Hospital East

Preface

Nearly ten months have passed from the unforgettable '3-11 disasters' in north-east Japan. I would like once again to deliver my sincere condolences and prayers for the earthquake and tsunami victims and their families.

Fortunately the degree of damage to the hospital buildings due to the earthquake was minimal. No patients and no staff members sustained any serious injury. Considering the days after the disaster, all members of the hospital labored under many difficulties including the planned electric power outages, the so-called rolling power outages, and stringent electricity-saving initiatives during the summertime. The problems associated with the nuclear power plants in Fukushima prefecture still continue to the present day. Kashiwa city is one of the radioactive 'hot spot' areas even though it is around 200 km away from Fukushima and is the home to our NCCHE Kashiwa campus, but I am glad to report that radioactive contamination measured at several spots in the hospital area has recently reached a relatively stable level.

Apart from the natural disasters of 2011, we had some internal ones of our own. In April, 2011 the number of the staff members of in our Anesthesiology Division dropped from 2 to 1 with the loss of the Division chief. We had to limit the number of operations until a new chief came to the division. Now three staff members work hard to bring the number of operations up to where it should be with the help of two part-timers.

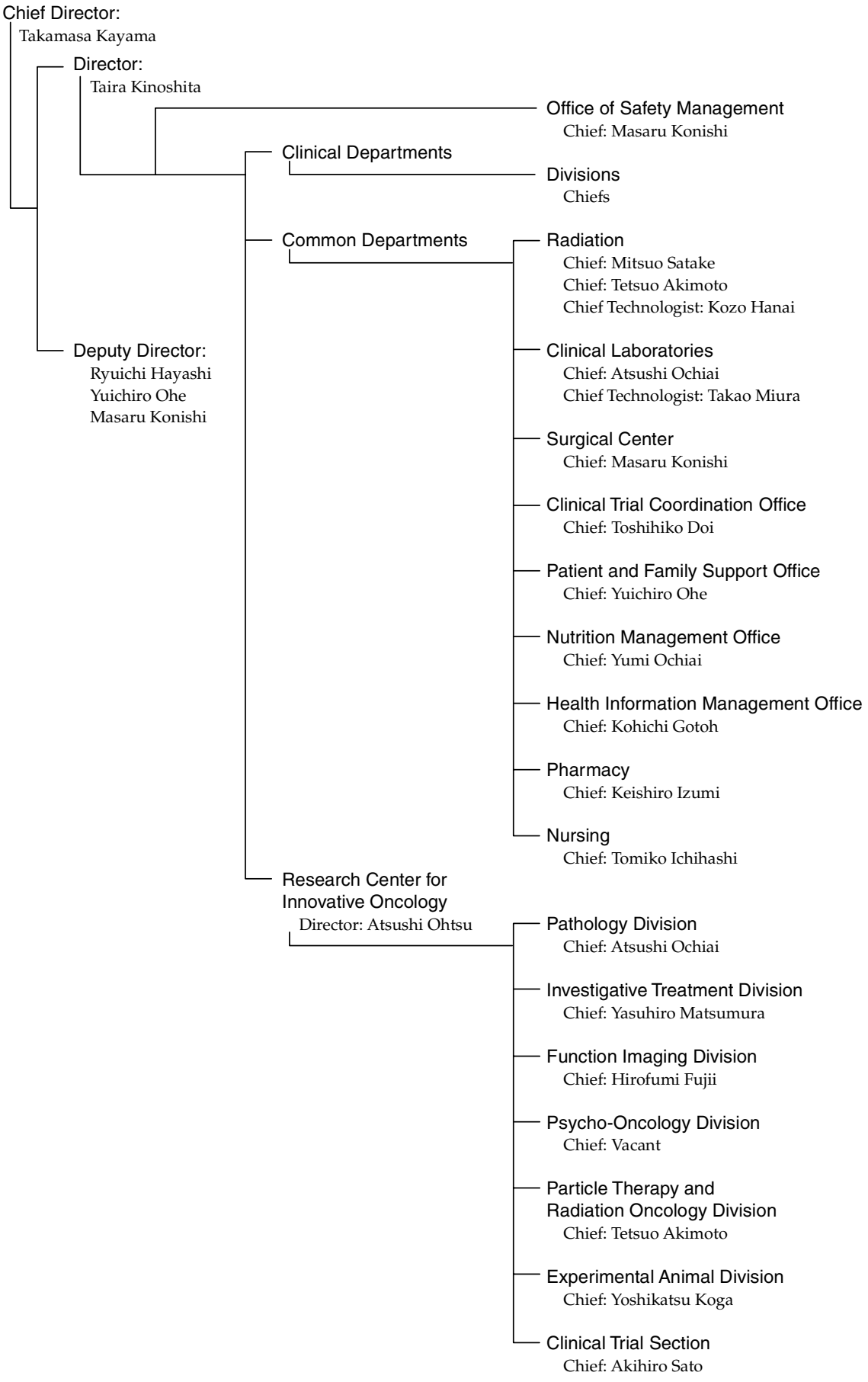
2011 was also a year of expansion and change. In the operating theater, the number of laparoscopic surgeries as a less invasive procedure has been increasing. The Palliative Care Unit changed its remit from terminal care to control of the symptoms before the terminal stage to extend the opportunity to use the limited number of beds for increasing patients. In the Research Center for Innovative Oncology several clinical trials of new anticancer drugs, peptide vaccine and endoscopic instrument are successfully ongoing.

We are in the second year of a new Independent Administrative Institution putting administrative reforms into place under the powerful chief director, Dr. Takamasa Kayama. In this situation, the Hospital East has had to show a different flag from that flown by Central Hospital. Hospital East has been trying to promote innovative works together with the Research Center for Innovative Oncology. I would like to congratulate them on their gaining of a strategic foothold regarding early phase trials from the government to accelerate their innovative activity in the development of new drugs and medical instruments.

2012 is a memorial year, encompassing both the 50th anniversary of the National Cancer Center and the 20th anniversary of the Hospital East. It is my great pleasure and honor to present the summary of the achievements of 2011 in the Hospital East, which were only accomplished through the hard work of the NCCHE staff members. I would like to express my sincere thanks and to send my warmest regards to all the members of the NCCH. At the same time I express my appreciation to all the member of the Tsukiji Campus for their extensive corporation.

Taira Kinoshita M.D., Ph.D.
Director, National Cancer Center Hospital East

Organization



Clinical Departments

Director:

Taira Kinoshita

- **Department of Head and Neck Oncology and Plastic and Reconstructive Surgery**
  - Chief: Ryuichi Hayashi
  - Chief: Shin Tahara
  - Chief: Minoru Sakuraba
  - Head and Neck Surgery Division
  - Head and Neck Oncology Division
  - Plastic and Reconstructive Surgery Division
- **Department of Breast Oncology and Hematology/Medical Oncology**
  - Chief: Kuniaki Ito
  - Chief: Noriaki Wada
  - Breast Surgey Division
  - Hematology/Breast and Medical Oncology Division
- **Department of Thoracic Oncology**
  - Chief: Kanji Nagai
  - Chief: Yuichiro Ohe
  - Chief: Hironobu Ohmatsu
  - Thoracic Surgery Division
  - Thoracic Oncology Division
  - Respiratory Endoscopy Division
- **Department of Gastrointestinal Oncology**
  - Chief: Taira Kinoshita
  - Chief: Norio Saito
  - Chief: Atsushi Ohtsu
  - Chief: Mitsuyo Nishimura
  - Chief: Toshihiko Doi
  - Chief: Kazuhiro Kaneko
  - Esophageal Surgery Division
  - Gastric Surgery Division
  - Colorectal Surgery Division
  - Gastrointestinal Medical Oncology Division
  - Gastrointestinal Endoscopy Division
- **Department of Hepatobiliary and Pancreatic Oncology**
  - Chief: Masaru Konishi
  - Chief: Masafumi Ikeda
  - Hepatobiliary and Pancreatic Surgery Division
  - Hepatobiliary and Pancreatic Medical Oncology Division
- **Department of Urology**
  - Chief: Vacant
- **Department of Anesthesiology and Intensive Care Unit**
  - Chief: Yasuko Miwa
  - Anesthesiology Division
  - Intensive Care Unit
- **Department of Palliative Medicine and Psycho-Oncology**
  - Chief: Hiroya Kinoshita
  - Chief: Asao Ogawa
  - Palliative Medicine Division
  - Psycho-Oncology Division
- **Department of Diagnostic Radiology**
  - Chief: Mitsuo Satake
- **Department of Radiation Oncology**
  - Chief: Tetsuo Akimoto
- **Department of Pathology and Clinical Laboratories**
  - Chief: Atsushi Ochiai
  - Pathology Division

Activities of the Departments

DEPARTMENT OF HEAD AND NECK ONCOLOGY AND PLASTIC AND RECONSTRUCTIVE SURGERY, HEAD AND NECK SURGERY DIVISION

Masakazu Miyazaki, Ryuichi Hayashi, Takeshi Shinozaki, Mitsuru Ebihara, Wataru Okano, Kensuke Suzuki, Shinya Jinnouchi

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 (further details are available in the annual report of the Plastic and Reconstructive Surgery Division).

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 2011, 271 new patients were treated: 419 patients underwent surgery under general anesthesia and 32 patients under local anesthesia. Ninety-one 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, are also being increasingly performed.

The outpatient service of the Division is available from Monday to Friday. Endoscopic, radiographic, and ultrasonic examinations are routinely performed. The dental service is also available to improve the quality of life after ablative surgery using maxillofacial prostheses, to prevent severe odontogenic infection during chemotherapy and / or radiotherapy, and to reduce local infection after major surgery for head and neck cancer.

Research Activities

1. Exploration of factors related to dilation of intraepithelial blood vessels or angiogenesis in the lesions of early-stage esophageal and head and neck cancers

RNA and DNA were extracted from biopsy specimens of cancerous and noncancerous tissues obtained from 13 new subjects using a laser microdissection system. The level of expression of MET, CXCR7, and CD44 was higher in the cancerous tissues than in the noncancerous tissues. In 4 (30.8%) of 13 subjects, p53 mutation was found in the cancerous tissue specimens, and the frequency of mutation was almost the same as that of esophageal squamous intraepithelial neoplasia. It is suggested based on the histopathological findings that the genes identified in this study, which were highly expressed in relation to angiogenesis and induction of inflammation, have an effect leading to carcinogenesis.

2. Study of polyglycolic acid sheet as a wound dressing material

The potential of polyglycolic acid sheet (PGA sheet) as a pharyngeal wound dressing material was studied. The PGA sheet was used in 6 patients with oral and oropharyngeal cancer who underwent peroral resection. Dislocation of the sheet occurred in 2 of 6 patients. In the remaining 4 patients without dislocation, good pain control was obtained. The PGA sheet was usable in 4 patients although touching or scraping frequently occurred in the oral cavity and oropharynx. Thus, the PGA

sheet can be used as a wound dressing material in patients who have undergone endoscopic resection of pharyngeal cancer.

Clinical Trials

1. Multicenter study to establish a suitable approach to resection of advanced tongue cancer

The aim of this study was to establish the pull-through approach as the standard approach for the resection of advanced tongue cancer. 74 patients with T3/4 tongue cancer were enrolled. The pull-through approach was used in 68 patients, whereas the mandibular swing approach was used in only 1 patient. The local control rate did not differ between the partial and total resections performed with the pull-through approach. Thus, the less invasive pull-through approach is considered to be the standard approach for the resection of advanced tongue cancer.

2. Symptom prevalence and functional status among patients with advanced head and neck cancer

A multicenter prospective study is being conducted. The overall QOL of advanced head and neck cancer patients with EORTC-QLQ-C15-PAL, the amount of airway secretions and typical symptoms of head and neck cancer are evaluated. The patient enrollment for this study is ongoing.

Published Papers

1. Ebihara M, Kishimoto S, Hayashi R, Miyazaki M, Shinozaki T, Daiko H, Saikawa M, Sakuraba M, Miyamoto S. Window resection of the trachea and secondary reconstruction for invasion by differentiated thyroid carcinoma. Auris Nasus Larynx, 38:271-275, 2011

2. Shinozaki T, Hayashi R. Nutrition and palliative surgery for head and neck cancer. In: Victor RP (ed), Diet and nutrition in palliative care, USA, CRC Press, pp283-288, 2011

Table 1. Number of new patients

Tongue	58
Oral cavity excluding tongue	48
Oropharynx	35
Hypopharynx	53
Cervical esophagus	15
Larynx	20
Nasal cavity and paranasal sinuses	2
Thyroid gland	33
Major salivary gland	2
unknown	3
Others	2
Total	271

Table 2. Type of procedure

Glossectomy	74
Resection of oral cavity	49
Oropharyngectomy	28
Hypopharyngectomy	27
Cervical esophagectomy	20
Laryngectomy	21
Resection of the nasal and/or paranasal sinuses	8
Thyroidectomy	50
Parotidectomy	17
Submandibulectomy	2
Endoscopic resection	40
Neck dissection	74
Others	41
Total	451

Table 3. 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

DEPARTMENT OF HEAD AND NECK ONCOLOGY AND PLASTIC AND RECONSTRUCTIVE SURGERY, PLASTIC AND RECONSTRUCTIVE SURGERY DIVISION

Minoru Sakuraba, Shogo Nagamatsu, Megumi Taji, Nobuko Suesada, Masahide Fujiki

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 pedicled flaps, local flaps, skin grafts, 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 the combination of functional and morphological reconstruction.

Routine Activities

Five plastic surgeons cover reconstructive operations both in the NCCH East in Kashiwa and the NCCH in Tokyo, and train the residents in the two hospitals. These reconstructive surgeries are performed in cooperation with the surgeons of another department of the hospital, such as Head and Neck Surgery, Breast Surgery, Orthopedic Surgery, Esophageal Surgery, Colorectal and Urological Surgery, *et cetera*. In the NCCH East, Head and Neck reconstruction is the most frequently performed operation accounting for 65% of the reconstructive surgery. In the Head and Neck region, a free jejunal graft and a rectus abdominis musculocutaneous flap are the most frequently used procedures. A weekly conference is held with doctors of the Departments of Head and Neck surgery, Radiation Oncology, and Gastro Intestinal Oncology. Breast reconstruction using autologous tissue transfer was employed in 2005, and since then, patients' needs for breast reconstruction have been increasing. Nineteen cases of breast reconstruction were performed in 2011, and a free deep inferior epigastric artery perforator (DIEP) flap transfer is the most frequently used procedure.

Research Activities

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

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

With the objective of addressing these four aspects, establishing a standard of reconstructive surgery and developing new techniques of reconstructive surgery are the most important aims of our studies. Multi-institutional analyses of postoperative complication and swallowing function after total pharyngolaryngo esophagectomy and reconstruction with a free jejunal graft are continuously performed. This study was supported by a Grant in-Aid for Cancer Research. The aim of the study was to clarify the relationship between surgical procedures and postoperative complications and function. We clarified the importance of the tensile strength of the transferred jejunum for better postoperative swallowing functions. Long term results after microsurgical head and neck reconstruction were evaluated to elucidate the risk factors associated with reconstructive failure. We clarified that reconstructive surgery in patients with previous surgical intervention, including reconstructive microsurgery, is at high risk of reconstructive failure. Furthermore, previous radiation therapy was closely related as a risk factor for reconstructive failure.

Table 1. Cooperation with other divisions

NCCH East	No. of patients
Head & Neck surgery	114
Orthopedic surgery	1
Esophageal surgery	2
Breast surgery	42
Dermatology	----
Urologic surgery	1
HB & P surgery	0
Ophthalmic surgery	----
Colorectal surgery	5
Gastric surgery	0
Thoracic surgery	7
Gynecology	----
Plastic & Reconstructive	2
Total	174

Table 2. Operative Procedures

NCCH East	No. of flaps
Microvascular free flap	103
Jejunum	34
RAMC or DIEP	36
Anterolateral thigh	18
Fibula bone	7
Latissimus Dorsi	1
Radial Forearm	0
Other flaps	7
Other Microsurgery	1
Supercharge	0
Nerve Graft	0
Limb Salvage	0
Hepatic Artery	0
Others	1
Subtotal	104
Pedicled flaps	18
PMMC	7
Latissimus Dorsi	3
RAMC	0
Other flaps	7
Other Procedures	52
Total	174

Published Papers

1. Onoda S, Sakuraba M, Asano T, Miyamoto S, Hayashi R, Asai M, Kimata Y. Thoracoacromial vessels as recipients for head and neck reconstruction and cause of vascular complications. Microsurgery, 31:628-631, 2011

2. Tanaka K, Sakuraba M, Miyamoto S, Hayashi R, Ebihara M, Miyazaki M, Shinozaki T, Daiko H, Yano T. Analysis of operative mortality and post-operative lethal complications after head and neck reconstruction with free tissue transfer. Jpn J Clin Oncol, 41:758-763, 2011

3. Onoda S, Kimata Y, Yamada K, Sugiyama N, Sakuraba M, Hayashi R. The best salvage operation method after total necrosis of a free jejunal graft? Transfer of a second free jejunal graft. J Plast Reconstr Aesthet Surg, 64:1030-1034, 2011

4. Tsuchiya S, Sakuraba M, Asano T, Miyamoto S, Kimata Y, Hayashi R, Nakatsuka T. Morphologic study of mandibles in Japanese patients for mandibular reconstruction with fibula free flaps. Head Neck, 33:383-388, 2011

5. Onoda S, Sakuraba M, Asano T, Miyamoto S, Beppu Y, Chuman H, Kawai A, Nakatani F, Kimata Y. Use of vascularized free fibular head grafts for upper limb oncologic reconstruction. Plast Reconstr Surg, 127:1244-1253, 2011

DEPARTMENT OF BREAST ONCOLOGY, HEMATOLOGY, AND MEDICAL ONCOLOGY, HEMATOLOGY AND STEM CELL TRANSPLANTATION DIVISION

Takeshi Yamaguchi, Yoichi Naito, Nobuaki Matsubara, Shunji Nagai, Masahiko Nezu, Hirofumi Mukai, Kuniaki Itoh

Introduction

The Hematology Division is part of the Division of Oncology and Hematology. The staff physicians and residents of this Division carry out clinical and research activities related to chemotherapy of patients with hematological and non-hematological tumors. The overall inpatient care system comprises the management of both oncology and hematology teams, namely, while a monthly rotating attending physician out of three staff physicians is responsible for all inpatient care and education of residents in the oncology team, all physicians including two hematology staff physicians and residents attend to manage all of the inpatient care in the hematology team. In 2011, approximately 180 patients with hematological malignancies, including 23 patients seeking a second opinion, visited the Division for consultation. High-dose chemotherapy with autologous peripheral blood hematopoietic stem cell transplantation is considered the standard treatment for patients with relapsed malignant lymphoma previously responsive to salvage chemotherapy and younger patients with multiple myeloma. Clinical engineers, in collaboration with staff physicians, perform stem cell harvesting by apheresis and cell processing.

