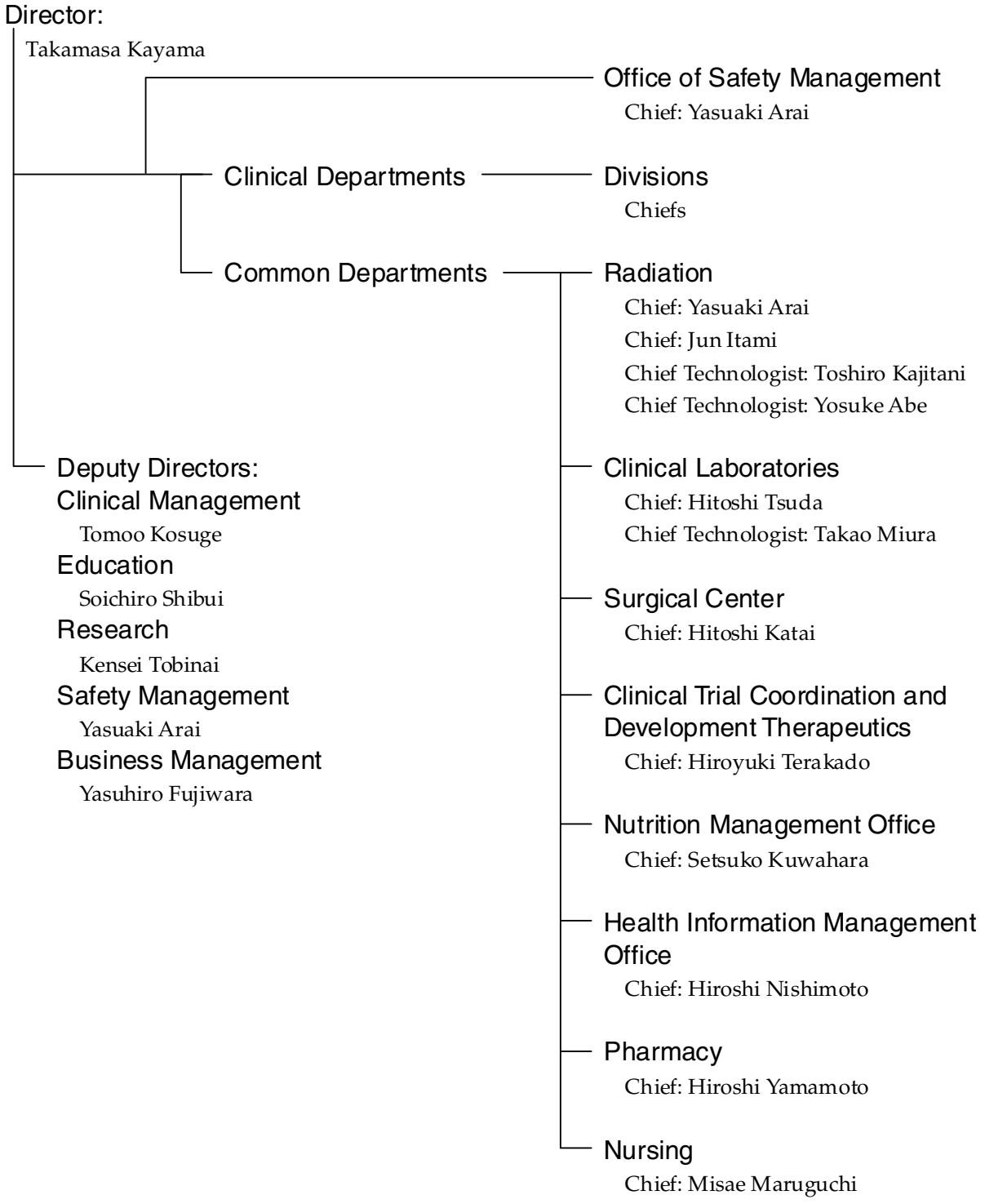
Hospital

Organization



Clinical Departments

Director:
Takamasa Kayama

- Department of Neurosurgery and Neuro-Oncology
  - Chief: Soichiro Shibui
  - Chief: Yoshitaka Narita
- Department of Ophthalmic Oncology
  - Chief: Shigenobu Suzuki
- Department of Head and Neck Oncology and Plastic and Reconstructive Surgery
  - Chief: Masao Asai
  - Chief: Shimpei Miyamoto
  - Head and Neck Surgery Division
  - Plastic and Reconstructive Surgery Division
- Department of Breast Oncology and Medical Oncology
  - Chief: Yasuhiro Fujiwara
  - Chief: Takayuki Kinoshita
  - Breast Surgery Division
  - Breast and Medical Oncology Division
- Department of Thoracic Oncology
  - Chief: Hisao Asamura
  - Chief: Tomohide Tamura
  - Chief: Masahiro Kaneko
  - Thoracic Surgery Division
  - Thoracic Oncology Division
  - Respiratory Endoscopy Division
- Department of Gastrointestinal Oncology
  - Chief: Hitoshi Katai
  - Chief: Yoshihiro Moriya
  - Chief: Yasuhiro Shimada
  - Chief: Yuji Tachimori
  - Chief: Yutaka Saito
  - Esophageal Surgery Division
  - Gastric Surgery Division
  - Colorectal Surgery Division
  - Gastrointestinal Medical Oncology Division
  - Gastrointestinal Endoscopy Division
- Department of Hepatobiliary and Pancreatic Oncology
  - Chief: Tomoo Kosuge
  - Chief: Takuji Okusaka
  - Hepatobiliary and Pancreatic Surgery Division
  - Hepatobiliary and Pancreatic Oncology Division
- Department of Urology
  - Chief: Hiroyuki Fujimoto
- Department of Gynecology
  - Chief: Takahiro Kasamatsu
- Department of Orthopedic Surgery
  - Chief: Hirokazu Chuman
- Department of Dermatologic Oncology
  - Chief: Naoya Yamazaki
- Department of Hematology and Hematopoietic Stem Cell Transplantation
  - Chief: Kensei Tobinai
  - Chief: Takahiro Fukuda
  - Hematology Division
  - Hematopoietic Stem Cell Transplantation Division
- Department of Pediatric Oncology
  - Chief: Atsushi Makimoto
  - Sarcoma Outpatient
- Department of Internal Medicine
  - Chief: Ken Ohashi
  - Diabetology, Cardiology, General Internal Medicine, Genetic Counseling, Dental
- Department of Anesthesiology and Intensive Care Unit
  - Chief: Tetsufumi Sato
  - Chief: Daisuke Yamaguchi
  - Anesthesiology Division
  - Intensive Care Unit
- Department of Palliative Care and Psycho-Oncology
  - Chief: Motohiro Matoba
  - Chief: Ken Shimizu
  - Palliative Care Division
  - Psycho-Oncology Division
- Department of Diagnostic Radiology
  - Chief: Yasuaki Arai
  - Chief: Masahiko Kusumoto
- Department of Radiation Oncology
  - Chief: Jun Itami
- Department of Pathology and Clinical Laboratories
  - Chief: Hitoshi Tsuda
  - Chief: Ryuji Tanosaki

Activities of the Departments

DEPARTMENT OF NEUROSURGERY AND NEURO-ONCOLOGY

Soichiro Shibui, Yoshitaka Narita, Yasuji Miyakita, Makoto Ohno, Yoshiko Okita

Introduction

Patients with primary and metastatic brain tumors are treated by five neurosurgeons in the Neurosurgery Division. Three hundred and thirteen patients were admitted and 92 craniotomies for tumor removal were carried out in 2011 including 35 gliomas, 39 metastatic brain tumors, 6 primary CNS lymphomas, and 5 meningiomas (Table 1). Ten ventriculo-peritoneal shunts and 7 neuroendoscopic surgeries for the IIIrd ventriculostomy or biopsy were also carried out for patients with hydrocephalus. Every craniotomy was carried out with the aid of a surgical navigation system (Stealth station). The site of the craniotomy and the extent of tumor removal were visualized on the CRT of this system in real time, contributing to safer and more precise surgery. Intraoperative monitoring with motor- and sensory evoked potential (MEP and SEP) recording as well as preoperative functional MRI and MR tractography were also used to preserve patient neurological function. Nine awake surgeries were also performed, particularly for removal of gliomas near the speech center. Postoperative radiotherapy and chemotherapy using high-dose methotrexate were carried out for malignant tumors. In order to design a more effective chemotherapy regimen, molecular biological studies for drug resistance, growth factors, cell kinetic studies on individual tumors and several clinical trials are ongoing.

Routine Activities

A weekly conference is held with doctors of the Department of Radiation Oncology on diagnosis and treatment of the patients with brain tumors. Usually 20 patients are hospitalized and two or three of them undergo surgical treatment every week. The Stealth navigation system is used for surgical planning during every craniotomy. The patients with malignant brain tumors receive postoperative radiotherapy and chemotherapy. Statistical analysis revealed that surgical removal of as much of the tumor as possible yielded better survival rates even for the most malignant glioblastomas, which usually recur soon after the surgery without radiotherapy. Concomitant use of chemotherapy is considered to enhance the anti-tumor effect of radiotherapy. Temozolomide has been given to all malignant glioma patients during radiotherapy and repeated every month for 2 years. The 1-year and 5-year survival rates of the patients with anaplastic astrocytomas were 86.7% and 34.3%, respectively, which were better than those recorded in the Brain Tumor Registry of Japan. But the 1-year and 5-year survival rates of patients with glioblastomas has remained at 58.3% and 11.9%, respectively (Table 2). High dose methotrexate is administered to the patients with primary CNS lymphoma before radiotherapy.

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

Research Activities

Patients with brain tumors have been registered in the Brain Tumor Registry of Japan (BTRJ) since 1969. More than 100,000 patients have been registered and followed up. The Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, contributes as a managing office of the BTRJ and established on-line registration using the University Hospital Medical Information Network (UMIN) system in 2009.

An analysis of gene expression profiles in malignant gliomas is being carried out in order to determine specific genes that have an influence on the effects of chemotherapy and radiation therapy in cooperation with the Genetics Division of the National Cancer Center Research Institute. Tumor samples of malignant gliomas were collected and were analyzed with a DNA microarray. FISH analysis using 1p/19q/EGFR/PTEN probes and the determination of the methylation status of O^6-methylguanine-DNA methyltransferase (MGMT) are also carried out to predict the prognosis of the patients with malignant gliomas.

Clinical Trials

The Japan Clinical Oncology Group (JCOG)-Brain

Table 1. Number of surgeries by year, 2009-2011

	2011	2010	2009
Glioma	35	51	46
Metastatic brain tumor	39	42	27
Meningioma	5	9	5
Primary CNS lymphoma	6	4	3
Other brain tumor	7	6	7
Others	31	33	25
Total	123	145	113

Table 2. Survival rates

Diagnosis	No	MST (mo)	5-yr (%)
Pilocytic astrocytoma	7	n.v.	100
Diffuse astrocytoma	47	n.v.	70.7
Oligoastrocytoma	21	n.v.	95.2
Anaplastic oligoastrocytoma	22	n.v.	65.8
Anaplastic astrocytoma	47	28.2	34.3
Glioblastoma	104	13.9	11.9

Op. year, 1995.1-2005.12; MST, median survival time; n.v., not verified

Tumor Study Group was organized in 2002 and a multi-institutional randomized controlled trial entitled "A randomized controlled phase II/III study of chemoradiotherapy using ACNU versus procarbazine and ACNU for astrocytoma grade 3 and 4" was carried out. The overall survival of both arms was longer than that of a Temozolomide (TMZ) study conducted by EORTC, but adverse events such as granulocytopenia and thrombocytopenia were observed more frequently. In April 2010 a randomized study was started entitled "A multicenter randomized phase II trial of Interferon-beta and Temozolomide combination chemoradiotherapy for newly diagnosed glioblastomas (JCOG 0911)". A clinical trial for metastatic brain tumors is also still ongoing: "Randomized phase III trial of postoperative whole brain radiation therapy compared with salvage stereotactic radiosurgery in patients with one to four brain metastasis (JCOG 0504)". The efficacy of the gamma knife will be compared to that of whole brain irradiation. A new clinical trial for primary CNS lymphoma and grade 3 glioma will start in 2012. These studies, under the surveillance of JCOG, aim to set a standard protocol for treating malignant brain tumor patients. Moreover, a proper methodology for performing randomized studies will be established in the field of neuro-oncology.

Published Papers

1. Terasaki M, Shibui S, Narita Y, Fujimaki T, Aoki T, Kajiwara K, Sawamura Y, Kurisu K, Mineta T, Yamada A, Itoh K. Phase I trial of a personalized peptide vaccine for patients positive for human leukocyte antigen--A24 with recurrent or progressive glioblastoma multiforme. J Clin Oncol, 29:337-344, 2011
2. Sunayama J, Sato A, Matsuda K, Tachibana K, Watanabe E, Seino S, Suzuki K, Narita Y, Shibui S, Sakurada K, Kayama T, Tomiyama A, Kitanaka C. FoxO3a functions as a key integrator of cellular signals that control glioblastoma stem-like cell differentiation and tumorigenicity. Stem Cells, 29:1327-1337, 2011
3. Ohno M, Narita Y, Miyakita Y, Ueno H, Kayama T, Shibui S. Reactivation of hepatitis B virus after glioblastoma treatment with temozolomide--case report. Neurol Med Chir, 51:728-731, 2011
4. Hashimoto K, Narita Y, Miyakita Y, Ohno M, Sumi M, Mayahara H, Kayama T, Shibui S. Comparison of clinical outcomes of surgery followed by local brain radiotherapy and surgery followed by whole brain radiotherapy in patients with single brain metastasis: single-center retrospective analysis. Int J Radiat Oncol Biol Phys, 81:e475-480, 2011

DEPARTMENT OF OPHTHALMIC ONCOLOGY

Shigenobu Suzuki

Introduction

Our Department is one of the rare groups specializing in ocular tumors, especially intraocular tumors. Recently, more than 60% of patients nationwide with retinoblastoma, which is the most frequent intraocular malignancy in childhood, and more than 50% of patients with uveal melanoma, which is the most frequent primary intraocular malignancy in adults, have been referred to the department.

Routine Activities

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

1) Retinoblastoma

Unless the patient's family has anxiety about preserving the affected eye, if the eye has already suffered from complication such as uveitis or secondary glaucoma, or if extraocular extension of the retinoblastoma is strongly suspected, we can offer the family eye-preserving treatment. Initial systemic chemotherapy and additional local therapies, called "chemoreduction therapy", comprise the main strategy. If the tumor is localized in the peripheral retina, plaque brachytherapy radiation using ruthenium-106 is also available. Transpupillary thermotherapy or cryotherapy is also used in cases with localized small tumors. Patients with extraocular extension, recurrence or metastasis who need systemic chemotherapy are treated with dedicated support from the Department of Pediatric Oncology.

2) Uveal melanoma

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

3) Conjunctival tumors

Conjunctival malignant tumors are treated by excisional resection with a safety margin combined with cryotherapy at the resection margin. Diffuse conjunctival tumors or tumors with orbital invasion are treaded with orbital exenteration.

4) Orbital tumors

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

5) Eyelid tumors

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

Clinical Trials

One of the unique techniques in our department is

local chemotherapy for retinoblastoma via selective ophthalmic artery infusion using a balloon catheter. Injection of melphalan (7.5 mg/m^2) directly into the affected side of the ophthalmic artery can be performed for two to three patients a week. From 1987 to 2007 1470 injections for 408 retinoblastoma eyes were examined, and the procedure success rate was 98.8%. This technique has been modified and performed until 2009 in more than 20 countries. We are planning the clinical trial on selective ophthalmic artery injection therapy for initial treatment methods.

Direct injection of diluted melphalan (0.016 mg/0.05 ml) into the vitreous cavity is performed for retinoblastoma eyes with vitreous seeding. Vitreous seeding can be cured for eyes with vitreous seeds after other treatment modalities, and about 65% eyes were rescued using this strategy.

Neoadjuvant chemotherapy for eye-preservation in retinoblastoma cases is available in selected patients in collaboration with the Department of Pediatrics, the Jikei University School of Medicine. A reduction of systemic chemotherapy using selective ophthalmic artery injection and vitreous injection strategies is now ongoing.

Published Papers

1. Suzuki S, Yamane T, Mohri M, Kaneko A. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. Ophthalmology, 118:2081-2087, 2011

Table 1. Number of patients

Retinoblastoma	48
Choroidal melanoma	14
Other intraocular tumors	22
Eyelid tumor	15
Conjunctival tumor	16
Orbital tumor	22
Others	5

Table 2. Operative procedure

Retinoblastoma	
Selective ophthalmic arterial injection	106
Laser and/or vitreous injection	118
Ruthenium brachytherapy	43
Enucleation	16
Choroidal melanoma	
Ruthenium brachytherapy	8
Enucleation	2
Resection of eyelid tumor	6
Resection of conjunctival tumor	6
Resection of orbital tumor	13
Orbital exenteration	1
Others	2

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

Masao Asai, Sei-ichi Yoshimoto, Hiroki Umezawa, Natsuki Matsunaga

Introduction

The strategy of head and neck cancer treatment is to improve the patient's survival rate while preserving the significant functions including speech, mastication, swallowing, and cosmetic appearance. In order to achieve this strategy, our division has tried to select the best treatment modality and devise new surgical strategies based on the clinico-pathological findings and the large database of our head and neck cancer patients.

Our divisions have developed and performed original surgical procedures of partial laryngectomy for newly-diagnosed and radiation-failed early glottic cancer, partial hypopharyngectomy for early hypopharyngeal cancer and total glossectomy without total laryngectomy for advanced tongue cancer. These surgical approaches can be performed without sacrificing the larynx. Compared with the results of conventional surgery, the wound apparently heals with fewer complications. Patients can resume social activities more easily when they maintain their ability to communicate by speech. We have recently started a new treatment trial of concurrent chemo-radiotherapy for advanced and resectable head and neck cancer at the National Cancer Center Hospital East.

Routine Activities

The Head and Neck Division of the NCCH consists of two head and neck surgeons and two plastic surgeons as regular staff, and two residents. In our outpatient service, an NCCH East a plastic surgeon is also engaged in routine outpatient activities, including regular follow-up care, and a resident of the Head and Neck Division of NCCH East performs general and local anesthetic operations, and supportive care of inpatients. Many operations with or without major microsurgical reconstructive surgery under general and local anesthesia and radiotherapy are performed at NCCH, but only chemo-radiotherapy for the head and neck cancer is mainly performed at NCCHE.

In 2011, 264 patients with head and neck cancer had undergone surgery under general and local anesthesia and 45 patients had undergone major surgery with reconstructive surgery in our division. Seventy five of these patients were over 75 years old, ranging from 75 to 90. The oldest patient who was treated with microsurgical reconstructive surgery was 87 years old. There were one serious postoperative complications in 264 cases. With the increasing numbers of high-risk patients, we need to establish a treatment policy for these patients in due course.

Our divisions performed neck dissection, total pharyngo-laryngo-esophagectomy with or without micro-surgical reconstructive surgery and various other surgical procedures in cooperation with other divisions. Over 10 patients have been operated on for other divisions in this year.

Our outpatient service is available from Monday to Friday, and the total number of newly registered patients has exceed 400 annually. The number of new patients in 2011 was similar to 2010. Endoscopic examinations and pharyngo-radiography are routinely performed once a week, and cervical echography twice a week. A weekly clinical head and neck conference is held every Tuesday attended by the head and neck surgeons, radio-oncologists, plastic surgeons, and a dentist. A clinico-pathological meeting is held every Friday to clarify and comprehend the oncological behavior of head and neck tumors.

Research Activities

Our divisions are taking part in multi-institutional studies related to neck dissection and the standardization of function preservation therapeutic strategy for head and neck carcinoma. Although neck dissection in our field is a very popular surgical procedure, the standard therapy has not been established until recently. Our divisions are currently investigating the neck dissection area and recurrences of oral cavity carcinoma, and taking part in multi-institutional studies of sentinel lymph node examination of tongue cancer from this year. There is currently no established standardized function-preserving treatment for head and neck carcinoma that will have an improvement on survival, loco-regional control, and preservation of various functions necessary for life. We conducted a research on the relationship between treatment procedures and the

pattern of recurrence/metastasis of various primary sites of head and neck carcinoma, and came up with the best treatment method with function preservation for each patient.

Clinical Trials

Our divisions were able to perform partial laryngectomy in 2 cases of supraglottic carcinoma and partial hypo-pharyngectomy with free radial forearm flap or free jejunum in 7 cases of pyriform sinus and posterior wall hypopharyngeal carcinoma. Voice function was able to be preserved in all the cases. We have started endoscopic mucosal resection (EMR) for small and superficial hypopharyngeal carcinomas in corporation with the Endoscopic Division from 2006, and 19 cases were treated in 2011. The rate of voice preservation surgery of hypopharyngeal cancer was very high (74%), probably No. 1 in Japan.

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

Tongue	29
Mesopharynx	22
Hypopharynx	35
Larynx	9
Oral cavity (without tongue)	32
Nasal and paranasal cavity	11
Thyroid	16
Major salivary gland	12
Neck metastasis (primary unknown, eyelid, melanoma, etc.)	18
Others	2
Total	186

Table 2. Type of procedures

Glossectomy (partial, hemi, subtotal) (+ reconstruction)	29 (6)
Resection of mesopharyngeal tumor (+ reconstruction)	22 (8)
Total pharyngolaryngectomy (TPLE) (+ reconstruction)	9 (9)
Partial hypopharyngectomy (preserve larynx) (+ reconstruction)	7 (6)
EMR	19
Total laryngectomy	8
Partial laryngectomy	0
Extended resection of larynx (+ reconstruction)	1 (1)
Resection of tumor of oral cavity (+ reconstruction)	32 (5)
Maxillectomy (+ reconstruction)	11 (4)
Thyroidectomy (hemi, total)	16
Parotidectomy, etc.	12
Neck dissection	18
Neck tumor	1
Reconstruction and plastic surgery only	16
Tracheotomy	5
Lymphadenectomy	55
Others	3
Total	264

Table 3. Operative morbidity and mortality

Major complications *(major leakage, bleeding, flap necrosis, etc.)*	1 cases (0.4% in total, 1 [2.2%] in 45 major surgeries)
Minor complications *(high fever, infection, pneumonia, minor leakage, etc.)*	10 cases (3.8%)
Operative death within 30 days	0 cases
Postoperative hospital death	0 cases

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

Shimpei Miyamoto, Shuji Kayano, Minoru Sakuraba, Shogo Nagamatsu, Hiroki Umezawa

Introduction

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

Routine Activities

Two plastic surgeons cover reconstructive operations. Every week three to five reconstructive operations are performed. These reconstructive surgeries are performed in cooperation with the surgeons of another division of hospital, such as Head and Neck Surgery, Orthopaedic Surgery, Esophageal Surgery, Breast Surgery, Dermatology, and so on. We started immediate breast reconstruction with autologous tissue transfer from April, 2010, and the number of the patients who receive breast reconstruction is increasing. Limb reconstruction after limb preservation surgery has increased in accordance with the establishment of the Sarcoma Treatment Group.

Research Activities

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

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

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

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

Other developments of reconstructive procedures in cooperation with the other divisions such as orthopedic surgery, breast surgery, et cetera, are ongoing.

Table 1. Cooperative projects with other divisions

Head & Neck surgery	50
Orthopaedic surgery	32
Esophageal surgery	11
Breast surgery	77
Dermatology	8
Urologic surgery	0
HB&P surgery	7
Ophthalmic surgery	0
Colorectal surgery	2
Gastric surgery	0
Thoracic surgery	0
Neurosurgery	1
Gynecology	2
Total	190

Table 2. Operative Procedures

Microvascular free flap	111
DIEP	35
Anterolateral thigh	24
Jejunum	22
Latissimus Dorsi	12
RAMC	8
Scapula bone	6
Fibula bone	3
Other flaps	1
Other Microsurgery	18
Supercharge	5
Nerve Graft	1
Limb Salvage	3
Hepatic Artery	7
Others	2
Subtotal	129
Pedicled flaps	43
Latissimus Dorsi	22
PM or PMMC	7
RAMC	3
Anterolateral thigh	3
Other flaps	8
Other Procedures	62
Total	227

Published Papers

1. Miyamoto S, Sakuraba M, Asano T, Hayashi R, Ebihara M, Miyazaki M, Daiko H, Shinozaki T, Kimata Y. Free jejunal patch graft for reconstruction after partial hypopharyngectomy with laryngeal preservation. Arch Otolaryngol Head Neck Surg, 137:181-186, 2011
2. Miyamoto S, Sakuraba M, Nagamatsu S. Reconstruction after partial hypopharyngectomy with larynx preservation. Plast Reconstr Surg, 128:327-328, 2011
3. Miyamoto S, Sakuraba M, Nagamatsu S. Reliable option for salvage pharyngoesophageal reconstruction. Plast Reconstr Surg, 127:1734-1735, 2011
4. Miyamoto S, Sakuraba M, Nagamatsu S, Hayashi R. Current role of the iliac crest flap in mandibular reconstruction. Microsurgery, 31:616-619, 2011
5. Miyamoto S, Sakuraba M, Nagamatsu S, Hayashi R. Salvage total pharyngolaryngectomy and free jejunum transfer. Laryngoscope, 121:947-951, 2011

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

Yasuhiro Fujiwara, Masashi Ando, Kenji Tamura, Chikako Shimizu, Kan Yonemori, Mayu Yunokawa, Makoto Kodaira

Introduction

The Breast and Medical Oncology Division is engaged in the clinical management and research of adult malignancies including breast cancer, gynecologic cancer, soft-tissue sarcoma, tumors of unknown primary sites and other rare types of solid tumors. Our activities involve patient care, clinical and translational research, and the education of young oncologists and co-medical staff.

