1.13 to 10.8) and cognitive impairment (odds ratio, 5.45; 95% CI, 1.26 to 23.6) as the factors associated with mental incapacity. A substantial portion of patients diagnosed as having lung cancer showed impairments in their capacity to consent to treatment. Results suggest that many advanced lung cancer patients fail to fully understand physicians' recommendations due to age-related functional cognitive impairment. Future studies should investigate brief and effective assessments of capacity and determine whether specific interventions can improve informed consent.

Division of Radiation Oncology and Particle Therapy

Tetsuo Akimoto, Sadatomo Zenda, Teiji Nishio, Ryosuke Kohno, Tomoko Kawagishi, Kenji Hotta

Introduction

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

Research activities

(a): PBT as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study. The aim of this pilot study was to assess the clinical benefit of PBT for mucosal melanoma of the head and neck. Patients with mucosal melanoma of the head and neck with histologically confirmed malignant melanoma and N0 and M0 disease were enrolled. PBT was delivered three times per week with a planned total dose of 60 Gy equivalents (GyE) in 15 fractions. Fourteen consecutive patients were enrolled from January 2004 through February 2008. Patient characteristics were as follows: median age 73 years old (range, 56 to 79 years); male/female ratio, 7/7; and T stage 1/2/3/4, 3/2/0/9. All patients were able to receive the full dose of PBT. The most common acute toxicities were mucositis (grade 3, 21%) and mild dermatitis (grade 3, 0%). As for late toxicity, 2 patients had a unilateral decrease in visual acuity, although blindness did not occur. No treatment-related deaths occurred throughout the study. The initial local control rate was 85.7%, and, with a median follow-up period of 36.7 months, median progression-free survival was 25.1 months, and 3-year overall survival rates were 58.0%. The most frequent site of first failure was the cervical lymph nodes (6 patients), followed by local failure in 1 patient and lung metastases in 1 patient. On follow-up, 5 patients died of disease, 4 died due to cachexia caused by distant metastases, and 1 patient by carotid artery perforation caused by lymph nodes metastases. PBT showed promising local control benefits and would benefit from ongoing clinical study.

(b): Phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer: To evaluate the feasibility of proton beam therapy (PBT) for stage III non-small cell lung cancer, especially focusing on acute toxicities and related dose volume histogram (DVH) parameters for the organ at risk. (Preliminary results) Twenty-three of the patients (96%) completed the planned treatment course except one patient who developed distant metastases during PBT. Regarding acute toxicities, grades of radiation pneumonitis were grade 0-1 in 23 (96%) and grade 2 in one patient, respectively. Those of esophagitis were grade 0-1 in 16 (62%), grade 2 in 6 (25%) and grade 3 in 2 patients (13%), respectively. All patients who developed grade 2-3 esophagitis were treated with concurrent chemotherapy. No other severe acute radiation-related toxicities were observed. The DVH parameters of all patients were as follows: average lung V20 Gy; 23% (16 to 32%), V10 Gy; 30% (19% to 50%), V5 Gy; 34% (20 to 52 %), mean whole lung dose; 16 GyE (6 to 19 GyE), mean dose to the heart; 7 GyE (4.9 to 22.5 GyE), esophagus V50 GyE; 11 GyE (0 to 47.2 GyE), mean whole esophageal dose; 22 GyE (1.9 to 30.4 GyE), the maximum dose to the spinal cord; 37 GyE (34.7 to 48 Gy). The lung V20 Gy and whole lung dose of the one patient who developed grade-2 radiation pneumonitis were 29% and 16.4 Gy, respectively. There was no statistical difference in the esophageal V50 Gy ($p=0.97$) and esophageal whole mean dose ($p=0.76$) between the patients with grade 0-1 esophagitis and those with grade 2-3.

(c): Proton dose distribution measurements using a MOSFET detector with a simple dose-weighted correction method for LET effects.

We experimentally evaluated the proton beam dose reproducibility, sensitivity, angular dependence and depth-dose relationships for a new Metal Oxide Semiconductor Field Effect Transistor (MOSFET) detector. The detector was fabricated with a thinner oxide layer and was operated at high-bias voltages. In order to accurately measure dose distributions, we developed a practical method for correcting the MOSFET response to proton beams. The detector was tested by examining lateral dose profiles formed by protons passing through an L-shaped bolus. The dose reproducibility, angular dependence and depth-dose response were evaluated using a 190 MeV proton beam. Depth-output curves produced

using the MOSFET detectors were compared with results obtained using an ionization chamber (IC).