Routine Activities

The Division manages patients with various types of hematological malignancies, including non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, macroglobulinemia, acute leukemia, and chronic leukemia. Recently, a tendency has been noted towards an increased number of elderly patients with hematological malignancies. Moreover, the Division is currently providing routine chemotherapy as an outpatient service to an increasing number of patients with both hematological and non-hematological tumors. All patients undergoing aggressive chemotherapy and autologous peripheral blood hematopoietic stem cell transplantation are managed in laminar airflow rooms in the designated ward on the eighth floor. Besides managing patients, the Division also provides consultation on hematological abnormalities. Morning case conferences on inpatient care are held on Mondays and Thursdays, and a weekly case conference on new patients visiting the clinics at the Division is held on Thursday evenings. A weekly conference, including an educational review on hematology, is also conducted on Tuesday evenings. On Wednesday evenings, a weekly joint conference on hematological disorders is held with pathologists. Morning journal clubs also meet on Wednesdays and Fridays at the Division of Oncology and Hematology.

Research Activities and Clinical Trials

Clinical studies on hematological malignancies performed by the Division 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 the local hematology group in Chiba prefecture. The Division also conducts pharmaceutical company-sponsored clinical trials of new anticancer agents 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 (JCOG0601); a randomized phase II trial of biweekly rituximab-CHOP or biweekly rituximab-CHOP/cyclophosphamide, cytarabine, dexamethasone, etoposide and rituximab (CHASER) followed by high dose melpharan, cyclophosphamide, etoposide and dexamethasone (LEED) with autologous peripheral blood hematopoietic stem cell transplantation in patients with newly diagnosed poor risk CD20+ diffuse large B cell lymphoma (JCOG0908); a phase II trial of rituximab-high-CHOP/CHASER followed by high dose LEED with autologous peripheral blood hematopoietic stem cell transplantation in patients with newly diagnosed mantle cell lymphoma (JCOG0406); and a randomized phase II trial of dexamethasone with bortezomib or thalidomide in patients with multiple myeloma in relapse (JCOG0904). An Asian phase II study was

completed on MK-0683 (volinostat), which is a novel inhibitor of histone deacetylase, for patients with low-grade B-cell lymphoma or mantle cell lymphoma in relapse. A randomized double blinded phase III trial of polyethylene glycol (PEG) G-CSF or filograstim for prophylactic use was completed in patients with relapsed malignant lymphoma who were treated with cyclophosphamide, cytarabine, etoposide and dexamethasone (CHASE). A randomized, double-blind study of RAD001 (everolimus), an inhibitor of the mammalian target of rapamycin, is ongoing for poor risk patients with diffuse large B-cell lymphoma in complete remission after first-line treatment with rituximab-CHOP. A global randomized phase III trial of CMC544 (intuzumab ozogamicin) and rituximab or bendamustin and rituximab in patients with relapsed CD22 positive diffuse large B cell lymphoma, who are not eligible for autologous stem cell transplantation, is also ongoing.

Published Papers

1. Tanaka R, Kimura S, Ashihara E, Yoshimura M, Takahashi N, Wakita H, Itoh K, Nishiwaki K, Suzuki K, Nagao R, Yao H, Hayashi Y, Satake S, Hirai H, Sawada K, Ottmann OG, Melo JV, Maekawa T. Rapid automated detection of ABL kinase domain mutations in imatinib-resistant patients. Cancer Lett, 312:228-234, 2011

Table 1. Number of patients

Non-Hodgkin's lymphoma	126
Hodgkin's lymphoma	6
Multiple myeloma	5
Acute leukemia	14
Chronic leukemia	10
Others	21
Total	182

Table 2. Type of procedure

PBSCT non-Hodgkin's lymphoma in relapse	2
Multiple myeloma	2
Total	4

DEPARTMENT OF BREAST ONCOLOGY, HEMATOLOGY, AND MEDICAL ONCOLOGY, INVESTIGATIONAL DRUG DEVELOPMENT FOR SOLID TUMORS DIVISION

Takeshi Yamaguchi, Yoichi Naito, Nobuaki Matsubara, Shunji Nagai, Masahiko Nezu, Hirofumi Mukai, Kuniaki Itoh

Introduction

Patients with different types of cancer, including those with breast and genitourinary tract cancers and malignant lymphomas, are treated with standard chemotherapy and/or managed in clinical trials in daily medical practice at the Division of Oncology and Hematology. 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, particularly for breast cancer and hematological malignancies, developmental therapeutics with 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 diseases of the Division comprised breast cancer and malignant lymphomas. Eligible patients with these cancers were invited to participate in large phase II/III studies. Presently, there is an increasing number of patients with cancers of the genitourinary tract and cancer of unknown primary origin. The Division also treated 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 2011, about 700 patients with different types of cancer, including hematological malignancies, visited the Division for consultation. Approximately 400 patients per month received routine chemotherapy as an outpatient service by the Division. The overall inpatient care system of the Division comprises management of both oncology and hematology teams, namely, a monthly rotating attending physician out of three staff physicians is responsible for all inpatient care and education of residents in oncology team, and all physicians including two hematology staff and residents attend to manage of all the inpatient care in the hematology team. Morning case conferences on inpatient care are held on Mondays and Thursdays, and a weekly case conference on new patients visiting the clinics at the Division is held on Thursday evenings. A weekly educational review on oncology and hematology is also conducted on Tuesday evenings. Moreover, a biweekly joint conference with breast surgeons is held on Wednesday evenings and a monthly urological conference with urologists is held on Monday evenings. Morning journal clubs also meet on Wednesdays and Fridays at the Division of Oncology and Hematology.

Research Activities and Clinical Trials

Phase I/II studies of new anticancer agents for specific disease targets are conducted in collaboration with pharmaceutical companies. Phase I studies of the following anticancer agents were conducted: cabazitaxel (a new taxane derivative) for patients with hormone refractory prostate cancer, abiraterone acetate (a CYP17 inhibitor for androgen antagonist) for patients with castration-resistant prostate cancer who have not received chemotherapeutic agents, eribulin (synthetic halichondrin) for patients with advanced or metastatic breast cancer in whom HER-2 was overexpressed, and NK105 (polymer micelles of paclitaxel) for patients with advanced or metastatic cancer for which standard chemotherapy was unavailable. For patients unresponsive to chemotherapy and those with cancers for which standard chemotherapy was unavailable, a combination phase I study of afatinib with vinorelbine is in progress. Phase II studies of the following anticancer agents were also conducted: AG-013736 (an inhibitor of VEGF receptor tyrosine kinases) as a second-line treatment for patients with metastatic renal cell cancer; and neratinib (erbB1/2/4 inhibitor) as an adjuvant chemotherapy for patients with breast cancer. A phase II study of eribulin for patients with soft tissue sarcomas is

Table 1. Number of patients

Breast cancer	262
Hematological malignancies	182
Genitourinary cancer	171
Gynecological cancer	19
Cancer of unknown primary origin	32
Others	44
Total	710

ongoing.

In addition, a randomized placebo controlled trial of RAD001 (an mTOR inhibitor, everolimus) combined with paclitaxel and trastuzumab is ongoing for patients with HER-2 positive metastatic and/or locally advanced breast cancer in as a primary treatment. BOLERO-3, a randomized placebo controlled trial of RAD001 with vinorelbine and trastuzumab is being conducted for patients with HER-2 positive, trastuzumab-resistant breast cancer in whom taxane therapy has been carried out. A randomized phase III study of neratinib versus a combination with lapatinib and capecitabine for patients with HER-2 positive metastatic and/or locally advanced breast cancer is also being conducted. A randomized phase III study of taxane-based chemotherapy with lapatinib or trastuzumab as a first line therapy for patients with HER-2 positive metastatic breast cancer is also being conducted. In addition, to select an effective chemotherapeutic regimen (SELECT-BC) for patients with metastatic breast cancer in whom hormone therapy has failed and trastuzumab is not indicated, a prospective randomized study of anthracycline versus TS-1 as a front-line chemotherapy is ongoing.

Published Papers

1. Tahara M, Minami H, Kawashima M, Kawada K, Mukai H, Sakuraba M, Matsuura K, Ogino T, Hayashi R, Ohtsu A. Phase I trial of chemoradiotherapy with the combination of S-1 plus cisplatin for patients with unresectable locally advanced squamous cell carcinoma of the head and neck. Cancer Sci, 102:419-424, 2011
2. Ohsumi S, Shimozuma K, Ohashi Y, Shinji M, Hozumi Y, Mukai H, Takatsuka Y, Aihara T. Health-related quality of life and psychological distress of breast cancer patients after surgery during a phase III randomized trial comparing continuation of tamoxifen with switching to anastrozole after adjuvant tamoxifen for 1-4 years: N-SAS BC 03. Breast Cancer Res Treat, 127:143-152, 2011
3. Shigeta K, Miura Y, Naito Y, Takano T. Cabazitaxel for castration-resistant prostate cancer. Lancet, 377:121; author reply 122-123, 2011
4. Shigeta K, Naito Y, Takano T. Early prostate cancer--treat or watch? N Engl J Med, 365:568-569, 2011

DEPARTMENT OF BREAST ONCOLOGY, HEMATOLOGY, AND MEDICAL ONCOLOGY, BREAST SURGERY DIVISION

Noriaki Wada, Kimiyasu Yoneyama, Chisako Yamauchi* (* part-timer)

Introduction

The Breast Surgery Division is responsible for the care of patients with operable breast cancers. The Division is committed to providing the latest, most comprehensive breast treatments for patients in cooperation with other breast care specialists. The multidisciplinary approach to diagnosis and treatment includes working closely with a team of surgeons, radiologists, pathologists, plastic surgeons, medical oncologists, specialized nurses, and technicians.

The division mainly focuses on "minimally invasive surgery" and carries out a thorough investigation for an oncologically safe approach, less morbidity and good cosmesis. In particular, sentinel lymph node (SLN) biopsy has already been established as a standard care for clinical node negative patients. This procedure can be a reasonable alternative to unnecessary axillary lymph node dissection (ALND). On the other hand, preoperative systemic therapy provides the opportunity for curative operation or breast-conserving surgery to avoid mastectomy. Moreover, we can provide breast reconstructive surgery in collaboration with the Plastic Surgery Division. These procedures will contribute to a better quality of life of patients with breast cancer.

Routine Activities

For the regular activities of the Division, a daily morning routine round is scheduled for inpatients by all staff and residents. Moreover, Our weekly film conference on breast cancer is conducted every Monday evening to discuss the diagnosis and surgical treatment planning for each patient. Multidisciplinary case conferences with the other breast care team members are held twice a month. A monthly pathological conference on breast cancer is also conducted on the last Friday of each month. At those conferences, the patients' 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 operated patients with breast cancer are shown in Table 1. A total of 285 patients with primary breast cancer and 23 patients with recurrence or other breast disease were operated on. Sixteen immediate breast reconstruction surgeries were included. Of the patients with primary breast cancer, 63 (22%) underwent primary systemic therapy. The types and number of operative procedures performed in 2011 are shown in Table 2. The rate of breast-conserving surgeries (including three radiofrequency ablation alone case) was 72% (204/285). Sentinel node biopsy was performed in 216 patients, and 173 patients were spared from ALND.

Clinical and Research Activities (Trials)

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

A feasibility study on RFA followed by partial mastectomy was performed for T1N0 breast cancer patients with no extensive intraductal components using a Cool-tip electrode system. Moreover, a phase II trial of RFA for the nonsurgical treatment of breast cancer is currently about to start.

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

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

3. Long term results of SLN negative patients without ALND.

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

4. Effectiveness of primary tumor resection for metastatic breast cancer.

In this multicenter clinical trial (JCOG 1017), the primary tumor resection plus systemic therapy arm is compared to the systemic therapy alone arm in metastatic breast cancer.

Published Papers

1. Ohtani S, Kochi M, Ito M, Higaki K, Takada S, Matsuura H, Kagawa N, Hata S, Wada N, Inai K, Imoto S, Moriya T. Radiofrequency ablation of early breast cancer followed by delayed surgical resection--a promising alternative to breast-conserving surgery. Breast, 20:431-436, 2011

Table 1. Number of primary breast cancer patients operated on during 2002-2011

Clinical stage	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Stage 0	8	18	14	29	34	27	23	38	39	43
Stage I	73	97	100	89	79	94	84	86	80	86
Stage II	110	104	97	94	103	87	87	122	137	112
Stage III	24	33	24	35	34	25	33	42	32	43
Stage IV, unknown	1	1	2	2	1	4	0	3	1	1
Total	216	253	237	249	251	237	227	291	289	285

Table 2. Types of operative procedures performed in 2011 for primary breast cancer

Type of operation	N
BT+SNB	42
BT+SNB→ALND	13
BT+ALND	25
BT alone	1
BP+SNB	128
BP+SNB→ALND	30
BP+ALND	32
BP alone	11
RFA+SNB	3
Total	285

Total mastectomy with immediate breast reconstruction was performed in six-teen 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 2005

Clinical stage	**N**	**5 yr. OS**	**10 yr. OS**
Stage 0	87	99%	93%
Stage I	570	97%	94%
Stage II	1104	90%	80%
Stage III	214	66%	51%
Stage IV, unknown	22	32%	11%
Total	1997		

median follow up period: 104 months [2-218]

DEPARTMENT OF THORACIC ONCOLOGY, THORACIC SURGERY DIVISION

Kanji Nagai, Junji Yoshida, Tomoyuki Hishida, Keiju Aokage, Akikazu Kawase, Masayuki Nakao, Tomohiro Haruki

Introduction

The Thoracic Surgery Division has three missions: surgical treatment, surgical resident training, and clinical research.

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

The Thoracic Surgery Division of the National Cancer Center Hospital East ranks second in Japan following the National Cancer Center Tokyo in providing surgical treatment of primary lung cancer. Since its establishment in 1992, the Division has been one of the most active leaders in the field of lung cancer in Japan. Moreover, it has been an active participant in international and national scientific venues. This year, in addition to 16 scientific papers published in English, and 1 in Japanese, the Division made 59 presentations: 15 international, 37 national, and 7 regional.

Routine Activities

To maintain its leadership position, the Division was seeking more consultant surgeons since Dr. Nagai, chief of the Division, was promoted to hospital management in 2006 and has since then been engaged mostly in administrative duties. After almost 4 years, a new consultant surgeon joined the Division. At the beginning of April, the Division welcomed Dr. Keiju Aokage, one of our former senior residents. The Division is presently composed of 4 consultant surgeons and 5 or 6 residents.

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

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

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

The surgical procedures of the Division have generally remained similar for the past several years, but we started to employ port-access thoracoscopic surgery more often last year. Approximately 10% of the surgeries are completed via a 3-port access, and 80% of the surgeries are thoracoscopically assisted. To date, the average postoperative hospital stays of patients in the Division have improved and became 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, 30-day operative

mortality occurred in 1 (0.3%) patient undergoing surgery for primary lung cancer.

Research Activities

In November 2003, the Thoracic Surgery Division initiated a new limited resection trial for small pulmonary ground-glass opacity (GGO) lesions. Patient selection was based solely on high-resolution CT (HRCT) findings: a pure or mixed GGO lesion of 2 cm diameter or smaller in the lung periphery with a tumor disappearance ratio (TDR) of 0.5 or higher on HRCT. TDR is defined as 1−DM/DL, where DM is the maximum tumor diameter on the mediastinal setting and DL on the lung setting. In November 2006, the Department of Thoracic Oncology, Kanagawa Cancer Center Hospital, Yokohama, Kanagawa, Japan, joined the trial, and we achieved our goal of 100 patients in November 2009. We are reviewing the enrolled patients radiologically and pathologically. In view of possible delayed cut-end recurrence cases among patients enrolled in the previous study, diagnosing using the Noguchi classification by intraoperative frozen section, we will have to survey these patients until 10 years after surgery.

The Division is also continuing a negative resection margin technique trial using lavage cytology examination for primary and metastatic lung cancer patients treated with limited resection. This method involves washing the used stapler cartridges followed by intraoperative cytological evaluation of the washed saline sediment.

Clinical Trials

1. Surgical margin lavage cytology examination in limited resection for primary and metastatic lung cancer patients [observational].
2. Member of an organized trial of TS-1 vs. UFT adjuvant chemotherapy for completely resected pathologic stage I (>2 cm) non-small cell lung cancer [phase III].
3. Member of an organized trial of limited resection for small GGO lung tumors [phase II].
4. Member of an organized trial of segmentectomy for peripheral T1aN0M0 non-small cell lung cancers [phase III].
5. Member of an organized trial of CDDP + DOC followed by TS-1 adjuvant chemotherapy for completely resected pathologic stage II/III non-small cell lung cancer [phase II].
6. Member of an organized trial of recMAGE-A3 + AS15 antigen-specific cancer immunotherapeutic as adjuvant therapy in patients with completely resected MAGE-A3 positive stage IB-IIIA non-small cell lung cancer [phase III].
7. Member of an organized trial of WT1 peptide vaccination as adjuvant therapy in patients with completely resected WT1/HLA-A*2402 positive stage IB-II non-small cell lung cancer [randomized phase II].

Table 1. Number of patients

Lung cancer	337
Metastatic lung tumor	55
Mediastinal tumor	17
Others	45
Total	454

Table 2. Type of procedure - Primary lung cancer

Pneumonectomy	26
Lobectomy	256
(Bronchoplasty)	(5)
Limited resection	45
Exploratory thoracotomy	10
Total	337

Table 3. Overall survival rates for resected primary lung cancer (as of 2010)

Pathologic stage#	Number of patients	MST (months)	5-yr survival rate (%)
IA	896	NR	87.9
IB	405	99.9	67.6
IIA	262	65.8	54.1
IIB	120	41.1	43.3
IIIA	306	37.7	37.9
IIIB	32	24.4	35.0

Surgery between 2000 and 2007; #: Stages according to TNM Classification, 6th edition; NR: Not reached.