Our goal is to provide comprehensive, state-of-the-art medical care to individual patients. An evidence-based, research-oriented and multi-disciplinary approach is the core value of our practice.

Routine Activities

Our Division consists of seven full-time attending physicians, two part-time staff physicians, two chief residents and one - three clinical residents. We also provide educational opportunities for short-term residents. Full-time attending physicians are on duty at the outpatient clinic one to three days a week. Residents, especially chief residents, are encouraged to take leadership in the clinical management of inpatients. They also undertake clinical and translational research projects under the supervision of attending physicians. Three board-certified Breast Cancer Specialist Nurses help provide seamless and comprehensive care to breast cancer patients. A pharmacist and a pharmacy resident routinely support patients receiving chemotherapy.

Most patients are treated in an outpatient setting in cooperation with the Ambulatory Chemotherapy Center and Pharmacy Division. New patients are referred from both inside and outside the NCCH. Terminally-ill patients are transferred to palliative care units outside the NCCH. 19 patients passed away in 16A ward in 2011. Other patients were referred to outside hospices or in-home care clinics. Post-operative patients have been encouraged to be referred to local breast cancer specialists participating in the Tokyo Breast Consortium network (http://breastcons.com/).

We regularly have 30-40 inpatients. The Briefing Conference is held every morning to discuss the up-to-date, evidenced-based care for individual patients. A Breast Cancer Specialist Nurse in the clinic and pharmacists attends those conferences. A Grand Round is scheduled every Monday, Wednesday, and Friday and a Phase I conference is held every Monday.

We are supporting the “Cosmetic Program” which encourages self-support for change of appearance due to cancer treatments since 2005. The program is held every 2nd and 4th Wednesday in the 16A-Ward and at the clinic in addition to occasional consultations from other wards by the Appearance Support Team.

Multidisciplinary Case Conferences with diagnostic radiologists, surgeons, and pathologists are held once a week for breast and gynecologic cancer patients. A Breast Cancer Conference is held once a month with the participation of the multidisciplinary specialists to discuss recent topics and new research results in breast oncology and to develop institutional treatment guidelines. The treatment guidelines for primary breast cancer were updated in 2011 following multidisciplinary discussion and distributed as a pocket booklet. The treatment guidelines for metastatic breast cancer are now under revision.

Research Activities

The goal of our research activities is to develop new therapeutic strategies for adult solid tumors based on the biology of neoplasia. We value cancer survivorship not only in the clinic but also as themes of research to develop comprehensive care program. We have conducted several retrospective chart reviews and qualitative studies focusing on fertility issues, appearance, spiritual needs and end-of-life care.

We continued to put our efforts into phase I studies by enhancing team communication through the Phase I conference. An investigator-initiated registration-directed trial that aims to evaluate the activity of carboplatin in HER-2 negative breast cancer in the preoperative setting has terminated its accrual in Autumn, 2011. We actively participate in

global trials as well as studies of national multi-institute clinical trialists' groups such as the Japan Clinical Oncology Group (JCOG), JGOG (the Japanese Gynecologic Oncology Group), and the Japan Breast Cancer Research Group (JBCRG). With the cooperation of Shien Lab, the Research Institute, or other multi-institutional research groups, we have launched several translational research programs that aim to discover biomarkers for patient enrichment, drug-resistance, and potential drug targets. We initiated a clinical study to explore SNPS related to taxane-induced peripheral neuropathy in cooperation with the Tokyo Metropolitan Institute of Medical Science in 2011. A ^{64}Cu-labeled trastuzumab molecular imaging study in cooperation with the RIKEN Center for Molecular Imaging Science is in steady progress since its kick-off in 2010. Other clinical studies including the above-mentioned trials are listed in Table 2.

Table 1. Demographics of Patients at their 1st Visit to the Clinic of the Breast and Medical Oncology Division (Jan-Dec, 2011)

No of 1st Visits	n	%
Total	700	
Breast	372	53
GYN	141	20
Cancer of primary unknown	96	14
Sarcoma	54	8
Others	37	5
Purpose of consultation		
2nd opinion	37	5
Treatment at NCCH	162	23
Referrals from other hospitals	130	19
Referrals from other divisions in NCCH	371	53
Breast surgery	256	
GYN	73	
Urology	6	
Orthopedics	7	
Others	29	
Others	0	0

Published Papers

1. Hashimoto K, Yonemori K, Shimizu C, Hirakawa A, Yamamoto H, Ono M, Hirata T, Kouno T, Tamura K, Katsumata N, Ando M, Fujiwara Y. A retrospective study of the impact of age on patterns of care for elderly patients with metastatic breast cancer. Med Oncol, 28:434-440, 2011
2. Tamura K, Shimizu C, Hojo T, Akashi-Tanaka S, Kinoshita T, Yonemori K, Kouno T, Katsumata N, Ando M, Aogi K, Koizumi F, Nishio K, Fujiwara Y. FcgammaR2A and 3A polymorphisms predict clinical outcome of trastuzumab in both neoadjuvant and metastatic settings in patients with HER2-positive breast cancer. Ann Oncol, 22:1302-1307, 2011
3. Katsumata N, Hirai Y, Kamiura S, Sugiyama T, Kokawa K, Hatae M, Nishimura R, Ochiai K. Phase II study of S-1, an oral fluoropyrimidine, in patients with advanced or recurrent cervical cancer. Ann Oncol, 22:1353-1357, 2011
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Table 2. Active Clinical Trials (Jan. 2011-Dec. 2011)

Disease	Clinical setting	Phase	Protocol	Regimen	status
Breast	Adjuvant	III	BEATRICE	CTx vs CTx + bevacizumab	Active, not recruiting
		III	ALTTO	lapatinib vs HCN vs lapa/HCN	Active, not recruiting
		III	CREATE-X	capecitabine vs none post-NAC	Active
		III	D-CARE	Denosumab vs placebo	Active
	NAC	R-II	CBDCA (IND trial)	neo.PTX +/- CBDCAf/b FEC	Active
		III	JCOG1017	Surgery vs no surgery for primary Stage IV BC	Active
		III	denosumab vs zolodronate	denosumab vs zolodronate	Active
		III	MARIANNE	RO5304020+/- RO4368451 vs HCN/PTX	Active
		III	RAD001	exemestane +/- RAD001	Active, not recruiting
	Metastatic	III	HKI272 (Neratinib)	HKI272 vs lapa/capecitabine	Active, not recruiting
		II	Avastin/PTX	bevacizumab/paclitaxel	Active, not recruiting
		II	ABI-007	ABI007 vs DTX	Active
		II	RO5304020	RO5304020	Active
		II	lapaHER	lapatinib/HCN	Active
		I/II	CAPIRI	capecitabine/CPT-11	Active
		I/II	S1/docetaxel	S1/docetaxel	Active
		Ib	RO5304020/RO4368451	RO5304020/RO4368451	Active
Ovary	Advanced	III	JCOG0602	primary surgery vs NAC	Active
		III	JGOG3017	TC vs. CDDP/CPT-11	Active
		III	GOG213	TC +/- bevacizumab	Active
		III	GOG218 (RDT)	TC +/- bevacizumab	Active
		III	AMG386	PTX+/-AMG386	Active
		III	GW786034	pazopanib	Active
		II	AZD2281	TC +/- Olaparib	Active
		II	JCOG0503	CPT-11/oral etoposide	Active
		I	BIBF	BIBF/CBDCA/Doxil	Active
Endometrial cancer	Advanced	III	JGOG2043	AP vs. DP vs. TCP	Active
	Advanced	III	JCOG0505	TC vs. TP (1st line)	Active
Cervical cancer	Advanced	III	S1/CDDP	S1/CDDP vs CDDP (1st line)	Active
		II	BKM120	BKM120	Active
		I	S1/CDDP	S1/CDDP chemoradiation	Active
		Feasibility	S1/CDDP	S1/CDDP	Active
Primary unknown cancer		II	CBDCA/S1	CBDCA/S1	Active
PNET/Ewing's sarcoma		II	CDDP/CPT-11 for refractory PNET	CDDP/CPT-11	Active
Solid tumor		I	MORAb-003	MORAb-003	Active
		I	MK2206	MK2206	Active
		I	MK4827	MK4827	Active
		I	AZD5363	AZD5363	Active
Soft tissue sarcoma		I	ET-743	ET-743	Active
CIPN SNPs		translational	Paclitaxel induced peripheral neuropathy	Paclitaxel	Active
Molecular Imaging		0	Molecular imaging JST/MEXT-	nano-dose, radio-labeled trastuzumab	Active

DEPARTMENT OF BREAST ONCOLOGY AND MEDICAL ONCOLOGY, BREAST SURGERY DIVISION

Takayuki Kinoshita, Sadako Akashi, Takashi Hojo, Sota Asaga, Junko Suzuki, Eriko Iwamoto, Nobuko Tamura, Kenjiro Jimbo

Introduction

The Breast Surgery Division deals with treatment of breast cancer, as well as diagnosis of breast diseases and lymph nodes in the axillary and clavicular region which are suspected of being metastatic foci. There was a remarkable change in surgical methods this year. In cooperation with plastic surgeons, immediate breast reconstruction became one of the choices for breast cancer patients since April 2010. While the percentage of breast-conserving surgery decreased to 51.0%, a total of 74 immediate breast reconstructions were performed in 2011, which comprised more than 14% of all the cases. Sentinel lymph node (SLN) biopsies were performed in 81.4% of the cases. Among these cases after SLNB, 71.9% of the cases (58.5% of all the cases) could omit axillary lymph node (ALN) surgery with negative SLN findings. In conjunction with the one-step nucleic acid amplification (OSNA) assay, more positive nodes, including micrometastases, have been detected, compared to traditional diagnosis by frozen section alone, and 28.1% of the cases after SLNB needed additional ALN dissection.

Routine Activities

This Division consists of four staff surgeons, two chief residents, and three or four rotating residents. There have been 3 staff surgeons till March, two new staff breast surgeons joined in April, and one surgeon left in September.

All the staff and the residents go the rounds together for all the inpatients from 7:30 every morning. A journal club and research conference are scheduled for every Tuesday morning after rounds. A weekly conference is held on Wednesdays from 17:00 to 19:00 for shared discussions with surgeons, medical oncologists, radiologists, and medical and radiological technologists. The diagnostic images of pre-operative patients are reviewed and compared to pathological reports in every post-operative patient. A breast pathology conference is held on the last Wednesday of each month from 18:00 to 18:30 to discuss a monthly theme (e.g., problems with diagnostic imaging, pathologically interesting cases). A conference about studies, institutional treatment guidelines and recent topics regarding breast cancer is held once a month by a multidisciplinary team. Treatment Guidelines for primary and metastatic breast cancer have been updated regularly through this multidisciplinary discussion since 2003, and they were updated in 2010.

Breast-Conserving Therapy (BCT) usually consists of local excision of the tumor followed by postoperative irradiation of the remaining breast. BCT is indicated for a tumor smaller than 3 cm. Patients with multi-focal lesions or extensive micro-calcifications detected by mammography are not suitable for BCT. Neo-adjuvant chemotherapy (NAC) and neo-adjuvant endocrine therapy (NAET) for operable advanced breast cancer are performed to avoid mastectomy and to test the sensitivity to therapeutic agents. This year, NAC or NAET was performed in about 11% of all patients. Patients receive adjuvant chemo-endocrine therapy depending upon their prognostic and predictive factors, which include the number of lymph nodes involved, histological grade of the tumor and secondary prognostic markers (HER2/neu, ER, PgR, etc.). Widely accepted factors that predict a response to a specific therapy are estrogen and progesterone receptors for hormone therapy and HER2 for trastuzumab.

Research Activities

New protocols for evaluating the survival merit of primary tumor removal in patients with metastatic breast cancer (Dr. Kinoshita) and the efficacy of sentinel lymph node biopsies after neoadjuvant chemotherapy for primary breast cancer patients who are node-positive (Dr. Hojo) are under consideration. With the recent advance in the development of an aromatase inhibitor, neoadjuvant endocrine therapy (NAET) may become the standard-bearer of tailored treatment. We have conducted a prospective neoadjuvant endocrine study since 1998. A new protocol to evaluate the optimal duration of NAET (4 M vs 6 M) has started (PTEX46). As indications for NAC

become more widespread, the question arises if SLNB is appropriate for axillary staging in patients after NAC. The accuracy and feasibility of SLNB after NAC have been evaluated (Kinoshita et al.). A feasibility study to establish the standard surgery for breast tumors using diagnostic images during surgery in an MRX operating room is ongoing (Hojo et al.). A study to evaluate the utility of the impact of supine MRI on surgical decision making was conducted. Supine MRI had more accuracy in the measurement of invasive ductal carcinoma compared to prone MRI, suggesting the usefulness of supine MRI before breast conserving surgery (Kinoshita et al.). A feasibility study using Real-time Virtual Sonography (RVS) is also being planned for breast conserving surgery. RVS can synchronize the US images and the MRI or CT images using a position tracking system with a magnetic sensor. It is thought to be useful for making an accurate excision line when US cannot detect suspicious daughter lesions or intraductal spread as identified on MRI or CT imaging.

Table 1. Number of patients

		n
Primary breast cancer		497
c Stage	0	100
	I	186
	II	180
	III	29
	IV	1
	unknown	1
Other malignant breast disease		1

Clinical Trials

1) Radiofrequency ablation (RFA)
Non-surgical therapy for early breast cancer has recently attracted attention. We started a Phase 3 trial of image-guided radiofrequency ablation which has been ongoing for early-stage breast carcinomas of less than 1 cm in diameter.
2) Denosumab adjuvant treatment (D-CARE)
A phase 3 multi-center, randomized, double blind, placebo controlled study has started. This study is to compare the treatment effect of denosumab with that of a placebo on prolonging bone metastasis-free survival in subjects with early-stage breast cancer at high risk of disease recurrence.
3) Scalp-cooling device during chemotherapy
A feasibility study to test the use of a scalp-cooling device that breast cancer patients will wear while undergoing chemotherapy treatment has started in order to slow or halt hair loss during chemotherapy.
4) Sentinel lymph node (SLN) biopsy
A multi-center feasibility study to test the SLN identification rate using radioisotope (RI) vs indocyanine green (ICG) has started.

Table 2. Type of procedure

	2007		2008		2009		2010		2011	
Total number of operations	546		462		462		482		576	
Mastectomy (%)	249	(46.7)	197	(44.0)	209	(45.6)	213	(44.2)	250	(47.6)
Breast-conserving surgery (%)	284	(53.3)	251	(56.0)	249	(54.4)	269	(55.8)	269	(51.2)
Radiofrequency ablation (%)									6	(1.1)
Axillary lymph node dissection (ALND) (%)	155	(29.1)	100	(22.3)	89	(19.4)	136	(28.2)	205	(41.5)
Sentinel lymph node biopsy (SLNB) (%)	373	(70.0)	342	(76.3)	368	(80.3)	316	(65.6)	402	(81.4)
ALND after SLNB (%)									113	(22.9)
Immediate breast reconstruction (%)	0		0		0		13	(2.7)	74	(14.1)
Neoadjuvant therapy	70	(13.1)	108	(24.1)	105	(22.9)	72	(14.9)	57	(10.9)

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DEPARTMENT OF THORACIC ONCOLOGY, THORACIC SURGERY DIVISION

Hisao Asamura, Shun-ichi Watanabe, Hiroyuki Sakurai, Mitsumasa Kawago

Introduction

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

Routine Activities

The division has four attending surgeons. Three subteams with attending surgeons and residents perform all of the inpatient care, operations, examinations, and outpatient care. In 2011, we performed a total of 520 operations; for lung cancer in 378 patients, metastatic tumor in 83, mediastinal tumor in 19, and others in 40.

The first year of our two-year fellowship program is devoted to patient care as a chief resident, and the second year is devoted to clinical/basic research. We have annually adopted one or two residents who want to major in general thoracic surgery.

In addition to weekly division meetings for the preoperative evaluation and postoperative inpatient review on Friday and for the journal club on Wednesday, the chest group has a plenary meeting to share basic information about the current issues for diagnosis and treatment of patients with lung malignancy on Thursday.

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

For metastatic lung tumors, resection has been attempted on the basis of Thomford's criteria: eligible patients are those who are at good risk, with no extrathoracic disease, with the primary site in control, and with completely resectable lung disease. Metastasis from colorectal carcinomas is the most common. For mediastinal tumors, thymic epithelial tumors are most commonly encountered for resection. In the mediastinum, where a variety of tumor histologies can arise, the treatment must be carefully determined by the cytologic/histologic diagnosis before surgery. For this purpose, CT-guided needle biopsy is replacing the formerly common biopsy under X-ray fluoroscopy. For patients with thymoma, we have recently adopted video-assisted resection of the tumor. VATS resection of mediastinal tumor is indicated exclusively for small thymomas.

Research Activities

We started a new modality, radiofrequency ablation (RFA), for malignant tumors of the lung in 2007. This modality should be effective for patients in whom it would be difficult to perform surgical resection, radiotherapy, or chemotherapy because of their poor risk. We are now conducting a clinical trial to evaluate the feasibility of RFA for poor-risk patients with malignant tumors of the lung. More than 100 patients have enrolled so far.

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

Minimally invasive surgery with the thoracoscope for thoracic malignancies is also an important

challenge in our division. In particular, the indications and surgical techniques of video-assisted surgery for early lung cancer are of special interest because of the increased incidence of such minute tumors due to improvements in CT devices and CT screening.

Clinical Trials

Due to the advent of new technologies in CT scanning, small-sized lung cancers are being found in a screening setting and also by chance. They usually present as "ground-glass opacity (GGO)" on CT, and pathologically they are considered early adenocarcinoma. The surgical management of such GGO-type lung cancer remains undetermined in terms of the extent of pulmonary parenchymal resection and lymph node dissection. Some cases might be followed up with careful monitoring by CT, since indolent tumors are known to exist. We are seeking the appropriate way to manage these patients. A clinical trial to determine the appropriateness of limited resection for early adenocarcinoma had been planned in the Japan Clinical Oncology Group (JCOG)- Lung Cancer Study Group, and two clinical trials (a phase III trial, JCOG 0802; a phase II trial, JCOG 0804) have been conducted since the end of 2009. In total, 40 cases and 31 cases have been registered for JCOG 0802 and 0804 from our division, respectively.

As for postoperative adjuvant therapy, a phase III clinical trial to compare the effectiveness of UFT with that of TS-1 for stage IA more than 2 cm and IB NSCLC planned in JCOG (JCOG 0707) has been conducted since 2008. Twenty six cases have been registered for this trial from our division.

Lung cancer consists of non-small (NSCLC) and small cell lung cancer (SCLC). Large cell carcinoma, which is one of the most common histologies of lung cancer, has been classified as NSCLC. Recently, some large cell carcinomas have been reported to have neuroendocrine features, and this lung cancer is called "large cell neuroendocrine carcinoma (LCNEC)". Sometimes it is difficult to discriminate the histology of LCNEC from that of SCLC. Asamura et al. reported the prognosis of resected LCNEC of the lung. The prognosis of this histology is similar to that of SCLC, and this report stated that both SCLC and LCNEC should be classified into the same category: "high-grade neuroendocrine tumor". The appropriate management of LCNEC is going to be investigated, and the role of adjuvant chemotherapy following resection should be discussed in the near future. A phase II clinical trial of adjuvant chemotherapy for LCNEC is on-going.

(by Shun-ichi Watanabe)

Table 1. Number of patients

Primary lung cancer	378
Metastatic lung tumor	83
Mediastinal tumor	19
Pleural disease	8
Chest wall tumor	6
Benign lung nodule	15
Others	11
Total	520

Table 2. Type of procedure

Lung resection	458
Lobectomy	281
Pneumonectomy	7
Segmentectomy	62
Wedge resection	108
Tracheal resection	0
Surgery for mediastinal tumors	21
Surgery for pleural tumors	14
Surgery for chest wall tumors	8
Others	19
Total	520

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

Pathological stage (TNM-7)	No. of pts	5-yr survival (%)
IA	723	92.7
IB	210	83.9
IIA	195	67.7
IIB	118	70.9
IIIA	222	41.1
IIIB	13	34.6
IV	39	22.8
Total	1,520	

Operation period: 2000.1-2004.12

Published Papers

1. Asamura H. Identity, similarity, and difference between large cell neuroendocrine carcinoma and small cell carcinoma. J Thorac Oncol, 6:1774; author reply 1776, 2011

2. Asamura H. Surgery after induction chemotherapy or chemoradiotherapy for locally advanced lung cancer: a technical challenge. J Thorac Oncol, 6:1458-1459, 2011

3. Rice D, Rusch V, Pass H, Asamura H, Nakano T, Edwards J, Giroux DJ, Hasegawa S, Kernstine KH, Waller D, Rami-Porta R. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. J Thorac Oncol, 6:1304-1312, 2011

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DEPARTMENT OF THORACIC ONCOLOGY, THORACIC ONCOLOGY DIVISION

Tomohide Tamura, Noboru Yamamoto, Hiroshi Nokihara, Shintaro Kanda, Hidehito Horinouchi, Shinji Nakamichi

Introduction

The incidence of lung cancer in Japan is increasing, especially in the female and elderly populations, and lung cancer has been the most common death from cancer since 1994. The majority of lung cancer patients are diagnosed at the advanced stage, and the prognosis of these patients is still poor. The goals of the Thoracic Oncology Division are to provide the highest quality treatment and to establish new effective treatments against lung cancer and other thoracic malignancies.

The Thoracic Oncology Division includes 6 staff physicians. A total of 3 chief residents, 8 residents, 2 short-term residents and 2 trainees joined the division during 2011. The Phase I Study Group was organized in 1996. Three staff physicians and 1 chief resident of the Thoracic Oncology Division are also core members of the Phase I Study Group.

Routine Activities

The staff physicians attend outpatient services for thoracic diseases, and the division has approximately 80 beds in the hospital. Inpatient care is carried out by five teams. Each team consists of one staff physician and one or two chief resident/resident/trainee.

Protocol and case conferences are scheduled every Monday morning and afternoon, respectively. The journal club is scheduled on Thursday mornings. The chest conference is held on Thursday evenings to discuss cases with thoracic surgeons, pathologists, radiologists and radiation oncologists.

A total of 305 new patients were admitted in 2011. The diagnosis for these patients and initial treatments for 260 lung cancer patients are listed in Tables 1-2. Thirty-six percent of 208 lung cancer patients receiving chemotherapy or chemoradiotherapy as their initial treatments participated in clinical trials. Survival outcomes of lung cancer patients treated in the Division are shown in Table 3. For the Phase I Study Group, 64 patients with miscellaneous solid tumors were admitted and participated in 10 phase I studies.

Research Activities

The Research activities of the Thoracic Oncology Division can be divided into five subjects: (1) multi-institutional phase III studies to establish new standard treatments against thoracic malignancies; (2) phase I/II studies to develop new effective chemotherapy regimens including new drugs against thoracic malignancies; (3) phase I studies to evaluate new drugs against solid tumors; (4) pharmacokinetic and pharmacodynamic (PK/PD) studies to investigate interpatient variability and optimal drug exposure; and (5) translational research for the development of biomarkers and innovative treatment strategies.

Clinical Trials

Clinical trials carried out in 2011 are shown in Table 4. Some studies were based on the JCOG research program, and some were carried out under contract with pharmaceutical companies.

