Hospital

Preface

The National Cancer Center Hospital (NCCH) has always set goals in accordance with the principles of striving for the highest level of patient care and clinical research.

The role of the NCCH should cover all facets of medical practice, such as diagnosis and treatment, as well as clinical research to explore better treatment procedures. To provide the most suitable patient care in cancer to all the people in Japan, we must develop new modalities, then evaluate, standardize and share them with domestic and international hospitals. Medical practice should be a constantly advancing field, so our mission includes the development of new agents, devices, techniques and methods for diagnosis and treatment, and also patient support such as palliative symptom control, mental care, family care, appearance care, and so on. We endeavor to be the most active and example of a state-of-the-art cancer hospital in Japan.

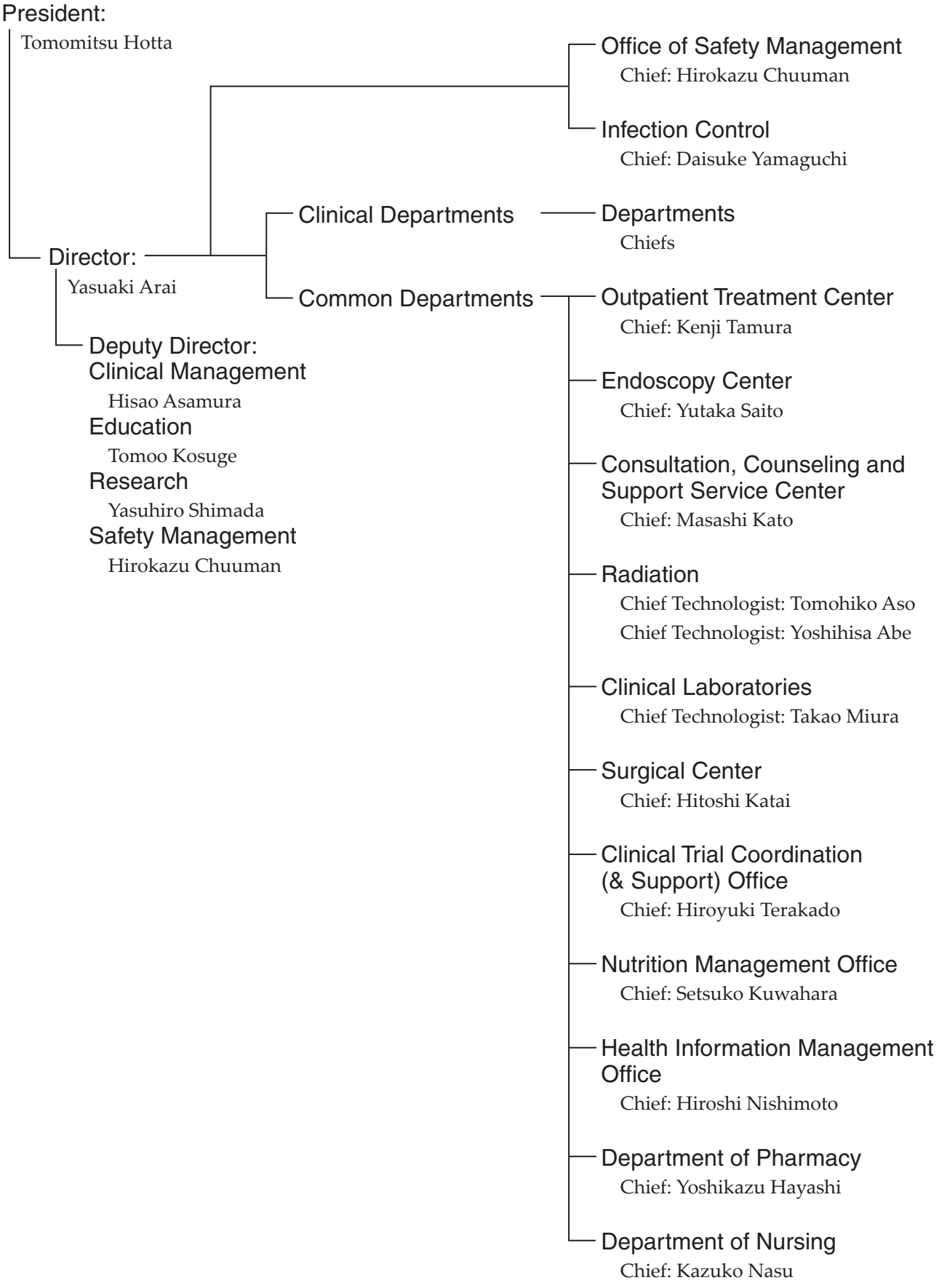
On July 2012, we reorganized the department structures into 30 clinical sections and 11 central clinical facilities to clarify each of their roles and to allow each of them to devote their full attention to their responsibilities.