Published Papers

1. Nakao M, Hishida T, Ishii G, Nagai K. Malignant pleural mesothelioma with osteosarcomatous differentiation: characteristic bone scintigraphy findings associated with enhanced tumorous osteogenesis. Eur J Cardiothorac Surg, 39:421, 2011
2. Ohtaki Y, Yoshida J, Ishii G, Aokage K, Hishida T, Nishimura M, Takeyoshi I, Nagai K. Prognostic significance of a solid component in pulmonary adenocarcinoma. Ann Thorac Surg, 91:1051-1057, 2011
3. Shimada Y, Yoshida J, Aokage K, Hishida T, Nishimura M, Nagai K. Complete left-sided pericardial defect in a lung cancer patient undergoing pneumonectomy without closure of the defect. Ann Thorac Cardiovasc Surg, 17:67-70, 2011
4. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Poor prognostic factors in patients with stage IB non-small cell lung cancer according to the seventh edition TNM classification. Chest, 139:855-861, 2011
5. Ohtaki Y, Ishii G, Hasegawa T, Nagai K. Adult neuroblastoma arising in the superior mediastinum. Interact Cardiovasc Thorac Surg, 13:220-222, 2011
6. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Prognostic impact of histology on early-stage non-small cell lung cancer. Chest, 140:135-145, 2011
7. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. The prognostic impact of cigarette smoking on patients with non-small cell lung cancer. J Thorac Oncol, 6:735-742, 2011
8. Maeda R, Ishii G, Yoshida J, Hishida T, Nishimura M, Nagai K. Influence of cigarette smoking on histological subtypes of stage I lung adenocarcinoma. J Thorac Oncol, 6:743-750, 2011
9. Suzuki K, Koike T, Asakawa T, Kusumoto M, Asamura H, Nagai K, Tada H, Mitsudomi T, Tsuboi M, Shibata T, Fukuda H, Kato H. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). J Thorac Oncol, 6:751-756, 2011
10. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Risk factors for tumor recurrence in patients with early-stage (stage I and II) non-small cell lung cancer: patient selection criteria for adjuvant chemotherapy according to the seventh edition TNM classification. Chest, 140:1494-1502, 2011

DEPARTMENT OF THORACIC ONCOLOGY, THORACIC ONCOLOGY DIVISION

Yuichiro Ohe, Hironobu Ohmatsu, Koichi Goto, Seiji Niho, Kiyotaka Yoh, Shigeki Umemura, Yuki Yamane, Toshihiro Shiozawa, Yoko Yamaguti, Masami Itho

Introduction

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

Routine Activities

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

Research Activities

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

Especially, whole genome analysis of 100 adenocarcinomas of the lung to detect new driver mutations is 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, some data demonstrated the usefulness of maintenance chemotherapy using pemetrexed orerlotinib for NSCLC but the efficacy has never been definitively established. Thus, an in-house feasibility study of maintenance chemotherapy with TS-1 for stage IV non-small cell lung cancer (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.

Crizotinib is a newly developing ALK and MET inhibitor and very effective for EML4-ALK positive NSCLC, although 4-5% of NSCLC are positive for EML4-ALK fusion protein. A global multi-institutional randomized phase 3 study of crizotinib has been started and we are participating in this study. JCOG0509 was a randomized phase 3 study comparing irinotecan with cisplatin vs amrubicin with cisplatin for extensive disease small cell lung cancer (SCLC). The interim analysis of JCOG0509 could not demonstrate non-inferiority of cisplatin and amrubicin compared with cisplatin and irinotecan.

Number of patients in 2011

Lung Cancer		361
	Small cell lung cancer	83
	Adenocarcinoma	174
	Squamous cell carcinoma	53
	Large cell carcinoma	8
	NSCLC NOS	36
	Others	7
Thymic cancer		5
Thymoma		2
Malignant pleural mesothelioma		4

Initial treatment of lung cancer in 2011

Chemotherapy	205
Chemoradiotherapy	54
Surgery followed by chemotherapy	48
Radiotherapy	19
Palliative care	30
Others	5

Survival of lung cancer patients treated in 2004-2008

Disease	Stage	Treatment	N	Survival rate (%)				
				1y	2y	3y	4y	5y
NSCLC	III	Chemoradiotherapy	255	78	49	36	32	26
NSCLC	IIIB-IV	Chemotherapy	830	47	27	15	9	5
SCLC	LD	Chemoradiotherapy	87	80	40	24	17	17
SCLC	ED	Chemotherapy	138	33	2	2	2	0

JCOG0605, a randomized phase 3 study comparing nogitecan vs weekly cisplatin, irinotecan and etoposide for previously treated SCLC and JCOG0901, a phase 2 study of amrubicin for refractory SCLC, have completed patient accrual. JCOG1011 is a newly started randomized phase 2 study for LD-SCLC comparing cisplatin and amrubicin with the CODE regimen (weekly cisplatin, vincristine, Adriamycin, etoposide) after induction chemoradiotherapy with cisplatin and etoposide.

Published Papers

1. Naito Y, Kubota K, Ohmatsu H, Goto K, Niho S, Yoh K, Ohe Y. Phase II study of nedaplatin and docetaxel in patients with advanced squamous cell carcinoma of the lung. Ann Oncol, 22:2471-2475, 2011

2. Nyberg F, Ogiwara A, Harbron CG, Kawakami T, Nagasaka K, Takami S, Wada K, Tu H-K, Otsuji M, Kyono Y, Dobashi T, Komatsu Y, Kihara M, Akimoto S, Peers IS, South MC, Higenbottam T, Fukuoka M, Nakata K, Ohe Y, Kudoh S, Clausen IG, Nishimura T, Marko-Varga G, Kato H. Proteomic biomarkers for acute interstitial lung disease in gefitinib-treated Japanese lung cancer patients. PLoS One, 6:e22062, 2011

3. Nyberg F, Barratt BJ, Mushiroda T, Takahashi A, Jawaid A, Hada S, Umemura T, Fukuoka M, Nakata K, Ohe Y, Kato H, Kudoh S, March R, Nakamura Y, Kamatani N. Interstitial lung disease in gefitinib-treated Japanese patients with non-small-cell lung cancer: genome-wide analysis of genetic data. Pharmacogenomics, 12:965-975, 2011

4. Niho S, Kubota K, Yoh K, Goto K, Ohmatsu H, Nihei K, Ohe Y, Nishiwaki Y. Clinical outcome of small cell lung cancer with pericardial effusion but without distant metastasis. J Thorac Oncol, 6:796-800, 2011

5. Suyama K, Naito Y, Yoh K, Niho S, Goto K, Ohmatsu H, Nishiwaki Y, Ohe Y. Development of Cushing's syndrome during effective chemotherapy for small cell lung cancer. Intern Med, 50:335-338, 2011

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, GASTRIC SURGERY DIVISION

Taira Kinoshita, Masaru Konishi, Shinichiro Takahashi, Takahiro Kinoshita, Naoto Gotohda, Yuichiro Kato, Teruhisa Sakamoto

Introduction

Patients with gastric tumors are treated by the Gastric Surgery Division in the Upper Abdominal Surgical Oncology Group. Our group consists of six staff surgeons, three senior residents and nine resident surgeons. The gastric tumors which we manage include not only common gastric adenocarcinomas but also adenocarcinomas of the esophagogastric junction (AEG), the incidence of which is increasing recently, and gastric submucosal tumors (GISTs), and so on. Annually 260-300 patients are operated on, either with conventional laparotomy or with laparoscopic surgery. The procedure of laparoscopic gastrectomy with nodal dissection was introduced to the division in 2010 to pursue minimal invasiveness and better quality of life (QOL) for the patients. The recent high-definition laparoscopic field of view enables more meticulous and accurate maneuvers. In 2011, about 50% of gastrectomies were performed under laparoscopy, which tendency may continue towards next year. 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 diseases associated with dismal prognoses (scirrhous gastric cancer or with progressive lymph nodes metastasis) through a surgical approach combined with recent advanced chemotherapy regimen.

Routine Activities

Usually 12-14 patients are hospitalized and 5-7 patients undergo operations per week. A weekly film conference is held every Monday from 17:00 with doctors from the the Department of Diagnostic Radiology and Department of Gastrointestinal Oncology, discussing diagnosis of the patients with gastric tumors from oncological, surgical, endoscopic and radiologic aspects, to determine the optimal treatment strategy for each patient. In principle, patients with superficial gastric cancer lesions (cT1a) of the intestinal histologic type showing a clear margin are treated with endoscopic submucosal dissection (ESD). Some are required to undergo subsequent completion laparoscopic surgery with nodal dissection based on the pathological findings of the specimen obtained with ESD. As the initial interventions, laparoscopic surgery with nodal dissection is indicated for other patients with c-stage I gastric cancer. Not only distal gastrectomy but also total gastrectomy or function preserving procedures (pylorus-preserving gastrectomy or proximal gastrectomy with jejunal interposition/double-tract) can be performed laparoscopically. Basically, all of the procedures, mobilization, lymphadenectomy and reconstruction are carried out under laparoscopy, which we refer to as total laparoscopic procedures. Open gastrectomy with D2 nodal dissection is indicated for patients with c-stage II or III gastric cancer. When the tumor has infiltrated adjacent organs (liver, pancreas, etc.), extended radical operations (pancreaticoduodenectomy, plus hepatectomy) are chosen. For AEGs, when the tumor is over 3 cm long and involves the distal esophagus exceeding, the left thoracoabdominal approach is selected. Otherwise, the abdominal approach with transhiatal dissection is chosen according to the results of JCOG 9502. When the patients are diagnosed as having p-stage II or III in the final postoperative pathological findings, they are subsequently recommended to undergo adjuvant chemotherapy according to the Gastric Cancer Treatment Guidelines (Japanese Gastric Cancer Association).

We place importance on education of gastric surgeons, including those from other institutions, as well as hands-on training for resident surgeons in our hospital. Surgeons from various hospitals regularly visit our division to learn surgical techniques.

Research Activities and Clinical Trials

We aggressively publish our clinical research data in domestic or international congresses. In addition, we participate in multi-institutional clinical trials conducted by the Japan Clinical Oncology Group (JCOG)-Gastric Surgery Study Group. Patients with gastric cancer are, if eligible for a particular 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 the appearance of large-sized lesions type 3 or type 4. In this trial, the neoadjuvant chemotherapy arm is being compared with the precedent surgery 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, the palliative gastrectomy arm is compared to the 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 to expand the indication to early gastric cancer of the undifferentiated type

Published Papers

1. Aizawa M, Gotohda N, Takahashi S, Konishi M, Kinoshita T. Predictive value of baseline neutrophil/lymphocyte ratio for T4 disease in wall-penetrating gastric cancer. World J Surg, 35:2717-2722, 2011
2. Nobuoka D, Gotohda N, Kato Y, Takahashi S, Konishi M, Kinoshita T. Influence of excess body weight on the surgical outcomes of total gastrectomy. Surg Today, 41:928-934, 2011

Table 1. Number of patients

Gastric cancer	268
Others (GIST etc.)	16

Table 2. Type of procedure

Open gastrectomy	129
Distal Gastrectomy	57
Pylorus-preserving Gastrectomy	0
Proximal Gastrectomy	6
Total Gastrectomy	63
Pancreaticoduodenectomy	1
Partial Gastrectomy	1
Others (bypass, exploration, etc.)	17
Laparoscopic Surgery	111
Distal Gastrectomy	82
Pylorus-preserving Gastrectomy	3
Proximal Gastrectomy	16
Total Gastrectomy	5
Partial Gastrectomy	5
Others (exploration, etc.)	7

Table 3. Survival rates of gastric cancer

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

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

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, COLORECTAL SURGERY DIVISION

Norio Saito, Masanori Sugito, Masaaki Ito, Akihiro Kobayashi, Yusuke Nishizawa

Introduction

The Colorectal and Pelvic Surgery Division was established 13 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 10 residents. The outpatient clinic is open 5 days a week. More than 350 new patients with colorectal carcinomas and more than 150 new patients with other pelvic malignancies visited this Division during the last year. Treatment plans are discussed at a weekly conference on GI malignancies and at another weekly conference on pelvic malignancies. Many treatment modalities, such as local excision with or without adjuvant chemo- or radiotherapy and other minimally invasive forms of surgery using laparoscopy, have been introduced for the treatment of patients in the early stages of cancer. Laparoscopy-assisted operations (Lap-Ops) with wider lymphadenectomy of up to more than D2 are also increasingly being performed in patients with advanced colorectal carcinomas. Abdominoperineal resection (APR) has, in the past, been the standard surgery in patients with very low rectal cancer; however, partial anal sphincter preserving surgery such as intersphincteric resection (ISR) has been performed in about 300 patients with very low rectal tumors and has resulted in cure, preservation of anal function, and better QOL.

Research Activities and Clinical Trials

1) A prospective randomized trial for extending the indications for Lap-Op (JCOG0404 CRC Surg-LAP vs. Open). The criteria for inclusion into this trial include: (1) T3 and T4 tumors located at C, A, and S in the colon and Rs in the rectum; (2) stage N0-2; (3) stage M0; and (4) a maximum tumor size ≤ 8 cm. A total of 77 patients have been registered in this Division. This study is currently in progress.
2) Intersphincteric resection study (ISR Study). APR has been the standard surgery for very low rectal cancer located within 5 cm of the anal verge. However, permanent colostomy causes severe impairment of the 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 regarding the potential functional adverse effects after ISR preoperatively. 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 33 patients with primary or recurrent tumors. This technique permits conservative surgery in selected patients with advanced rectal cancer involving the prostate and/or seminal vesicles without compromising local control. The QOL of these patients appears to be better. This study is also in progress.
4) A prospective randomized trial for the feasibility and effect of lateral node dissection in low rectal cancer – (Total) Mesorectal Excision (ME) vs. Lateral Node Dissection with preservation of autonomic nerves (D3 with nerve-sparing) [JCOG0212 CRC Surg.]. This study aims to

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

5) Local excision with postoperative chemoradiotherapy for T1･T2 rectal cancer. This study aims to evaluate preoperatively the feasibility and the oncologic outcome of local therapy for T 1 and a part of T2 rectal cancer without lymph node metastases. In this study, 32 patients have been registered, and itis currently in progress.
6) 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)

Table1. Number of patients (2011.1-2011.12)

Colorectal cases			Other cases		Total
Colon	Rectum	Sub-total	Gastro-intestinal	Others	
140	173	313	7	103	423

Tables 2. Type of procedure
Operative Procedures (2011.1-2011.12)

Colon N=140 Laparoscopic (LAP) : 110, Open : 30		
Sigmoidectomy	44	(LAP:43)
Right (hemi) colectomy	34	(LAP:33)
Ileocecal resection	8	(LAP: 8)
Limited colectomy	26	(LAP:23)
Hartmann procedure	0	
High anterior resection	0	
Low anterior resection	2	
Left (hemi) colectomy	2	(LAP:2)
Stoma	3	
Other	21	

Rectum N=173 Laparoscopic (LAP) : 79, Open : 94		
Low anterior resection	75	(LAP:45)
Abdominoperineal resection(AAR)*	47	(LAP:22)
High anterior resection	11	(LAP:11)
Abdominoperineal resection (APR)	15	
Hartmann procedure	6	
Local excision	5	
Total pelvic exenteration	3	
Stoma	4	
Others	7	

*Conventional coloanal anastomosis : 4
Partial intersphincteric resection (ISR) : 19
Subtotal ISR : 17
Total ISR : 7
Partial external sphincter resection (ESR) : 3

Table 3. Survival rates

Stage	Colon No. of pts	Colon 5-yr survival (%) overall	Colon 5-yr survival (%) cancer specific	Rectum No. of pts	Rectum 5-yr survival (%) Overall	Rectum 5-yr survival (%) cancer specific
Stage0	7	100	100	10	100	100
Stage I	155	96.1	100	119	94.1	99.1
Stage II	239	91.5	95.2	158	83.9	89.9
Stage IIIa	158	82.7	86.3	132	82.2	84.3
Stage IIIb	50	64.9	64.9	89	59.3	62
Stage IV	133	14.3	15.4	77	23.6	23.9

Op:1999.1-2005.12

Published Papers

1. Shiomi A, Ito M, Saito N, Ohue M, Hirai T, Kubo Y, Moriya Y. Diverting stoma in rectal cancer surgery. A retrospective study of 329 patients from Japanese cancer centers. Int J Colorectal Dis, 26:79-87, 2011
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DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, ESOPHAGEAL SURGERY DIVISION

Hiroyuki Daiko, Mitsuyo Nishimura

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, with regard to surgery for esophageal cancer, since transthoracic esophagectomy with 3-field lymphadenectomy has become more safe, reliable, and radical, the Division is striving to improve the surgical procedure further in order to lower the high incidence of postoperative mortality and morbidity that occur following this procedure. The Division is conducting a study to define the role of surgery in the multimodal approach to the treatment of esophageal cancer.

Routine Activities

The Esophageal Surgery Division consists of 2 staff surgeons, 1 chief resident 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 3 patients are operated upon every week. In 2011, 103 patients underwent esophagectomy. Transthoracic esophagectomy with extended lymph node dissection was performed on 59 nontreated cases or with neoadjuvant chemotherapy before surgery, and modified transthoracic esophagectomy was performed as a salvage procedure in 3 patients in whom other therapeutic modalities had failed. Thoracoscopic esophagectomy in the prone position with radical lymph node dissection was undertaken in 31 cases and transhiatal esophagectomy without thoracotomy was performed in 10 cases. Postoperatively, within 30 days, 1 patient died due to complications after a salvage operation.

Clinical Activities

The prognosis of patients with intramural metastasis or with involvement of more than 4 lymph nodes is very poor compared with patients without these factors. Currently, the Division is examining the role of pre- or postoperative chemotherapy in such patients, in whom two cycles of 5-fluorouracil and cisplatin preoperatively and postoperatively are administered.

For patients without lymph node metastasis in the thoracic inlet, thoracoscopic esophagectomy in the prone position with radical lymph node dissection is being attempted.

Cisplatin and 5-fluorouracil are administered preoperatively to patients with stage II/III esophageal cancer according to the outcome of the JCOG 9907 study. Furthermore, we have developed more effective neoadjuvant therapy for clinical stage II/III; a feasibility trial of neoadjuvant chemotherapy with docetaxel, cisplatin and fluorouracil for clinical stage II/III thoracic esophageal carcinoma has been completed.

For treating patients aged over 80 years who are unable to receive definitive chemoradiotherapy or undergo surgery, transhiatal esophagectomy with upper and middle to lower mediastinal lymph node dissection to as great an extent as possible is being attempted.