Table 1. Number of New Inpatients in 2011

Non-small cell lung cancer	217
Adenocarcinoma	170
Squamous cell carcinoma	29
Others	18
Small cell lung cancer	43
Mesothelioma	6
Thymic cancer	5
Others	34
Total	305

Table 2. Initial Treatments for New Inpatients with Lung Cancer in 2011

Chemotherapy	174
Chemoradiotherapy	34
Adjuvant chemotherapy following surgery	25
Preoperative chemoradiotherapy	2
Thoracic radiotherapy	5
Supportive care alone (including palliative radiotherapy)	20
Total	260

Table 3. Survival Outcomes

Non-small cell lung cancer			
Unresectable stage III	204 patients treated with concurrent chemoradiotherapy in 1994-2005	Median	24.0 mo
		1-Year	75.5 %
		3-Year	34.7 %
		5-Year	22.8 %
Stage IV	480 patients treated with initial chemotherapy in 2000-2006	Median	13.2 mo
		1-Year	52.7 %
		3-Year	14.8 %
		5-Year	13.1 %
Small cell lung cancer			
limited disease	50 patients treated with concurrent chemoradiotherapy in 2001-2004	Median	28.8 mo
		2-Year	60.0 %
		5-Year	31.7 %
Extensive disease	108 patients treated with initial chemothrapy in 2001-2004	Median	12.1 mo
		2-Year	15.7 %
		3-Year	5.6 %

Table 4. Clinical Trials in 2011

Target disease	Stage	Phase	Treatment
NSCLC	Advanced	III	S-1 vs. DTX
NSCLC	Advanced	III	PF-00299804 vs. Erlotinib
NSCLC-ALK fusion	Advanced	III	PF-02341066 vs. PEM/CDDP
NSCLC-ALK fusion	Advanced	II	PF-02341066
NSCLC-EGFR mutation	Advanced	II	Erlotinib vs. Erlotinib/Bevacizumab
NSCLC-LCNEC	Advanced	II	CDDP/CPT-11
NSCLC	Advanced	II	Erlotinib vs. Erlotinib/ARQ197
NSCLC-ALK fusion	Advanced	I/II	CH5424802
NSCLC	Advanced	I	CBDCA/PTX+Ipilimumab
NSCLC	Locally advanced	II	CDDP/VNR+high-dose TRT
NSCLC	Locally advanced	II	CDDP/PEM+TRT
NSCLC	Locally advanced	I/II	EMD531444
NSCLC	Post operative	III	JCOG0707: S-1 vs. UFT
SCLC	Extensive	III	PCI vs. observation
SCLC	Recurrent	III	JCOG0605: wkly CDDP/ETP/CPT-11 vs. NGT
SCLC	Recurrent	II	AMR
SCLC	Limited	ii	JCOG1101: CRT- CDDP/AMR vs. CODE
Lung cancer	Advanced	II	CDDP short hydration
Lung cancer	Advanced	PK/PD	AMR
Lung cancer	Advanced	Translational	Circulating endothelial cells
Sokid tumor (Phase I study group)	Advanced	III	Antiemetics
Solid tumor	Advanced	I	10 New agents

DTX; docetaxel, CDDP; cisplatin, PEM; pemetrexed, CPT-11; irinotecan, CBDCA; carboplatin, PTX; paclitaxel, TRT; thoracic radiotherapy, VNR; vinorelbine, AMR; amurubicin, PCI; prophylactic cranial irradiation, EPT; etoposide, NGT; nogitecan, CRT; chemoradiotherapy, CODE; CDDP/vincristine/doxorubicin/etoposide

Published Papers

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DEPARTMENT OF THORACIC ONCOLOGY, RESPIRATORY ENDOSCOPY DIVISION

Takaaki Tsuchida, Shinji Sasada

Introduction

In the field of bronchoscopy, bronchoscopic treatments are coupled with computerized tomography (CT) for the treatment of airway stenosis, minute peripheral lung cancer, and so on. For respiratory diseases, we have focused on the accurate and less-invasive diagnosis of minute peripheral malignancies detected by CT, which can lead to earlier surgical treatment and less-invasive treatments including bronchoscopic therapies. This is facilitated by a multi-purpose bronchoscopy system consisting of a flat-panel fluoroscope, as well as with the patient's cooperation and appropriate support by medical personnel. Endobronchial malignancies are diagnosed with videobronchoscopy, together with an endobronchial ultrasound system, and a high-resolution flat-panel fluoroscope. In addition, imaging diagnosis, including that with high-resolution CT, is also a routine activity for bronchoscopy, which leads to more accurate and safer diagnoses and the earlier detection of tracheobronchial malignancies.

Routine Activities

A weekly film-reading conference is held. Furthermore, we attend all clinical conferences in the Surgery, Oncology, Radiology and Pathology Divisions to discuss and decide upon treatment strategies. Four hundred and eighteen cases of transbronchial biopsy were performed. Twenty five cases of bronchio-alveolar lavage were performed. Endobronchial ultrasonography (EBUS) is used not only to evaluate mediastinal or hilar malignant lesions but also to evaluate whether the biopsy devices could lead to the occurrence of peripheral lung lesions. Fifty four cases of EBUS-TBNA (EBUS-trans bronchial needle aspiration) were performed as a less invasive procedure to improve diagnosis for patients with mediastinal or hilar lymph node swelling. Ten endobronchial lesions were treated with endobronchial ablation (2 cases), tracheobronchial prosthesis (6 cases), and transbronchial resection (2 cases).

Research Activitiesa

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

Table 1. Number of patients

Adenocarcinoma	148
Squamous cell carcinoma	55
Small cell carcinoma	29
Other malignant tumor	46
Inflammation	64
Others	76
Total	418

Table 2. Type of procedure

Transbronchial biopsy	418
Conventional procedure	(276)
Endobronchial ultrasound	(142)
Observation	173
Bronchoalveolar lavage	25
Medical thoracoscopy	7
Ablation of tumor	2
Stent	6
Other therapies	2
Total	633

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, ESOPHAGEAL SURGERY DIVISION

Yuji Tachimori, Hiroyasu Igaki, Nobukazu Hokamura

Introduction

More than 300 new patients with esophageal tumors are admitted to the National Cancer Center Hospital every year. The multidisciplinary treatment plans are determined by the stage of the tumor in close cooperation with other teams. The Esophageal Surgery Division particularly cooperates with the Gastrointestinal Oncology Division and the Radiation Oncology Division for preoperative chemotherapy and chemoradiotherapy and salvage surgery after definitive chemoradiotherapy. We also maintain close cooperation with the Head and Neck Surgery Division for cervical esophageal carcinomas and with the Gastric Surgery Division for adenocarcinomas in the esophagogastric junction. In Japan, squamous cell carcinomas still constitute the largest proportion of esophageal tumors, and the proportion of adenocarcinomas was 5% in our institution in 2010.

Routine Activities

The Esophageal Surgery Division consists of three staff surgeons, one chief resident and three rotating senior residents. A multidisciplinary conference is held weekly in which surgeons, medical oncologists, radiation oncologists, endoscopists, radiologists, and pathologists who are involved in the treatment of esophageal diseases meet and discuss the diagnosis, staging, and treatment plans for patients with esophageal tumors. A bimonthly conference for pretreatment clinical diagnosis and a pathology demonstration of resected esophageal tumors is held to discuss a wide range of topics.

Every week, three patients with esophageal cancer undergo esophageal surgery. One hundred twelve patients underwent esophagectomy including 3 patients with cervical esophageal cancer and 8 with adenocarcinoma in the esophagogastric junction, and also including two with melanoma and one with GIST. Of the 100 patients who underwent surgery as primary therapy, a curative resection was completed for 96%, which reflects strict preoperative staging, with three hospital deaths due to an operative complication. Preoperative chemotherapy was recommended for 45 patients and preoperative chemoradiotherapy was recommended for 25 patients with resectable Stage II-IV esophageal squamous cell cancer. A three-field dissection, including the whole upper mediastinum and supraclavicular in addition to the lower mediastinum and abdomen, is our standard procedure. Video-assisted thoracic surgery was introduced for esophagectomy as minimally invasive surgery in 39 patients. Increase of laryngeal nerve palsy is serious concern. Feasibility will be evaluated upon morbidity and survival results.

The number of patients who receive definitive chemoradiotherapy as their primary treatment for resectable tumor is decreasing after the report of a clinical trial on definitive chemoradiotherapy (JCOG9906). Persistent or recurrent local disease is not infrequent after chemoradiotherapy. Twelve patients underwent salvage esophagectomy after the failure of definitive chemoradiotherapy without surgery-related death in 2011. A three-field dissection is avoided for salvage esophagectomy.

Clinical Trials

The results of a multi-institutional randomized controlled trial (JCOG9907) confirmed preoperative chemotherapy with cisplatin and 5FU before esophagectomy as standard therapy for resectable Stage II-III esophageal cancer. Preoperative chemotherapy with docetaxel, cisplatin and 5FU and preoperative chemoradiotherapy with cisplatin, 5FU and 41.4 Gy irradiation were conducted as feasibility study for the next trial. In addition, a Phase II trial for definitive chemoradiotherapy with or without salvage esophagectomy (JCOG0909) was started. For a Stage I lesion, a multi-institutional randomized controlled comparison between surgery and definitive chemoradiotherapy (JCOG0502) is continuing registration.

Table 1. Type of surgery

Esophagectomy	100
Salvage esophagectomy	12
Gastric conduit cancer surgery	6
Tumor enucleation	1
Salvage lymphadenectomy	2
Bypass surgery	2
Cervical esophagostomy	1
Exploration	3

Table 2. Type of esophagectomy

Rt. thoracotomy with 3-field	53
Rt. thoracotomy with 2-field	12
Video-assisted with 3-field	31
Video-assisted with 2-field	8
Lt. thoracotomy	1
Transhiatal	1
Cervical	3
Abdominal	3

Table 3. Survival rates after esophagectomy

Clinical stages before preoperative chemo and/or radiotherapy	No. of pts	MST (mo)	5-yr survival (%)
cStage I	151	n.v.	76.8
cStage IIA	161	63	51.4
cStage IIB	124	128	67.2
cStage III	406	32	35.7
cStage IVA	35	14	14.3
cStage IVB	98	23	26.5

Operation period: 1997.1-2006.12 n.v.: not verified

Published Papers

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DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, GASTRIC SURGERY DIVISION

Hitoshi Katai, Takeo Fukagawa, Shinji Morita, Masaki Ohashi, Michihiro Ishida, Yukie Yoda

Introduction

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

Routine Activities

The Division includes four staff surgeons, two chief residents and three or four rotating residents at any given time. Nine to eleven patients are operated upon every week. The Division shares a ward with the Gastrointestinal Medical Oncology Division, so that specialists from both divisions can treat patients with gastric cancer. Patients with stage I disease are followed-up without adjuvant chemotherapy. Adjuvant S-1 chemotherapy is used for patients with stage II and III disease.

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

We consider the education of foreign surgeons is to be an important function. In 2011, more than 20 surgeons from various countries visited this division for 2 weeks to 12 months to learn about the management of gastric cancer patients, especially surgical techniques for lymph node dissection and postoperative care. All staff surgeons have sufficient experience in teaching in English.

Research Activities

Several translational studies are being carried out in cooperation with the National Cancer Center Research Institute. Genomic scanning in gastric cancer is being carried out. The Millennium Genomic Project, which entails the analysis of single nucleotide polymorphisms (SNPs) to investigate susceptibility to gastric cancer, is also ongoing. DNA methylation as a gastric cancer metastasis risk factor has been investigated. A mini-chip assay of peritoneal washings for prediction of gastric cancer recurrence is being developed. Research on the detection of small amounts of cancer cells in peripheral blood and bone marrow of gastric cancer patients is being carried out in cooperation with Kyusyu University and Hamburg-Eppendorf University.

Clinical Trials

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

Table 1. Number of Patients

Adenocarcinoma	411
GIST	11
Others	29
Total	451

Table 2. Operative morbidity and mortality after gastrectomy

	Number of patients	%
Major complications	43	11.7
Minor complications	72	19.7
Postoperative hospital deaths	0	0
Total	366	100

Gastrectomy includes total, proximal, distal, and pylorus-preserving gastrectomy.
Major complications include pancreatic fistulae, leakage, and intra-abdominal abscesses
Minor complications include wound infection, urinary tract infection, line infection, etc.

Table 3. Operative Procedures

Distal gastrectomy	133
Total gastrectomy	115
Pylorus-preserving gastrectomy	54
Proximal gastrectomy	28
Wedge resection	10
Pancreaticoduodenectomy	1
Laparoscopic distal gastrectomy	16
Laparoscopic pylorus preserving gastrectomy	18
Laparoscopic total gastrectomy	1
Other (bypass, exploration, etc.)	75
Total	451

Table 4. Survival Rates

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

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

Published Papers

1. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol, 29:4387-4393, 2011
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3. Yamashita H, Katai H, Morita S, Saka M, Taniguchi H, Fukagawa T. Optimal extent of lymph node dissection for Siewert type II esophagogastric junction carcinoma. Ann Surg, 254:274-280, 2011
4. Saka M, Morita S, Fukagawa T, Katai H. Present and future status of gastric cancer surgery. Jpn J Clin Oncol, 41:307-313, 2011
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DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, COLORECTAL SURGERY DIVISION

Yoshihiro Moriya, Takayuki Akasu, Shin Fujita, Seiichiro Yamamoto, Ryo Inada

Introduction

The Colorectal Surgery Division deals with colorectal cancer and allied malignancies in the colon and rectum. Liver metastasis from colorectal cancer is treated in cooperation with the Hepatobiliary and Pancreatic Surgery Division. Although surgery is the main treatment modality for colorectal cancer, multi-disciplinary treatments including radiotherapy and chemotherapy are important in advanced cancer. We have multi-disciplinary meetings with the Gastrointestinal Oncology Division, Endoscopy Division and Radiology Division every week, and discuss treatment plans for preoperative patients.

Routine Activities

There are four staff surgeons, one chief resident, and four or five rotating residents. Every morning (8:20-8:50), we have a morning conference and rounds in wards 8B and 15A, B. Every Tuesday evening (18:30-19:30), a conference is held for the diagnosis of colorectal cancer: colorectal surgeons, endoscopists, and radiologists discuss the diagnosis for preoperative patients. Every Wednesday evening (17:00-18:30), a conference is held for the treatment of colorectal cancer: colorectal surgeons and medical oncologists discuss treatments for preoperative and postoperative patients.

Twelve operations are performed a week in our division. Thus, we operate upon 600 patients with colorectal cancers and allied diseases annually. Patients with clinical stage I colon and rectal cancers mainly undergo laparoscopic surgery. Patients with clinical stage II or III colon cancer are treated with laparoscopic or conventional surgery. Other patients with T3 or T4 colon cancers are treated with conventional techniques or the no-touch isolation technique as part of a clinical traial (JCOG1006 study). Patients with advanced rectal cancers are treated with conventional surgery. Adjuvant chemotherapy is being used in stage III colorectal cancer patients in a clinical trial (JCOG0910 study). Although preoperative radiotherapy is not performed routinely for advanced rectal cancer, patients with T4 rectal cancers or rectal cancers with multiple lymph node metastases are treated with preoperative chemoradiotherapy and surgery. Patients with symptoms caused by nonresectable tumors are treated with palliative surgery including palliative resection, bypass, and stoma before chemotherapy. Patients with resectable liver metastasis are treated in cooperation with the Hepatobiliary and Pancreatic Surgery Division and adjuvant chemotherapy regimens are being evaluated in a clinical trial (JCOG0603 study).

Research Activities

As described in “Routine Activities”, clinical trials are integrated into our routine work. Four clinical trials are underway, and the details are described in “Clinical Trials”. We are evaluating new surgical procedures, including intersphincteric resection (ISR) for very low rectal cancer, laparoscopic surgery, and surgery for pelvic recurrence of rectal cancer. We also carry out basic research in cooperation with scientists at the National Cancer Center Research Institute and the identification of a suitable treatment based on such a prediction is one of our important goals. In 2011, we published 5 papers, and the results of our research in 2011 are summarized as follows.

Clinical research

In multi-institutional retrospective and prospective studies, we clarified the indications of diverting stoma for patients with rectal cancer. Diverting stoma is recommended for an anastomosis within 5.0 cm of the anal verge and very strongly for a very low anastomosis within 2.0 cm.

A multi-institutional randomized trial of adjuvant chemotherapy for colorectal cancer (NSAS-CC) demonstrated that adjuvant chemotherapy with UFT improved the survival of patients with rectal cancer but not of those with colon cancer.

We demonstrated that laparoscopic ISR for lower rectal cancer provides benefits in the early postoperative period without increasing morbidity or mortality in a case-control study.

A case of ceacal schwannoma treated with lapalosocopic wedge resection was reported.

Clinical Trials

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

1. JCOG0205: A randomized study that compares adjuvant oral UFT + LV to intravenous 5-FU + lLV for pathological stage III colorectal cancer. One thousand, one hundred and ten eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
2. JCOG0212: A randomized study that compares mesorectal excision (ME) to ME with pelvic lateral lymph node dissection for clinical stage II or stage III lower rectal cancer patients. Seven hundred and one eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
3. JCOG0404: A randomized study that compares laparoscopic to open colectomy for clinical stage II or stage III colon cancer located at the cecum, ascending colon, sigmoid colon or rectosigmoid cancer. One thousand and fifty-seven eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
4. JCOG0603: A randomized study that compares adjuvant modified FOLFOX (5-FU + lLV + Oxaliplatin) to surgery alone after hepatic resection for liver metastasis from colorectal cancer. One hundred and seven patients have been enrolled and recruitment continues.
5. JCOG0910: A randomized study that compares adjuvant Capecitabine to TS-1 for pathological stage III colorectal cancer. Three hundred and nine patients have been enrolled and recruitment continues.
6. JCOG1006: A randomized study that compares conventional techniques to the no-touch isolation technique for clinical T3 or T4 colon cancer. One hundred and fifty two patients have been enrolled and recruitment continues.

Published Papers

1. Hamaguchi T, Shirao K, Moriya Y, Yoshida S, Kodaira S, Ohashi Y. Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC). Cancer Chemother Pharmacol, 67:587-596, 2011
2. Matsumoto T, Yamamoto S, Fujita S, Akasu T, Moriya Y. Cecal schwannoma with laparoscopic wedge resection: report of case. Asian J Endosc Surg, 4:178-180, 2011

DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, GASTROINTESTINAL MEDICAL ONCOLOGY DIVISION

Yasuhiro Shimada, Yasuhide Yamada, Tetsuya Hamaguchi, Ken Kato, Satoru Iwasa, Yoshitaka Honma, Natsuko Okita, Hitoshi Nishitani, Kohei Akiyoshi

Introduction

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

Routine Activities

The staff of the GI Medical Oncology Division consists of 5 medical oncologists, 2 senior residents, and 3 or 4 residents. We hold a daily case conference together at 8 am before the morning rounds. Inter-group meetings with each surgical division (Colorectal, Gastric, and Esophageal Surgery Divisions) and the Radiation Oncology Division are held weekly to decide upon treatment strategies for each individual case or to discuss future treatment strategies for the disease. Palliative care that considers the physical and psychological aspects of each case is another important issue discussed in staff meetings. The Palliative Care team and psycho-oncologists advise us on how to minimize patient discomfort and anxiety throughout end-of-life care. In 2011, we treated 2,139 hospitalized patients (568 of whom were newly diagnosed). Of these patients, 230 were entered in protocol studies.

Research Activities

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

We also quantitatively measured the mRNA levels of possible predictive biomarkers in paraffin-embedded GI cancer specimens obtained from surgical resection or endoscopic biopsy, and investigated the correlation between enzymes related to anti-cancer drug metabolism and clinical outcomes with a real-time RT-PCR assay using laser-captured microdissection. Some of these molecules will be validated with cancer tissues of 365 patients in a large randomized clinical trial

(JCOG9912) to establish a chemotherapeutic regimen tailored for patients according to genotype, and a new protocol for metastatic gastric cancer compares docetaxel/S-1/cisplatin versus standard S-1/cisplatin with further examination of molecular profiles from endoscopic biopsy specimens.

Clinical Trials

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

1. Colorectal Cancer

A regimen of infusional 5-fluorouracil (5-FU) and levofolinate (l-LV) with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) is the standard care as first- and second-line chemotherapy for patients with metastatic colorectal cancer. However, infusional 5-FU with l-LV has the disadvantages of inconvenience, cost, and morbidity related to the use of a portable infusion pump and a central venous catheter-port system. We investigated establishing combination chemotherapy regimens based on the oral fluoropyrimidine, S-1 (S-1/oxaliplatin/BV, S-1/irinotecan/BV), for metastatic disease. A phase III study of S-1/oxalipaltin/BV (SOXB) is on-going to compare this approach with modified FOLFOX6/BV in first-line chemotherapy. Combination treatment with oral fluoropyrimidines is an important candidate to improve patient QOL, medical cost and medical staff burden.

In the adjuvant setting, JCOG0205 finished and has now been followed for 5 years. The final results of disease-free survival and overall survival determined at the end of December, 2011, were clearly superior to overseas clinical data. The findings suggested that the Japanese strategy of D3 dissection followed by oral fluoropyrimidines might be better than that of strategies from overseas. A new adjuvant trial, JCOG0910, comparing S-1 with one of the standard regimens, capecitabine alone, started in March 2010. At the end of 2011, more than 800 patients had been accrued from JCOG hospitals. JCOG0603, a randomized study of adjuvant chemotherapy with mFOLFOX6 after complete resection of liver metastasis from colorectal cancer, was restarted with minor revisions. The phase I stage of JCOG0903, a phase I/II trial of chemoradiation with S-1/MMC for anal canal squamous carcinoma, was also completed in 2011.

2. Gastric Cancer

A phase III study comparing three regimens (5-FU vs CPT-11/CDDP vs S-1) (JCOG9912) was already published in 2009. This was a pivotal study that established a new standard care protocol for advanced gastric cancer and cited the "New Japanese guidelines for diagnosis and treatment of carcinoma of the stomach", 2010 edition. Another phase III study (JCOG0106) of methotrexate/5-FU or 5-FU monotherapy against peritoneal dissemination of gastric cancer was presented at ASCO 2008. Methotrexate/5-FU did not prove superior to 5-FU alone in survival. A randomized phase II study of best-available 5-FU versus weekly paclitaxel as second-line therapy against peritoneal dissemination of gastric cancer (JCOG0407) was presented at ASCO 2010. A phase I/II study of 5-FU/l-LV/paclitaxel (FLTAX) combination therapy as first-line therapy against this population has finished. A phase III study of FLTAX is under preparation now for advanced gastric cancer with peritoneal metastases. S-1 has become a new standard treatment in the adjuvant setting for stage II/III gastric cancer. A feasibility study of modified S-1/CDDP after gastrectomy was completed, showing improved tolerability and preliminary favorable survival results.

Molecular-targeted drugs for advanced gastric cancer as well as colorectal cancer have been investigated. An international phase III study with CDDP plus capecitabine, which is also an oral fluoropyrimidine, with or without BV (AVAGAST), was reported with negative results. Trials on lapatinib (EGFR/HER2, a dual tyrosine kinase inhibitor) and RAD001 (an mTOR inhibitor) are ongoing. A phase I study of S-1/CDDP/sorafenib was completed, revealing additional toxicities. The activity of trastuzumab for HER2 positive gastric cancer was reported in a first-line ToGA study. We started to evaluate the second-line activity of trastuzumab with weekly paclitaxel.

3. Esophageal Cancer

The results of our phase III study of preoperative versus postoperative 5-FU/CDDP (FP) (JCOG9907) were reported in 2007. Preoperative FP was proven to be significantly superior to postoperative FP with regard to overall survival. Based on the results of this trial, the standard care for stage II/III esophageal cancer has been changed to preoperative FP followed by surgery. A phase II study on the FP/RT (50.4 Gy) regimen in stage II or III esophageal cancer was completed with similar

activity and tolerability. The next JCOG phase III study is being planned in the preoperative adjuvant setting to compare preoperative FP versus preoperative chemoradiation versus preoperative intensive docetaxel with FP in stage II or III esophageal cancer.

4. Other

A phase I study of weekly NK105 (a micellar nanoparticle formulation of taxol) for GI cancer, and a phase II study with NK012 (a micellar nanoparticle formulation of irinotecan) for second-line colorectal cancer have finished. A phase II study of AMN107 against gastrointestinal stromal tumors has also finished.

UGT1A1, a key enzyme in the metabolism of irinotecan, has been validated in a prospective trial. This is an important milestone for genotype-tailored chemotherapy, since homozygotes of UGT1A1*28 or *6 exhibit a higher incidence of severe neutropenia. The dose of irinotecan based on genetic information can be adjusted before the first administration to avoid severe toxicity.

Number of Patients Treated

Disease/stage	Total no. of hospitalized pts.	No. of newly diagnosed pts.	No. of pts. enrolled in the protocol
1) Esophageal cancer	859	195	
Neo CRT			8
Stage I FP+RT vs surgery　JCOG0502 (phase III)			10
Stage II/III S-1/CDDP+RT　JCOG0604 (phase I)			1
Stage I EMR+5FU/CDDP+RTJCOG0508 (phase II)			2
5FU/CDDP+RT for Ce Esophageal Cancer			2
Docetaxel+FP(DCF)-EC　JCOG0807 (phase I/II)			2
Stage II/III EC-CRT+Salvage　JCOG0909 (phase II)			4
T4/M1LYM DCF (phase I/II)			5
S-488410 (phase I/II)			1
DE766 (phase I)			3
2) Gastric cancer	695	149	
S-1/oxaliplatin （SOX） vs S-1/cis p latin （SP）(phase III)			40
Paclitaxel ± lapatinib (phase III)			1
Cetuximab/cis p latin/capecitabine （phase III）			1
NK105 (phase II)			1
Paclitaxel ±IMC-1121B (ramucirumab/placebo) (phase III)			10
Neo S1/CDDP　JCOG0501(phase III)			2
wPTX/Tmab (phase II)			3
3) Colorectal cancer	509	196	
Capecitabine vs S-1　JCOG0910 (phase III)			41
5FU//-LV/oxaliplatin/bevacizumab vs S-1/oxaliplatin/bevacizumab (phase III)			18
NK012 (phase II)			2
Regorafenib vs BSC （phase III）			9
JCOG0603 (phase II/III)			4
Tri-weekly XELIRI+BV (BIX Study)			6
SOX-RT (phase I)			1
Stage II/III S-1/MMC　JCOG0903 (phase I/II)			2
Sunitinib+5FU//-LV/oxaliplatin vs bevacizumab+5FU//-LV/oxaliplatin (phase IIb)			1
mFOLFOX/bevacizumab　TRICC0808 (phase II)			1
Panitumumab/CPT-11 or Panitumumab (phase II)			34
FOLFOX or FOLFIRI/Panitumumab　Paff-J (phase II)			5
4) Others	76	28	
NK105 weekly (phase I)			6
AMN107 vs imatinib (phase III)			2
Regorafenib vs BSC (GIST) (phase III)			2
total	2139	568	230

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DEPARTMENT OF GASTROINTESTINAL ONCOLOGY, GASTROINTESTINAL ENDOSCOPY DIVISION

Yutaka Saito, Takahisa Matsuda, Ichiro Oda, Takeshi Nakajima, Shigetaka Yoshinaga, Haruhisa Suzuki, Satoru Nonaka and Taku Sakamoto (National Cancer Center Hospital)
Yasuo Kakugawa, Yosuke Otake and Minori Matsumoto (Screening Technology and Development Division)

Introduction

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

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

Routine Activities

Various diagnostic techniques including chromoendoscopy, magnifying endoscopy and endoscopic ultrasonography (EUS) are used to detect and evaluate early malignant lesions. Capsule endoscopy also has been accepted as being far less invasive. In our facility, small intestine capsule endoscopy has been performed since 2005. In order to obtain more accurate endoscopic diagnosis of gastrointestinal disease, we routinely use the recently developed narrow-band imaging (NBI) system. A total of 10,810, 2,924, 372, 59, 41 and 35 screening and/or diagnostic procedures by gastroscopy, colonoscopy, EUS, EUS-fine needle aspiration (EUS-FNA), endoscopic retrograde cholangiopancreatography (ERCP) and capsule endoscopy, respectively, were performed in 2011.