All members of staff continue to make a full effort to develop better cancer patient care and to be the most reliable medical partner for patients as professionals.

It is my great pleasure and honor to present the summary of our achievements in 2012, and I appreciate your understanding of our recent efforts and results in our ongoing progress towards the continuous advancement of cancer patient care.

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

Organization



Clinical Departments

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

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  Chief: Soichiro Shibui
- Department of Ophthalmic Oncology
  Chief: Shigenobu Suzuki
- Department of Head and Neck Surgery
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- Department of Plastic and Reconstructive Surgery
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  Chief: Masahiko Kusumoto
- Department of Radiation Oncology
  Chief: Jun Itami
- Departments of Pathology, Clinical Laboratories
  Chief: Hitoshi Tsuda

Activities of the Departments

Department of Neurosurgery and Neuro-Oncology

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

Introduction

Patients with primary and metastatic brain tumors are treated by six neurosurgeons in the Neurosurgery Division. Two hundred fifty-seven patients were admitted and 98 craniotomies for tumor removal were carried out in 2012 including 47 gliomas, 33 metastatic brain tumors, 4 primary CNS lymphomas, and 7 meningiomas (Table 1). Nine ventriculo-peritoneal shunts and 4 neuroendoscopic surgeries 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. Five awake surgeries were also performed, particularly for removal of gliomas near the speech center. We started work with our intraoperative MRI system in February 2012 and 80 craniotomies were carried out with use of this system. 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 patients with brain tumors. Usually 20 patients are hospitalized and two or three of them undergo surgical treatment every week. The Stealth navigation system is used for surgical planning during every craniotomy. The patients with malignant brain tumors receive postoperative radiotherapy and chemotherapy. Statistical analysis revealed that surgical removal of as much of the tumor as possible yielded better survival rates even for the most malignant glioblastomas, which usually recur soon after the surgery without radiotherapy. Concomitant use of chemotherapy is considered to enhance the anti-tumor effect of radiotherapy. Temozolomide has been given to all malignant glioma patients during radiotherapy and repeated every month for 2 years. The 5-year survival rates of the patients with anaplastic astrocytomas and glioblastomas were 66.1% and 10.1%, respectively, which were better than those recorded in the Brain Tumor Registry of Japan. (Table 2). High dose methotrexate is administered to the patients with primary CNS lymphoma before radiotherapy.

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

Research activities

Patients with brain tumors have been registered in the Brain Tumor Registry of Japan (BTRJ) since 1969. More than 100,000 patients have been registered and followed up. The Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, contributes as a managing office of the BTRJ and established on-line registration using the University Hospital Medical Information Network (UMIN) system in 2009. Clinical data during 2001 and 2004 were collected and the report will be published in 2013 as a supplement of the official journal of the Japan Neurosurgical Society.

An analysis of gene expression profiles in malignant gliomas is being carried out in order to determine specific genes that have an influence on the effects of chemotherapy and radiation therapy in cooperation with the Division of Cancer Genomics, the National Cancer Center Research Institute. Tumor samples of malignant gliomas were collected and were analyzed with a DNA microarray. FISH analysis using 1p/19q/EGFR/PTEN probes, the determination of the methylation status of O^6-methylguanine-DNA methyltransferase (MGMT) and the mutation of IDH1/2 are also carried out to predict the prognosis of the patients with malignant gliomas.