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.

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

Table 1. Type of Operation

Esophagectomy	103
GIST	3
Carcinoma of the reconstructed gastric tube	1
Salvage lymph node dissection	6
Exploratory thoracotomy	3
Emergency operation	4
Others	2
Total	122

Table 2. Type of Approach for Esophageal Cancer

Rt-Transthoracic Esophagectomy	62
Thoracoscopic Esophagectomy	31
Transhiatal Esophagectomy	10
Total	103

Published Papers

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DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, GASTROINTESTINAL ONCOLOGY DIVISION

Atsushi Ohtsu, Toshihiko Doi, Takayuki Yoshino, Nozomu Fuse, Takashi Kojima

Introduction

In 2011, approximately 500 patients were treated by 5 medical oncologists and 7 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 367 patients are hospitalized and the hospital stay with chemotherapy or palliative therapy was short. Our activities for each type of GI cancer in 2011 are shown in Table 1 (Number), Table 2 (Treatment), and Table 3 (efficacy). In clinical trials, both 58 sponsored initiated trials which consisted of 34 phase I trials including first-in-human, first-in-class drugs in a global fashion and 24 phase2/3 global trials to approve investigational new drugs (INDs) were conducted.

Research Activities

Esophageal Cancer (EC)

The result of a multicenter phase II trial of neo-adjuvant combination chemotherapy with docetaxel, cisplatin and 5-FU (DCF) in stage II/III EC was presented at the ASCO (American Society of Clinical Oncology) meeting, 2011. A multicenter phase II trial of neo-adjuvant chemoradiotherapy (CRT) in stage II or III EC, a multicenter phase I/II trial of induction-chemotherapy combination with DCF followed by CRT for advanced EC with T4 or M1, and a multicenter phase I/II trial of chemotherapy combination with DCF in stage IV EC (JCOG0807) have been completed. The enrollment of a multicenter phase I/II trial of CRT concurrent with S-1 and cisplatin in stage II or III EC (JCOG0604) was closed before the registration of the targeted number of patients due to slow accrual.

Gastric Cancer (GC)

The result of the AVAGAST study which evaluated the efficacy of bevacizumab was published in Journal of Clinical Oncology. The results of a global randomized phase II trial comparing irinotecan with nimotuzumab to irinotecan alone was presented at the 9th International Gastric Cancer Congress. The GASTRIC group project which evaluated the surrogacy of progression-free survival for overall survival in gastric cancer patients using individual patient data analysis on 4,102 patients from 20 randomized trials was presented at the 9th annual meeting of Japanese Society of Medical Oncology.

Colorectal Cancer (CRC)

We reported the results of company-sponsored trials, as a randomized phase II trial comparing TAS-102 with BSC (best supportive care), TAS-102 showing overall survival benefit over a placebo. In a global randomized phase III trial comparing regorafenib with a placebo, regorafenib showed survival benefit over the placebo. We also reported the results of investigator-initiated trials, as a cross-sectional study to elucidate *KRAS* mutation in 5,000 CRC, a registration trial to evaluate the Luminex *KRAS* test, an international consortium and a domestic multicenter trial in chemo-refractory KRAS wild-type metastatic CRC patients to evaluate the correlation between the efficacy of cetuximab and FcGR polymorphism and a retrospective trial to evaluate the efficacy of cetuximab to p. G13D *KRAS* mutation.

Others

We also treated GI rare cancers (GIST, NET etc.) as best practice. Recently our division has focused more on early stage clinical development, especially cutting edge phase I trials. Over 100 patients have been registered in phase I or I/II trials as company driven trials. Several results of trials, such as a (PLK1 inhibitor (MK-1496), an IGF-1R inhibitor (AMG 479), a PI3K inhibitor (BKM120), a pan HER inhibitor (TAK285), etc.) were presented at international meetings and published.

Table1. Number of patients

Tumor Type	Number of new patients	Number of hospitalized patients
Esophageal	196	136
Gastric	214	124
Colorectal	313	76
Other type of tumors	58	31
Total	781	367

Table2. Treatment

Tumor Type	Treatment	Number of patients
Esophageal Cancer	Chemotherapy(include CRT*)	118
Gastric Cancer	Chemotherapy	115
	Adjuvant chemotherapy	67
Colorectal Cancer	Chemotherapy	220

*chemoradiation

Table3. Survival of patients who received standard chemotherapy

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

Clinical Trials (Describing Only Ongoing Disease-specific Trials)

Esophageal Cancer (EC)

A multicenter phase III trial comparing surgery with CRT concurrent with 5-FU and cisplatin in stage I EC (JCOG0502), and a multicenter phase II trial of combined treatment with endoscopic mucosal resection and chemo radiotherapy for clinical Stage I EC (JCOG0508) are ongoing. A multicenter phase II trial of S-488410 (vaccination with multiple peptides) in stage IV EC is going as a company-led trial.

Gastric Cancer (GC)

The enrollment for a multicenter phase III trial (G-SOX) comparing S-1 plus oxaliplatin with S-1 plus cisplatin (SP) has been completed and the follow-up is ongoing. The follow-up of a multicenter global phase III trial comparing capecitabine plus cisplatin (XP) with cetuximab to XP (EXPAND) and a multicenter global phase III trial comparing everolimus to placebo (GRANITE) are ongoing. The enrollment for a multicenter global phase III trial comparing paclitaxel plus placebo to paclitaxel plus ramucirumab, a multicenter phase II trial of SP plus cetuximab, a multicenter randomized phase II trial of S-1 plus leucovorin (SL), SL plus oxaliplatin and SP, and multicenter phase II trial of neoadjuvant chemotherapy with docetaxel, S-1 plus cisplatin (JCOG 1102) has been opened.

Colorectal Cancer (CRC)

A global randomized phase III trial comparing ramucirumab with placebo in combination with FOLFIRI is ongoing. A phase Ib trial to evaluate FOLFIRI with CS-7017 regimen is ongoing. A phase I/II trial to evaluate capecitabine with perifosine is ongoing. In an adjuvant setting, a multicenter trial to evaluate the FOLFOX regimen is ongoing.

Published Papers

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DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, DIGESTIVE ENDOSCOPY DIVISION

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

Introduction

The Digestive Endoscopy Division covers the fields of the gastrointestinal (GI) tract and head and neck regions. In 2011, a total of 10,830 examinations were performed. A narrow band imaging (NBI) system using the LUCERA spectrum (Olympus Optical Co., Ltd.) has been included for routine examination in 5 of 6 endoscopy rooms since September 2009. Furthermore, endoscopic treatments such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), percutaneous endoscopic gastrostomy (PEG), endoscopic balloon dilation (EBD), radial incision and cutting (RIC), and photodynamic therapy (PDT) have been performed.

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

Routine Activities

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

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

Research Activities

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. Furthermore, detection of circulating tumor cells (CTCs) is performed using blood and tissue samples from esophageal, gastric, and colorectal cancer patients.

In contrast, developing research into novel endoscopy systems is being performed. A Micrometer Volumetric Optical Imaging System (μVOIS) is based on Optical Coherence Tomography. In the μVOIS, the three-dimensional microstructure of the intramucosal layer and muscularis mucosa can be visualized in a horizontal direction. Second is hypoxia imaging for neoplastic lesions of the head and neck and alimentary tracts, with blue visualized images. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and nanoparticles of the rare earth, doped

yttrium oxide. This system is capable of penetrating through the intestinal wall and obtaining images. Furthermore, molecular imaging endoscopy for the use of this system with InGaAs CCD has been developed, since nanoparticles of rare earth act as fluorescent agents. With a low-temperature atmospheric pressure plasmas system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnosis system using photosensitizing agents, such as hypericin and 5ALA, has been constructed. Moreover, research is ongoing into the development of a new electrosurgical knife as an endoscopic device, which will be used in ESD for esophageal and gastric cancer.

Clinical Trials

A wide range of many prospective clinical trials is ongoing into the endoscopic treatment of cancers of the esophagus, stomach, and colorectum, as follows: multicenter clinical trials of a follow-up study after EMR of m1-3 esophageal cancers; a phase I/II study of PDT using Laserphyrin in residual/recurrent cases followed by chemoradiation for esophageal cancers; a phase III randomized trial regarding the efficacy of a proton pump inhibitor followed by EMR for esophageal cancer; a phase II trial of combined treatment of endoscopic mucosal resection and chemoradiotherapy for clinical stage I esophageal carcinoma (JCOG0508); a multicenter clinical study for enrollment of early gastric cancer following endoscopic treatment for enrollment system using the Web; a multicenter clinical trial of ESD for undifferentiated gastric cancer (JCOG1009); a multicenter clinical study regarding residual/recurrent rates and observation periods of endoscopic piecemeal mucosal resection (EPMR) for colorectal neoplastic lesions; and the Japan Polyp Study (JPS) for determination of observation periods after endoscopic treatment for colorectal polyps.

Published Papers

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DEPARTMENT OF HEPATOBILIARY AND PANCREATIC ONCOLOGY, HEPATOBILIARY AND PANCREATIC SURGERY DIVISION

Taira Kinoshita, Masaru Konishi, Shinichiro Takahashi, Takahiro Kinoshita, Naoto Gotohda, Yuichiro Kato, Kazuteru Monden, Motokazu Sugimoto, Teruhisa Sakamoto

Introduction

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

With the refinements in laparoscopic instruments and advances in surgical experience, laparoscopic hepatectomy is a safe alternative for selected patients with hepatic neoplasms, and has fulfilled its indications. In our division, this procedure has been performed since 2002.

Routine Activities

In the National Cancer Center Hospital East, surgeons in the Upper Abdominal Surgical Oncology Group operate on all patients with gastric, hepatobiliary and pancreatic cancer. Our group is composed of 6 attending surgeons, 3 chief residents, and 4–6 residents. The outpatient clinic is open 5 days a week. Staff meetings are held 3 times a week during which treatment strategies from the medical and surgical points of view are discussed. A case conference on imaging diagnosis is conducted every Tuesday in cooperation with radiologists and medical oncologists, and a pathology conference is held every month with pathologists. In 2011, 228 patients with hepatobiliary and pancreatic diseases underwent surgical treatment at our Division.

Research Activities and Clinical Trials

1) Pancreatic cancer

JASPAC-01 is a randomized phase III trial to compare orally administered S-1 with intravenous gemcitabine as adjuvant chemotherapy for patients with curatively resected pancreatic cancer. Three hundred and fifty-eight patients have been enrolled and recruitment is complete. Follow-up is on-going.

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

JASPAC-05 is a phase II study on neoadjuvant S-1 and concurrent radiotherapy for patients with borderline resectable pancreatic cancer. This study starts in this year.

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.

BTCS is a phase II feasibility study on adjuvant chemotherapy with S-1 for patients with resected biliary tract cancer. Thirty-three patients have been enrolled and recruitment is complete. The high rate of treatment completion and mild toxicity indicated that S-1 chemotherapy is feasible for patients with resected BTC. A multicenter RCT in to compare S-1 and observation is now under preparation.

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. Follow-up is on-going.

Recruitment in a phase II trial on adjuvant immunotherapy with Glypican-3 for patients with hepatocellular carcinoma 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

Table 1. Number of patients

Invasive pancreatic cancer	30
Other pancreatic neoplasms	13
Hepatocellular carcinoma	41
Hepatic metastases	72
Intrahepatic cholangiocarcinoma	10
Bile duct cancer	20
Gallbladder cancer	5
Total	191

Table 2. Type of procedure

Pancreaticoduodenectomy	36
Distal pancreatectomy	18
Total pancreatectomy	3
Hepatectomy without biliary reconstruction	120
Hepatectomy with biliary reconstruction	8
Laparoscopic hepatectomy	19
Other procedures	24
Total	228

Table 3. Survival rates

Diagnosis	No. of pts	5-yr survival (%)
Invasive pancreatic cancer (2001~2009)	186	22.5
Hepatocellular carcinoma (2001~2005)	350	48.5
Hepatic metastases (2001~2009)	312	56.6
Intrahepatic cholangiocarcinoma (2001~2007)	38	47.2
Extrahepatic bile duct cancer (2001~2007)	83	29.5
Papilla Vater cancer (2001~2007)	45	51.4
Gallbladder cancer (2001~2007)	46	37.7

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.

Published Papers

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DEPARTMENT OF HEPATOBILIARY AND PANCREATIC ONCOLOGY, HEPATOBILIARY AND PANCREATIC ONCOLOGY DIVISION

Masafumi Ikeda, Shuichi Mitsunaga, Izumi Ohno, Satoshi Shimizu

Introduction

The Hepatobiliary and Pancreatic Oncology Division is responsible for the treatment and management of patients with hepatic, biliary, and pancreatic cancers. A multidisciplinary treatment strategy is important for the therapy of these cancers, and the treatment plan for each patient is carefully discussed by pharmacologists, surgeons, radiologists, radiation oncologists and medical oncologist. Our goal is to provide high-quality cancer treatment with sufficient palliative care and to develop novel and effective treatments through well-designed clinical trials and research projects.

Routine Activities

Our Division is composed of 4 staff oncologists, and 3 residents, and we have 35-45 beds in the hospital and conduct clinical rounds for admitted patients every morning and evening. Most of the new patients with unresectable hepatobiliary and pancreatic tumors are hospitalized for tumor diagnosis and treatment. Individual patient treatment strategies are discussed in weekly case conferences participated in by medical oncologists, surgeons, radiologists, radiation oncologists, and pharmacologists. For hepatocellular carcinoma (HCC), percutaneous ablation therapy is indicated as a standard treatment in patients with ≤ 3 tumors that are each < 3 cm in diameter. Transcatheter arterial chemoembolization (TACE) is usually used for treating advanced or recurrent HCC when hepatectomy or ablation therapy is not indicated. Sorafenib, an oral multikinase inhibitor, has been used for the treatment of advanced HCCs in patients with portal vein tumor thrombosis and/or distant metastases, or in whom TACE is not indicated. A medical team "Team Nexavar", which is composed of medical oncologists, pharmacologists, and nurses, provides supportive care for the toxicities of sorafenib. Intra-arterial chemotherapy is also available for the treatment of localized advanced HCCs, although it remains unclear whether sorafenib or intra-arterial chemotherapy is better for the treatment of advanced HCCs. For patients with advanced biliary tract cancer, gemcitabine and cisplatin therapy are recognized as the first-line therapies worldwide. S-1 has also been approved for biliary tract cancer, and is administered as the second-line chemotherapy. For patients with advanced pancreatic cancer, gemcitabine plus erlotinib, gemcitabine and S-1 have been approved for the treatment of pancreatic cancer. In our division, gemcitabine plus erlotinib is selected as the first line treatment, if the patient has good general condition. If the general condition is not so good, gemcitabine monotherapy is selected as the first-line chemotherapy. S-1 monotherapy is also considered as the second-line chemotherapy.

Furthermore, we are also responsible for all abdominal ultrasonographic examinations at our hospital, as well as ultrasound-guided biopsies of abdominal masses, particularly those in the liver and pancreas, performed for pathological diagnosis. Percutaneous transhepatic or endoscopic biliary drainage and stenting are performed to relieve jaundice and facilitate the removal of drainage tubes. The endoscopic approach, which is more comfortable than the percutaneous approach, has become the first choice this year, because our endoscopic skill has matured.

Research Activities

Hepatocellular carcinoma

No reliable data from a prospective clinical study for TACE are available in either Korea or Japan. We conducted a single-arm expanded treatment efficacy and safety study of TACE in Japan and Korea, and TACE could be demonstrated to exert a marked favorable efficacy in patients with unresectable HCC who were not suitable for curative treatment.

Sorafenib has been acknowledged as a standard chemotherapy for advanced HCC, but it has some troublesome toxicities including hand-foot syndrome and liver dysfunction. The usefulness of urea-content ointment for prevention of hand-foot syndrome and the efficacy and safety of sorafenib for HCC with Child Pugh B have been clarified.

Intra-arterial chemotherapy has been widely used for advanced HCC in Japan, but no chemotherapeutic agents or regimens have shown any survival benefit. To elucidate the survival benefit of intra-arterial chemotherapy, a

Table 1. Number of patients

Hepatocellular carcinoma	103
Biliary tract cancer	
Intrahepatic cholangiocarcinoma	23
Extrahepatic cholangiocarcinoma	18
Gallbladder cancer	28
Papilla of vater carcinoma	5
Pancreatic cancer	
Locally advanced disease	40
Metastatic disease	114
Other	27
Total	358

Table 2. Type of procedure

Hepatocellular carcinoma	
Radiofrequency ablation	80
Transcatherter arterial chemoembolization	181
Intra-arterial chemotherapy	79
Systemic chemotherapy	84
Proton	10
Biliary tract cancer	
Systemic chemotherapy	68
Radiotherapy	2
Pancreatic cancer	
Systemic chemotherapy	188
Chemoradiotherapy	10
Total	684

Table 3. Survival rates

Diagnosis	No.of pts	MST(mo)	2-yr survival(%)
Hepatocellular carcinoma			
Radiofrequency ablation	191	57.2	83.0
Transcatherter arterial chemoembolization	292	22.7	46.9
Intra-arterial chemotherapy	75	6.5	21.9
Systemic chemotherapy	16	4.7	0
Period:	1992/11-2005/12		
Biliary tract cancer			
Systemic chemotherapy	147	5.4	4.3
Period:	1997/11-2006/2		
Pancreatic cancer			
Locally advanced disease	154	11.2	14.3
Metastatic disease	442	4.8	1.6
Period:	1992/11-2007/3		

randomized trial comparing the combined administration of sorafenib with intra-arterial cisplatin with sorafenib alone is planned and now ongoing for advanced HCC.

Biliary tract cancer

To elucidate the additional efficacy of WT1 vaccine, a randomized trial comparing the combined administration of gemcitabine plus cisplatin with WT1 vaccine with gemcitabine plus cisplatin has been designed for the treatment of advanced biliary tract cancer.

Pancreatic cancer

S-1 with concurrent radiotherapy exerted extremely favorable activity with mild toxicity in patients with locally advanced pancreatic cancer. Based on this result, the two following clinical trials are ongoing: neoadjuvant S-1 and concurrent radiotherapy for borderline resectable pancreatic cancer, and S-1 and concurrent radiotherapy with versus without induction chemotherapy for locally advanced pancreatic cancer. For advanced pancreatic cancer, we have investigated the clinical significance of IL-6, IL-1 and the circulating CRP level, and the symptomatic changes to predict disease control by chemotherapy.