Due to the increasing number of patients with superficial gastrointestinal neoplasms, the number of therapeutic endoscopy procedures is also increasing in this field. In 2011, 1,914 endoscopic resections were carried out (pharynx 20, esophagus 193, stomach 366 and colon 1,335). Among these, ESD, which was developed for large en-bloc resections with a low-risk of local recurrence, was performed for 61 superficial esophageal cancers, 343 early gastric cancers and 125 superficial colorectal neoplasms. For colorectal ESDs and some esophageal ESDs, the newly developed ball-tip bipolar needle knife (B-knife) and insulation-tipped knife (IT-knife; KD-Y0009) were used together with CO_2 insufflation. These procedures and devices were originally developed by our colleagues.

ESD achieves a higher en-bloc resection rate compared to the standard EMR technique and is less invasive than a surgical operation while EUS-FNA provides a less invasive procedure to improve diagnosis for patients with pancreatic tumors, lymph-node swelling, submucosal tumors of the GI tract, etc. As for emergency endoscopic procedures, 446 endoscopies were performed for gastrointestinal bleeding and other emergencies.

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

Procedure	Number of Procedures Performed in 2011
Upper GI Endoscopy	10,810
Lower GI Endoscopy	2,924
Pharyngeal EMR/ESD	20
Esophageal EMR/ESD	132/61
Gastric EMR/ESD	23/343
Colorectal Polypectomy, EMR	1,210
Colorectal ESD	125
EUS/EUS-FNA/ERCP	372/59/41
Emergency Endoscopy	446
Capsule Endoscopy	35

Research Activities (Figure 1)

Our efforts have been focused on new diagnostic and therapeutic strategies. For more accurate endoscopic diagnosis of gastrointestinal disease, we are utilizing the NBI system that enables us to narrow the spectral transmittance bandwidth of the optical filters used in the light source of electronic

endoscope systems. In addition, we have recently conducted a trial study on an autofluorescence imaging (AFI) system. This system can identify lesions based on differences in tissue fluorescence properties and reveal gastrointestinal neoplasms that are not detectable with conventional endoscopy.

A multicenter randomized controlled trial (RCT) was conducted to compare the polyp detection rate between AFI and white light endoscopy (WLE). This large RCT in a multicenter referral setting did not show any objective advantage of AFI over WLE in terms of an improved adenoma detection rate. The use of NBI in the proximal colon, however, appeared to improve small adenoma detection and reduce the miss rate in our previous multicenter study so the combined use of NBI and AFI will play an important role in future colorectal cancer screening.

Gastric cancer is the second leading cause of cancer death worldwide. In order to improve the survival rate, early diagnosis is one of the optimal strategies, but it has been difficult to differentiate early gastric cancer from other non-neoplastic lesions using conventional WLE. We have conducted a multicenter prospective RCT and concluded that magnifying-NBI improved the diagnostic accuracy for discriminating gastric neoplasms from benign small depressed lesions. We reported this paper at a Plenary Session of the American Society for Gastrointestinal Endoscopy (ASGE) in 2011.

Endoscopic submucosal dissection (ESD) is accepted as a minimally invasive treatment for early gastric cancer although not widely used in the colorectum because of increased technical difficulty. We have conducted a multicenter prospective study at 10 specialized institutions to examine the current status of colorectal ESDs at specialized endoscopic treatment institutions. Our conclusion was that ESD performed by experienced endoscopists is an effective alternative treatment to surgery providing high en-bloc and curative resection rates for large superficial colorectal tumors based on a prospective series of 1,111 cases.

We have also participated in a further multicenter prospective study on endoscopic treatment of large early colorectal neoplasia conducted by the Colorectal Endoscopic Resection Standardization Implementation Working Group of the Japanese Society for Cancer of the Colon and Rectum. Our group enrolled the largest number of cases so we presented the study results in the Plenary Session of the 19th United European Gastroenterology Week (UEGW 2011) in Stockholm, Sweden where we received the Top Abstract Prize. The en-bloc resection rate for ESD was significantly higher than for EMR although complication rates were not significantly different. Despite longer procedure times, ESD is becoming a standard treatment in Japan for treatment of early colorectal neoplasms especially for larger lesions.

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

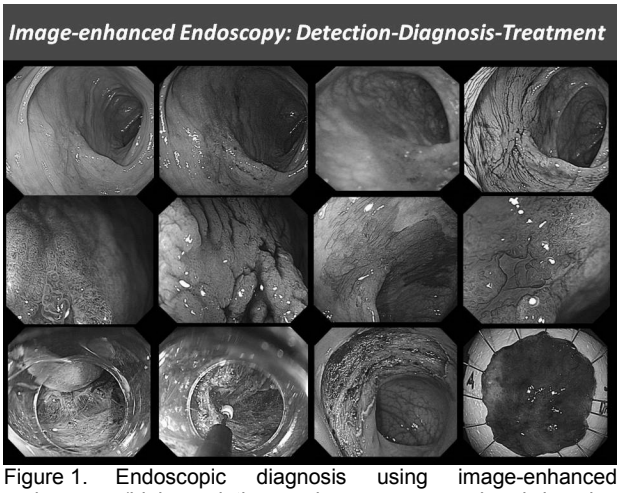

Figure 1. Endoscopic diagnosis using image-enhanced endoscopy (high-resolution endoscopy, narrow-band imaging and autofluorescence imaging) and endoscopic submucosal dissection (ESD) procedure for treating early colon cancer

Clinical Trials

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

A nationwide cancer registry system has been developed for early gastric cancer treated with EMR/ESD. A five-year multicenter prospective cohort study has been ongoing using this cancer

registry system since 2010. Our division has also cooperated as a participating institution in a Phase II trial of endoscopic submucosal dissection to expand the indications for early gastric cancer (JCOG 0607).

RCTs concerning colorectal neoplasms are ongoing as well. The Japan Polyp Study (JPS) was started in February 2003. The JPS is a multicenter RCT designed to evaluate colorectal cancer surveillance strategies in patients who have undergone complete colonoscopies on two occasions with the removal of all detected neoplasia including flat and depressed lesions using a high-resolution colonoscope. At present, 3,926 patients have been enrolled in this study. This multicenter RCT is scheduled to continue until 2012 and analysis of data will help to develop future recommendations for surveillance guidelines in Japan after the excision of polyps including flat and depressed lesions. The final step in the randomization process and complete histopathological assessments are ongoing at the present time.

In late 2009, we initiated an RCT comparing our proposed bowel preparation method for colon capsule endoscopy with the traditional approach. The aim of this trial is to clarify overall cleanliness and determine the anal excretion rate prior to the end of the capsule's battery life using our bowel preparation proposal and a previously reported method.

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

Tomoo Kosuge, Kazuaki Shimada, Minoru Esaki, Satoshi Nara, Youji Kishi, Seiji Oguro

Introduction

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

Routine Activities

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

Operation and perioperative care

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

Conferences

We have several clinical or educational conferences on the treatment of HBP malignancies. At the "Ward Conference", the clinical conditions of the perioperative patients and surgical strategies for preoperative cases are discussed. At the "Cherry Conference", surgeons and radiologists discuss imaging studies of selected patients. An "HBP Case Conference" is held by surgeons and medical oncologists to discuss the clinical course of both surgical and medical patients as well as common issues among HBP malignancies. The "Micro Conference" is a pathological conference on postoperative cases, where surgeons, radiologists, and pathologists participate in the discussion. In the "Journal Club", the latest articles on pancreatic disease are reviewed by surgeons, medical oncologists, radiologists and pathologists.

Surgical strategies for HBP malignancies

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

Pancreatic cancer: The prognosis of patients with invasive ductal carcinoma is poor even with aggressive surgical resection. Multidisciplinary treatments with adjuvant chemotherapy in the form of clinical trials have been used for this potentially noncurative disease. Resection of borderline malignancies, such as pancreatic cystic neoplasms and neuroendocrine tumors (NETS) is performed aggressively, since a favorable prognosis can be expected with surgical resection.

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

Research Activities and Clinical Trials

Dr. Kosuge et al. reported the results of a multicenter controlled trial to evaluate the effect of adjuvant gemcitabine administration after curative resection in cases of pancreatic cancer (JSAP-02, Ueno, Kosuge et al. Br J Cancer 2009). They are now conducting a randomized phase III study of adjuvant chemotherapy with combination therapy of gemcitabine and S-1 vs. gemcitabine alone in patients with resected pancreatic cancer (JSAP-04).

Dr. Shimada et al. are conducting 3 prospective randomized trials to evaluate the efficacy of surgical devices in HBP surgery: 1) Safety of stapler vs. non-stapler closure of the pancreatic remnant after distal pancreatectomy: a multicenter randomized controlled trial (SNS-RCT); 2) The impact of the use of an energy device during parenchyma transection of the liver: a multicenter randomized controlled trial (EPL-RCT); and 3) The

Table 1. Number of patients

	n
Invasive pancreatic cancer	71
Other pancreatic neoplasms	27
Hepatocellular carcinoma	35
Hepatic metastases	54
Intrahepatic cholangiocarcinoma	19
Bile duct cancer	29
Gallbladder cancer	12
Duodenal cancer	6
Others	46
Total	299

Table 2. Operative procedures

	n
Hepatectomy without biliary resection	105
Hepatectomy with biliary resection	25
Right hemihepatectomy and pancreaticoduodenectomy (HPD)	2
Classical Whipple (CW)	10
Pylorus-preserving pancreaticoduodenectomy (PPPD)	59
Distal pancreatectomy	34
Appleby operation	2
Medial pancreatectomy	6
Total pancreatectomy	3
Extended cholecystectomy	8
Other resections	20
No resection	25
Total	299

Table 3. Long-term survivals

Invasive ductal carcinoma (2000-2008)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	9	62	62
II	8	71	71
III	109	51	40
IVa	172	33	17
IVb	73	25	18
Total	371	38	26

Hepatocellular carcinoma (2000-2008)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	33	87	75
II	144	89	81
III	195	67	54
IV	72	61	44
Total	444	73	59

effect of stapled vs. hand-sewn duodenal reconstruction on delayed gastric emptying during pancreaticoduodenectomy: a dual-center randomized controlled trial (SH-RCT). Dr. Nara et al. are now carrying out a study to evaluate the feasibility of laparoscopic hepatectomy in our environment. These studies are supported by Grants-in-Aid for scientific research from the Ministry of Health, Labour and Welfare of Japan and the National Cancer Center Research and Development Fund.

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

Takuji Okusaka, Hideki Ueno, Chigusa Morizane, Shunsuke Kondo

Introduction

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

Routine Activities

The division consists of four staff oncologists and three to four residents. In 1990, the division began using percutaneous ethanol injection (PEI) to treat patients with small HCCs. In 1999, radiofrequency ablation therapy (RFA) was introduced clinically as an alternative to PEI. Based on long-term observations of PEI-treated patients, we have used percutaneous ablation therapy as a valuable alternative to surgery for most patients with 3 or fewer HCC nodules, all of which are smaller than 3 cm in diameter. We also perform transcatheter arterial chemoembolization (TACE), mainly in patients with multiple HCC nodules. In patients with unresectable pancreatic cancer or biliary tract cancer, chemotherapy is performed in clinical practice or as a clinical trial to develop active treatment. Patients with locally advanced pancreatic cancer may receive chemoradiotherapy, which has shown some clinical benefits for symptom control and survival.

Most patients with hepatobiliary and pancreatic tumors, whether they undergo surgical or nonsurgical treatment, are hospitalized in the Hepatobiliary and Pancreatic Ward. Case conferences are held weekly with surgeons and radiologists to determine treatment strategies for these patients. Rounds and conferences for patients admitted to the division are made by all staff oncologists and residents every morning and evening.

Research Activities

We conducted a multicenter phase II trial in patients with HCC to evaluate the efficacy and safety of SM-11355, using a Zinostatin stimalamer suspension in iodized oil as a reference (Okusaka et al.). Patients with unresectable HCC were randomized 2:1 to receive administration of the SM-11355 or Zinostatin stimalamer suspension into the hepatic artery. Efficacy was evaluated with CT and the therapeutic effect (TE) was categorized as grades V to I, where TE V was defined as disappearance or 100% necrosis of all treated tumors. The TE V rates were 26.5% (22/83) and 17.9% (7/39) in the SM-11355 and Zinostatin stimalamer groups, respectively. The adverse effects with the largest difference between the two groups were hepatic vascular injury (0 vs. 48.4%) and eosinophilia (84.3 vs. 41.0%). The 2-year and 3-year survival rates were 75.9% vs. 70.3% and 58.4% vs. 48.7%, respectively. The results suggest that SM-11355 in iodized oil has similar efficacy to Zinostatin stimalamer and that repeated dosing of SM-11355 is possible without hepatic vascular injury in cases of relapse.

We conducted a phase I/II trial of fixed dose rate infusion of gemcitabine (FDR-Gem) and S-1 (FGS) in patients with Gem-refractory pancreatic cancer (Morizane et al.). The patients received FDR-Gem on day 1 and S-1 orally twice daily on days 1-7. Cycles were repeated every 14 days. Patients were scheduled to receive Gem (mg/m^2/week) and S-1 (mg/m^2/day) at four dose levels in the phase I: 800/80 (level 1), 1,000/80 (level 2), 1,200/80 (level 3) and 1,200/100 (level 4). Forty patients were enrolled in the phase II study at the recommended dose, which was level 3. In the phase II trial, a partial response was confirmed in seven patients (18%). The median overall survival time and median progression-free survival time were 7.0 and 2.8 months, respectively. The common adverse effects were anorexia, leukocytopenia and neutropenia. This combination regimen of FGS is active and well tolerated in patients with Gem-refractory pancreatic cancer.

A multicenter phase II study was conducted to assess the efficacy and toxicity of Gem and S-1 combination therapy for metastatic pancreatic cancer (Ueno et al.). Chemotherapy-naïve patients

with histologically or cytologically proven metastatic pancreatic adenocarcinoma were eligible for this study. A total of 55 patients were included and the efficacy and toxicity were analyzed in 54 patients who received at least one dose of gemcitabine and S-1 combination therapy. Although no complete response was seen, a partial response was achieved in 24 patients, resulting in an overall response rate of 44.4%. The median progression-free survival was 5.9 months and the median overall survival was 10.1 months with a 1-year survival rate of 33.0%. The major Grade 3-4 toxicities were neutropenia (80%), leukopenia (59%), thrombocytopenia (22%), anorexia (17%) and rash (7%). Hematological toxicity was mostly transient and there was only one episode of febrile neutropenia ≥Grade 3. Gem and S-1 combination therapy produced a high response rate with good survival in patients with metastatic pancreatic cancer.

Clinical Trials

Twenty-six clinical trials are ongoing, including eight phase III trials, such as adjuvant chemotherapy versus placebo in HCC patients who had undergone hepatic resection or local ablation therapy, chemotherapy with new agents versus standard chemotherapy in unresectable HCC patients, and chemotherapy with new agents versus standard chemotherapy in advanced pancreatic cancer patients. Two studies are collaboration trials with the Department of Diagnostic Radiology, and one with the Department of Radiation Oncology. Two trials are being conducted to evaluate cancer immunotherapy.

Our studies are supported by Gan-kenkyu-kaihatsuhi (Grant No. 23-A-22, No. 23-A-2 Toku 2, No. 23-A-14, No. 23-A-22, No. 23-A-30, No. 23-A-37, No. 23-A-38), Health and Labour Sciences Research Grants, Clinical Cancer Research (Grant No. H22-ganrinsho-ippan-013,
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Table 1. Number of patients according to primary tumor site

	No. of pts
Pancreatic cancer	
Invasive ductal	147
Neuroendocrine	16
Others	6
Biliary tract cancer	
Extrahepatic bile duct	7
Gallbladder	29
Papilla of Vater	10
Liver cancer	
Hepatocellular	242
Intrahepatic cholangio	40

Table 2. Number of patients according to type of procedure

	No. of pts
Pancreatic cancer	
Systemic chemotherapy	103
Chemoradiotherapy	5
Biliary tract cancer and Intrahepatic cholangio carcinoma	
Systemic chemotherapy	45
Hepatocellular carcinoma	
Ethanol injection	13
Radiofrequency ablation	41
Transcatheter arterial (chemo)embolization	139
Intra-arterial chemotherapy	43
Systemic chemotherapy	42
Radiotherapy	9

Table 3. Survival

	MST (month)	Survival rate (%)
Pancreatic cancer		
Advanced	10.2	1-yr: 42.4
Biliary tract cancer and Intrahepatic cholangiocarcinoma		
Advanced	11.6	1-yr: 47.7
Hepatocellular carcinoma		
Radiofrequency ablation	NA	5-yr: 63.9
Transcatheter arterial (chemo)embolization	42.2	3-yr: 56.6
Systemic chemotherapy	8.5	1-yr: 40.9

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3. Okusaka T, Ueno H, Ikeda M, Morizane C. Phase I and pharmacokinetic clinical trial of oral administration of the acyclic retinoid NIK-333. Hepatol Res, 41:542-552, 2011

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9. Furuse J, Okusaka T. Review: Targeted therapy for biliary tract cancer. Cancers, 3:2243-2254, 2011

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DEPARTMENT OF UROLOGY

Hiroyuki Fujimoto, Tohru Nakagawa, Motokiyo Komiyama, Hiroyuki Nakanishi

Introduction

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

Routine Activities

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

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

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

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

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

(4) Testicular germ cell tumor (GCT). Stage I: careful observation regardless of any pathological element. Stage II or higher: EP (etoposide + CDDP) or BEP (BLM + etoposide + CDDP) chemotherapy as the 1st line. In nonseminomatous cases, salvage operation after induction chemotherapy. In seminoma cases, careful observation rather than surgery is selected.

Research Activities

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

1. Renal cell carcinoma: Improvement of the treatment outcome in metastatic renal cell carcinoma remains a major problem. Phase II and III studies using a VEGFR inhibitor (AG-013766) are also in progress.
2. Urothelial cancer: The effectiveness of a phase III study to confirm the efficacy of neoadjuvant M-VAC therapy for T2-3N0M0 bladder cancer (JCOG0209) is under review. For metastatic disease, a phase II study using a peptide vaccine (S288310) is in progress and a weekly CBDCA + PTX regimen has been indicated.
3. Prostate cancer: To identify the most effective treatment for the recurrence of PSA failure after radical prostatectomy, a phase III study to evaluate the efficacy of salvage irradiation vs hormone ablation for postoperative PSA failure in T1c-T2 prostate cancer (JCOG0401) is under review. A new operative method to achieve a complete surgical margin (extended radical prostatectomy) has been developed, and its efficacy in patients with specimen-confined disease has been evaluated without neoadjuvant endocrine therapy. To provide a more precise preoperative diagnosis, a new imaging strategy using 3.0 Tesla MRI has been developed. In local advanced disease, a phase III study to evaluate the survival benefit of continuous endocrine therapy after 3D conformal radiotherapy is still underway. For hormone-refractory prostate cancer, a study on a new hormonal regime with MDV3100 has completed enrollment.

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

Clinical Trials

We are actively involved in the following ongoing protocol studies;

1. Phase II & III studies: AG-013766 for metastatic renal cell carcinoma
2. A phase II study: S288310 peptide vaccine and weekly CBDCA+PTX for M-VAC-refractory metastatic urothelial cancer
3. A phase III study: Salvage radiation vs hormone ablation for postoperative PSA failure in T1c-T2 prostate cancer (JCOG0401)
4. A phase II study:MDV3100 for hormone-refractory prostate cancer
5. A phase II study: TIP for CDDP-refractory metastatic germ cell tumor.

Published Papers

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2. Fujimoto H, Nakanishi H, Miki T, Kubota Y, Takahashi S, Suzuki K, Kanayama H, Mikami K, Homma Y. Oncological outcomes of the prostate cancer patients registered in 2004: report from the Cancer Registration Committee of the JUA. Int J Urol, 18:876-881, 2011

Table1. Patients statistics: Major treatment

	2008	2009	2010	2011
Radical/partial nephrectomy	28	43	35	30
Nephroureterectomy	11	16	15	12
Total cystectomy	22	26	31	24
TURBT	161	163	130	140
M-VAC	31	42	62	50
GC		50	71	84
Radical prostatectomy	105	111	98	111
Prostatic biopsy	186	247	168	175
High orchiectomy	7	6	12	8
Retroperitoneal lymphadenectomy	10	7	8	13
Chemotherapy for testicular cancer	10	9	14	30
Retroperitoneal tumor resection	9	9	15	10

DEPARTMENT OF GYNECOLOGY

Takahiro Kasamatsu, Tomoyasu Kato, Takashi Onda, Shun-ichi Ikeda, Mitsuya Ishikawa, Shinich Togami

Introduction

The Gynecologic Oncology Division deals with tumors originating from the female genital and reproductive organs. Surgery is the main treatment modality for most gynecologic cancers, but multidisciplinary treatments consisting of radiotherapy and chemotherapy are routinely considered in close cooperation with therapeutic radiation oncologists and medical oncologists. The incidences of three common gynecologic cancers, *i.e.*, cervical, endometrial and ovarian cancer, are now on the rise in Japan. In our institution, the numbers of patients with endometrial and ovarian cancer have increased about 4-fold over the past 30 years. The number of patients with invasive carcinoma of the cervix had decreased by half during the same period, but this trend has reversed since the late 1990s. Consequently, invasive cervical cancer is still the most common gynecologic cancer in Japan.

Routine Activities

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

1) Treatment strategy for uterine cervical cancer. Either conization or simple total hysterectomy is the treatment of choice for persistent high-grade dysplasia, Stage 0 or Ia1 cervical cancer. Patients with stages Ia2 to IIIa usually undergo radical hysterectomy and pelvic lymphadenectomy. Postoperative total pelvic irradiation following radical hysterectomy is only considered for patients with metastasis to the pelvic nodes or parametrial tissue as confirmed by pathological examination. Radiotherapy alone or concurrent chemo-radiotherapy is given to patients at any stage. Chemotherapy is occasionally used for the treatment of distant metastasis.
2) Treatment strategy for endometrial cancer. The primary treatment choice is hysterectomy with bilateral salpingo-oophorectomy. Pelvic lymph node dissection is also performed for patients with a high risk of metastasis. Para-aortic node dissection is limited to those with biopsy-proven nodal metastasis. In our practice, positive peritoneal cytology is not a poor prognostic factor for patients with a well-differentiated tumor confined to the uterus, whereas postoperative chemotherapy is performed for patients with extra-uterine disease.
3) Treatment strategy for ovarian cancer. A simple total hysterectomy, bilateral salpingo-oophorectomy and omentectomy with or without combined resection of the involved intestine are the standard procedures for the treatment of ovarian cancer. When an intraperitoneal tumor can be optimally debulked and node metastasis is confirmed by pathologic sampling during the operation, combined pelvic and para-aortic lymph node dissection is indicated. For patients with advanced-stage cancer, surgery is followed by combination chemotherapy containing Carboplatin and Paclitaxel. Patients with more advanced stage III and IV disease, who are unlikely to be optimally debulked, are treated with primary chemotherapy. After several courses of chemotherapy, an interval debulking surgery is usually performed for these patients. Surgery alone can offer the chance of cure for patients with recurrence, but only when the disease is completely resectable. The type of surgical procedure, operative morbidity, and survival rates are shown in Tables 1, 2, and 3.

Research Activities

To assess the safety and efficacy of a splenectomy and to analyze the prognostic factors of Müllerian carcinoma with spleen metastasis, Uehara and Onda et al (1). reviewed the medical records of patients with Müllerian carcinoma who underwent a splenectomy between 1997 and 2007 at NCCH. It was concluded that a splenectomy can be performed safely and effectively during debulking surgery for appropriately selected patients with

Table 1. Type of procedure

Procedure	No. of Patients
Radical hysterectomy	28
Simple hysterectomy	164
± Salpingo-oophorectomy	
± Lymphadenectomy	
± Omentectomy	
± Lymphadenectomy	
Radical vulvectomy	3
Conization	11
Others	18
Total	224

Table 2. Operative morbidity and mortality

Item	Value (as % of total patients)
Major complications[a]	2.2%
Minor complications[b]	5.8%
Operative death within 30 days	0
Postoperative hospital death	0

[a] Lymph cystitis requiring drainage, ureterovaginal fistula.
[b] Infection, hemorrhage, bladder atony requiring medication.