Since accurate measurements of proton dose distribution require correction for LET effects, we developed a simple dose-weighted correction method. The correction factors were determined as a function of proton penetration depth, or residual range. The residual proton range at each measurement point was calculated using the pencil beam algorithm. Lateral measurements in a phantom were obtained for pristine and SOBP beams. The reproducibility of the MOSFET detector was within 2%, and the angular dependence was less than 9%. The detector exhibited a good response at the Bragg peak (0.74 relative to the IC detector). For dose distributions resulting from protons passing through an L-shaped bolus, the corrected MOSFET dose agreed well with the IC results. Absolute proton dosimetry can be performed using MOSFET detectors to a precision of about 3% (1 sigma). A thinner oxide layer thickness improved the LET in proton dosimetry. By employing correction methods for LET dependence, it is possible to measure absolute values with a thinner oxide layer which was operated at high-bias voltages. In order to accurately measure dose distributions, we developed a practical method for correcting the MOSFET response to proton beams. The detector was tested by examining lateral dose profiles formed by protons passing through an L-shaped bolus. The dose reproducibility, angular dependence and depth-dose response were evaluated using a 190 MeV proton beam. Depth-output curves produced using the MOSFET detectors were compared with results obtained using an ionization chamber (IC).

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Clinical trials

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

1) A phase II study of PBT for malignant melanoma of nasal cavity.
2) A phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.
3) A phase I/II study of line scanning for localized prostate cancer

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

	Number of patients treated with radiotherapy during 2007-2011				
	2008	2009	2010	2011	2012
New patients	52	57	107	200	245
Head and neck cancers	13	24	39	49	49
Lung and mediastinal cancers	22	13	12	24	24
Hepatocellular carcinoma	6	6	12	27	27
Prostate cancer	11	14	42	93	93
Others	0	0	2	7	7

List of papers published in 2013
Journal

1. Tansho R, Takada Y, Kohno R, Hotta K, Hara Y, Mizutani S, Akimoto T. Experimental verification of dose calculation using the simplified Monte Carlo method with an improved initial beam model for a beam-wobbling system. Phys Med Biol, 58:6047-6064, 2013
2. Kawashima M, Ariji T, Kameoka S, Ueda T, Kohno R, Nishio T, Arahira S, Motegi A, Zenda S, Akimoto T, Tahara M, Hayashi R. Locoregional control after intensity-modulated radiotherapy for nasopharyngeal carcinoma with an anatomy-based target definition. Jpn J Clin Oncol, 43:1218-1225, 2013
3. Matsubara K, Kohno R, Nishioka S, Shibuya T, Ariji T, Akimoto T, Saitoh H. Experimental evaluation of actual delivered dose using mega-voltage cone-beam CT and direct point dose measurement. Med Dosim, 38:153-159, 2013
4. Kiyozuka M, Akimoto T, Fukutome M, Motegi A, Mitsuhashi N. Radiation-induced dimer formation of EGFR: implications for the radiosensitizing effect of cetuximab. Anticancer Res, 33:4337-4346, 2013
5. Okano S, Yoshino T, Fujii M, Onozawa Y, Kodaira T, Fujii H, Akimoto T, Ishikura S, Oguchi M, Zenda S, de Blas B, Tahara M, Beier F. Phase II study of cetuximab plus concomitant boost radiotherapy in Japanese patients with locally advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol, 43:476-482, 2013
6. Sugimoto M, Gotohda N, Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Kojima M, Ochiai A, Zenda S, Akimoto T, Konishi M. Pancreatic resection for metastatic melanoma originating from the nasal cavity: a case report and literature review. Anticancer Res, 33:567-573, 2013

Section of Experimental Animals

Yoshikatsu Koga

Introduction

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

Routine activities

- Health management of the experimental animals and maintenance of the animal laboratories.
  - Animal-breeding rooms: specific pathogen-free (SPF) rooms (8 rooms for mice and 1 room for rats), conventional rooms (1 room for mice, 1 room for rats, hamsters, and rabbits, and 1 room for pigs), and P2 animal laboratory.
- Approval of animal experiments and gene recombinant experiments in accordance with the regulations.
  - In 2013, 58 studies involving animal experiments and 25 studies with gene recombinant experiments were approved by the Committee of Experimental Animals and Gene Recombination.

List of papers published in 2013

Journal

1. Yamazaki N, Koga Y, Yamamoto S, Kakugawa Y, Otake Y, Hayashi R, Saito N, Matsumura Y. Application of the fecal microRNA test to the residuum from the fecal occult blood test. Jpn J Clin Oncol, 43:726-733, 2013
2. Koga Y, Katayose S, Onoda N, Kasamatsu T, Kato T, Ikeda S, Ishikawa M, Ishitani K, Hirai Y, Matsui H, Matsumura Y. Usefulness of immuno-magnetic beads conjugated with anti-EpCAM antibody for detecting endometrial cancer cells. J Cancer Ther, 4:1273-1282, 2013
3. Yasunaga M, Furuta M, Ogata K, Koga Y, Yamamoto Y, Takigahira M, Matsumura Y. The significance of microscopic mass spectrometry with high resolution in the visualisation of drug distribution. Sci Rep, 3:3050, 2013
4. Koga Y, Yamazaki N, Yamamoto Y, Yamamoto S, Saito N, Kakugawa Y, Otake Y, Matsumoto M, Matsumura Y. Fecal miR-106a is a useful marker for colorectal cancer patients with false-negative results in immunochemical fecal occult blood test. Cancer Epidemiol Biomarkers Prev, 22:1844-1852, 2013