Clinical Trials

Twenty-eight clinical trials (Sponsored, 15 trials; Investigator-initiated, 13 trials) are ongoing, and 8 clinical trials (Sponsored, 3 trials; Investigator-initiated, 5 trials) are planned for the upcoming year. A recent trend in clinical trials has been seen in new molecularly targeted agents for advanced HCC, and new combination chemotherapy for advanced biliary and pancreatic cancer.

Published Papers

1. Kudo M, Imanaka K, Chida N, Nakachi K, Tak W-Y, Takayama T, Yoon J-H, Hori T, Kumada H, Hayashi N, Kaneko S, Tsubouchi H, Suh DJ, Furuse J, Okusaka T, Tanaka K, Matsui O, Wada M, Yamaguchi I, Ohya T, Meinhardt G, Okita K. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer, 47:2117-2127, 2011

2. Iwasa S, Ikeda M, Okusaka T, Ueno H, Morizane C, Nakachi K, Mitsunaga S, Kondo S, Hagihara A, Shimizu S, Satake M, Arai Y. Transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization. Jpn J Clin Oncol, 41:770-775, 2011

3. Suzuki E, Furuse J, Ikeda M, Ishii H, Okusaka T, Nakachi K, Mitsunaga S, Ueno H, Morizane C. A phase I/II study of combined chemotherapy with mitoxantrone and uracil/tegafur for advanced hepatocellular carcinoma. Jpn J Clin Oncol, 41:328-333, 2011

4. Kanai F, Yoshida H, Tateishi R, Sato S, Kawabe T, Obi S, Kondo Y, Taniguchi M, Tagawa K, Ikeda M, Morizane C, Okusaka T, Arioka H, Shiina S, Omata M. A phase I/II trial of the oral antiangiogenic agent TSU-68 in patients with advanced hepatocellular carcinoma. Cancer Chemother Pharmacol, 67:315-324, 2011

5. Inaba Y, Arai Y, Yamaura H, Sato Y, Najima M, Aramaki T, Sone M, Kumada T, Tanigawa N, Anai H, Yoshioka T, Ikeda M. Phase I/II study of hepatic arterial infusion chemotherapy with gemcitabine in patients with unresectable intrahepatic cholangiocarcinoma (JIVROSG-0301). Am J Clin Oncol, 34:58-62, 2011

DEPARTMENT OF UROLOGY

Yasuyuki Sakai, Yoshinobu Komai

Introduction

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

Routine Activities

Outpatient activities: An outpatient clinic is open 2 days a week as a Urology Department. Flexible cystoscopy, abdominal ultrasonography, retrograde pyelography and some prostate biopsies are performed in the outpatient clinic. Superficial bladder cancer (G3, cis, or recurrent tumor) after TUR-Bt is treated by instillation of BCG into the bladder. Advanced urogenital cancers including stage D2 prostate cancer are referred to the medical oncology division for chemotherapy or hormone therapy. Extrinsic obstructions of the upper urinary tract that directly result from invasion of an adjacent malignancy or peritoneal metastasis are also treated. In most cases, internal stenting is better tolerated than percutaneous nephrostomy. Thirty-four patients newly received ureteral stents and 4 underwent nephrostomy for obstructive uropathy.

Inpatient activities: A daily conference is held with doctors of Department of Pelvic Surgery on diagnosis and treatment of the patients with colorectal and urological cancer. We performed about 50 combination surgeries with colorectal surgeons. In the department of urology, 78 general anaesthesia surgeries, 71 spinal anesthesia surgeries and 54 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 and Clinical Trials

Minimum incision endoscopic surgery was introduced from 2011, the surgery is a gasless, single-port access, cost-effective, and minimally invasive surgery. We intend to make this operation more sophisticated in coordination with the Department of Urology, Tokyo Medical and Dental University.

For those patients (intermediate and high-risk groups) who desired preservation of sexual function, bilateral sural nerve grafting was performed for the recovery of sexual functions. Sural nerve interposition grafting was performed in 46 patients from 2004, and they were followed up for 1 year. Overall, 10 men (22.2%) had return of erectile activity (partial erection).

Total pelvic exenteration (TPE) is the standard procedure for locally advanced rectal cancer involving the prostate and seminal vesicles. We evaluated the feasibility of bladder-sparing surgery as an alternative to TPE. We performed concomitant prostatectomy and cysto-urethral anastomosis (5 cases in 2011).

Published Papers

1. Komai Y, Fujii Y, Iimura Y, Tatokoro M, Saito K, Otsuka Y, Koga F, Arisawa C, Kawakami S, Okuno T, Tsujii T, Kageyama Y, Morimoto S, Toma T, Higashi Y, Fukui I, Kihara K. Young age as favorable prognostic factor for cancer-specific survival in localized renal cell carcinoma. Urology, 77:842-847, 2011

Table 1. Number of Patients in 2011

Prostate Cancer	35
Bladder Cancer	27
Renal cell carcinoma	19
Upper urothelial carcinoma	10
Testicular cancer	7

Table 2. Number of operative cases in 2006-2011

Section	2007	2008	2009	2010	2011
Radical nephrectomy	27	20	24	24	17
(laparoscopic)	(8)	(6)	(7)	(11)	(2)
(MIES)					(6)
Partial nephrectomy	2	1	4	8	5
(MIES)					(2)
Nephroureterectomy	3	10	5	7	9
(MIES)					(1)
Radical cystectomy	6	9	8	9	11
TUR-Bt	37	32	43	47	59
Radical prostatectomy	32	21	33	33	25

(MIES: Minimum Incision Endoscopic Surgery)

Table 3. Overall Survival Rate after operation (%)

	1 year	3 years	5 years
Prostate cancer	100	97.5	96.3
Renal cell carcinoma	95.8	89.7	76.7
Invasive bladder cancer	87.8	56.0	38.9

DEPARTMENT OF ANESTHESIOLOGY AND INTENSIVE CARE UNIT

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

Introduction

Perioperative care for cancer patients with limited vital organ function presents a major challenge for anaesthetists because anaesthesia and surgery itself may cause further deterioration in physical functions. The aim of modern anaesthesia is to protect patients from surgical stress by blocking the noxious stimuli of surgical trauma and enhances their recovery from the operation. The quality of life of the patients and medical ethics must be carefully taken into account.

In 2011, this department faced a crisis followed by the resignation of the senior consultant. However, our remaining young anaesthetist pulled through this difficult situation with the support of the surgeons, nurses, and other staff. Two more anaesthetists took up their posts in the summer. We therefore continue to endeavour to regenerate the department with a broad outlook. We would like to sincerely express our deep appreciation to all who encouraged us during our tough times in 2011.

Routine Activities

Staff members (3 anaesthetists, 2 visiting anaesthetists, 6 part-time anaesthetists and 3 residents serve in various capacities in the department. We performed 2366 cases in 2011 including significant numbers of crucial cases and the cases which had to be treated as difficult airway cases. The annual number of patients admitted to the intensive care unit was 1228.

Daily activity starts with a preanaesthesia case presentation. A journal club is held once a week to sustain up-to-date knowledge of all aspects of anaesthesia.

Research Activities and Clinical Trials

It is extremely important for an academic group to keep up with current research, and although we have been working in somewhat straightened circumstances we still managed to plan some clinical research. Dr Torigoe presented "Unilateral negative pressure pulmonary edema during anaesthesia with a laryngeal mask airway" at the 31st annual meeting of The Japan Society of Anaesthesia in Naha.

Table 1. Number of Patients Managed under General or Spinal/Epidural Anaesthesia

Type of Surgery	2007	2008	2009	2010	2011
Head & Neck	501	458	474	515	424
Thoracic	499	472	503	488	466
Esophageal				137	126
Gastric, Hepatobiliary, Pancreatic	537	508	566	542	556
Colorectal	417	453	418	491	426
Urological	77	59	79	88	78
Breast	247	233	282	297	291
Miscellaneous					2
Total	2278	2183	2322	2558	2366

Table 2. Number of Patients Admitted to the Intensive Care Unit

	2007	2008	2009	2010	2011
Number of the Patients Admitted to ICU	1210	1163	1167	1435	1228

DEPARTMENT OF PALLIATIVE MEDICINE AND PSYCHO-ONCOLOGY, PALLIATIVE CARE SERVICE

Hiroya Kinoshita, Yoshihisa Matsumoto, Mieko Fukui, Keiko Abe, Masao Ogawa, Kazuaki Hiraga

Introduction

The National Cancer Center Hospital East opened the palliative care unit in 1992 for the purpose of providing only palliative care service. 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 only designated inpatient setting unit for palliative care in the Toukatu-Hokubu region. Before 2007, the registry system for admittance was adopted wherein patients were admitted in the order of their application. This system was abolished because patients with severe symptoms had to wait for a long time before being admitted. In line with this, criteria for admitting patients were changed to ensure optimal use of limited resources and provide appropriate care to patients with severe physical symptoms and psychological problems. The waiting time for admission was reduced to 5 days.

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

2. Outpatient clinic

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

Research Activities

The department participates in the Outreach Palliative care Trial of Integrated regional Model (OPTIM), which is an intervention study for the purpose of dispersing palliative care in four typical regions in Japan.

Clinical Trials

A phase III study on oral buccal fentanyl is ongoing.

Table 1. New referrals to the outpatient clinic (n=395, January - December 2011)

		N (%)
Age	Mean±SD (median, range) (yr)	66.5±11.7 (68, 19-96)
Gender	(male/female)	205/190
Survivors or receiving anticancer therapy		79 (20.0)
Cancer site	Lung	120 (30.4)
	Breast	41 (10.4)
	Colorectal	40 (10.1)
	Head and Neck	35 (8.9)
	Pancreas	21 (5.3)
	Stomach	19 (4.8)
	Esophagus	15 (3.8)
	Liver	15 (3.8)
	Others	89 (22.5)

Table 2. Admission to the palliative care unit (n=378, January - December 2011)

		N (%)
Age	Mean±SD (median, range) (yr)	66.2±11.6 (67, 19-96)
Gender	(male/female)	204/174
Cancer site	Lung	104 (27.5)
	Colorectal	51 (13.5)
	Breast	40 (10.6)
	Head and Neck	26 (6.9)
	Pancreas	26 (6.9)
	Stomach	18 (4.8)
	Prostate	13 (3.4)
	Kidny/Bladder	13 (3.4)
	Others	87 (23.0)
Wating time for admission	Mean±SD (median, range) (days)	5.0±5.3 (3, 0-27)

DEPARTMENT OF PALLIATIVE MEDICINE AND PSYCHO-ONCOLOGY, PSYCHO-ONCOLOGY SERVICE

Asao Ogawa, Daisuke Fujisawa, Hiroyuki Takei, Daisuke Kiuchi, Junko Nouno, Harumi Koga

Introduction

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

Routine Activities

The Psycho-Oncology Division is composed of 2 attending psychiatrists, 2 clinical psychologists, and 2 psychiatry residents. The Division's 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 included individuals who were 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 2 university hospital is held on Thursdays. In August 2008, the Comprehensive Support Center for Cancer Patients and Families was developed outside the hospital as a part of the regional palliative care project.

Research Activities

Clinical trials

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

Table. Psychiatric consultation data (n=1028; January-December, 2011)

Section		N (%)
Age	Mean±SD (median, range) (yr)	64.9±12.6 (67,16～91)
Gender	(male/female)	614 (59.7%) / 414 (40.3%)
Inpatient / Outpatient		666 (64.8%) / 362 (35.2%)
Cancer patient / Family member		987 (96.0%) / 41 (4.0%)
Cancer site	Head and neck	215 (20.9%)
	Lung	208 (20.2%)
	Esophagus	108 (10.5%)
Stage	Recurrent or metastatic	678 (65.9%)
PS	0/1, 2/3, 4	311 (30.2%) / 486 (47.3%) / 231 (22.5%)
Pain	Present	211 (20.5%)
Psychiatric diagnosis	Delirium	309 (30.1%)
	Adjustment disorders	123 (12.0%)
	Major depression	68 (6.6%)
	Dementia	54 (5.3%)
	No diagnosis	176 (17.1%)

DEPARTMENT OF PALLIATIVE MEDICINE AND PSYCHO-ONCOLOGY, SUPPORTIVE CARE TEAM

Hiroya Kinoshita, Asao Ogawa, Daisuke Fujisawa, Yoshihisa Matsumoto, Mieko Fukui, Hiroyuki Takei, Yoichiro Higashi, Tomofumi Miura, Junko Nouno, Harumi Koga, Yuko Tanaka, Chiyuki Terada, Yukie Hosoda, Yasuhiko Ichida, Shinya Motonaga, Kyoko Okada, 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, a certified nurse specialist, 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 "Palliative Care Service" sections.

Table. Supportive Care Team consultation data (n = 839; January-December, 2011)

		N (%)
Age	Mean ± SD (range) (yr)	65.3 ± 12.8 (17-97)
Gender	(male/female)	545 (65%) / 294 (35%)
Service	Palliative care/ Psycho-oncology	173 / 666
Cancer site	Lung	205 (24%)
	Head and Neck	160 (19%)
	Esophagus	90 (11%)
	Colon	73 (9%)
	Stomach	65 (8%)
	Breast (mammary)	35 (4%)
Stage	I / II / III / IV	53 (6%) / 60 (7%) / 82 (10%) / 410 (49%)
	/ recurrence / unknown / others	/ 168 (20%) / 46 (5%) / 17 (2%)
Performance status	0/ 1/ 2/ 3/ 4	129 (15%) / 179 (21%) / 182 (22%) / 206 (25%) / 143 (17%)
Physical symptoms	Pain	343 (41%)
(moderate - severe)	Appetite loss	222 (26%)
	Fatigue	146 (17%)
	Respiratory distress	109 (13%)
Psychiatric diagnosis	Delirium	291 (44%)
(primary diagnosis)	Adjustment disorders	48 (7%)
	Dementia	28 (4%)
	Major Depressive Disorder	17 (3%)
Outcome	Discharge/ Hospital transfer	529 (63%) / 28 (3%)

DEPARTMENT OF DIAGNOSTIC RADIOLOGY

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

Introduction

The Diagnostic Radiology Division is committed to improving health through excellence in image-oriented patient care and research. Our Division performs more than 73,000 inpatient and outpatient procedures annually. The Division also conducts clinical scientific research as well as basic scientific studies, with the results translated directly into better patient care.

Routine Activities

Our division has four multislice 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 Multiaxis 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 multidetector 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 examination.

This division has 7 consulting radiologists and 32 technologists. As part of our routine activities, every effort is made to produce an integrated report covering almost all examinations, such as MMG, contrast radiologica1 procedures, CT, MRI, RI, PET, angiography and IVR, mainly transarterial chemo-embolization (TACE).

The number of cases examined in 2011 is shown in the Table below.

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

Research Activities and Clinical Trials

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

(1) Development of new Nuclear Medicine tracers

The small interfering RNA (siRNA) was 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 polyadenines using E. coli Poly(A) Polymerase (E-PAP) and ATP conjugated with DTPA and subsequently labeled with Tc-99m or Ga-68 under strict RNase-free conditions. The gene-silencing ability of the siRNA did not change after radiolabeling.

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

(2) Development of new CT technology

The accurate evaluation of cartilage invasion is essential for deciding upon appropriate treatment strategies for laryngeal and hypopharyngeal cancer. In dual-energy CT (DECT), two data sets acquired with different tube voltages can be fused to generate weighted-average CT images that have a similar image impression to conventional CT images obtained at 120 kV, in addition to generating images of the distribution of iodinated contrast medium alone. For these applications, the material-specific X-ray energy dependence of the absorption coefficient is used in image postprocessing to mathematically extract iodine and separately calculate color-coded iodine images and virtual non-contrast images.

Dual-energy CT images 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.

Table 1. Number of Cases Examined

	2007	2008	2009	2010	2011
Plain X-ray examination	35,339	33,913	33,841	34,330	35,032
Mammography (MMG)	2,338	2,272	2,388	2,595	2,434
Fluoroscopic Imaging (GI-series, etc.)	2,531	3,387	3,781	3,478	3,903
CT	18,356	18,014	19,543	21,128	21,967
MRI	4,817	5,053	5,723	5,830	5,708
RI	1,825	1,693	1,718	1,676	1,582
PET	1,541	1,585	1,670	2,048	2,239
Angiography	698	766	711	728	656
Total	67,445	66,683	69,375	71,813	73,521

DEPARTMENT OF RADIATION ONCOLOGY

Tetsuo Akimoto, Mitsuhiko Kawashima, Sadatomo Zenda, Masakatsu Onozawa, Satoko Arahira

Introduction

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

The primary aim of the Department of Radiation Oncology is to develop high precision RT such as intensity modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT) and proton beam therapy (PBT) and expand and establish the important role of RT in cancer treatment. Another important goal is to establish standard treatment and optimal irradiation techniques including PBT.

Routine Activities

At present, the staff of the Department consists of 5 consultant physicians (radiation oncologists), 12 radiation technologists, 4 medical physicists, 1 nurse, and 1 clerk. We have more than 1000 new cases for conventional RT and more than 100 new patients for proton beam therapy every year. Quality assurance for both conventional RT and PBT is performed by medical physicists and radiation technologists, and a conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. RT and PBT are routinely based on three-dimensional radiation therapy planning and PBT 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.

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 modalities for various cancers are in progress.

The Department is responsible for conventional (photon-electron) RT, the systems for which comprise 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 Department is also responsible for PBT, involving 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 Department. PBT is performed from 2 treatment rooms and both rooms are routinely used for rotational gantry treatment. The Department performs quality assurance and regular maintenance of the PBT machines for precise dose delivery and safe treatment.

Research Activities

In the Department of Radiation Oncology, the following research activities are in progress:

1) Establishment of optimal combined approaches including RT and chemotherapy for locally advanced head and neck cancer.
2) Establishment of the clinical usefulness of IMRT with or without chemotherapy for head and neck 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.
6) PBT for pediatric malignancies.
7) The role of gene polymorphism in the development of acute and late radiation-related complications.

Clinical Trials

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

1) JCOG0701: Accelerated fractionation vs. conventional fractionation radiation therapy for glottic cancer of T1-2N0M0: a phase III study.
2) JCOG0701-A1: Evaluation of single-nucleotide polymorphisms (SNPs) in the development of acute and late complications after accelerated fractionation and/or conventional fractionation radiation therapy for glottic cancer of T1-2N0M0.
3) JCOG0906: A multi-institutional phase II study on post-operative short-term radiation therapy for breast conserving therapy.
4) JCOG1015: A phase II study on intensity modulated radiation therapy (IMRT) with chemotherapy for loco-regionally advanced nasopharyngeal cancer (NPC).
5) A phase II study on PBT for malignant melanoma of nasal cavity.
6) A phase II trial of Concurrent Chemoradiotherapy with 5-FU plus Cisplatin for resectable squamous cellcarcinoma of cervical esophagus.