Table 3. Survival

FIGO	Cervical cancer[a]		Endometrial cancer[a]		Ovarian cancer[b]	
Stage	No. of patients	5-yr survival	No. of patients	5-yr survival	No. of patients	5-yr survival
I	425	87%	372	91%	80	86%
II	139	74%	62	86%	20	81%
III	120	58%	143	69%	131	32%
IV	46	36%	28	26%	73	16%
Totals	730		605		304	

[a]1993-2002
[b]1990-1999

primary or recurrent Müllerian carcinoma. Onda et al (2). reviewed the outcomes of neoadjuvant chemotherapy (NAC) for advanced ovarian cancer, and demonstrated that NAC followed by surgical cytoreduction is an acceptable management strategy for patients with advanced ovarian cancer.

Clinical Trials

A phase III study to compare treatment starting with neoadjuvant chemotherapy and primary cytoreductive surgery followed by postsurgical chemotherapy (JCOG 0602) for advanced ovarian cancer was completed. A phase II study on irinotecan and etoposide for patients with platinum-resistant taxan-pretreated ovarian cancer (JCOG 0503) is now ongoing. A phase I/II study on Heavy Ion Radiotherapy with concurrent chemotherapy for locally advanced cervical adenocarcinoma using the Heavy Ion Medical Accelerator is ongoing in Chiba (HIMAC, National Institute of Radiological Sciences).

Published Papers

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6. Toita T, Ohno T, Kaneyasu Y, Kato T, Uno T, Hatano K, Norihisa Y, Kasamatsu T, Kodaira T, Yoshimura R, Ishikura S, Hiraoka M. A consensus-based guideline defining clinical target volume for primary disease in external beam radiotherapy for intact uterine cervical cancer. Jpn J Clin Oncol, 41:1119-1126, 2011

DEPARTMENT OF ORTHOPEDIC SURGERY

Hirokazu Chuman, Yasuo Beppu, Akira Kawai, Fumihiko Nakatani, Tomoya Matsunobu, Naofumi Asano, Kunihiko Numoto, Shusa Oshika, Shoji Nagano

Introduction

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

Clinical Practices

The orthopedic surgery division of the NCCH consists of four staff doctors (Drs. Hirokazu Chuman, Yasuo Beppu, Akira Kawai, Fumihiko Nakatani, and Umio Yamaguchi) and five residents. Occasionally, several fellows from Japan and overseas join our group. Outpatient consults are held every weekday. About 30 patients are constantly hospitalized to undergo operation, chemotherapy or radiation therapy. Five or six major operations are routinely performed every week. In 2011, 304 operations were performed under general anesthesia, including palliative operations for pathological fractures or spinal cord compression from metastatic bone and soft tissue tumors. Sarcomas in the trunk, including the thoracic wall, retroperitoneal space and head and neck lesions were excised in cooperation with thoracic, general or head-neck surgeons, respectively. A total of 28 reconstructive operations was conducted in collaboration with plastic surgeons to achieve adequate soft tissue coverage after the resection of malignant tumors of the trunk or limb-salvage operations for sarcomas of the extremities. As a result, almost 90% of the operations were performed with a limb-sparing approach. With regard to the patients' postoperative course, we have been collaborating with a physical therapist to rehabilitate the musculoskeletal system in cancer- bearing-patients.

As for chemotherapy, we have been conducting neoadjuvant and adjuvant chemotherapy for high-grade bone and soft tissue tumors, palliative chemotherapy for metastatic bone and soft tissue sarcomas, occasionally in collaboration with a medical oncologist. Chemotherapy of children and adolescents with sarcomas is conducted by a pediatric oncologist.

Conferences

Every morning at 8:00 A.M., all staff doctors and residents meet for the morning conference and make rounds of hospitalized patients in the 13B and 12A ward. A weekly clinical conference is held every Monday morning and Tuesdays from 8:00 to 9:00 to discuss the diagnosis, operative procedure, pre-postoperative rehabilitation program, and chemotherapy regimen of each patient.

Research Activities

Since 2004, we have been collaborating with the Research Institute of the National Cancer Center to develop novel molecular target therapies or tailor-made treatments for sarcoma patients. With a genome-wide microarray system or a protein-wide two dimensional fluorescence difference gel electrophoresis (2D-DIGE) system, we have been analyzing the complete expression levels of mRNA and protein in the tumor samples from patients with Ewing's family tumors, osteosarcomas and sarcomas of soft tissues. Combined with each patient's clinical information, we have been establishing novel biomarkers for prediction of

Table 1. Numbers treated in our division from 2009 -2011

Year	Benign STT	Malignant STT	Benign BT	Malignant BT	Total
2009	48	142	28	65	283
2010	86	146	44	44	320
2011	57	156	41	69	323

STT, soft tissue tumor; BT, bone tumor

[Statistics]

	Soft tissue sarcoma	Bone Sarcoma	Benign Bone Tumor	Spine or Bone metastasis	biopsy or others	Total
Surgeries performed	95	39	41	21	106	302

	Soft tissue sarcoma	Bone sarcoma	Benign Bone Tumor	Bone metastasis	Total
New patients	116	32	39	24	211

patients' prognoses or effects of the chemotherapeutic agents. Using the same method, we also have been searching for new genes or proteins for the molecular-targeted treatment approach.

Clinical Trials

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

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

1. A multi-institutional phase clinical trial of multidrugs adjuvant chemotherapy for osteosarcomas (JCOG 0905) since 2010.
2. A multi-institutional phase study of ridaforlims (an mTOR inhibitor) for controlled sarcomas since 2009.
3. A multi-institutional phase study of Eribulin for uncontrolled sarcoma since 2010.

Published Papers

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DEPARTMENT OF DERMATOLOGIC ONCOLOGY

Naoya Yamazaki, Arata Tsutsumida, Ken-jiro Namikawa, Ryota Tanaka, Junji Kato, Wataru Omata

Introduction

The Department of Dermatologic Oncology has consistently served as the core hospital for the establishment of treatment strategies for malignant skin tumors since the National Cancer Center opened in 1962, and over 1500 cases of malignant melanoma have been accumulated thus far; an impressive number for a hospital or research institution in Japan. Today, patients are referred from throughout Japan. Most of the patients are examined and treated for skin cancer including malignant melanoma. Surgery is the main treatment modality for skin cancer, and multi-disciplinary treatments, consisting of chemotherapy, immunotherapy, and radiotherapy, are also routinely carried out. In addition, this department plays an active role in multicenter trials for skin cancer all over Japan.

Routine Activities

The department has three staff dermatologic oncologists and three residents. We are also engaged in routine outpatient activities on Wednesdays and Thursdays in the National Cancer Center East.

In 2011, a total of 290 patients were examined for the first time in the dermatology department for a malignant skin tumor. The numbers of patients with malignant melanoma (132) and extramammary Paget's disease (22) were particularly large, and were approximately 5 times and 2 times, respectively, the numbers of 15 years ago. There were also 9 cases of the rare cancer, angiosarcoma.

Rounds are made and case presentations are held every morning. A division conference is held every Monday to discuss the therapeutic principles for outpatients and inpatients. A clinicopathological conference that focuses on surgically removed skin specimens is held with pathologists once a month.

Research Activities

Malignant melanoma

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

It is extremely important to detect early malignant melanoma lesions accurately and the Department of Dermatologic Oncology adopts dermoscopy for a differential diagnosis. Dermoscopy is very useful for examination of the sole, which is the most frequent site of malignant melanoma in Japanese subjects, since early melanoma frequently shows a parallel ridge pattern, while a parallel furrow, a lattice-like or a fibrillar/filamentous pattern is typical of a pigmented nevus. Based on these findings, our study group proposed a algorithm for the management of acquired acral melanocytic lesions.

We have taken part in a Japanese multicenter joint study on sentinel lymph node (SLN) biopsy. At the Department of Dermatologic Oncology, SLN biopsies for malignant melanoma were performed with the injection of technetium tin colloid, blue dye plus fluorescence method (combination of indocyanine green and the Photodynamic Eye System) in 95 cases. The addition of a real-time fluorescence navigation system with indocyanine green as a new technique achieved a detection rate of 100%. Of all the patients in whom SLN was identified and biopsied, about 35% had metastasis.

We have conducted the DERMA study, the first global study for melanoma patients in Japan. The study investigational product is an Antigen-Specific Cancer Immunotherapeutic agent comprising the recombinant protein MAGE (Melanoma Antigen)-A3. We had a great difficulty in finding candidate patients as the subjects had to be stage IIIb and IIIc cutanous melanoma patients with macroscopic lymph node involvement. Moreover we took part in the study only after a 2-year delay. However, the number of recruited patients is 7 in Japan, a number which is highly regarded in the world. We will continue to follow-up 4 patients recruited in our department for regulatory approval.

Extramammary Paget's disease

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

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

Clinical Trials

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

(1) Sentinel lymph node detection in malignant melanoma patients using real-time fluorescence navigation with indocyanine green.
(2) Development and translational research of a peptide vaccine for advanced malignant melanoma.
(3) Serum 5-S-cysteinyldopa and melanoma inhibitory activity levels are periodically measured as tumor markers of malignant melanoma. We are studying their correlation with patient pathophysiological conditions.

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

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

Published Papers

1. Iizuka A, Komiyama M, Tai S, Oshita C, Kurusu A, Kume A, Ozawa K, Nakamura Y, Ashizawa T, Yamamoto A, Yamazaki N, Yoshikawa S, Kiyohara Y, Yamaguchi K, Akiyama Y. Identification of cytomegalovirus (CMV)pp65 antigen-specific human monoclonal antibodies using single B cell-based antibody gene cloning from melanoma patients. Immunol Lett, 135:64-73, 2011
2. Noro S, Yamazaki N, Nakanishi Y, Yamamoto A, Sasajima Y, Kawana S. Clinicopathological significance of sentinel node biopsy in Japanese patients with cutaneous malignant melanoma. J Dermatol, 38:76-83, 2011
3. Namikawa K, Yamazaki N. Sentinel lymph node biopsy guided by indocyanine green fluorescence for cutaneous melanoma. Eur J Dermatol, 21:184-190, 2011

Table 1. Number of New Patients

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Malignant melanoma	67	68	74	97	94	79	92	75	94	88	132
Squamous cell carcinoma	27	19	24	31	36	25	25	28	36	52	27
Basal cell carcinoma	40	29	31	47	33	23	25	33	31	28	28
Sweat gland carcinoma	3	10	7	8	10	17	6	10	10	9	9
Trichilemmal carcinoma	0	1	2	0	0	1	7	0	1	0	0
Paget's disease	10	16	13	12	18	16	19	20	21	19	22
Bowen's disease	16	8	7	12	9	8	4	2	10	3	9
Dermatofibrosarcoma protuberans	2	2	3	5	3	7	3	5	10	10	10
Angiosarcoma	7	5	3	3	5	9	6	12	9	9	9
Malignant fibrous histiocytoma	0	0	1	1	1	0	1	1	3	3	1
Epithelioid sarcoma	1	1	0	0	2	1	0	1	0	0	0
Malignant lymphoma	3	10	12	12	15	7	6	15	13	16	16
Merkel cell carcinoma	-	-	-	-	2	3	2	4	3	3	8
others	2	5	5	4	5	12	11	8	7	17	19
Total	178	175	182	232	233	208	207	214	248	257	290

Table 2. Operative Procedures (total number)

Wide local excision	125
Local excision	75
Sentinel node biopsy	36
Lymph node biopsy	12
Lymph node dissection	35
(neck)	5
(axilla)	10
(inguinal)	11
(groin)	8
(popliteal)	0
(epitrochlear)	1
Skin graft	29
Local flap	9
Free flap	5
Amputation	9
others (biopsy/debridement)	3

Table 3. New Agent Studies in 2010

Agent	Eligible Cancer Type	Trial Phase
ONO-4538	Melanoma	II
MAGE-A3	Melanoma	III
BCX1777	T/NK-Cell Lymphoma	I
E7777	Peripheral/Cutaneous T Cell Lymphoma	I
Lenalidomide	ATL, Peripheral T Cell Lymphoma	I
KW0761	T/NK-Cell Lymphoma	II
RO5126766	Solid Tumors	I
RO4987655	Solid Tumors	I
WT4869	Solid Tumors	I
IMC-11F8	Solid Tumors	I
Romidepsin	Peripheral/Cutaneous T Cell Lymphoma	I/II
PF-00299804	Lung Cancer	III

Table 4. Survival rates

	Stage	2002-2007 Number of Patients	5-year Overall Survival Rates
Malignant Melanoma	Stage IA	25	100
	Stage IB	41	100
	Stage IIA	21	85
	Stage IIB	11	65
	Stage IIC	11	76
	Stage IIIA	26	61
	Stage IIIB	29	49
	Stage IIIC	25	60
Squamous Cell Carcinoma	Stage I	39	100
	Stage II	30	96
	Stage III	21	53

DEPARTMENT OF HEMATOLOGY, AND HEMATOPOIETIC STEM CELL TRANSPLANTATION, HEMATOLOGY DIVISION

Kensei Tobinai, Yukio Kobayashi, Takashi Watanabe, Sung-Won Kim, Dai Maruyama, Noriyuki Morikawa, Suguru Fukuhara

Introduction

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

Routine Activities

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

In addition to patient care in the ward, our daily activities include management of hematology clinics and a diagnostic laboratory to perform bone marrow microscopic examination, and flowcytometric and molecular-genetic analyses. Five staff physicians, two chief residents, and one to three rotating residents are involved in these activities.

Research Activities

In addition to immunophenotypic analyses, molecular diagnosis is routinely performed, using polymerase chain reaction and fluorescence in-situ hybridization for the detection of t(8;14), t(14;18), t(11;18), t(9;22), t(8;21), t(15;17), and so on. Our recent research has focused on indolent B-cell non-Hodgkin lymphoma (B-NHL). Clinical as well as molecular and cytogenetic analysis of ocular adnexal mucosa-associated lymphoid tissue lymphoma cases led to the discovery of a new tumor suppressor gene deleted at 6q23; we identified the A20 gene as a tumor suppressor gene in various B-cell malignancies (Nature 2009;459:712-6). We are extending the study to determine the spectrum with the mutated A20 gene. We have studied the mechanism of toxicities of bortezomib (Br J Cancer 2010;103:1580-7).

In 2011, we published 20 original articles, and have contributed to the refinement of some subcategories of peripheral T-cell lymphoma (Blood 2011;117:3402-8 / Blood 2011;118:148-55).

Clinical Trials

In 2011, we participated in 39 new-agent studies including 10 international studies, and 7

Table 1. The number of patients with newly diagnosed hematologic malignancies who were managed in the Hematology Division

Disease	Year												
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Acute myelocytic leukemia (AML)	12	18	10	8	8	9	8	9	10	6	10	8	13
Acute lymphocytic leukemia (ALL)	6	3	8	3	2	1	2	4	9	8	2	2	1
Chronic myelocytic leukemia (CML)	15	9	24	11	7	5	6	10	11	3	3	2	2
Myelodysplastic syndrome (MDS)	9	9	8	5	6	5	3	3	9	8	20	9	3
Hodgkin lymphoma (HL)	10	10	14	15	16	9	13	21	11	12	7	11	16
Non-Hodgkin lymphoma (NHL)	133	204	215	268	291	299	278	265	210	208	151	185	243
Adult T-cell leukemia-lymphoma (ATL)	3	4	5	4	5	4	6	6	4	5	5	3	6
Chronic lymphocytic leukemia (CLL)	1	2	3	3	2	4	5	4	5	6	4	2	1
Multiple myeloma (MM)	7	7	8	6	9	19	14	9	8	10	12	9	10
Waldenström macroglobulinemia (WM)	3	1	1	1	1	1	0	0	2	3	1	2	2
Total	199	267	295	324	347	356	335	331	279	269	215	233	297

cooperative group studies (Tables 2 and 3). Almost all the new agents that are developed against hematological malignancies in Japan have been evaluated in our Division, and many of them have been approved by the Japanese Ministry of Health, Labour and Welfare (MHLW).

Bendamustine was recently approved by the MHLW, based on its high efficacy for relapsed indolent B-NHL and mantle cell lymphoma in our phase I and II trials (Cancer Sci 2010;101:2054-8 / Cancer Sci 2010;101:2059-64). The agent is now being applied to treat diffuse large B-cell lymphoma and multiple myeloma.

For myelodysplastic syndrome, a phase II study of a hypomethylating agent, azacitidine, was completed, leading to its approval by the MHLW (Cancer Sci 2011;102:1680-6). This year, a phase I study of oligopeptide vaccine against WT1 protein was initiated against acute myelocytic leukemia in complete remission. This is the first vaccine study against hematological malignancies aimed at approval in Japan.

For ATL, based on our published results of a phase III study, JCOG9801 (J Clin Oncol 2007;25:5458-64) and phase I and II studies of KW-0761, a humanized anti-CCR4 (CC chemokine receptor 4) antibody (J Clin Oncol 2010;28:1591-8), we completed patient enrolment to a randomized phase II study comparing an intensified regimen (mLSG15) with or without KW-0761. Based on the encouraging results of a pivotal phase II study against relapsed ATL (J Clin Oncol, in press), KW-0761 will soon be approved by the MHLW.

We have published the results of a phase II/III study to evaluate the dose-dense schedule of rituximab plus CHOP (R-CHOP) chemotherapy for untreated indolent B-NHL (JCOG 0203) (J Clin Oncol 2011;29:3990-8). Although the dose-dense R-CHOP-14 arm did not show superior progression-free survival to the standard R-CHOP-21 arm, the survival data are outstanding. JCOG 0203 has provided important evidence in the treatment of indolent B-NHL for the oncology society (J Clin Oncol 2011;29:3954-6).

Currently, a phase III trial for newly diagnosed diffuse large B-cell lymphoma (JCOG 0601) is

Table 2. Clinical trials for new agent development

Disease	Agents	Phase	Enrolled Patients in 2011	Enrolled Patients in Total
CML	Nilotinib	III	0	1
	Bostinib	I/II	0	2
MDS	Azacitidine	I/II	0	8
	Decitabine	I/II	0	7
AML	WT1 vaccine	I	1	1
MM	MP + Bortezomib	I/II	0	7
	Vorinostat + Bortezomib	I	0	2
	Bendamustine + PSL	II	0	1
	Carfilzomib	I	1	1
	Siltuximab	I	1	1
PTCL	Forodesine	I	0	2
	KW-0761 (ATL)	II	1	2
	KW-0761 (T/NK)	II	1	2
	Lenalidomide	I	1	2
	Romidepsin	I/II	0	0
	E7777	I	0	0
	Darinaparsin	I	0	0
CLL	Alemtuzumab	I	0	1
	Ofatumumab	I/II	0	1
FL	GA101	III	0	0
	CMC-544	III	3	3
	CMC-544 + R-CVP	I	3	8
	Rituximab	II	0	10
	Everolimus	I	0	4
	BM-ca	I	4	4
	Ofatumumab vs. Rituximab	III	10	10
Indolent B-NHL	Vorinostat	II	0	3
MCL	R + Bendamustine	II	0	0
	VcR-CAP	III	0	2
DLBCL	Enzastaurin	III	0	7
	Bendamustine + R	II	1	3
	Ofatumumab	III	0	0
	Everolimus	III	0	1
	CMC-544	III	3	3
CD30+ lymphoma	SGN-35	I	1	1
ML	Vorinostat	I	0	10
AML, ML, MM	OPB-51602	I	1	1

PTCL, peripheral T-cell lymphoma; FL, follicular lymphoma; B-NHL, B-cell non-Hodgkin's lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; ML, malignant lymphoma; MP, melphalan, prednisolone; PSL, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, PSL; R, rituximab; VcR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, PSL

ongoing, in which a dose-intense schedule of rituximab in R-CHOP is being compared with that of a standard 3-week R-CHOP regimen. We are also conducting a phase II study of a rituximab-incorporating dose-intensified chemotherapy for untreated mantle cell lymphoma (JCOG 0406).

To develop new effective treatments for B-cell malignancies, we have investigated an anti-CD22 chemoimmunoconjugate (Cancer Sci 2010;101:1840-5), as well as new generation anti-CD20 antibodies (Cancer Sci 2011;102:432-8). Recently we initiated several new agent studies for T-cell malignancies, including forodesine, lenalidomide, romidepsin, darinaparsin, pralatrexate and denileukin difititox. Our continuous efforts will contribute to the further improvement of therapeutic outcomes of patients with hematologic malignancies, world-wide.

Table 3. Cooperative group studies

Disease / Protocol	Phase	Year	No. of pts (a)	%CR (b)	OS (b)
AML					
JALSG-AML 95	III	(96-97)	6	81%	40% (4-yr)
JALSG-AML 97	III	(98-01)	15	79%	47% (5-yr)
JALSG-AML 201	III	(02-06)	13	78%	57%(5-yr)
JALSG-APL 97	III	(98-02)	2	95%	86% (4-yr)
JALSG-APL 204	III	(04-11)	2	NA	NA
Therapy-related leukemia	II	(96-99)	16	75%	40% (3-yr)
ALL/Lymphoblastic lymphoma					
JCOG 9004	II	(91-94)	14	83%	31% (7-yr)
JCOG 9402	II	(94-99)	10	81%	29% (5-yr)
JALSG-ALL 97	II	(98-01)	8	74%	32% (5-yr)
JALSG-ALL 202	II	(03-10)	9	NA	NA
CML					
JALSG-CML 207	III	(08-10)	1	NA	NA
Hodgkin lymphoma					
JCOG 9305	II	(93-97)	7	79%	89% (5-yr)
JCOG 9705	II	(98-00)	6	70%	81% (5-yr)
Aggressive non-Hodgkin lymphoma					
JCOG 9505	II(c)	(95-98)	2	56%	42% (4-yr)
JCOG 9506	II	(95-97)	6	50%	49% (5-yr)
JCOG 9508	II	(96-99)	19	80%	68% (5-yr)
JCOG 9809	III	(99-02)	55	62%	56% (8-yr)
JCOG 0601	III	(08-)	23	NA	NA
JCOG 0406	III	(08-)	4	NA	NA
JCOG 0908	III	(08-)	6	NA	NA
Indolent B-cell lymphoma					
JCOG 0203	II/III	(02-07)	52	77%	88% (6-yr)
Adult T-cell leukemia-lymphoma					
JCOG 9303	II	(94-97)	6	36%	31% (2-yr)
JCOG 9801	III	(98-03)	6	33%	19% (3-yr)
Nasal NK/T-lymphoma					
JCOG 0211-DI	I/II	(03-07)	8	77%	78% (2-yr)
Multiple myeloma					
JCOG 9301	III	(93-98)	10	50% (d)	50% (4-yr)
JCOG 0112	III	(02-05)	9	46% (d)	63% (2-yr)
JCOG 0904	Iic	(09-)	4	NA	NA

(a) the number of patients enrolled from our Division; (b) As the number of enrolled patients in our Division is relatively small, the %CR or OS for the entire group of patients enrolled in the JCOG or JALSG trials is shown here.
(c) randomized phase II study
(d) CR + PR rate. Abbreviations: JCOG, Japan Clinical Oncology Group; JALSG, Japan Adult Leukemia Study Group; LSG, Lymphoma Study Group; OS, overall survival; NA, not available

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DEPARTMENT OF HEMATOLOGY, AND HEMATOPOIETIC STEM CELL TRANSPLANTATION, HEMATOPOIETIC STEM CELL TRANSPLANTATION DIVISION

Takahiro Fukuda, Yuji Heike, Takuya Yamashita, Sung-Won Kim, Saiko Kurosawa, Nobuhiro Hiramoto

Introduction

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

Routine Activities

Six staff physicians (Drs. Heike, Yamashita, Kim, Kurosawa, Hiramoto, and Fukuda) participate in the transplant program. Children who undergo HSCT are managed in collaboration with the transplant team and Dr. Makimoto, the Chief of Pediatric Oncology Division. In 2011, a total of 101 transplantations were performed. The numbers of each type of HCST and those of HSCT recipients with each disease type in recent years are shown in Tables 1 and 2, respectively. Of note, 54 patients underwent HSCT from unrelated bone marrow donors in 2011, which was the highest level of activity in Japan. At the weekly conference on Monday afternoons, in collaboration with doctors of the Hematology Divisions, about 30 hospitalized HSCT patients and those who were referred for HSCT are reviewed for clinical management and a decision regarding their eligibility for HSCT. The transplant unit is staffed by 26 nurses trained in oncology and specialized supportive care for HSCT patients. The nursing unit has been assuming leadership in an effort to facilitate improved care for skin and gut graft-versus-host disease (GVHD), and establishment of a Long-term Follow-up Unit (LTFU) for the education of patients and their family members. At the weekly 12B ward meeting on Friday afternoons, all HSCT patients are reviewed in detail by all transplant team members including doctors, nurses, pharmacists, the nutritional support team, clinical research coordinators, and the transplant coordinator.

Research Activities and Clinical Trials

Our transplant team has been focusing on the development of comprehensive cellular immunotherapy, including a reduced-intensity stem cell transplant (Mini-transplant) for elderly patients. Three staff physicians (Drs. Heike, Yamashita, and Fukuda) are principal investigators for the Government supported grant projects. Dr. Heike has organized a cell processing facility on the adjoining 12th floor and a facility on the 11th floor specializing in gene therapy in compliance with good manufacturing procedures (GMP). Currently, two clinical trials of gene therapy using the HSV-TK suicide gene are ongoing: one is for donor lymphocyte infusion after related HSCT, and the other is for T-cell add-back following haploidentical HSCT. A clinical trial of post-transplant consolidation with the WT1 vaccine is also ongoing. We have been working on expansion of the indication of drugs used for the treatment of GVHD and infections. In May 2011, foscarnet, an anti-viral agent, was approved for cytomegalovirus infection after HSCT. A prospective feasibility study of the LTFU system after HSCT was approved by the institutional IRB, and will be started in 2012. A nationwide large survey of quality of life (QOL) has been conducted for patients with acute leukemia who received chemotherapy or HSCT. In the Division, about 13 clinical trials are ongoing. In 2011, we have published 7 articles in peer-reviewed international journals and 5 manuscripts have been accepted for E-pub or are in press for publication.