Published Papers

1. Kawashima M, Kohno R, Nakachi K, Nishio T, Mitsunaga S, Ikeda M, Konishi M, Takahashi S, Gotohda N, Arahira S, Zenda S, Ogino T, Kinoshita T. Dose-volume histogram analysis of the safety of proton beam therapy for unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys, 79:1479-1486, 2011

2. Zenda S, Kawashima M, Nishio T, Kohno R, Nihei K, Onozawa M, Arahira S, Ogino T. Proton beam therapy as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study. Int J Radiat Oncol Biol Phys, 81:135-139, 2011

3. Zenda S, Kohno R, Kawashima M, Arahira S, Nishio T, Tahara M, Hayashi R, Kishimoto S, Ogino T. Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses. Int J Radiat Oncol Biol Phys, 81:1473-1478, 2011

Table 1. Number of patients treated with radiotherapy during 2006-2010

	2006	2007	2008	2009	2010
New patients	1146	1097	1084	1384	1616
New treatments	1418	1363	1388	1363	1388
Head and neck cancers	270	249	289	281	320
Lung and mediastinal cancers	395	391	390	370	411
Breast cancers	300	296	264	297	406
Gastrointestinal cancers	242	202	221	202	228
Hepatobiliary tract cancers	54	63	47	46	54
Urological cancers	94	114	112	120	151
Bone and soft tissue cancers	6	8	8	6	15
Hematological cancers	38	25	33	27	6
Others	19	15	24	35	20
Proton therapy	76	75	81	90	56
IMRT		6	4	31	83

Changes in the number of patients treated with RT

DEPARTMENT OF PATHOLOGY AND CLINICAL LABORATORIES

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

Introduction

The Department of Pathology and Clinical Laboratories (DPCL) is composed of two divisions; the Pathology Division (PD) and the Clinical Laboratory Division (CLD). Both divisions play a fundamental role in routine hospital service, and support research activities as well as clinical trial studies at the National Cancer Center Hospital East (NCCHE).

Seven pathologists, including 6 pathologists board-certified by the Japanese Society of Pathology, are assigned to the PD. Two are full-time staff, and another is part-time. The remaining 4 pathologists originally belong to the Pathology Division at the Research Center for Innovative Oncology (RCIO), and are working concurrently at the DPCL. Also working in the division are 6 clinical laboratory technicians and 1 assistant. 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 12 full-time technicians are working at the CLD.

Routine Activities

The primarily routine activities in the PD involve surgical pathology. In 2011, 8,650 biopsy specimens, including 704 frozen sections and 787 review cases, and 2,156 surgically resected specimens were examined and pathologically diagnosed (see Table1 for details). Case conferences are held regularly with almost all of the clinical department/divisions, including 4 weekly case conferences with Head-and-Neck Surgery (Monday), Hematology and Chemotherapy (Wednesday), the Digestive Endoscopy Division (Tuesday) and Thoracic Surgery (Friday). Five thousand hundred and forty five cytology specimens, including 2,320 samples from respiratory organs, were evaluated (Table 2). Ten autopsies were performed, and all cases were presented and discussed in clinic-pathological conferences, which are held monthly. Conference-style training sessions are open every Thursday morning for the residents, where they learn how to present pathological findings through mock case-presentations.

The CLD provides accurate and reliable data to understand the patients' conditions and support prompt decision making for all clinicians working at the NCCHE. Most of the essential laboratory test

Table 1. Number of patholoy samples examined in the Pathology Division in 2011

Origin	Biopsy	Surgical specimen	Autopsy
Hepatobiliary and Pancreatic Oncology	291	1	2
Thoracic Oncology	398		2
Cardiovascular Division			
Thoracic Surgery	502	440	
Esophageal Surgery	86	104	
Breast Surgery	423	296	
Colorectal (Pelvic) Surgery	346	394	
Gastric Surgery	252	509	
Orthopedic Surgery	4		
Dermatology	13		
Urological Surgery	172	7	
Obstetrics and Gynecology	18		
Plastic Surgery	8	3	
Head and Neck Surgery	754	381	
Diagnostic Radiology	0		
Radiation Oncology	137		
Digestive Endoscopy Division	1572		
Gastrointestinal Oncology	3052		3
Hematology and Medical Oncology	403	1	2
Dental Division	2		
Outpatient Unit	177	18	
Palliative Care Unit	1	1	1
Others	39	1	
Total	8650	2156	10

Table 2. Number of cytology samples examined in the Pathology Division in 2011

Sample	
Gynecological	614
Respiratory organs	2320
Gastrointestinal tract	659
Urological	592
Body fluids	341
Hematorogical	95
Head and Neck	227
Breast	182
Skin, CNS, Eye and Soft tissue	35
Others	80
Total	5145

services are available on a-round-the-clock basis. The majority of the general laboratory tests for hematology, biochemistry, serology and urinalysis are performed by an automated analyzer, which enables the division to provide the results within one hour after samples submission. A special computer-based ordering system is equipped to ensure sample-processing and data-transfer to and from outside commercial laboratories. The daily activities of each subsection are as follows (also see Table3 for details):

i) The general laboratory medicine section examines urine (urinalysis) as well as stool, pleural effusion, ascites and spinal fluid samples. Urinalysis includes sugar, protein and blood contamination, 12 of which items are examined by an automated analyzer.
ii) The hematology section performs blood count, blood cell morphology and coagulation tests. Bone marrow samples are also examined morphologically for hematological malignancies.
iii) The biochemistry and serology section examines blood samples and measures protein, sugar, lipid and enzymes/metabolites associated with liver and kidney functions. Most of these tasks are performed by an automated analyzer. The section also performs immunological assays to detect several tumor markers.
iv) The physiology section performs electrocardiography, respiratory function tests, ultrasonography and electroencephalography.
v) The bacteriology section examines various clinical samples to identify the pathogens (bacteria, fungus and virus) which cause infection(s). The section also plays a pivotal role as a part of intramural infection control team at the NCCHE.
vi) The blood transfusion section consolidates any usages of blood preparation/products in the NCCHE. The section is also responsible for collecting and providing up-to-date information related to the safe usage of the blood preparation/products. Daily routine activities for each blood transfusion case include blood typing, irregular antibodies screening and cross-matching.

Research Activities

As a part of the National Cancer Center Biobank project, the DPCL plays a major role in collecting and storing tumor tissue and serum samples in the NCCHE. In 2011, 397 frozen tumor tissue samples from surgery-harvested materials were collected and stored.

All of the pathologists are involved in research activities at the RCIO. The research interests of each pathologist vary, but they all share the same concept; a better understanding of cancer biology to develop new strategies for treating cancer patients. Please refer to the corresponding section in this book for the details.

The laboratory technicians working at 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

In 2011, as a part of a Phase I Center project, the DPCL played an essential role in 126 clinical trials which were carried out at the NCCHE. The PD in particular participated in a total of 65 trials and supplied paraffin embedded tissue sections for 28 trials in 2011.

Table 3. Number of laboratory tests exmined in the Clinical Laboratory Division in 2006-2011

Section	2006	2007	2008	2009	2010	2011
General laboratory medicine	192,597	176,173	196,233	230,610	265,517	264,452
Hematology	473,416	488,908	527,567	560,110	589,144	622,666
Biochemistry	1,330,853	1,338,116	1,424,263	1,493,858	1,569,963	1,648,755
Serology	121,436	118,468	125,409	136,127	139,759	146,104
Bacteriology	17,834	17,799	21,822	22,466	21,978	21,657
Blood transfusion	20,047	20,240	21,378	24,181	22,441	21,895
Physiology	34,485	34,530	34,258	39,232	43,215	43,275
Total	2,186,307	2,208,652	2,211,641	2,506,584	2,652,017	2,768,804

PHARMACY DIVISION

Keishiro Izumi, Yasuhiko Ichida, Akio Hiroi, Takashi Uemura, Reiko Matsui, Masahito Yonemura, Sonoko Kobayashi, Hideki Funazaki, Ikuyo Ueda, Shinya Motonaga, Tomoka Hagihara, Kenji Kawasumi, Hiroko Ouchi, Mai Itagaki, Tomoko Ogawa, Isami Sakai, Shinya Suzuki, Kazushi Endo

Introduction

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

Our residents' training program started in 2006. In 2011, six residents joined the Division. Presently, the Division has a total of twenty residents. In addition, the Division has accepted two trainees from other institutions for our oncology-pharmacist training program. In 2010, the two and a half months training course (or an optional advanced training course) has started for the fifth-year pharmacy students on the six-year pharmacy education program in Japan. Our Division has established a special curriculum for them. Through this year, three terms of the training courses, we have educated fifteen pharmacy students and three advanced-training pharmacy students.

The Pharmacy Division provides various important services: controlling inventory; dispensing medications; preparing i.v. solutions for chemotherapy, which include the aseptic mixing of antineoplastic agents; collecting and providing drug information; managing therapeutic drug monitoring; checking treatment regimens for each patient's chemotherapy; and providing pharmaceutical management and counseling. The Division reviews the drugs taken by patients before and during their hospitalization. We also check anticoagulants taken by patients undergoing endoscopic mucosal resection. The Division provides a pharmacy outpatient service in which pharmacists check patients' adverse reactions and doses of antineoplastic agents, especially in the case of oral anticancer medications. Then we assess the necessity of the supportive-care medications and suggest them to physicians. Pharmacists are on duty at the Outpatient Chemotherapy Center as dedicated staff members. The pharmacists provide the Chemotherapy Hotline Service, which is a direct line for our outpatients who have any problems concerning their chemotherapy treatment. In the Outpatient Chemotherapy Center, pharmacists are always available to provide drug information for healthcare providers and patients. We also manage investigational drugs.

New Developments

Over the years, the services of our Division have been under continuous expansion and development. The Division has assigned one pharmacist as a dedicated staff member per ward to provide timely medication counseling and drug information for healthcare providers and patients, to pursue effective pharmaceutical care. The pharmacy outpatient service started reviewing the drugs taken by all patients to evaluate when patients have to stop their anticoagulants before their operation or when they have to stop metformin before examinations with iodinated-contrast material.

	2009	2010	2011
Number of Prescriptions			
Prepared in hospital pharmacy			
Total	82,557	84,492	86,643
Inpatients	77,013	78,327	80,837
Outpatients	5,544	6,165	5,806
Taken to outside pharmacies	49,192	50,731	55,826
(% of prescription filled outside)	(89.9%)	(89.2%)	(90.6%)
Injections			
Total	164,293	157,958	159,730
Inpatients	142,373	132,407	132,969
Outpatients	21,920	25,551	26,761
Number of Prescriptions			
(Investigational new Drugs)	2,997	4,435	4,676
Aseptic Preparation of Injection Mixture			
Anticancer drugs	34,283	32,007	35,082
Others	4,791	4,689	3,320
Number of medication counseling (for inpatients)			
Patients	4,619	5,063	5,067
Counseling sessions which earned a counseling fee	5,746	6,522	6,645
Number of medication counseling sessions (for outpatients)			
in the Outpatient Chemotherapy Center	5,016	5,705	6,364
in the pharmacy outpatient service		479	734
in the 'Sorafenib' outpatient service		416	583
Number of calls on the Chemotherapy Hotline	602	980	1,468
Number of checks on home medications	5,364	5,422	5,364

NURSING DIVISION

Tomiko Ichihashi

Introduction

Recently, In the development of giving better treatment to cancer patients, residential care and treatment has become an integral part of these patients' recovery and their quality of life. The nursing department has dealt with this issue by assigning nurses who exclusively specialized in helping patients go home safely. Our main task is to ensure that patients can be discharged without facing problems medically and physically.

Since 2010, twice a month each ward has organized meetings about residential care which are attended by nurses to support discharge. We have also offered some services to the nurses and care managers who support the patients at home by giving follow-up services on the telephone. Since April 2010 we have encouraged certified nurses to participate in the Nutrition Support Team (NST) to support patient's swallowing and eating processes, and this has made it possible for them to respond smoothly to their patient's nutritional needs. We have also succeeded in intensifying registered nurses' nutritional concerns, which accordingly help them to identify the nutritional problems of each patient. This in turn has led to the patients' awareness of their own dietary-related problems. We have also set up an outpatient section since September, 2010, which offers guidance to the patients on the list of all kinds of surgery for cancers in different sites, such as esophageal, epigastrial, abdominal, respiratory, head and neck and urinary cancer. Participants are given a lecture about prevention of complications after surgery. We work together with other sections to reduce the uneasiness and anxiety which patients experience pre- and postsurgery and to support the each patient's decision about his or her treatment. As for nurses, all wards have introduced a two-working-shift system since September, 2009, and we now have an additional short-time two-working-shift system in order to support nursing care.

Financially, we have contributed to increased profitability by establishing a 7 to 1 system to place nurses. We have a nursery home, which is on the go 24 hours a day. It can take care of a child whose parent has to start working early in the morning.

As part of our own self-help approach, we have established the following goals for the purpose of clarifying our mission and raise the quality of care, under the overall concept: "To shine with learning and act full of life"

1. Respect the patients' will and offer the proper care.
2. Advance medical and nursing skills for the benefit of patients.
3. Try to make our hospital a bright and energetic place to work.
4. Support each other and draw out our ability to achieve the best care for the patients.
5. Take an active part in the hospital's administration.

Routine Activities

In 2011, of the current 311 nurses, 46 were newly employed. The average number of outpatients per day was 769.4, while that of inpatients was 349.9. The average hospitalization term was 14.7 days. The number of chemotherapy treatments in The Medical Treatment Center per day was 66; the number of operations conducted was 2,734 (As of December 2011). We provided educational services to patients undergoing chemotherapy on how to deal with the side effects, and also provided one-on-one telephone-follow-up services and hot-line-telephone services to help solve each patient's problems and allay anxieties in their own home environment.

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.

The post of head nurse in charge of nurse's education has been established since April, 2010 to help nurses to study in the optimum way, nurse studying and to support the mental health of our nursing staff.

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

specialized cancer nursing course education programs. We have subsequently accepted trainees for study in the expert nurse course and certified expert nurse course.

Not only expert nurses and certified nurses, but also registered nurses in our hospital have carried out nursing-related research projects and attended external training programs. We gave 20 presentations at academic conference in 2011.

Table 1. The number of trainees (≥1 week)

Category	Year			
	2008	2009	2010	2011
Postgraduate Nurses	8	6	14	6
Certified Expert Nurses	12	13	12	17
Expert Nurses	6	5	4	3
Others	9	1	0	0
Total	35	25	30	26
Nursing Students	208	172	156	141

CLINICAL TRIAL MANAGEMENT OFFICE

Toshihiko Doi

Introduction

The mission of the Clinical Trials Management Office (CTMO) is to facilitate the conduct of quality clinical trials at NCCHE, especially those which are all conducted as a sponsored initiated trial, to achieve registration. The CTMO also will assist investigators with infrastructure support, including Institutional Review Board (IRB) and initial regulatory guidance. A total of 30 staff members support the CTMO: 10 Clinical Research Coordinators (CRCs) (7 Nurses and 3 Pharmacologist), 10 data managers, 4 medical technologists, 1 Free Nurse and 5 secretaries. The CRCs coordinate and conduct patient care visits to ensure that all procedures are conducted with the optimum protocol compliance. The CRC teams interact with the investigators to ensure that patients receive appropriate medical evaluation and care when needed and will alert the investigator of any serious adverse events throughout the course of the protocol study. The clinical data manager teams contribute to the setting up, running and reporting of clinical trials and processes data using a range of computer applications and database systems to support collection, cleaning and management of patient data. They interact with the client as necessary to establish data review guidelines and data flow procedures. The team will also communicate/coordinate with the database manager to ensure accuracy and completeness of the clinical data. Medical technologists conduct and supervise complex medical tests, clinical trials, and control complicated EKG/EUG pharmacokinetic/pharmacodynamic (PK/PD) sampling management. The secretarial team supports the activities of the other teams.

Routine Activities

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

1) Assist Principal Investigators in the activation and administration of clinical trials.
2) Provide centralized support for operational reviews and ongoing management
3) Provide training and education relevant to all aspects of study management to clinical staff and new investigators.
4) Communicate the availability of clinical trials to physicians, referring physicians and the public
5) Prepare records for internal and external quality and compliance audits, to ensure high-quality standards for data collection and management of clinical trials and to provide a resource for the clinical trial process
6) Assist clinicians in screening and enrolling, managing, and following patients for clinical trials
7) Coordinate and ensure the completion of patient-specific study requirements
8) Provide data management support for clinical trials, including serious adverse events (SAEs)
9) Process, store and ship specimens & support PK/PD sampling
10) Preparing for Audit and Inspection by company and regulatory authorities

A routine staff meeting is held on Fridays to share relevant matters in the management of ongoing clinical trials. An operational committee is also formed and meets with other core members including primary investigations from the clinical laboratory division, pharmacy division and nurse division, and the clinical study support office for the purpose of proper management of trials.

New Achievements and Performance

The number of supported trials and patients under their administration increased in 2011 as in previous years. The CTMO has conducted and supported in excess of 100 registration trials as company sponsored trials. Among them, the numbers of phase 1 clinical trials have increased remarkably over the last few years. We have in particular joined/managed complicated and more early phase clinical trials (1 'first in man' clinical trial and 5 multinational simultaneous phase1 trials, and 1 food effect interaction trial for US-FDA

approval). In 2012, we will be challenged with tougher, more leading edge clinical trials.

In this year, government will provide support to the NCCH & NCCHE with plans to create an infrastructure enabling early-stage and exploratory clinical trials of new drugs and medical devices sponsored by industry and research institutions. We are creating the infrastructure required for exploratory, early-stage clinical trials (for development by specific prospective companies). To realize these trials, Phase 1-specific teams have been started in collaboration with oncology experts to share updated patient and trial information, through regular Phase 1 meetings for patient recruitment, and brief meetings for information sharing.

Drug development is a costly and risky affair and involves lot of money and time. Many compounds that are screened initially fail to make it to the next stage of development. In the past few years, so many phase 3 trials did not meet the endpoint. Many companies re-consider clinical development strategies and have changed their focus (biomarker driven enrichment, IIR for screening etc). The CTMO will meet and overcome the challenge of newer and advanced trials such as combination of unapproved multi-drug trials and new biomarker driven trials. Furthermore, we will contribute to the worldwide network system for phase1 trials to establish the acceleration of the pre-clinical and clinical development of investigational anti-cancer medicines.

PATHOLOGY DIVISION

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

Introduction

The research activities of the Pathology Division of the Research Center for Innovative Oncology currently focus on the application of the morphological study of cancer tissue to the clinical course of the patient. These activities aim to: I) elucidate the new biological roles of cancer epigenetics and cancer-stromal interaction; II) develop a new cancer treatment strategy (Preclinical study); and III) set up and perform experimental and clinicopathological studies on cancer. Prognostic factors and clinicopathological characteristics of various cancers have also been investigated in collaboration with the Department of Pathology and Clinical Laboratories of the National Cancer Center Hospital East (NCCHE) and other institutions.

New Biological Roles of Cancer Epigenetics and Cancer-Stromal Interaction

Overexpression of the polycomb group protein EZH2 (enhancer of zeste homolog 2) occurs in various malignancies and is associated with a poor outcome. EZH2 is an enzyme that controls epigenetical expression of important genes such as E-cadherin and RUNX3 by increasing histone H3K27 tri-methylation. To elucidate the mechanism of EZH2 overexpression in various cancer cells, a promoter analysis of the EZH2 gene was performed and we investigated whether a survival signal that is upregulated in cancer cells could be related to overexpression at the transcription level. The clinical relevance of the signaling pathway that leads to EZH2 overexpression in breast cancer was investigated and the results demonstrated that the MEK-ERK1/2-Elk-1 pathway leads to EZH2 overexpression. The triple-negative and ERBB2-overexpressing subtypes of breast cancer are known to contain more rapidly proliferating breast cancer cells. The signaling pathway connected to EZH2 overexpression was associated with both aggressive subtypes of breast cancer (1). In addition to breast cancer, EZH2 expression and its clinicopathological relationship were investigated in esophageal cancer (2).

Cancer tissue is composed of cancer and stromal cells. The cancer microenvironment generated by the cancer-stromal interaction plays important roles not only in carcinogenesis but also in cancer progression as well as metastasis. Cancer stroma consists of various kinds of cells: fibroblasts, endothelial cells, lymph vessels, macrophages and matrices. The most abundant stromal cells are fibroblasts, however, the origin and biological roles of cancer stromal fibroblasts are still unclear. During the metastatic process, cancer cells interact with vascular adventitial fibroblasts (VAF), which are the main components of the outermost connective tissue layer of blood vessels. The subcutaneous co-injection of human lung adenocarcinoma cell lines (A549, PC-14, and CRL-5807) and human VAF (hVAF) resulted in a high rate of tumor formation. High expression of podoplanin in hVAFs was observed, and sorted podoplanin-positive hVAFs displayed enhanced tumor formation, lymph node metastasis, and lung metastasis of A549 cells. Knockdown and overexpression of podoplanin in hVAFs indicated that podoplanin plays an important role in promoting A549 cancer progression and metastasis. Furthermore, the analysis of small-sized human lung adenocarcinoma (n = 112) revealed that patients with podoplanin-positive cancer-associated fibroblasts had a significantly higher rate of lymph node metastasis and a high risk of recurrence. These results indicate a promotive effect of hVAFs mediated by podoplanin on cancer progression and suggest that the perivascular environment may constitute a specific niche for tumor progression (3). In addition to the importance of fibroblasts on adenocarcinoma progression, squamous cell carcinomas (SqCCs) with a fibrous stroma displayed a higher invasive phenotype and were associated with a significantly poor prognosis. The current results indicate the microenvironment created by both SqCC cells and the peritumoral fibroblasts may facilitate cancer aggressiveness (4).

Development of a New Cancer Treatment Strategy

Trastuzumab is a recombinant antibody drug that is widely used for the treatment of HER2-overexpressing breast and gastric carcinoma. Despite encouraging clinical results, many HER2-overexpressing carcinomas have been primarily resistant to trastuzumab. One of the major roles for trastuzumab in the treatment of

cancer is antibody-dependent cellular cytotoxicity (ADCC) activity with activation of NK cells. To explore trastuzumab resistance, HER2-overexpressing carcinoma cells which were expressing E-cadherin were used to investigate the role of ADCC through the killer cell lectin-like receptor G1 (KLRG1), an inhibitory receptor expressed on subsets of natural killer (NK) cells which recognizes E-cadherin as ligands on NK cells in vitro and in vivo. The results indicated that HER2-overexpressing carcinoma cells were killed by trastuzumab-mediated ADCC and the ADCC activity reflected the degree of E-cadherin expression on carcinoma cells.The results indicated that expression of E-cadherin was shown to be a predictor of the response to trastuzumab-based treatment for HER2-overexpressing carcinomas, furthermore, trastuzumab-mediated ADCC was markedly enhanced by KLRG1-negative peripheral blood mononuclear cells (5).

Experimental and Clinicopathological Studies on Cancer in Collaboration with the Diagnostic Pathology Section

Primary lung adenocarcinomas predominantly composed of goblet cells (APGCs) are relatively rare, and the clinicopathological characteristics have remained unclear. To clarify the clinicopathological characteristics of APGCs, adenocarcinomas with a goblet cell-type component of ≥ 90% from 2228 cases of surgically resected primary lung adenocarcinoma were examined and the clinicopathological characteristics of APGCs (46 cases) were analyzed. APGCs showed a significantly higher rate of tumor location on the left side, in the lower lobe and pathological stage I, when compared with the other types of adenocarcinoma. Furthermore, APGCs displayed a lower frequency of central fibrosis, plural invasion, pulmonary metastasis, lymphatic permeation, and vascular invasion. APGCs demonstrated local recurrence in two of 46 cases (4.3%) and no incidents of distant metastasis. APGCs formed a distinct subset and should be considered separately from lung adenocarcinoma based on frequent involvement of the left and lower lung and lack of central fibrosis (6).

The histological predictive and prognostic factors for gastrointestinal tract cancers such as colon (7, 8), pancreatic tumors (9) and other histologic types of lung cancers (10, 11) were also investigated and reported in collaboration with the clinical divisions of the NCCHE and other institutions.

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INVESTIGATIVE TREATMENT DIVISION

Yasuhiro Matsumura, Masahiro Yasunaga, Yoshikatu Koga, Misato Takigahira, Hikaru Machida, Toshifumi Obonai, Hirobumi Fuchigami, Yoshiyuki Yamamoto, Yohei Hisada, Ryuta Sato, Ryo Tsumura, Yuki Fujiwara, Kengo Oguruma, Kaoru Shiina, Mamiko Shimada, Yukie Katayori

The main goal of the research in this Division is to develop innovative strategies for cancer diagnosis and treatment based on the better understanding of the physiology and biology of cancer tissues and the interaction between cancer and the host. The improvement of preexistent modalities of cancer diagnosis and treatment is also within the scope of our research activity.

Drug Delivery Systems in Cancer Chemotherapy

The main objective of investigating drug delivery systems (DDSs) in cancer chemotherapy is to find methods by which anticancer agents can selectively target solid tumors. The enhanced permeability and retention (EPR) effect in solid tumor tissue was named according to the following pathophysiological characteristics: (a) hypervasculature; (b) incomplete vascular architecture; (c) several vascular permeability factors stimulating extravasation within the cancer; and (d) minimal drainage of macromolecules and particulates (1). Polymeric micelles were expected to increase the accumulation of drugs in tumor tissues utilizing the EPR effect and to incorporate various kinds of drugs into the inner core by chemical conjugation or physical entrapment with relatively high stability. There are several anticancer agent-incorporated micelle carrier systems under clinical evaluation (1, 2).

However, most human solid tumors possess abundant intercellular connective tissue, hindering diffusion of such macromolecules including antibodies. That is why immunoconjugate therapy for stroma rich common solid cancers has not yet proved successful in clinical application. In this context, we have proposed a successful new strategy that overcomes the above contradictory drawbacks by conjugating a small molecular cytotoxic drug with an antibody against particular components of the tumor stroma. In our strategic concept of cancer stroma targeting (CAST) therapy, stromal-targeting immunoconjugates bound to the stroma to create a scaffold, from which sustained release of the cytotoxic agent occurred allowing subsequent diffusion throughout the tumor tissue to damage both tumor cells and tumor vessels (3, 4).

Noninvasive Diagnostic Test for Uterus Cancer

The present medical examination for detecting uterine endometrial cancer has not been proved to be useful. Therefore, we attempted to develop an autoscan-cytology system for detecting endometrial cancer without relying on judgment by the human eye. Our newly developed autoscan-cytology for exfoliated endometrial cells showed overall sensitivity for endometrial cancer patients and overall specificity for healthy volunteers of 53.3% and 94.6%, respectively. This new autoscan-cytology for endometrial cancer deserves further clinical evaluation (5).

Pharmacogenomics Study

Effects of genetic polymorphisms/variations of various genes were analyzed on paclitaxel.

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CANCER PHYSIOLOGY PROJECT

Katsuya Tsuchihara, Chika Miyoshi, Eriko Tomitsuka, Sachiyo Mimaki, Tomomitsu Nasuno, Hiroyasu Esumi

Introduction

Both environmental and genetic factors affect the characteristics of tumor cells. Cancer cells might adapt themselves to the tumor microenvironment by altering their genomes and epigenomes. The Cancer Physiology Project has focused on such adaptations, especially, alterations in the metabolic regulation of cancer cells. Recently developed comprehensive genome and epigenome analyses are powerful tools to reveal the underlying molecular mechanisms for such adaptations as well as exploring novel biomarkers to predict the prognosis of cancers and therapeutic effects of anti-cancer therapies. The final goal of the project is the application of these findings to the development of the rationale of anti-cancer strategies.

Research Activities

Development of Anti-austeric Drugs

Cancer cells in solid tumors frequently encounter a hypoxic and nutrient-deficient microenvironment. The cytotoxicity of conventional anti-cancer drugs was significantly impaired under culture conditions mimicking the tumor microenvironment. Austerity, which is resistance to nutrient starvation, is a characteristic feature of various cancer cells. Since most non-cancerous tissues seldom encounter such nutrient-deficient circumstance, targeting austerity is a promising new strategy for selective cancer treatment. Arctigenin, a major component of *Arctium lappa* (the greater burdock) which is used in traditional herbal medicine, is one of the anti-austerity compounds previously identified in this project. As well as purified arctigenin, a crude extract of *Arctium lappa* possessed equivalent anti-austeric abilities which were exhibited both in culture cell and xenograft models of pancreatic cancer. With the aim of the clinical application of *Arctium lappa*, a phase I/II clinical trial recruiting advanced pancreatic cancer patients has been started, which will examine the efficacy and possible toxicity and determine the appropriate dose for further trials.

Implication of biomarkers for cancer therapy

KRAS mutation testing for metastatic colorectal cancer patients scheduled to receive anti-EGFR antibody treatment has been carried out as a part of the Advanced Medical Technology Programs approved by the Ministry of Health, Labour and Welfare in 2009 and 2010. One-hundred fifty nine tests were performed under the program. Following up the patients who were diagnosed with the KRAS test and received anti-EGFR antibody treatment revealed that sensitive and quality controlled KRAS testing provided improved predictive power to determine the efficacy of the treatment. To further explore more effective genomic biomarkers for anti-EGFR antibody treatment, a multi-centered retrospective study combined with whole exon sequencing and copy number variation analyses has been started.

Molecular epidemiology of lung adenocarcinoma

Whole exon sequencing was adopted to clarify the mutation profiles of Japanese lung adenocarcinoma. Somatic mutations of 97 cases of archived lung adenocarcinoma specimens were identified. An ethnicity-specific mutation profile of known driver mutations was revealed. Furthermore, largely diverse mutation patterns of individual tumors were exhibited.

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CANCER IMMUNOTHERAPY PROJECT

Tetsuya Nakatsura

Introduction

The Cancer Immunotherapy Project aims to investigate evidenced-based cancer immunotherapy, repeating basic research and translational research.

Research Activities

We attempted to compare the induction of the Glypican-3 (GPC3)-specific T-cell-mediated immune response after locoregional therapies in hepatocellular carcinoma (HCC) patients and tumor-bearing mice. Circulating GPC3-specific cytotoxic T lymphocytes (CTLs) were increased in 5 of 9 patients after radiofrequency ablation (RFA) and in 4 of 9 patients after transcatheter arterial chemo-embolization (TACE), but in only 1 of 9 patients after surgical resection. All 7 patients with GPC3-expressing HCCs exhibited an increase in GPC3-specific CTLs after RFA or TACE, whereas none of the 7 patients did after surgical resection. The number of increased GPC3-specific CTLs after RFA was significantly larger than that after surgical resection (P=0.023). Similarly, the frequency of GPC3-specific CTLs after RFA was significantly greater than that after surgical resection in the mouse model (P=0.049). We validated for the first time the stronger effect on the immune system achieved with RFA compared with surgical resection for HCC patients and tumor-bearing mice. Combined treatment with RFA and immunotherapy is a reasonable strategy against HCC. We carried out a phase I clinical trial of HLA-A2-restricted GPC3 (144-152) peptide vaccine in 14 patients with advanced HCC. Immunological responses were analyzed with an *ex vivo* γ-interferon enzyme-linked immunospot assay. The frequency of GPC3 (144-152) peptide-specific CTLs after vaccination (mean, 96; range, 5-441) was significantly larger than that before vaccination (mean, 6.5; range, 0-43) ($P < 0.01$). An increase in the GPC3 (144-152) peptide-specific CTL frequency was observed in 12 (86%) of 14 patients after vaccination. Additionally, there was a significant correlation between the maximum value of GPC3 (144-152) peptide-specific CTLs after vaccination and the dose of the peptide injected ($P = 0.0166$, $r = 0.665$). Moreover, we established several GPC3 (144-152) peptide-specific CTL clones from PBMCs of patients vaccinated with GPC3 (144-152) peptide by single cell sorting using Dextramer and a CD107a antibody. These CTL clones had high avidity (the recognition efficiency showing 50% cytotoxicity was 10(-10) or 10(-11) M) and could recognize HCC cell lines expressing GPC3 in an HLA-class I-restricted manner. These results suggest that GPC3 (144-152) peptide vaccine can induce high avidity CTLs capable of killing HCC cells expressing GPC3 (1). The HLA-A2-restricted GPC3 (144-152) peptide-specific CTL clone recognized naturally processed GPC3-derived peptide on ovarian CCC cells in a HLA class I-restricted manner. Moreover, we confirmed that the level of GPC3 expression was responsible for CTL recognition and that subtoxic-dose chemotherapy made tumor cells more susceptible to the cytotoxic effect of CTL. Thus, it might be possible to treat ovarian CCC patients by combining chemotherapy with immunotherapy. Our data suggest that GPC3 could be an effective target for immunotherapy against ovarian CCC (2). Lengsin is an eye lens protein with a glutamine synthetase domain. Lengsin protein is overexpressed irrespective of the histological type of lung carcinoma, but not in normal tissues other than the lens. Therefore, to significantly extend the use of Lengsin-based T-cell immunotherapy approaches for the treatment of patients with lung carcinoma, we searched for HLA-A*0201-restricted epitopes from this protein by screening predicted Lengsin-derived candidate peptides for the induction of tumor-reactive CTLs. Two of the immunizing peptides, Lengsin (206-215) (FIYDFCIFGV) and Lengsin (270-279) (FLPEFGISSA), induced peptide-specific CTLs in HLA-A*0201 transgenic (HHD) mice, and thus were used to stimulate human peripheral blood lymphocytes *in vitro*. Lengsin (206-215) and Lengsin (270-279) also induced human peptide-specific CTLs, and we were able to generate Lengsin (206-215)- and Lengsin (270-279)-specific CTL clones. The Lengsin (270-279)-specific CTL clone specifically recognized peptide-pulsed T2 cells, COS-7 cells expressing HLA-A*0201 and Lengsin, and HLA-A*0201+/Lengsin+ lung carcinoma cells in an HLA-A*0201-restricted manner. These results suggest that Lengsin (270-279) is naturally processed and presented by HLA-A*0201 molecules

on the surface of lung carcinoma cells and may be a new target for antigen-specific T-cell immunotherapy against lung cancer (3). Dysregulation of the phosphatidylinositol-3-kinase (PI3K)/mammalian target of the rapamycin (mTOR) pathway frequently occurs in human tumors, and is therefore considered to be a good molecular target for treatment. In HCCs, overexpression of p-Akt and decrease of PTEN expression have been reported. NVP-BEZ235 is a novel dual inhibitor of PI3K and mTOR; however, its effect on HCCs has not been documented. Consequently, we investigated the effects of NVP-BEZ235 on the PLC/PRF/5, HLE, JHH7 and HepG2 HCC cell lines *in vitro* and *in vivo*. NVP-BEZ235 decreased the levels of p-Akt and p-p70S6K and inhibited cell proliferation in all HCC cell lines in a dose-dependent manner. Flow cytometric analysis revealed that inhibition of cell proliferation by NVP-BEZ235 was accompanied by G1 arrest in all cell lines, and that NVP-BEZ235 induced apoptosis in PLC/PRF/5 and HLE cells. Tumor growth was suppressed without body weight loss when NVP-BEZ235 was orally administered to JHH-7 tumor-bearing mice for 11 days. These results suggest that NVP-BEZ235 is a potential new candidate for targeted HCC therapy (4).

Clinical Trials

We are performing a Phase II study of GPC3 peptide vaccine as adjuvant treatment for HCC after surgical resection or RFA, and a clinical study to evaluate the immunological efficacy of GPC3 peptide vaccine in patients with advanced HCC.

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FUNCTIONAL IMAGING DIVISION

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

Introduction

The Functional Imaging Division actively investigated mainly 2 kinds of imaging modalities, namely, radionuclide imaging and magnetic resonance (MR) imaging, to establish strategies for minimally invasive and personalized cancer therapies. For radionuclide imaging, some experimental studies were performed using a small animal single photon emission computed tomography (SPECT) scanner to develop new probes for hypoxia imaging and so on. For MR imaging, some experimental studies were done using both a 9.4T scanner dedicated for small animal imaging and a 3.0T whole-body scanner.