Table 1. Number of each type of HSCT

Year		2008	2009	2010	2011
Allogeneic		77	93	90	76
Unrelated	Bone marrow transplantation	48	59	60	54
	Peripheral blood stem cell transplantation	1	0	0	0
	Cord blood transplantation	1	5	1	4
Related	Bone marrow transplantation	5	2	5	2
	Peripheral blood stem cell transplantation	22	27	24	16
Autologous		8	18	19	25
Total		85	111	109	101

Table 2. Number of patients who underwent HSCT between 2008 and 2011.

Diagnosis	Allogeneic	Autologous
Acute myeloid leukemia	137	1
Myelodysplastic syndrome	29	
Acute lymphocytic leukemia	48	
Malignant Lymphoma (including ATL)	114	39
Multiple Myeloma		16
Solid tumors	2	14
Others	6	
Total	336	70

Published Papers

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DEPARTMENT OF PEDIATRIC ONCOLOGY

Atsushi Makimoto, Ako Hosono, Hiroshi Kawamoto, Yuki Yamamoto, Koji Suzuki, Chika Tanaka

Introduction

Pediatric oncology includes a wide variety of malignancies in children and adolescents such as acute leukemias and malignant lymphomas, as well as solid tumors such as soft tissue sarcomas, neuroblastomas, Wilms tumors and retinoblastomas. All diseases are usually highly chemo-sensitive and curable with appropriate multi-disciplinary treatment. Doctors in the Pediatric Oncology Division manage pediatric cancer patients who are treated with multi-agent chemotherapy, which is usually more toxic than that in adult oncology, as well as with surgery and radiotherapy, which is always radical and sometimes toxic. Hematopoietic stem cell transplantation (SCT) is sometimes indicated in both hematologic malignancies and solid tumors. Regardless of the disease, pediatric oncologists face all of the medical and psychosocial problems in children with cancer with the support of nurses and other medical staff.

The Pediatric Oncology Division includes three staff physicians and two chief residents. The number of doctors does not increase due to the rarity of the diseases. This division handles about 80 patients with pediatric malignancies per year, who are referred from hospitals located throughout Japan and other Asian countries. Due to the need for intensive chemotherapy, most of the patients have to be hospitalized in the pediatric ward (12A). If a patient needs allogeneic SCT, he/she will be transferred to the transplantation ward (12B).

A special nursing care system in the ward helps young patients and their families physically as well as psychologically. Nurses provide appropriate information to help patients and families maintain an ideal relationship. To enhance the quality of hospital life for young patients, educational opportunities ranging from elementary school to high school are available in the pediatric ward, where 8 teachers work daily.

Routine Activities

The pediatric outpatient service is open from Monday through Friday to treat new patients and to provide follow-up treatment to patients who have completed intensive treatment. The pediatric staff and trainees discuss various issues regarding pediatric inpatients on daily rounds. Patients undergo various procedures in a timely manner, sometimes under IV sedation. These procedures include diagnostic bone marrow aspiration/biopsy, central venous catheter placement, and lumbar puncture/intrathecal chemotherapy. A Pediatric Conference is held every morning, mainly to decide upon individual treatment plans. Inter-department conferences between orthopedics, radiation oncology, and palliative care are individually scheduled on a biweekly basis.

The common approach to these diseases is "risk-adapted therapy" regarding long-term life expectancy. Patients receive multidisciplinary therapy, including surgical removal of the tumor, radiation therapy, chemotherapy, and sometimes SCT, as indicated.

The Sarcoma Hot-line, which accepts inquiries and consultations from outside doctors and patients (both children and adults) by phone, is open from Monday to Friday under the management of this division.

Research Activities

I. Designing and planning of clinical trials in a multicenter setting

The Pediatric Data Center (DC) for collaborative pediatric groups, which is independent of the Japan Clinical Oncology Group (JCOG), was established in 2004 with a Grant-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare. Although the DC was transferred to the non-profit organization "Support Unit for Childhood Cancer with Effective Strategy and Solution (SUCCESS)" in 2009, management of the DC is one of the research activities. The DC provides expertise in data management and facilitates administrative matters related to clinical trials. Moreover, the DC studies the methodology of clinical trials. Currently, this DC is managing 2 clinical trials, which are described in the following section.

II. Ancillary studies associated with retrospective case series and clinical trials

(1) Pathology review of case series to identify

correlations between specific molecules and survival.
(2) Determination of the diagnostic value of PET scans for pediatric solid tumors.
(3) Establishment of standard supportive and palliative care for pediatric cancer patients including a special "cosmetic program" for adolescent patients.

Clinical Trials

This department is expanding its focus to include treatment development using relatively new off-label drugs. One of the objectives of the following trials is gathering data on, and assessing the safety and efficacy data of, such off-label drugs.
(1) Phase I-II trial of the combination of topotecan and ifosfamide for recurrent pediatric solid tumors.
(2) Randomized phase II study of two cross-over sequences comprising vinorelbine/cyclophosphamide and temozolomide/etoposide in the outpatient setting for relapsed or refractory solid tumors in children and young adults.
(3) Phase I trial of immunotherapy using HLA-A2- and A24-restricted glypican-3 peptide vaccine for pediatric tumors.

Published Papers

1. Araki Y, Matsuyama Y, Kobayashi Y, Toyokawa S, Inoue K, Suzuki S, Makimoto A. Secondary neoplasms after retinoblastoma treatment: retrospective cohort study of 754 patients in Japan. Jpn J Clin Oncol, 41:373-379, 2011

Table 1. Number of patients

Diagnosis	Newly diagnosed	Pretreated
Rhabdomyosarcoma	7	3
Ewing sarcoma family	6	2
Osteosarcoma	6	2
Neuroblastoma	3	3
Retinoblastoma*	1	1
Germ cell tumor	3	0
Other solid tumors	9	3
Acute lymphoblastic leukemia	0	1
Acute myeloid leukemia	1	1
Non-Hodgkin lymphoma	4	1
Other hematologic diseases	1	0
Total	33	22

*; extended case only

Table 2. Type of procedures

chemotherapy	49
chemotherapy and stem cell transplantation	7
surgery	20
others	3

Table 3. Survival rates (acturarial, 2000-2005)

Diagnosis	Number of pts	5-yr survival (%)
Rhabdomyosarcoma	31	51
Ewing sarcoma family	17	70
Osteosarcoma	8	63
Neuroblastoma	9	44
Non-Hodgkin's Lymphoma	26	85
Acute lymphoblastic leukemia	22	77
Acute myeloid leukemia	8	63

DEPARTMENT OF INTERNAL MEDICINE, GENERAL INTERNAL MEDICINE DIVISION

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

The Department of Internal Medicine was reorganized in October 2010 to better serve the diverse needs of cancer patients and provide more comprehensive, patient-centered care. The Department consists of the following three divisions.

Indroduction

The increasing number of cancer patients who visit the National Cancer Center Hospital have a wide range of non-cancer related medical problems such as diabetes, hypertension, heart diseases, and kidney diseases. Cancer or its treatment can aggravate the pre-existing medical conditions and sometimes can cause these problems. These medical issues must be addressed and managed along with the cancer itself so that our patients can go through optimal cancer therapies and have a better outcome. In 2011, four specialists joined the team. Our staffs have experience and expertise in their respective field and provide comprehensive management of these issues.

Routine Activities

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

In 2011, we have expanded diabetes consultation service into NCC Hospital East, improving the quality of diabetes care there.

DEPARTMENT OF INTERNAL MEDICINE, GENETIC COUNSELING DIVISION

Teruhiko Yoshida, Kokichi Sugano

Introduction

Cancer, like many other multi-factorial or common diseases, arises through a complex interplay among life style/environmental factors, genetic predisposition and aging. Cancers are typical polygenic diseases, and an obvious family history (such as 3 or more patients with the same or related cancer types within the 2nd-degree relatives) is not evident in more than 95% of the so-called sporadic cases. However, monogenic Mendelian inheritance patterns have been recognized for certain cancer families. Clinical cancer genetics has been a part of the outpatient service in the National Cancer Center Hospital (Tsukiji) since 1998 as a close collaboration with the Division of Genetics, National Cancer Center Research Institute.

Routine Activities

The major mission of the clinic in a daily practice is to provide cancer genetic counseling in a broad sense, and the clinic accepts any request for information, consultation and other assistance to deal with the clients' concern regarding their own genetic risk or that of their family members. The presence of a nurse with an interest and training in clinical genetics is critical to assist the counseling sessions. Based on a family history, age at diagnosis, type and pattern of cancer development such as multiple primaries, and other accompanying signs and symptoms, genetic risk for the possible hereditary cancer syndromes will be assessed for the clients, followed by explanation of available and appropriate genetic testing, if applicable. Both pre- and post-genetic test counseling is essential to make the genetic testing useful and fruitful to the clients in the long run.

Research Activities

The Division has been participating in several multi-center research activities related to the psychological impact of genetic testing, spectrum of manifestations of hereditary cancer syndromes, and evaluation and development of genetic testing methods. One of the major targets is hereditary retinoblastoma, because about half of the newly diagnosed cases in Japan will visit National Cancer Center Hospital to seek the highly advanced treatment available at the Department of Ophthalmic Oncology. Incidence of retinoblastoma

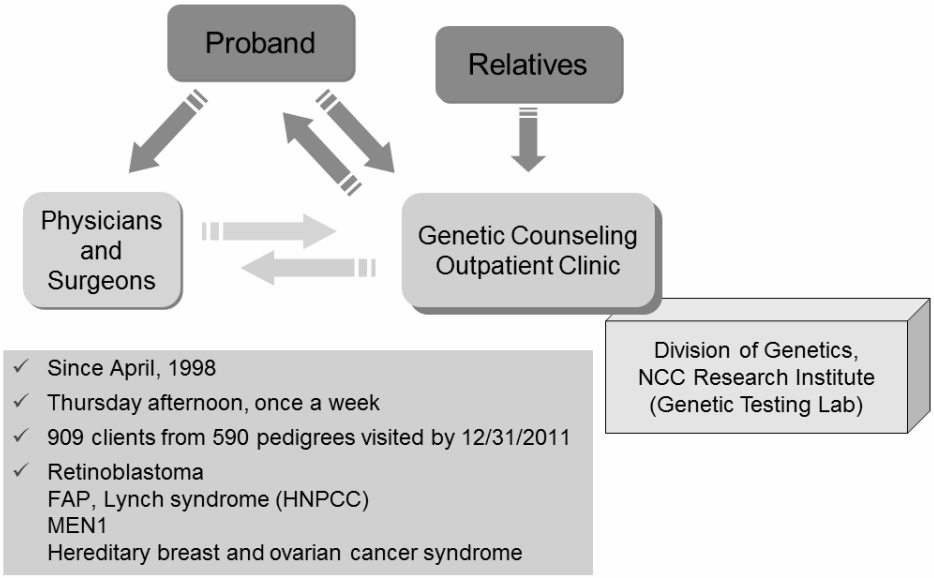

Figure 1. An outline of genetic counseling clinic at NCC hospital

is about 1/16,000-20,000 births, and all bilateral and 10-15% of unilateral retinoblastomas are hereditary with a germline inactivating mutation of the *RB1* gene. Fig. 1 illustrates the current scheme of *RB1* genetic testing. The overall detection rate of the accumulated cases was 64/67 (96%) for bilateral cases and unilateral cases with family history but 3/29 (10%) for unilateral cases without family history. Carrier diagnosis was performed on 93 individuals, including 14 newborns from 11 pedigrees using cord blood samples. Because sensitivity is not sufficient for each single test, and detection of mosaicism and splicing aberration requires FISH and RT-PCR, respectively, the combination of multiple tests is necessary.

Clinical Trials

No clinical trial was performed in 2011.

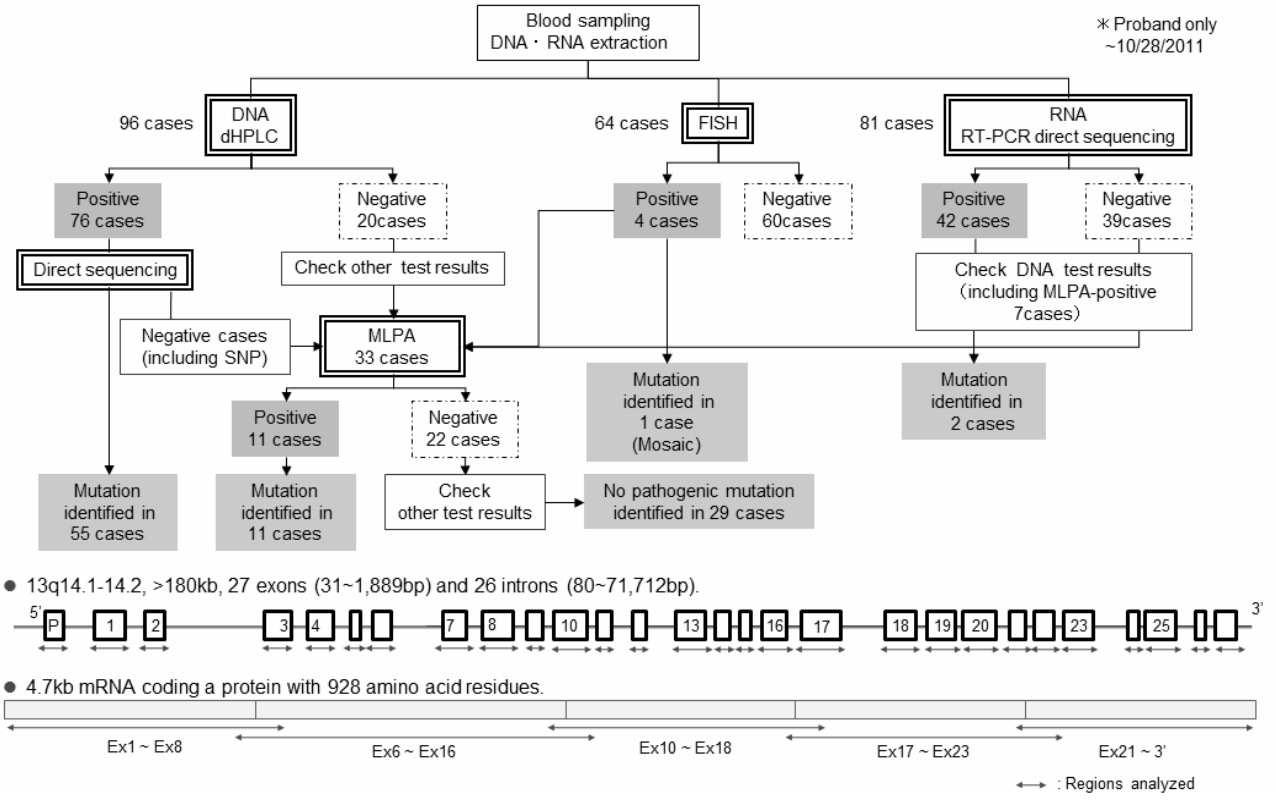

Figure 2. Flowchart of genetic tests for hereditary retinoblastoma.

Table. Number of patients

Type of Disease	Proband	Relative	Total
Lynch syndrome (Hereditary Non-Polyposis Colon Cancer; HNPCC)	11	8	19
Familial Adenomatous Polyposis (FAP)	5	4	9
Retinoblastoma	6	14	20
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	8	3	11
MEN I (Multiple Endocrine Neoplasia Type I)	0	0	0
Other diseases	7	0	7
Counseling only	1	0	1
Total	34	15	49

DEPARTMENT OF INTERNAL MEDICINE, DENTAL DIVISION

Takao Ueno

Introduction

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

Routine Activities

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

Research Activities

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

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

Table. Number of patients

Management of oral complications	622
Introduction to the cooperation dental clinic（oral health care before operation）	306
Total	928

DEPARTMENT OF ANESTHESIOLOGY AND INTENSIVE CARE UNIT, ANESTHESIOLOGY DIVISION

Tetsufumi Sato, Yoko Kinoshita, Tsukasa Satake, Nobuko Yokokawa, Rie Suzuki, Minako Arai, Nohito Tanioka, Yosuke Kawaguchi, Shinji Sugita, Fumie Yamazaki, Keisuke Ishikawa, Kazuhito Mietani, Masashi Yanagi, Megumi Sekikawa

Introduction

The purpose of anesthesiology is to preserve breathing, circulation, and a consistent metabolic state necessary for a person to survive perioperatively. As anesthetists we must prevent any noxious vital reaction due to surgical stress and we must maintain the optimum and safe environment in which the patient is to undergo surgery. The main function of our Division is anesthesia management in the operating room, and we normally perform general anesthesia for 4,000 cases a year or more, and additionally give sedation (approximately 100 a year) during the endoscopic operations performed out of the operating room.

The Division is currently getting ready to introduce improved and state-of-the-art clinical monitoring and information integration systems, namely ORSYS (Philips Japan), designed to automate most intraoperative documentation, and PIMS (Philips Japan) designed to handle the clinical information of patients in the ICU. We will be able to focus even more than before on our patients.

Routine Activity

We hold daily conferences every morning and examine the case of the day, and host a journal club twice a week. An average of 30 daily elective operations are managed, and our Division is ready at any time to support emergency surgery. Preoperative evaluation of the next day's cases and postoperative rounds are performed after surgery.

Research Activity

1) Examination of safe sedative methods for endoscopic operations
2) In cooperation with fundamental university-based studies, we are examining the pituitary function in various kinds of pain

Clinical Trials

1) Examination of the scoring induction for preoperative risk

Table. Number of patients

Surgery in the operation room	4520
General anesthesia	1487
General anesthesia with epidural anesthesia	2450
Epidural anesthesia	6
Epidural anesthesia with spinal anesthesia	5
Spinal anesthesia	144
Others	2

DEPARTMENT OF ANESTHESIOLOGY AND INTENSIVE CARE UNIT, INTENSIVE CARE UNIT

Daisuke Yamaguchi, Yousuke Kawaguchi, Shinji Sugita, Keisuke Ishikawa, Kazuhito Mietani, Tetsufumi Satou

Introduction

The Division of Intensive Care Medicine consists of 6 full time staff members and 5-6 rotating residents who receive critical care medicine training. Since June 2009, we have conducted all patient managements in ward 8A at all hours as a closed management ICU. Compared with other cancer centers in Japan, by providing the largest number of professional staff including intensivists and anesthesiologists, we provide multidisciplinary intensive care. In addition to post surgical patients, without regard to surgical or medical, we treat severe and life-threatening inpatients with acute respiratory failure, septic shock, acute kidney injury, acute hepatic failure, or multiple organ dysfunction which are caused by various types of pathophysiological entities.

Routine Activities

A division conference is held every morning which is attended by intensivists, anesthesiologists, surgeons, physicians, psychiatrists, ICU nurses, staff of the medical engineer division, and other specialists who are involved in the intensive care treatment. We discuss the treatment plans for all ICU patients of the day, with particular attention to critical or life-threatening cases. For these patients, careful management with multidisciplinary cooperation is essential. We are frequently consulted about patients in critical condition who require intensive care, and we discuss these cases at any time. The timing of ICU admission and the treatment plan in our division are also discussed at this conference.

Highly-advanced medical treatments in our ICU include some types of mechanical ventilation especially for acute lung injury patients, renal replacement therapy including continuous hemofiltration and plasma exchange, cardiovascular support for patients with the use of various vasoactive and inotropic agents, temporary pacing devices, and even percutaneous cardiopulmonary bypass (A-V ECMO systems). In performing and delivering these ICU treatments, we observe evidence-based critical care medicine according to the latest guidelines.

From April 2010 to March 2011, 306 new patients were admitted to the ICU, with a total of 1,294 patients treated in our ICU. Of these, although 60% of the admissions were post-surgical status, we treat not only surgical patients but sudden medical change inpatients or outpatients who require chemotherapy, and even oncology emergency patients who have been brought to the ER by ambulance.

With the exception of routine post surgical management, the most frequent cases which require admission to our division are patients with severe respiratory failure as typified by acute lung injury (ALI/ARDS), acute exacerbation of idiopathic pulmonary fibrosis (IPF) and acute interstitial pneumonitis (AIP). As these severe respiratory failure patients often require prolonged mechanical ventilation, we aggressively provide early mobilization of mechanical ventilated patients in cooperation with physiotherapists even if they are intubated and sedated.

Secondly, severe sepsis and septic shock in post surgical patients or neutropenic patients who have hematological disease or who are given chemotherapy have accounted for more than 70 cases per year. We provide sepsis treatments following the Surviving Sepsis Campaign Guidelines (so called “SSCG2008”), and sometimes resuscitate patients with life-threatening sepsis.

Blood purification therapy is one of the important functions in our ICU. In cooperation with the medical engineering division, we provided renal replacement therapy (mainly continuous venovenous hemodiafiltration), plasma exchange, and polymyxin B hemoperfusion for more than 80 cases since June 2009.

If a cardiovascular event occurs, for example acute coronary syndrome or severe congestive heart failure which requires catheter intervention or mechanical cardiac support devices, our intensivists transfer these patients to a cardiac specialized hospital with thorough medical safety management, as if it were a “mobile ICU”.

Critical Care Medical (CCM) training to rotating residents is also important work for us. Both surgical and medical residents must receive CCM training for 2 or 3 months during their first year. Our ICU is a really adequate environment for them to learn oncology emergency and critical care

medicine. We restrict resident duty hours according to the recommendations of The Accreditation Council for Graduate Medical Education (ACGME) in the USA, and provide CCM training program with reference to the educational guidelines of Society of Critical Care Medicine (SCCM) in the USA.

Perspective

In recent years, as the number of operations performed in our hospital has rapidly increased, a concomitant increase has also been seen in the number of patients who require intensive care treatment. Therefore, the significance of the function of our ICU in the hospital has been well-recognized.

Since December 2010, the Rapid Response System (so called "ER call") was established, and at the same time our Medical Emergency Team was organized with a core of intensivists.

The number of ICU beds was expanded from 4 to 8 in November 2011. We are totally prepared to go to greater effort for all cancer patients who require critical care.

Department of Palliative Care and Psycho-Oncology, Palliative Care Division

Motohiro Matoba, Osamu Saito, Satoshi Murakami, Kosuke Miura, Chio Shuto

Introduction

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

Routine Activities

The main routines of the team are to manage the symptoms of terminal patients and to educate the residents to get them to acquire the knowledge and skills required of a palliative care physician. We are usually in charge of about 30 inpatients, and make a morning round and hold conferences twice-daily. In the outpatient department, we treat approximately 20 patients per week. Besides conventional drug therapy, we perform various neuronal blockades, place emphasis on mental support for the patient and their families and sometimes refer the patients to the Division of Psycho-Oncology, Department of Orthopedic Surgery, Department of Pediatric Oncology and Department of Diagnostic Radiology to attain better symptom management. For the porpose of equilibration of palliative medicine, bimonthly conferences are held, and consequently coordination with the community palliative care in the vicinity is strengthened.

Education for Residents

With regard to their clinical education and training, all the residents of the NCCH are required to train with our team for 1 month, within which a one-week home hospice course is mandatory. In total, 25 residents trained with our team during 2011. The course is whole-person-care oriented. The home hospice course offers an opportunity to understand the role of various occupations other than doctors, such as visiting nurses and care managers. Moreover, a summer training program is carried out for medical students and junior residents. Four medical students and 2 junior residents participated in the program during 2011.

Research Activities

Several translational studies are ongoing in collaboration with the Cancer Pathophysiology Division in the National Cancer Center Research Institute, Hoshi University, Chiba University, and Nihon University.

The effect of lidocaine on the adverse symptoms of cancerous peritonitis, the impact of adjuvant analgesics on sleep disturbance associated with neuropathic pain, the effects of ketamine on pain on movement using the novel spinal bone metastasis model which was developed by us, impact of capsaicin on TRPV-1, and the role of glia cells in cancer pain have been investigated.

Clinical Trials

The main purpose of our clinical trials is to develop a standard therapy to ameliorate terminal symptoms. We have been investigating the usefulness and efficacy of adjuvant analgesics for neuropathic pain, the effect of ketamine on the pain of patients with spinal bone metastasis, the palliation of breathlessness with intravenous trometamol and inhaled furosemide, and the efficacy of oral transmucosal fentanyl citrate (OraVescent fentanyl; OVF). In addition, we have investigated the efficacy and safety of oxicodene injection and presented our findings at the 12th congress of the European Association for Palliative Care.

Table 1. Number of patients.