Research Activities

As tumor hypoxia is associated with a poor prognosis and resistance to chemotherapy and radiotherapy, its *in vivo* imaging is quite useful to determine the optimal treatment of cancer. In the experimental radionuclide studies, we developed two different types of hypoxia imaging probes. The first one was a novel ^{99m}Tc-labeled probe containing a 4-nitrobenzyl ester group. It was specifically reduced in hypoxic cells, and the resulting product, carboxylate anions, were successfully trapped in hypoxic cells because of their hydrophilicity and negative charge (1). The other candidate was a ^{125}I-labeled hypoxia-inducible factor 1 (HIF-1) -mimic protein. HIF-1 is a key transcriptional regulator in response to hypoxia. The mimic protein was designed to be stable under hypoxic conditions specifically and degraded in the same manner as HIF-1α under normoxic conditions. *In vivo* SPECT/CT imaging, autoradiography and double-fluorescent immunostaining for HIF-1α and pimonidazole were studied, and it was confirmed that the tumor uptake of this probe corresponded to the HIF-1 expression. Thus, it would be a useful probe for the molecular imaging of HIF-1-activity in tumors (2).

Radiolabeled liposomes are promising radiopharmaceuticals for tumor imaging and radionuclide therapy because of their high affinity to tumors. On the other hand, conventional liposomes also accumulate in the reticuloendothelial systems (RES), such as the liver and spleen. This has hindered their clinical application. In order to solve this problem, we developed a new liposome, the ^{111}In-EC-carrying liposome. It was rapidly washed out and excreted to urine after trapping by the RES, due to the nature of ^{111}In-EC. When ^{111}In was substituted by ^{90}Y, radionuclide therapy could be expected. A patent was applied for ^{111}In-EC-carrying liposomes.

For the early detection of pancreatic cancer, the usefulness of an imaging probe of alpha v beta 3 ($\alpha_v\beta_3$) integrin called ^{111}In-DOTA-c(RGDfK) in SPECT imaging was investigated using a hamster pancreatic carcinogenesis model. ^{111}In-DOTA-c(RGDfK) could clearly visualize pancreatic cancers as small as 3 mm in diameter. ARG analysis and histopathological examination revealed the uptake of ^{111}In-DOTA-c(RGDfK) was strongly correlated with $\alpha_v\beta_3$ integrin expression. On the contrary, no clear uptake of ^{111}In-DOTA-c(RGDfK) was demonstrated in inflammatory lesions. Our findings suggested that SPECT imaging using ^{111}In-DOTA-c(RGDfK) has great potential for early and accurate detection of pancreatic cancer.

Although, MR imaging is originally capable of showing high tissue contrast resolution, administration of contrast agents can further enhance it. We have developed a new contrast agent to visualize mouse tumors in collaboration with The University of Tsukuba (PI: Professor Nagasaki). This contrast agent consisted of iron-oxide nano-particles coated with a plentiful amount of polyethylene glycol (PEG) molecules. These PEG molecules prevent the binding of iron-oxide nano-particles to serum proteins after intravenous administration. As a result, they are not rapidly eliminated from the blood stream by phagocytosis of hepatic and splenic macrophages, and thereby many of them reach the tumor vasculature. We confirmed these iron-oxide nano-particles accumulated very well in subcutaneous mouse tumors on Prussian blue-stained specimens. In addition, we observed the negative enhancement effect of these iron-oxide nano-particles in these tumors on T_2-weighted MR images (3).

Another iron-oxide nano-particle, ferucarbotran, is a clinically approved contrast agent.

Ferucarbotran-enhanced interstitial lymphography has been considered as a useful technique for differentiating metastatic and non-metastatic lesions within sentinel lymph nodes, because it can visualize metastatic and non-metastatic tissues as high and low signal areas, respectively. This technique has, however, a pitfall that radiologists should keep in mind. We investigated inflamed lymph nodes of mice using this technique, and found that non-metastatic tissues like inflammatory tissues can show high signals that are misinterpreted as metastasis. The lack of iron-laden macrophages in inflamed paracortical areas might be the cause of these high signals.

Although MR imaging is a useful tool for preclinical studies, on the negative side, it takes a rather long acquisition time. To improve the though-put of MR imaging, a simultaneous acquisition method with multiple animals is under investigation. We developed a multi-channel coil and simultaneously imaged up to 8 tumor bearing mice using this coil. Our initial study revealed this system could accurately measure the volume of multiple tumors with an acquisition time one third shorter than the conventional method (4).

Clinical Trials

Clinical trials of hypoxia PET tests were ongoing using 2 kinds of radiopharmaceuticals: one was F-18 labeled fluoroarabinofuranosyl nitroimidazole (FAZA) and the other was Cu-62 labeled diacetyl methyl-thiosemicarbazone (ATSM). Patients with lung cancer and those with head and neck cancer were tested to investigate clinical and pathological features of tumors with high avidity to these radiopharmaceuticals.

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

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PSYCHO-ONCOLOGY DIVISION

Asao Ogawa, Hiroya Kinoshita, Ken Shimizu, Daisuke Fujisawa

Introduction

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

Research Activities

Research and Development of Interventions for Depression

Major depressive disorders (MDDs) and adjustment disorders (ADs) are common psychiatric disorders in cancer patients but are often overlooked in clinical oncology settings. We developed the 'Distress Screening Program' as a practical means of screening for and facilitating the treatment of major depression and adjustment disorders in cancer patients. We introduced a clinical screening program utilizing the Distress and Impact Thermometer (DIT) to identify MDD and AD in cancer outpatients receiving chemotherapy.

As part of this program, pharmacists administered the DIT to consecutive patients undergoing chemotherapy at an outpatient clinic. Psychiatric treatment was recommended to all the patients with positive screening results. The proportion of patients referred to the Psychiatric Service during the program period was then compared with that during a usual care period.

Of the 520 patients who started chemotherapy during the 6-month program period, 5.0% (26/520) were referred to the Psychiatric Service and 2.7% (15/520) were diagnosed as having an MDD or AD. No statistically significant difference in the referral rates was observed between the two periods (2.7 vs 1.0%, $p = 0.46$). However, the period from the first chemotherapy treatment until the visit to the Psychiatric Service was significantly shorter during the program period than during the period of usual care (12.9±13.2 days vs 55.6±17.6 days, $p<0.001$).

The proportion of patients referred to the Psychiatric Service for the treatment of MDDs or ADs during the program period was not different from that during the usual care period. However, the program was useful for introducing psychiatric treatment at an earlier stage. Further modifications to the program to improve the referral rate are necessary.

Research and Development of the Psychological Support Program for Cancer Patients in Designated Cancer Hospitals

Collaboration between psychiatry and palliative medicine has the potential to enhance the quality of medical practice. The integration between palliative care and psychiatry has been attempted only in discrete medical settings and is not yet firmly established as an institution.

In Japan, the Cancer Control Act was approved in 2006, and prefectural and local cancer hospitals were designated by the government. The designated cancer hospitals were required to provide a hospital-based palliative care team, with a palliative care specialist, a consultation-liaison psychiatrist and a certified advanced nurse practitioner as core members. In addition, national medical insurance covers the services provided by qualified palliative care teams that fulfill the necessary conditions: palliative care teams must be interdisciplinary teams composed of full-time core members with a palliative care specialist, a consultation-liaison psychiatrist, a certified advanced nurse practitioner and hospital pharmacists. The approval of palliative care teams by the insurance plan encourages the dissemination of palliative care service in practice. We investigated the availability and degree of integration between psychiatric consultation-liaison services and palliative care in Japan.

A survey questionnaire was mailed to consultation-liaison psychiatrists at 375 government-designated cancer hospitals regarding their consultation-liaison services. A total of 375 survey questionnaires were sent to consultation-liaison psychiatrists, with a response rate of 64.8%. Designated cancer hospitals with approved palliative care teams were significantly more likely to have a consultation-liaison

psychiatrist in the palliative care team than those in non-approved palliative care teams [80/80 (100%) versus 110/153 (73%); P < 0.008]. Approved palliative care teams had double the number of referrals, conducted rounds more frequently and held conferences more frequently. Psychiatrists of the approved palliative care teams spent more of their time on palliative care consultations, adhered more closely to consultation processes and contributed more actively to the integration of developmental perspectives in treatment plans. In Japan, most designated cancer hospitals with approved palliative care teams were more likely to integrate psychiatric consultation-liaison services into their palliative care programs. Systematic strategies for integration between palliative care and consultation-liaison psychiatry would contribute to the provision of appropriate psychosocial care for cancer patients and families at all stages.

PARTICLE THERAPY AND RADIATION ONCOLOGY DIVISION

Teiji Nishio, Ryosuke Kohno, Satoru Kameoka, Shie Nishioka, Sadamoto Zenda, Mitsuhiko Kawashima, Tetsuo Akimoto

Introduction

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

Research Activities

(a): Proton beam therapy 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 proton beam therapy 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. Proton therapy 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 proton therapy. 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. Proton beam radiotherapy showed promising local control benefits and would benefit from ongoing clinical study.

(b): Dose-volume histogram analysis of the safety of proton beam therapy for unresectable hepatocellular carcinoma

To evaluate the safety and efficacy of radiotherapy using PRT for unresectable hepatocellular carcinoma, sixty consecutive patients who underwent PRT between May 1999 and July 2007 were analyzed. There were 42 males and 18 females, with a median age of 70 years (48-92 years). All but 1 patient had a single lesion with a median diameter of 45 mm (20-100 mm). Total PRT dose/fractionation was 76-cobalt Gray equivalent (CGE)/20 fractions in 46 patients, 65 CGE/26 fractions in 11 patients, and 60 CGE/10 fractions in 3 patients. The risk of developing proton-induced hepatic insufficiency (PHI) was estimated using dose-volume histograms and an indocyanine-green retention rate at 15 minutes (ICG R15). None of the 20 patients with ICG R15 of less than 20% developed PHI, whereas 6 of 8 patients with ICG R15 values of 50% or higher developed PHI. Among 32 patients whose ICG R15 ranged from 20% to 49.9%, PHI was observed only in patients who had received 30 CGE (V30) to more than 25% of the noncancerous parts of the liver (n = 5) Local progression-free and overall survival rates at 3 years were 90% (95% confidence interval [CI], 80-99%) and 56% (95% CI, 43-69%), respectively. A gastrointestinal toxicity of Grade $\geq$2 was observed in 3 patients. ICG R15 and V30 are recommended as useful predictors for the risk of developing PHI, which should be incorporated into multidisciplinary treatment plans for patients with this disease.

(c): Development of an activity pencil beam algorithm using measured distribution data of positron emitter nuclei generated by proton irradiation of targets containing ^{12}C, ^{16}O, and ^{40}Ca nuclei in preparation of clinical application

The purpose of this study is to develop a new calculation algorithm that is satisfactory in terms of the requirements for both accuracy and calculation time for a simulation of imaging of the proton-irradiated volume in a patients body in clinical proton therapy. The activity pencil beam

algorithm (APB algorithm), which is a new technique to apply the pencil beam algorithm generally used for proton dose calculations in proton therapy to the calculation of activity distributions, was developed as a calculation algorithm of the activity distributions formed by positron emitter nuclei generated from target nuclear fragment reactions. In the APB algorithm, activity distributions are calculated using an activity pencil beam kernel. In addition, the activity pencil beam kernel is constructed using measured activity distributions in the depth direction and calculations in the lateral direction. ^{12}C, ^{16}O, and ^{40}Ca nuclei were determined as the major target nuclei that constitute a human body that are of relevance for the calculation of activity distributions. In this study, "virtual positron emitter nuclei" was defined as the integral yield of various positron emitter nuclei generated from each target nucleus by target nuclear fragment reactions following irradiation with a proton beam. Compounds, namely, polyethylene, water (including some gelatin) and calcium oxide, which contain plenty of the target nuclei, were irradiated using a proton beam. In addition, depth activity distributions of virtual positron emitter nuclei generated in each compound from target nuclear fragment reactions were measured using a beam ON-LINE PET system mounted on a rotating gantry port (BOLPs-RGp). The measured activity distributions depend on depth or, in other words, energy. The irradiated proton beam energies were 138, 179, and 223 MeV, and measurement time was about 5 h until the measured activity reached the background level. Furthermore, the activity pencil beam data were made using the activity pencil beam kernel, which was composed of the measured depth data and the lateral data including multiple Coulomb scattering approximated by the Gaussian function and were used for calculating activity distributions. The data of measured depth activity distributions for every target nucleus by proton beam energy were obtained using BOLPs-RGp. The form of the depth activity distribution was verified, and the data were constructed in consideration of the time-dependent change of the form. Time dependence of an activity distribution form could be represented by two half-lives. The Gaussian form of the lateral distribution of the activity pencil beam kernel was decided by the effect of multiple Coulomb scattering. Thus, the data of the activity pencil beam involving time dependence could be obtained in this study. The simulation of imaging of the proton-irradiated volume in a patient body using target nuclear fragment reactions was feasible with the developed APB algorithm taking time dependence into account. With the use of the APB algorithm, it was suggested that a system of simulation of activity distributions that has levels of both accuracy and calculation time appropriate for clinical use can be constructed (1).

(d): A feasibility study of a molecular-based patient setup verification method using a parallel-plane PET system

A feasibility study of a novel PET-based molecular image guided radiation therapy (m-IGRT) system was conducted by comparing PET-based digitally reconstructed planar image (PDRI) registration with radiographic registration. We selected a pair of opposing parallel-plane PET systems for the practical implementation of this system. Planar images along the in-plane and cross plane directions were reconstructed from the parallel-plane PET data. The in-plane and cross-plane FWHM of the profile of 2 mm diameter sources was approximately 1.8 and 8.1 mm, respectively. Therefore, only the reconstructed in-plane image from the parallel-plane PET data was used in the PDRI registration. In the image registration, five different sizes of 18F cylindrical sources (diameter: 8, 12, 16, 24, 32 mm) were used to determine setup errors. The data acquisition times were 1, 3 and 5 min. Image registration was performed by five observers to determine the setup errors from PDRI registration and radiographic registration. The majority of the mean registration errors obtained from the PDRI registration were not significantly different from those obtained from the radiographic registration. Acquisition time did not appear to result in significant differences in the mean registration error. The mean registration error for the PDRI registration was found to be 0.93±0.33 mm. This is not statistically different from the radiographic registration which had a mean registration error of 0.92±0.27 mm. Our results suggest that m-IGRT image registration using PET-based reconstructed planar images along the in-plane direction is feasible for clinical use if PDRI registration is performed at two orthogonal gantry angles (2).

(e): 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 proton dose using MOSFET detectors (3).

(f): Multi-institutional Retrospective Analysis of the Inhomogeneity Correction for Radiation Therapy of Lung Cancer

The purpose of this work is to retrospectively analyze the effect of the inhomogeneity correction using a clinically treated plan for stage III non-small-cell lung cancer within multiple institutions in Japan. Twenty-five patients among five radiation therapy facilities were registered for this study. The isocenter dose or D95 of PTV or other important values were compared with and without an inhomogeneity correction using a model-based algorithm. The differences in isocenter dose were 4% average and 10% maximum for the first Anterior-Posterior opposed field plan to 40 Gy and 6% average and 11% maximum for the off-cord boost oblique field plan of 20 Gy. The differences in D95 dose were 1% average and 9% maximum for the first plan and 1% average and 6% maximum for the boost plan. D95 prescription seemed to be a superior method; however, its reliability depends on each clinical case. Additionally, maximum dose, minimum dose and mean dose for both the primary tumor and the metastatic lymph node were analyzed, and the minimum dose had the most impressive results. In some cases, the target volume had an unintended underdose of more than 10%. Finally, an analysis of the organ at risk was added, and this showed no meaningful differences for the V20 of the lung and the maximum dose of the spinal cord. These results provide a standard for the effects of the inhomogeneity correction (4).

Published Papers

1. Miyatake A, Nishio T, Ogino T. Development of activity pencil beam algorithm using measured distribution data of positron emitter nuclei generated by proton irradiation of targets containing ^{12}C, ^{16}O, and ^{40}Ca nuclei in preparation of clinical application. Med Phys, 38:5818-5829, 2011
2. Yamaguchi S, Ishikawa M, Bengua G, Sutherland K, Nishio T, Tanabe S, Miyamoto N, Suzuki R, Shirato H. A feasibility study of a molecular-based patient setup verification method using a parallel-plane PET system. Phys Med Biol, 56:965-977, 2011
3. Kohno R, Hotta K, Matsuura T, Matsubara K, Nishioka S, Nishio T, Kawashima M, Ogino T. Proton dose distribution measurements using a MOSFET detector with a simple dose-weighted correction method for LET effects. J Appl Clin Med Phys, 12:3431, 2011
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CLINICAL TRIAL SECTION

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Introduction

Established in 2008, the Clinical Trial Section supports the Investigator Initiated Clinical Trials (IITs) Program at the National Cancer Center Hospital East (NCCHE) through the Clinical Data Center. Our section consults on development strategy, supports project management and protocol development. The Section consists of the CRC Office for IITs, Clinical Data Center, Protocol Development (Medical Writing) Team, Research Concierge Office, IRB Office and Regulatory Affairs.

Routine Activities

CRC Office for IITs
- Support IITs that are conducted in the NCCHE

Clinical Data Center
- Provides direct oversight of Institutional Investigator Initiated Early-Phase Clinical Trials
- Data Management
- Central Monitoring
- Site Visit Monitoring through direct access to electronic medical records

Protocol Development Team
- Support for protocol writing
- Support for consent form writing
- Consultation on clinical development strategy
- Consultation on trial methodology

Research Concierge Office
- Support for informed consent for genetic research
- Support for trans rational research using genome information.

IRB Office
- Oversees all IRB activities
- Management of Contents of clinical trials on web site
- Call Center for clinical trials
- Intellectual Properties Rights Management commenced in 2010

Regulatory Affairs
- Consultation on regulatory affairs throughout the whole process of drug development by regulatory affairs experts
- All experts have experience either as reviewers in the Minister of Health, Labor and Welfare (MHLW) or in the Pharmaceuticals and Medical Devices Agency (PMDA).

Research Activities and Clinical Trials

CRC Office for IITs
- CRCs, in 2010 supported 34 IITs including a Sponsor Investigator IND trial. A total of 696 patients participated in the IITs.

Clinical Data Center
- Two clinical studies, a medical device and new anticancer drag study, and first-in-man phase 0 study, are active as of 2011.
- Three clinical studies, two medical device studies, and a study on anti-cancer drug are in preparation.

Research Concierge Office
- RCs, in 2011 supported about 3,000 informed consents in 2011.

Protocol Development Team
- Medical writing support and project management were provided for all IITs that were overseen by the Clinical Data Center.