Lung cancer	43
Sarcoma	38
Rectal cancer	21
Breast cancer	20
Leukemia	16
Uterine cancer	16
Renal cancer	13
Gastric cancer	9
Pancreatic cancer	8
Colon cancer	8
Gallbladder cancer	8
Bladder cancer	8
Esopahageal cancer	8
Malignant lymphoma	6
Primary unknown cancer	6
Prostate cancer	5
Multiple melanoma	4
Ovarian cancer	4
Malignant melanoma	2
Liver cancer	2
CNS cancer	2
Skin cancer	2
Bone cancer	2
Head and neck cancer	2
Others	36
Total	289

Table 2. Type of procedure

Adjustment of non-opioid analgesics	76
Commencement of opioid analgesics	22
Adjustment of opioid analgesics	92
Opioid rotation	38
Adjustment of adjuvant analgesics	61
Nerve block	13
Management of side effect of analgesics	71
Other symptom management	6
Reference to other specialists	8
Others	2

Published Papers

1. Takemura Y, Yamashita A, Horiuchi H, Furuya M, Yanase M, Niikura K, Imai S, Hatakeyama N, Kinoshita H, Tsukiyama Y, Senba E, Matoba M, Kuzumaki N, Yamazaki M, Suzuki T, Narita M. Effects of gabapentin on brain hyperactivity related to pain and sleep disturbance under a neuropathic pain-like state using fMRI and brain wave analysis. Synapse, 65:668-676, 2011

2. Narita M, Niikura K, Nanjo-Niikura K, Narita M, Furuya M, Yamashita A, Saeki M, Matsushima Y, Imai S, Shimizu T, Asato M, Kuzumaki N, Okutsu D, Miyoshi K, Suzuki M, Tsukiyama Y, Konno M, Yomiya K, Matoba M, Suzuki T. Sleep disturbances in a neuropathic pain-like condition in the mouse are associated with altered GABAergic transmission in the cingulate cortex. Pain, 152:1358-1372, 2011

3. Hirai K, Kudo T, Akiyama M, Matoba M, Shiozaki M, Yamaki T, Yamagishi A, Miyashita M, Morita T, Eguchi K. Public awareness, knowledge of availability, and readiness for cancer palliative care services: a population-based survey across four regions in Japan. J Palliat Med, 14:918-922, 2011

4. Murakami S, Matoba M. The methods of the opioid introduction: choice of opioids. Jpn J Hosp Palliat Care, 21:25-29, 2011

5. Murakami S. Palliative medicine for the lung cancer. Popular Medicine, 270:103-108, 2011

DEPARTMENT OF PALLIATIVE CARE AND PSYCHO-ONCOLOGY, PSYCHO-ONCOLOGY DIVISION

Ken Shimizu, Yu Yamada, Masashi Kato, Yoshio Oshima

Introduction

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

Routine Activities

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

The range of psychiatric diagnoses is based on the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) shown in the Table. In 2011, a total of 641 patients were referred for psychiatric consultation. The mean age was 66 years and 22.8% percent of the referrals were outpatients. Three hundred and thirty-three (52.0%) of the total number of referred patients were males. The most common psychiatric diagnosis was delirium (26.4%), followed by adjustment disorders (25.4%), and major depression (8.3%), while 8.0% of the referrals had no psychiatric diagnosis. The three common mental disorders, adjustment disorder, major depression and delirium, were responsible for half of the psychological problems. The most common cancer referrals were patients with hematological cancer (11.7%), followed by lung cancer (11.2%), breast cancer (8.6%), esophageal cancer (7.6%) and stomach cancer (6.7%).

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

Research Activities

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

Table 1. Patient demographics

Patients	Total number	641	
	Age	66 years	
	Male	333	52.0%
	Inpatients	495	77.2%

Table 2. Number of cancers by site

Cancer site	Hematological	75	11.7%
	Lung	72	11.2%
	Breast	55	8.6%
	Esophageal	49	7.6%
	Stomach	43	6.7%

Table 3. Breakdown of diagnoses

Diagnosis	Delirium	169	26.4%
	Adjustment Disorders	163	25.4%
	Major Depression	53	8.3%
	No Diagnosis.	51	8.0%

Published Papers

1. Ito T, Shimizu K, Ichida Y, Ishibashi Y, Akizuki N, Ogawa A, Fujimori M, Kaneko N, Ueda I, Nakayama K, Uchitomi Y. Usefulness of pharmacist-assisted screening and psychiatric referral program for outpatients with cancer undergoing chemotherapy. Psychooncology, 20:647-654, 2011

2. Shimizu K, Akizuki N, Nakaya N, Fujimori M, Fujisawa D, Ogawa A, Uchitomi Y. Treatment response to psychiatric intervention and predictors of response among cancer patients with adjustment disorders. J Pain Symptom Manage, 41:684-691, 2011

3. Kobayakawa M, Inagaki M, Fujimori M, Hamazaki K, Hamazaki T, Akechi T, Tsugane S, Nishiwaki Y, Goto K, Hashimoto K, Yamawaki S, Uchitomi Y. Serum brain-derived neurotrophic factor and antidepressant-naive major depression after lung cancer diagnosis. Jpn J Clin Oncol, 41:1233-1237, 2011

DEPARTMENT OF DIAGNOSTIC RADIOLOGY

Yasuaki Arai, Masahiko Kusumoto, Yoshito Takeuchi, Yasunori Mizuguchi, Kenichi Takayasu, Gen Iinuma, Hiroaki Kurihara, Hirokazu Watanabe, Tomoko Manabe, Yoko Kawawa, Kentaro Shibamoto, Keitaro Sofue, Mototaka Miyake, Hiroaki Onaya

Introduction

The Department of Diagnostic Radiology offers a wide range of modalities, including interventional radiology (IR), general radiology, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, mammography and nuclear medicine. We seek individuals with outstanding leadership capabilities, proven academic and administrative experience, the vision to build and sustain programs at the forefront of imaging research, and a commitment to clinical experience.

Routine Activities

	Modality	Number of examinations
1	CT	38,857
2	MRI	7,731
3	IR	4,025
4	RI	4,294
5	Ultrasound	12,003
6	Radiograph	78,397
7	Gastrointestinal study	2,493

Research Activities

Because of their increased signal to noise ratio, 3.0 T MR machines have improved the ability to detect disease. We have been studying the efficacy of high resolution MR mammography using 3.0 T MRI for the detection and the lesion distribution of invasive ductal cancer or DCIS. Nowadays, we are also investigating the efficacy of the prediction of neo-adjuvant chemotherapy using breast MR spectroscopy.

We have also been performing studies into the efficacy of the detection of liver metastases using Gd-EOB-DTPA-enhanced 3.0 T MR imaging. Prospective studies were performed to compare the images on Gd-EOB-DTPA-enhanced MR imaging for chronic liver disease with 1.5 T and 3.0 T systems.

We have correlated the MR imaging findings with the histopathological findings of ovarian endometrioid tumors, borderline malignancy and ovarian mucinous borderline tumors of the intestinal type to clarify the characteristics of these diseases and to make accurate diagnoses.

CT colonography (CTC) has been developed in the NCC as a new diagnostic technology for the evaluation of colorectal lesions. With the use of 64 multi-slice CT, more than 500 early colorectal cancers have been examined using CTC from 2008 to 2011. We have started a collaboration study with Chicago University to investigate computer-aided detection (CAD) in CTC since last year. Moreover, we have accomplished tagging and electronic cleansing, also CO_2 insufflation systems for standard and efficient CTC preparation. We successfully introduced CTC into colorectal screening in our screening center in 2010, and are now further developing the effective diagnostic methods for the screening process.

Another new CAD systems for lung cancer using MDCT data have been developed in collaboration with Faculty of Engineering in Tokushima University. A newly developed software for lung nodule detection was revised, and a new method of quantitative classification based on CT histogram analysis of lung cancer was proposed.

The Japan RECIST working group improved the tumor response evaluation computer system, which is capable of semiautomatic RECIST evaluation and is compliant with DICOM (Digital Imaging and Communications in Medicine) data.

A multi tracer consisting of F-18 FDG, C-11 choline, C-11methionine and Cu-64 DOTA-antibody PET imaging has been studied for cancer patients to improve the sensitivity and specificity of detecting tumor sites or tumor characteristics. F-18 FDG dynamic PET sampling with Patrak-plot analysis allows us to calculate the glucose metabolic rate of the tumor site. Respiratory-gated PET/CT was evaluated to reduce breathing-induced artifacts using a four-dimensional PET/CT protocol. It provided better localization and quantization of tumors around the lower thorax to the upper abdomen. Another radiopharmaceutical for PET, F-18 FBPA, a derivative of phenylalanine and also an essential evaluator for BNCT, has been synthesized in the hospital, and is waiting for IRB approval for clinical use.

TACE is widely performed for patients with unresectable HCC and has recently been

recommended for those with 2 or 3 tumors >3cm or >=4 tumors in a treatment algorithm proposed by Japanese guidelines. In 4966 HCC patients with no vascular invasion or extrahepatic metastasis who underwent TACE, patients were stratified to two categories of TACE and survival rates were evaluated. The three-year survival for 2 or 3 tumors >3cm or >=4 tumors was 55% and 46% in Child-Pugh A, respectively and 30% and 22% in class B, respectively. These results would help in comparing the outcome of TACE in the East and West, since the treatment algorithm of Japanese guidelines and Barcelona Clinic Liver Cancer (BCLC) staging system might be almost identical.

Clinical Trials

In addition to many company oriented clinical trials, ten clinical trials on interventional radiology are ongoing in the NCC as the flagship hospital of a multi-institutional cooperative study group (JIVROSG: Japan Interventional Radiology in Oncology Study Group): a phase I/II study of RFA for intrapelvic malignant tumors (JIVROSG-0204); a phase I/II study of RFA for malignant bone tumors (JIVROSG-0208); a phase III study evaluating the efficacy of hepatic arterial infusion chemotherapy for metastatic colorectal cancer patients with unresectable liver metastases (JIVROSG-0606); a phase I/II study of RFA for malignant renal tumors (JIVROSG-0701); a phase I/II study of RFA for malignant lung tumors (JIVROSG-0702); a phase III study evaluating the efficacy of peritoneo-venous shunting (JIVROSG-0803); a phase III study evaluating the efficacy of percutaneous vertebroplasty for painful bone metastases (JIVROSG-0804); a phase III study evaluating the efficacy of percutaneous trans-esophageal gastric tubing (JIVROSG-0805); a phase III study evaluating the efficacy of stenting for malignant colorectal stricture (JIVROSG-0806); and a phase III study evaluating the efficacy of stenting for SVC/IVC syndrome (JIVROSG-0807).

Published Papers

1. Arai Y, Inaba Y, Sone M, Saitoh H, Takeuchi Y, Shioyama Y, Nakajima Y. Phase I/II study of transjugular transhepatic peritoneovenous venous shunt, a new procedure to manage refractory ascites in cancer patients: Japan Interventional Radiology in Oncology Study Group 0201. AJR Am J Roentgenol, 196:W621-W626, 2011

2. Arakawa H, Johkoh T, Sakai F, Kusumoto M, Hataji O, Taguchi O. Exacerbation of radiation fibrosis with erlotinib: another pattern of radiation recall phenomenon. Jpn J Radiol, 29:587-589, 2011

3. Fujiwara H, Sekine S, Onaya H, Shimada K, Mikata R, Arai Y. Ring-like enhancement of focal nodular hyperplasia with hepatobiliary-phase Gd-EOB-DTPA-enhanced magnetic resonance imaging: radiological-pathological correlation. Jpn J Radiol, 29:739-743, 2011

4. Hamaguchi T, Shirao K, Ohtsu A, Hyodo I, Arai Y, Takiuchi H, Fujii H, Yoshida M, Saito H, Denda T, Koizumi W, Iwase H, Boku N. A phase II study of biweekly mitomycin C and irinotecan combination therapy in patients with fluoropyrimidine-resistant advanced gastric cancer: a report from the Gastrointestinal Oncology Group of the Japan Clinical Oncology Group (JCOG0109-DI Trial). Gastric Cancer, 14:226-233, 2011

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11. Eguchi S, Kanematsu T, Arii S, Omata M, Kudo M, Sakamoto M, Takayasu K, Makuuchi M, Matsuyama Y, Monden M. Recurrence-free survival more than 10 years after liver resection for hepatocellular carcinoma. Br J Surg, 98:552-557, 2011

12. Maruyama S, Kemuriyama T, Manabe T, Takahata T, Shoji I, Nishida Y. Severe hypotension during the decreasing phase of Gz stress in anesthetized rats wearing an anti-G suit. Aviat Space Environ Med, 82:1030-1036, 2011

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DEPARTMENT OF RADIATION ONCOLOGY

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Introduction

The role of the Department is to provide state of art radiation therapy for all relevant patients, to educate and develop the expertise of radiation oncologists, and to lead new developments in radiation oncology both in Japan and worldwide. All Departmental Activities are dedicated to Cancer Patients. In this year, a new building for hospital-based boron neutron capture therapy (BNCT) using an accelerator was begun, and will be finished in 1.5 years. The Department will be fully involved in the development of BNCT.

Routine Activities

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

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

Research Activities

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

The staff in the Division are actively engaged in various prospective trials including JCOG studies.

Clinical Trials

Brain tumors: A multicenter phase II/III trial on

interferon-beta and temozolomide combination therapy for newly diagnosed glioblastomas.

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

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

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

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

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

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

Development of an Adaptive Radiation Therapy System

Table 1. Number of Radiation Treatment Plans

Primary Sites	No. of All Treatment Plans					
	2006	2007	2008	2009	2010	**2011**
Head & neck	87	111	115	95	128	**166**
Brain	51	90	117	99	113	**97**
Lung	343	357	397	431	429	**348**
Breast	437	523	549	452	487	**503**
Esophagus	190	276	220	213	265	**237**
Stomach	29	30	34	29	25	**15**
Colorectal	60	101	86	78	66	**119**
Pancreas and hepatobiliary	82	60	38	48	69	**68**
Gynecological	88*	154*	255	331	274	**328**
Genitourinary	137	118	128	159	192	**169**
Bone & soft tissue	55	64	75	69	103	**92**
Skin	12	19	16	26	58	**71**
Pediatric	19	25	22	32	25	**66**
Hematological	141	145	137	220	159	**157**
Other	31	35	47	52	19	**14**
Total	1762	2108	2236	2334	2412	**2450**

*: No. of Cases

Table 2. Purpose of Radiation Therapy

	No. of All Treated Patients					
	2006	2007	2008	2009	2010	**2011**
No. of Treatment Plans	1762	2108	2236	2334	2412	**2450**
Curative Intent	1033	1393	1535	1500	1587	**1662**
Palliative Treatment	729	715	701	834	825	**788**
Curative/Palliative	1.42	1.95	2.19	1.80	1.92	**2.11**
New Patients	1197	1234	1181	1210	1277	**1690**

Table 3. Special Radiation Therapy

	No. of Treated Patients			
	2008	2009	2010	**2011**
IORT	0	0	0	**1**
TBI	23	38	41	**52**
SRT-Brain	4	6	3	**2**
SRT-Body	10	20	33	**45**
Intracavitary RT ^{192}Ir-HDR	32	41	50	**49**
Intracavitary RT ^{192}Ir-LDR	1	0	0	**0**
Interstitial RT ^{192}Ir-HDR	10	22	6	**25**
Interstitial RT ^{192}Ir-LDR	0	0	0	**0**
Interstitial RT ^{198}Au-LDR	6	6	6	**4**
Interstitial RT ^{125}I-LDR	0	16	26	**16**
Interstitial RT ^{106}Ru-LDR	27	7	10	**13**
Non-Sealed Radionuclide Therapy ^{89}Sr	3	3	5	**12**
Non-Sealed Radionuclide Therapy ^{131}I	0	1	14	**21**

IORT ; intraoperative radiotherapy
TBI ; total body irradiation

Published Papers

1. Okamoto H, Kohno T, Kanai T, Kase Y, Matsumoto Y, Furusawa Y, Fujita Y, Saitoh H, Itami J. Microdosimetric study on influence of low energy photons on relative biological effectiveness under therapeutic conditions using 6 MV linac. Med Phys, 38:4714-4722, 2011

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4. Kuroda Y, Hosoya T, Oda A, Ooki N, Toyoguchi Y, Murakami M, Kanoto M, Sugawara C, Honma T, Sugai Y, Nemoto K. Inverse-direction scanning improves the image quality of whole carotid CT angiography with 64-MDCT. Eur J Radiol, 80:749-754, 2011

DEPARTMENT OF PATHOLOGY AND CLINICAL LABORATORIES, PATHOLOGY DIVISION

Hitoshi Tsuda, Ryoji Kushima, Koji Tsuta, Akiko Maeshima, Hirokazu Taniguchi, Masayuki Yoshida, Akihiko Yoshida, Yuko Sasajima

Introduction

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

Routine Activities

In 2011, a total of 15 board-certified pathologists, 6 residents and 11 medical technologists, including 10 cytotechnologists, cooperatively performed routine histological and cytopathological diagnosis of specimens obtained at the National Cancer Center Hospital (NCCH) and the Research Center for Cancer Prevention and Screening, and education of the residents. Seven pathologists working exclusively in the NCCH also shared management of the division with regard to infrastructures, risk and human errors, improvement of environment including ventilation of formalin and noxious organic solvents, and so on. Another 7 pathologists were concurrently the staff of the NCC Research Institute (NCCRI) and another one was also the staff of the Center for Cancer Control and Information Services (CCCIS).

1. Surgical pathology

A total of 18,413 histological diagnoses were provided consisting of 15,288 biopsy specimens including 1,858 intraoperative frozen sections and 3,642 surgically resected specimens. The intraoperative frozen sections comprised primary tumors, regional lymph nodes, and surgical margins of specimens. The one-step nucleic acid amplification (OSNA) assay was performed for 374 sentinel lymph nodes to examine metastasis intraoperatively.

2. Cytopathology

Cytopathological diagnoses were provided for a total of 10,232 patients including 402 for intraoperative diagnosis. The specimens comprised smears, sputa, body fluids, urine, and needle aspirates submitted from various departments. Intraoperative cytological examination of body fluids was utilized for disease staging and treatment decisions in the fields of gastric surgery and gynecology.

3. Autopsy

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

4. Conferences

Clinicopathological case conferences were held periodically by diagnostic and treatment groups for cancers of specific organs. The members also participated in the tumor board. We had also monthly joint conferences with the Pathology Division, the NCC East, and trimonthly multi-institutional pathology TV conferences.

Research Activities

In order to improve the quality of pathology practice in future, research projects were conducted in various fields. To establish the basis for the promotion of research activities, we were involved in the construction of the Tsukiji Biobank and reference data base in collaboration with other departments.

1. Gastrointestinal tract

Staff members contributed to multicenter studies on the extramural discontinuous cancer spread in colorectal cancer and on the risk of lymph node metastasis of pedunculated-type early colorectal cancer. The 9th Japan-Korea gastrointestinal-meeting was held, and interobserver variation in the diagnosis of gastric dysplasia and carcinoma was analyzed. The HER2 status and molecular detection of lymph-node metastasis of gastric cancer were studied.

2. Lung and mediastinal tumors

Clinicopathological features of lung carcinomas with *ALK* translocations were studied in the largest case series so far, and diagnostic criteria were proposed for the detection of *ALK* translocation by an *in situ* hybridization test. The utilities of EGFR mutation-specific antibody and of an antibody panel to differentiate squamous cell carcinoma from adenocarcinoma were examined. The diagnostic significances of mitotic counting, phosphohistone H3 immunohistochemistry, and spindle cell and oncocytic features were evaluated in neuroendocrine lung carcinoma. Hormone receptor expression was detected in thymic tumors.

3. Breast and gynecological pathology

MET amplification and PIK3CA mutation were shown to be involved in the genesis and progression of ovarian clear cell carcinoma (OCCC). Histological criteria were proposed for grading OCCC for the purpose of prognosis and for evaluating the therapeutic effect of radiofrequency ablation in early breast cancer. A study to standardize the diagnostic criteria of lobular endocervical glandular hyperplasia of the uterine cervix was conducted in collaboration with gynecologists, diagnostic radiologists, and pathologists.

4. Hematological and soft tissue tumors

Cases of follicular lymphoma with monocytoid/plasmacytoid differentiation and a case of pulmonary epithelioid hemangioendothelioma were reported.

Central pathology review in clinical trials and quality assessment

Central pathology review was performed in clinical trials of breast and gynecological cancers. A study of nationwide quality assurance program for HER2 and hormone receptor tests has been launched.

Table 1. Numbers of Cytopathological Specimens Diagnosed in the Pathology Section in 2011

Field	Number of specimens
	Total
Gynecology	3656
Urology	2872
Respiratory organs	1175
Gastrointestinal tracts	679
Hepatobiliary and Pancreas	380
Head and Neck	175
Breast	130
Hematology	117
Others	159
Research Center for Cancer Prediction and Screening	889
Total	10232

Table 2. Numbers of Autopsies Performed in the Pathology Section in 2011

Department/Division	Number
Hematology and Hematopoietic Stem Cell Transplantation	9
Breast and Medical Oncology	5
Urology	5
Thoracic Oncology	4
Dermatology	3
Neurosurgery	1
Esophageal Surgery	1
Total	28

Table 3. Case Conferences Held Periodically at the Pathology Section

Day	Time	Name of conference	Participants	Frequency
Mon.	16:00-17:00	Monday conference (Jan.-Mar., Sep.-Dec.)	All staff, NCC Hospital East	Monthly
	17:00-18:00	Autopsy conference	All staff, physicians in charge	Monthly
Tue.	17:00-18:00	Gynecological pathology conference	Gynecology Group	Monthly
	1700-19:00	Lymphoma conference	Hematology group	Weekly
	18:00-19:30	Breast cancer pathology workshop	Breast cancer group	Monthly
	12:00-13:00	Pulmonary cytology conference	Pulmonary endoscopy group	Weekly
Wed.	14:00-17:00	GI gross conference	Gastroenterology group	Weekly
	17:30-18:30	GI endoscope conference	Gastroenterology group	Weekly
	18:00-19:00	Gastric histopathology conference	Gastroenterology group	Monthly
	18:30-19:30	Urologic pathology conference	Urology group	Monthly
Thu.	14:00-15:00	Brain tumor pathology conference	Neurosurgery group	Monthly
	18:00-20:00	Hepatobiliary and pancreatic pathology conference	Hepatobiliary and pancreas group	Biweekly
	18:00-19:00	Bone and soft tissue tumor conference	Orthopedics group	Monthly
Fri.	07:15-08:30	Gastric pre-surgery case conference	Gastric surgery group	Weekly
	07:30-08:30	Pulmonary pre-and post-surgery case conference	Pulmonary surgery group	Weekly
	14:30-15:30	Skin tumor pathology conference	Dermatology group	Monthly
	18:00-20:00	Esophageal histopathology conference	Esophageal surgery group	Monthly

Published Papers

1. Ueno H, Mochizuki H, Shirouzu K, Kusumi T, Yamada K, Ikegami M, Kawachi H, Kameoka S, Ohkura Y, Masaki T, Kushima R, Takahashi K, Ajioka Y, Hase K, Ochiai A, Wada R, Iwaya K, Nakamura T, Sugihara K. Actual status of distribution and prognostic impact of extramural discontinuous cancer spread in colorectal cancer. J Clin Oncol, 29:2550-2556, 2011

2. Kushima R, Kim K-M. Interobserver Variation in the Diagnosis of Gastric Epithelial Dysplasia and Carcinoma between Two Pathologists in Japan and Korea. J Gastric Cancer, 11:141-145, 2011

3. Tsuta K, Kalhor N, Raso MG, Wistuba II, Moran CA. Oncocytic neuroendocrine tumors of the lung: histopathologic spectrum and immunohistochemical analysis of 15 cases. Hum Pathol, 42:578-585, 2011

4. Tochigi N, Tsuta K, Maeshima AM, Shibuki Y, Asamura H, Hasegawa T, Tsuda H. Malignant pulmonary epithelioid hemangioendothelioma with hilar lymph node metastasis. Ann Diagn Pathol, 15:207-212, 2011

5. Tsuta K, Raso MG, Kalhor N, Liu DC, Wistuba II, Moran CA. Sox10-positive sustentacular cells in neuroendocrine carcinoma of the lung. Histopathology, 58:276-285, 2011

6. Tsuta K, Raso MG, Kalhor N, Liu DD, Wistuba II, Moran CA. Histologic features of low- and intermediate-grade neuroendocrine carcinoma (typical and atypical carcinoid tumors) of the lung. Lung Cancer, 71:34-41, 2011

7. Hatanaka K, Tsuta K, Watanabe K, Sugino K, Uekusa T. Primary pulmonary adenocarcinoma with enteric differentiation resembling metastatic colorectal carcinoma: a report of the second case negative for cytokeratin 7. Pathol Res Pract, 207:188-191, 2011

8. Tsuta K, Kalhor N, Wistuba II, Moran CA. Clinicopathological and immunohistochemical analysis of spindle-cell carcinoid tumour of the lung. Histopathology, 59:526-536, 2011

9. Kozu Y, Tsuta K, Kohno T, Sekine I, Yoshida A, Watanabe S, Tamura T, Yokota J, Suzuki K, Asamura H, Furuta K, Tsuda H. The usefulness of mutation-specific antibodies in detecting epidermal growth factor receptor mutations and in predicting response to tyrosine kinase inhibitor therapy in lung adenocarcinoma. Lung Cancer, 73:45-50, 2011

10. Mimae T, Tsuta K, Takahashi F, Yoshida A, Kondo T, Murakami Y, Okada M, Takeuchi M, Asamura H, Tsuda H. Steroid receptor expression in thymomas and thymic carcinomas. Cancer, 117:4396-4405, 2011

11. Tsuta K, Liu DC, Kalhor N, Wistuba II, Moran CA. Using the mitosis-specific marker anti-phosphohistone H3 to assess mitosis in pulmonary neuroendocrine carcinomas. Am J Clin Pathol, 136:252-259, 2011

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DEPARTMENT OF PATHOLOGY AND CLINICAL LABORATORIES, CLINICAL LABORATORIES DIVISION

Ryuji Tanosaki, Koh Furuta

Introduction

The Clinical Laboratories Division, together with the Pathology Division, provides an important service as in-hospital diagnostic unit by examining laboratory specimens and screening for disorders. This division is largely divided into 5 subdivisions. The first subdivision is the clinical laboratory assembly including urinalysis, hematology, biochemistry, endocrinology, immunology, tumor markers and molecular diagnostics. The other subdivisions are the phlebotomy section, the bacteriology laboratory, the blood transfusion service, and physiologic examination facilities consisting of ultrasonography, electrocardiography, electroencephalography, and respiratory function. Along with the transition of our hospital status to an Independent Administrative Institution (IAI), the Clinical Laboratory Division was reorganized and is mainly supervised by 2 medical doctors since June 2010; one medical doctor (K.F.) is responsible for the clinical laboratory assembly, and the other (R.T.) manages the blood transfusion service and supervises the phlebotomy section. The phlebotomy section, which is located adjacent to the outpatient clinics on the 2nd floor, has officially belonged to our division since 2010. The bacteriology laboratory is also supervised by a staff physician of the Infectious Control Team (ICT). The physiologic examination facilities are managed by staff physicians from the corresponding departments.

All the clinical laboratories support clinicians in patient care by providing laboratory data, which are subject to strict quality control, and by accepting consultations from members of the medical staff.

Since last year, we have been preparing to obtain an ISO 15189, which is a medical laboratory-oriented accreditation for quality and competence by the International Organization for Standardisation's Technical Committee 212 (ISO/TC 212). This will be a good opportunity to reorganize and maintain a high-quality management system.

Routine Activities

Two medical doctors, 35 full-time and 8 part-time medical technologists, and 4 assistants provide services. An administrative meeting is held weekly, attending members of which consist of three medical doctors from the Pathology Division and two medical doctors from the Clinical Laboratory Division, and the head and vice-head medical technologists. The laboratory management meetings are regularly held twice a month for quality control of laboratory operations. Our Division also participates in several domestic and international programs for inter-laboratory standardization and quality control including the CAP (College of American Pathologists) Survey.

In the molecular diagnostic laboratory, the examinations for mutations, which might exist in certain genes such as epidermal growth factor receptor (EGFR), are performed using fluorescence in situ hybridization (FISH) and high-resolution melting analysis (HRMA) to determine the eligibility of the targeted therapy. As the number of target diseases increases, the kinds and the number of these molecular tests are also increasing.

The phlebotomy section is equipped with an automated system, BC ROBO™, which enables the automatic labeling and selection of blood collection tubes. It facilitates the blood sampling and also allows us to analyze the number and the waiting time of each patient. The working group meeting, consisting of medical doctors, all chief medical technologists and the chief outpatient nurse, is held once a month in order to provide better services to patients and to secure procedural safety.

The blood transfusion service specifically employs 4 medical technologists, including 1 transfusion-accredited member. An absolute hemo-vigilant system has been established in our institution. Reports regarding any adverse events, which might occur associated with blood transfusion, are automatically sent to the blood transfusion laboratory, and a medical technologist makes a round in the ward to collect precise information. Because about 5% of platelet transfusions are associated with non-hemolytic adverse events probably due to certain substances in the plasma of the blood products, the removal of the supernatant is performed by request of clinical

physicians. Special attention is paid to confirming the ABO types of blood products, as many patients undergo allogeneic hematopoietic stem cell transplantation from an ABO-mismatched donor in our institution, to whom mismatched ABO-blood products are intended to be transfused to prevent adverse immunologic reactions.

Research Activities

An in-hospital bio-bank, which was established in 2002, has been maintained for use by various researchers, and more than 800,000 samples have been cryo-preserved as of the end of 2011.

The project of another larger-scale comprehensive bio-bank is underway in collaboration with the CCCIS, NCCRI, and NCC for the purpose of future progress in cancer research, and our division will contribute to it in phlebotomy and processing of clinical materials (see also the Pathology Division).

Flow cytometers are used for analysis of the surface markers of leukemia and lymphoma cells and for confirmation of blood cell types for routine examinations as well as for research purposes: investigations are performed into the kinetic analysis of infused platelets, enumeration of hematopoietic stem cells and analysis of donor-chimerism after HLA-mismatched hematopoietic stem cell transplantation. The project of development of a new enumeration technique of hematopoietic stem cells, which was started in 2006, is continuing in collaboration with a medical diagnostic company.

The chief doctor (R.T.) participates in the establishment of nationwide guidelines for standard cell-processing procedures as a committee member of the corresponding academic societies. He also contributes to transplantation activities, especially for adult T-cell leukemia-lymphoma, and in cord blood transplantation with the support of a grant for an Anti-Cancer Project from the Ministry of Health, Welfare and Labour of Japan, and as a member of the National Marrow Bank.

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SURGICAL CENTER

Hitoshi Katai

Introduction

The Surgical Center deals with all kinds of malignant neoplasm. Our mission is to provide safe surgical care to the patients (Safe Surgery Saves Lives). Several groups collaborate to ensure the best surgical care, consisting of anesthesiologists, surgeons from 15 surgical oncology groups, nurses, and medical-technical staff with support staff from Radiology and the Laboratory. The Plastic Surgery and Pediatric Surgery Groups have newly joined this year.

Routine Activities

During 2011, the Surgical Center supported more than 4,500 surgical cases and more than 3,900 general anesthesia surgical cases, a slight increase in the number of cases and a 2.4% increase in general anesthesia cases over 2010. Sentinel node navigation surgery in breast cancer, autonomic nerve preservation proximal gastrectomy with jejunal interposition in early gastric cancer, hepatectomy and pancreatectomy in patients with hepato-biliary and pancreas diseases, and placement of an artificial urinary sphincter for bladder incontinence after prostate cancer treatment are unique treatments in our institution (http://www.ncc.go.jp/jp/about/mission.html), and occasionally performed in the Surgical Center. Over the years, minimally invasive procedures have increased remarkably. Endobronchial brachytherapy under general anesthesia in lung cancer and endoscopic resection under general anesthesia in GI cancer are also unique treatments (http://www.ncc.go.jp/jp/about/mission.html), and are carried out in the Surgical Center.

A new operative field monitor and operation room monitor have been introduced to ensure safe operations. Peri-operative information management systems have been introduced into the clinical practice to facilitate the anesthesiologists' and nurses' work.

The Surgical Center staff works as part of a multidisciplinary team active in planning the best utilization of operating rooms. Scheduling, equipment usage, and staffing in the 15 operating suites were evaluated to establish an optimal work flow, streamline room turnover, and improve start times.

Education and Training

All surgical oncology groups have their own training programs for their fellows with the support of the Surgical Center staff. Our center also provides virtual reality simulators to allow fellows to develop the skills used in laparoscopic and thoracoscopic surgery. About 40 foreign doctors have visited our surgical center.

Table 1. Total number of operations

	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Anesthesia													
General	113	111	132	116	126	130	127	143	109	119	136	128	1487
General and epidural	201	219	226	203	178	192	180	205	224	209	201	212	2450
Epidural and lumbar	0	0	1	0	0	1	2	0	1	0	0	0	5
Epidural and lumbar	0	0	0	0	0	2	2	1	0	1	0	0	6
Lumbar	12	13	15	10	15	11	13	14	7	8	19	7	144
Local	37	32	31	35	27	39	31	33	27	47	38	49	426
Others	0	2	0	0	0	0	0	0	0	0	0	0	2
Total	363	377	405	364	346	375	352	396	368	384	394	396	4520

Table 2. Number of general anesthesia cases

	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Neurosurgery	8	8	12	11	11	7	8	16	10	9	10	10	120
Opthalmology	21	21	24	27	23	27	23	25	30	25	24	23	293
Head & Neck Surgery	11	12	18	11	9	10	13	16	11	13	12	13	149
Breast Surgery	43	41	47	36	42	44	42	45	29	37	38	35	479
Thoracic Surgery	41	38	32	43	34	41	35	41	42	41	45	58	491
Esophageal Surgery	12	10	13	12	12	8	11	11	17	16	15	11	148
Gastric Surgery	38	38	43	38	31	34	36	37	38	34	42	46	455
Colorectal Surgery	42	54	53	47	37	38	40	44	50	47	40	41	533
Hepatobiliary & Pancreatic Surgery	15	19	23	22	28	21	20	20	22	23	20	26	259
Gynecology	19	19	24	22	16	13	16	18	17	17	18	11	210
Urology	21	19	24	18	19	27	21	18	21	24	21	19	252
Dermatology	7	8	8	8	8	8	6	14	6	8	12	7	100
Orthopedic Surgery	18	17	17	17	20	22	20	30	28	20	27	25	261
Others	18	26	20	7	14	22	16	13	12	14	13	15	190
Total	314	330	358	319	304	322	307	348	333	328	337	340	3937

CLINICAL TRIAL COORDINATION (& SUPPORT) OFFICE

Hiroyuki Terakado

Introduction

the Clinical Trial Coordination (& Support) Office aims to promote clinical trials on unapproved drugs and medical devices, with the goal of allowing patients to receive the benefits arising from life science research as quickly as possible.

The task of the Clinical Trial Coordination (& Support) Office is to facilitate smooth implementation of industry-sponsored registration trials ("*Chiken*"), physician-initiated registration directed clinical trials ("*Ishi-shudou-chiken*") and other clinical research studies (investigator-initiated trials)

This office consists of 3 divisions (the Clinical Trial Coordination Division, the Physician-initiated Registration-directed Clinical Trials Support Division and the Clinical Data Management Division). The staff members, nurses, pharmacists and laboratory technologists, participate in this division independently from outpatient divisions, wards, the nursing division and pharmacy, thus breaking through the conventional framework of profession-based organizations.

Routine Activities

The Clinical Trial Coordination (& Support) Office supports a lot of the industry-sponsored registration trials ("*Chiken*") as well as the physician-initiated registration directed clinical trials ("*Ishi-shudou-chiken*"). A total of 22 CRCs (clinical research coordinators), support these trials. The number of the industry-sponsored registration trials is increasing year by year, and we supported 165 registration-directed clinical trials including 4 physician-initiated registration directed clinical trials in 2011 (Table 1). The Clinical Data Management Division supports 20 clinical trials.

The number of the supported clinical trials is increasing as previously described, and the supporting area covered by the CRCs will be expanded to include not only registration trials but also other investigator-initiated clinical trials. Therefore, the expansion of CRC staff members is highly anticipated. In view of the plan for our hospital, all members of this Office will work together to contribute to reinforcing the clinical research capabilities of our hospital and to making this Office a valuable unit for all members of this hospital.

Table 1. Registration-directed Clinical Trials ("*Chiken*") including Investigator-initiated Registration-directed Clinical Trials

Department	Eligible Cancer Type	Trial Phase	number of trials
Department of Neurosurgery and Neurooncology			4
	Glioma	Phase II	1
		Phase III	1
	Glioblastoma	Phase III	2
Department of Breast Oncology and Medical Oncology			
Breast and Medical Oncology Division			24
	Breast cancer	Phase I	1
		Phase II	3
		Phase III	6
		Post-marketing	2
	Ovarian cancer	Phase II	1
	Ovarian cancer/Fallopian tube cancer/Peritoneal cancer	Phase I	1
		Phase III	2
	Cervical cancer	Phase III	1
	Uterine corpus cancer	Phase II	1
	Soft tissue tumors	Phase I	1
	Solid tumors	Phase I	4
	Neutropenia	Phase III	1
Breast Surgery Group			1
	Breast cancer	Phase III	1

Department of Thoracic Oncology			
Thoracic Oncology Division			30
	Solid tumors	Phase I	12
	Lung cancer	Phase I	4
		Phase I/II	2
		Phase II	3
		Phase III	7
		Post-marketing	2
Thoracic Surgery Division			1
	Lung cancer	Phase III	1
Department of Gastrointestinal Oncology			
Gastrointestinal Medical Oncology Division			17
	Colon cancer	Phase II	2
		Phase III	1
		Post-marketing	1
	Gastric cancer	Phase III	6
	Esophageal cancer	Phase I	1
		Phase I/II	2
		Phase II	1
	GIST	Phase III	2
	Solid tumors	Phase I	1
Department of Hepatobiliary and Pancreatic Oncology			
Hepatobiliary and Pancreatic Oncology Division			27
	Hepatocellular cancer	Phase I	1
		Phase I/II	3
		Phase III	9
	Pancreatic cancer	Phase I/II	1
		Phase II	4
		Phase II/III	1
		Phase III	1
		Post-marketing	1
	Pancreatic endocrine tumors	Phase II	1
		Phase III	1
	Neuroendocrine tumor	Phase I/II	1
	Solid tumors	Phase I	3
Department of Urology			5
	Renal cell cancer	Phase II	2
		Phase III	1
	Bladder cancer	Phase I/II	1
	prostatic cancer	Phase I/II	1
Department of Orthopedic Surgery			3
	Soft tissue sarcoma	Phase II	1
		Phase III	1
	Soft tissue tumors, Bone tumors	Phase II	1
Department of Dermatologic Oncology			2
	Malignant melanoma	Phase II	1
		Phase III	1
Department of Hematology, and Hematopoietic Stem Cell Transplantation			
Hematology Division			38
	Malignant lymphoma	Phase I	9
		Phase I/II	2
		Phase II	6
		Phase III	8
	Leukemia	Phase I	3
		Phase I/II	2
		Phase II	1
		Phase III	1
	Multiple Myeloma	Phase I	2
		Phase I/II	2
	MDS	Phase I/II	1
	Hematopoietic organ tumor	Phase I	1
Hematopoietic Stem Cell Transplantation Division			2
	Allogenic stem cell transplant	Phase I	1
		Phase I/II	1
Department of Pediatric Oncology			3
	Nausea/Vomiting	Phase III	1
	Candidiasis, Aspergillosis	Phase II	1
	malignant tumor	Phase I	1
Department of Palliative Care and Psycho-Oncology			
Palliative Care Division			1
	Cancer pain	Phase III	1
Department of Diagnostic Radiology			4
	Hepatocellular cancer	Phase II	2
	hypervascular cancer	medical device	2
Department of Radiation Oncology			1
	Nausea/Vomiting	Phase II	1
Total			165

As of December 2011

NUTRITION MANAGEMENT OFFICE

Setsuko Kuwahara, Masahiro Sunaga, Hiroki Matsubara, Hiroko Takashima

Introduction

2011 was the year for working on a number of research activities for the Nutrition Management Office.

Improving taste disorders as development of supportive care was initiated as a research project. During cancer treatment, many patients have experienced a decrease in appetite and QOL, and it is believed that improving appetite could improve successful treatment rates.

In addition, dietitians and chefs, in order to enhance the ward activities, began ward catering. This aims to review how to improve our team medical care as well as to deliver nutrition care directly and immediately to patients and families. This initiative will enhance the Nutrition Support Team (NST) activity. Five years ago, our Office began working on the nutritional assessment of cancer patients, including the measurement of resting metabolic changes in patients during treatment, and we have continued to accumulate data on post-surgical status following, for example, esophageal surgery and hepatobiliary-pancreatic surgery. In addition, the Office has placed a strong emphasis on planning meals, menu improvements and personal support, based on the comments received from patients regarding their food on a dedicated Food Comments Form: in fact, this form as of December 2011 was being returned by 54% of patients, so the rich data from these comments has been of great assistance to the office, and we believe that our actions on the feedback help to complement the patients' total treatment.

Routine Activities

Dietary meals totaled 549,511 in 2011, and we gave nutrition-related dietary advice to 2,025 persons. There have been 599 requests for consultation to the NST 50 per month on average, and this aspect of the Office has shown strong growth by 20% annually. Following the establishment of the Departments of Gastroenterology and Stem Cell Transplantation, they became in particularthe most active as far as consultations was concerned, as seen in Table 1. The Office also aims to enhance our nutritional teaching content. Following our experience of publishing two books for 100-day recipes for patients who have undergone ovarian cancer surgery and uterine colorectal surgery, we were involved in the publication of a 100-day recipe book for those who have undergone esophageal surgery, designed as a reference book for the nutritional management of patients after discharge. As for food service, improvements were carried out regarding breakfasts. In the field of human resource development, we have a strong commitment to education and training and we conducted 10 University courses for registered dietitians within the University. By strengthening our cooperation with universities, our aim is to enhance research activities in the future through the development of human resources.

Research Activities and National Workshops

1) The Nutritional Management Workshop for Cancer Patients continues educational activities to underline the importance of nutritional management and giving opportunities to learn practical techniques to maintain such management. In 2011, it celebrated its 30th anniversary, in Okayama, with "Nutrition Past, Present and Future" being the title of the the President's lecture.
2) The Hospital Group for Disease Prevention Study Group of Japan, under the slogan Beneficial and Smooth Formula Diet", investigated the development of the effective use of rice powder in a study of hospital food intake.
3) In cooperation with nutritionists of the Nutritional Management of Cancer Course we held lectures to help target the general public regarding a cancer-preventative diet (Venues: Akita, Tokyo, Toyama, Nagano, Iwate, band Kanagawa)
4) Research project
   ① Survey of dysgeusia
   ② Full medical team. Enhance and expand the role of the dietitian
   ③ Studies on nutrition in the surgical treatment of esophageal cancer
   ④ Perioperative nutritional assessment after pancreaticoduodenectomy

Future Prospects

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

Table 1. Number of NST consultations in 2011

Clinical Departments	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sept	Oct	Nov	Dec	total
Esophageal Surgery	5	4	4	2	2	1	4	3	5	4	2	2	38
Head and Neck Surgery		2	1	2	3	1	1	2	1	2			15
Gastrointestinal Medical Oncology	18	14	6	11	11	8	11	5	7	8	9	6	114
Hematopoietic Stem Cell Transplantation	12	8	10	11	11	8	9	9	9	10	14	5	116
Thoracic Oncology	5	4	8	2	6	4	5	6	2	1	5	2	50
Thoracic Surgery			1	1			1	1	2	1			7
Hepatobiliary and Pancreatic Oncology	2	2	1	1		4	8	2	3	4	1		28
Hepatobiliary and Pancreatic Surgery	4	1	5	2	3	4	3	4	2	1	1	1	31
Breast Oncology and Mecal Oncology	1	2	1	2	8	10	7	5	5	4	6	7	58
Gynecology			1	2	2	5		1	1	2	1		15
Neurosurgery and Neuro-Oncology	1			1	1		1		2			2	8
Gastric Surgery	2		1		1			1	1	2	2		10
Colorectal Surgery	2	2	1	1	1	1	1		1	1			11
Urology	3	3	3	6	1	3	2	3	2	1	2	4	33
Pediatric Oncology		2		1	1	1						5	10
Orthopedic Surgery	1	1	1	1				2		3	1		10
Dermatologic Oncology			1	1	4	2	2	1	1	1			13
Hematology			1	2	2	1			2	3	2	3	16
Radiation Oncology	1	1	1	1	1	2	1	1	1	4		2	16
Total	57	46	47	50	58	55	56	46	47	52	46	39	599
												mean	50

HEALTH INFORMATION MANAGEMENT OFFICE

Hiroshi Nishimoto, Shinobu Fukuoka, Hisayo Nishizawa

Introduction

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

Routine Activities

Auditing Discharge Summary (Quantitative inspection)

Data on discharge summaries should be entered by the attending physician. We inspected and checked about 10,000 summaries and, where required, gave some advice regarding correct input.

National Cancer Center Hospital Cancer Registry (Hospital-based Cancer Registry)

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

Table. National Cancer Center Hospital Cancer Registry

Year of Diagnosis	Number of New Cancer Cases		
	Total	Male	Female
2008	6,684	3,929	2,755
2009	6,721	3,895	2,826
2010	6,636	3,926	2,710

DEPARTMENT OF PHARMACY

Hiroshi Yamamoto

Introduction

The Pharmacy stores and dispenses drugs, prepares injections (including aseptic mixtures), collects and disseminates drug information and provides patients with guidance regarding the proper use of drugs. Its services have improved in response to the hospital's goal of envisaging the highest quality of medical care, practice and research. A state-of-the-art computerized system and other pharmacy-related equipment ensure quality control and inventory management, promote the proper use of drugs, and enhance the efficiency and quality of our services.

Routine Activities

As part of the fundamental function of the hospital, the Pharmacy prepares and dispenses oral and topical medicines and injections for individual patients. All outpatients and inpatients are provided with aseptic mixtures of injectable chemotherapy agents prepared in the Pharmacy. The importance of providing drug information to patients has been widely acknowledged. Clinical pharmacists visit inpatients and give advice on taking medicine, focusing especially on pain control with opioids, and participate in the palliative-care support team. The Pharmacy also provides outpatients with guidance in the proper use of opioids and anti-cancer agents.

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

A physician places an order through the hospital's computerized electric medical record system. The prescription order is then redirected to the medicine-package-printing system which provides drug information. The medicine-package information and easy-to-understand-by-patients explanations and instructions for the proper use of drugs, such as regarding efficacy and effectiveness, precautions, and guidance concerning symptoms at the early stage of adverse reactions, are automatically printed out for patients when a prescription is ordered.

The injection-order is directly linked to an automatic "picking system" device, and this linkage ensures that injections are made properly and efficiently. This injection-ordering system contains an additional function, a regimen-ordering system for anti-cancer drugs which makes it possible to check the dose as well as the interval of chemotherapy. In 2011, Pharmacy acquired a robot which prepares injection preparations without human assistance.

Research Activities

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

Information Services

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

the general public and medical experts outside the hospital.

Education and Training

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

Table 1. Number of Prescriptions

	FY 2010	FY 2009
1) Oral and topical preparations		
Prepared in the hospital pharmacy	141,536	134,627
Inpatients	128,566	122,391
Outpatients	12,970	12,236
Taken to outside pharmacies	66,080	63,528
(% of prescription filled outside)	83.6	83.8
2) Injections		
Inpatients	289,568	299,950
Outpatients	34,097	34,936

Table2. Amounts of Drugs Consumed

	FY 2010 (including sales tax)	(%)	FY 2009 (including sales tax)	(%)
Total	4,564,239	100.0	4,901,870	100.0
Internal medicines	407,375	8.9	364,297	7.4
External	33,747	0.7	44,716	0.9
Injection	3,129,818	68.6	3,478,960	71.0
Narcotics	154,469	3.4	153,149	3.1
Blood	430,021	9.4	413,673	8.4
X-ray imaging	249,640	5.5	297,318	6.1
RI	108,945	2.4	91,941	1.9
Others	50,223	1.1	57,816	1.2

Unit:1000 yen

Table 3. Aseptic Preparation of Injectable Drugs

	FY 2010	FY 2009
Anticancer Drugs	59,552	51,071
Others	32,112	34,936

Table 4. House Preparations

	FY 2010	FY 2009
Sterilized	103	93
Nonsterilized	138	131

Table 5. Investigational Drugs

	FY 2010	FY 2009
Newly registered	46	52
Ongoing study	109	106
Total	155	158

NURSING DIVISION

Misae Maruguchi

Activities of the Nursing Division

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

1) Continuous Nursing for Cancer Survivorship

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

We adopted the two-shift nursing system in 10 units, comprising an 8-hour day shift and a 16-hour night shift. Inpatient unit nurses work together more as closely than nurses in an outpatient clinic. Moreover, we have strengthened the support for the patient discharge process so that patients can return earlier to their own home or area.

We are accepting and meeting the challenge to provide many patient education programs produced by Certified Nurse Specialists and Certified Nurses. We have 10 patient education programs. Many patients and families have participated in the educational program for their self-care and survivorship in their daily life.

2) Educational Activities

(1) Assist and support new nurses

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

(2) Development knowledge and skills for cancer nursing

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

We have 9 specialized nurse training courses: Cancer chemotherapy nursing I and II; Clinical trial nursing; Palliative care nursing I and II; Lymphedema care; Wound care nursing; Dysphagia nursing; and Radiotherapy and IVR nursing. A total of 198 nurses have participated, all of whom have over 4 years' nursing experiences. Many nurses want to participate in the courses. Through evaluation of the result of these courses this year, issues in the future are to improve the educational content for nurses to enable career development.

3) Certified Nurse Specialists and Certified Nurses

Currently, 7 certified nurse specialists and 22 certified nurses are working at the National Cancer Center Hospital. They represent the role model for cancer nursing practice in both the inpatient and outpatient settings. The number of consultations is increasing, which proves that the use of Certified Nurse Specialists and Certified Nurses is being accepted by the nurses in this hospital.

As members of teams where different professionals work together in special areas, such as infection control, palliative care, nutritional support, and care of decubitus ulcers, these Certified Nurses contribute to effective cooperation. The identification of problems and discussions from the point of view of multidisciplinary teams serve as a good model for other nurses and provide an important educational role in the clinical setting.

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

staffs.

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

4) Research Activities and Publications

We presented 10 studies on nursing at some annual conferences in 2011. One of those studies was "Problems and needs related to physical and psychosocial rehabilitation at long-term follow-up nursing consultation for allogeneic hematopoietic stem cell transplantation recipients in Japan", which was presented by our Certified Nurse Specialist in Cancer Nursing at the ASBMT/CIBMTR annual conference in the US.

This year, we organized the Nursing Research Committee, the members of which must have a master's degree or a doctor's degree. They must also have sufficient experience regarding nursing research activities. They support nurses to challenge nursing research based on their clinical questions. We expect our nurses from the National Cancer Center Hospital to create and develop cancer nursing to even higher levels of proficiency and expertise.