Clinical trial

The Japan Clinical Oncology Group (JCOG)-Brain Tumor Study Group was organized in 2002 and a multi-institutional randomized controlled trial entitled "A randomized controlled phase II/III study of chemoradiotherapy using ACNU versus procarbazine and ACNU for astrocytoma grade 3 and 4" was 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: "A Randomized phase III trial of postoperative whole brain radiation therapy compared with salvage stereotactic radiosurgery in patients with one to four brain metastasis (JCOG 0504)". The efficacy of the gamma knife will be compared to that of whole brain irradiation. A new clinical trial for primary CNS lymphoma and grade 3 glioma will start in 2013. These studies, under the surveillance of JCOG, aim to set a standard protocol for treating malignant brain tumor patients. Moreover, a proper methodology for performing randomized studies will be established in the field of neuro-oncology.

Table 1. Number of surgeries by year, 2010-2012

	2012	2011	2010
Glioma	47	35	51
Metastatic brain tumor	33	39	42
Meningioma	7	5	9
Primary CNS lymphoma	4	6	4
Other brain tumor	5	7	6
Others	36	31	33
Total	132	123	145

Table 2. Survival rates

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

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

List of papers published in 2012
Journal

1. Momota H, Narita Y, Miyakita Y, Shibui S. Intravascular lymphoma of the central nervous system presenting as multiple cerebral infarctions. Nagoya J Med Sci, 74:353-358, 2012
2. Okita Y, Narita Y, Miyakita Y, Ohno M, Nagai S, Shibui S. Management of cytomegalovirus infection in a patient with malignant glioma treated with temozolomide and steroids. Intern Med, 51:2967-2971, 2012
3. Okita Y, Narita Y, Yoshida A, Miyakita Y, Ohno M, Saio M, Yoshimi N, Shibui S. The late recurrence of ganglioneuroma 21 years after initial presentation with neuroblastoma. Pediatr Hematol Oncol, 29:647-651, 2012
4. Ohno M, Narita Y, Miyakita Y, Okita Y, Kayama T, Shibui S. Development of secondary skull sarcoma after treatment for childhood acute myeloid leukemia. Asia Pac J Clin Oncol, 8:e49-52, 2012
5. McCarthy BJ, Shibui S, Kayama T, Miyaoka E, Narita Y, Murakami M, Matsuda A, Matsuda T, Sobue T, Palis BE, Dolecek TA, Kruchko C, Engelhard HH, Villano JL. Primary CNS germ cell tumors in Japan and the United States: an analysis of 4 tumor registries. Neuro Oncol, 14:1194-1200, 2012
6. Matsuda K, Sato A, Okada M, Shibuya K, Seino S, Suzuki K, Watanabe E, Narita Y, Shibui S, Kayama T, Kitanaka C. Targeting JNK for therapeutic depletion of stem-like glioblastoma cells. Sci Rep, 2:516, 2012
7. Ohno M, Narita Y, Miyakita Y, Okita Y, Matsushita Y, Yoshida A, Fukushima S, Ichimura K, Kayama T, Shibui S. Histopathological malignant progression of grade II and III gliomas correlated with IDH1/2 mutation status. Brain Tumor Pathol, 29:183-191, 2012
8. Okita Y, Narita Y, Miyakita Y, Ohno M, Fukushima S, Maeshima A, Kayama T, Shibui S. Long-term follow-up of vanishing tumors in the brain: how should a lesion mimicking primary CNS lymphoma be managed? Clin Neurol Neurosurg, 114:1217-1221, 2012
9. Fukushima S, Narita Y, Shinomiya A, Ohno M, Miyakita Y, Okita Y, Hanakawa K, Ide T, Kayama T, Shibui S, Tsuda H. A case of unclassified high-grade glioma with polar spongioblastoma pattern. Neuropathology, 32:604-610, 2012
10. Okita Y, Narita Y, Miyakita Y, Ohno M, Fukushima S, Kayama T, Shibui S. Pathological findings and prognostic factors in recurrent glioblastomas. Brain Tumor Pathol, 29:192-200, 2012
11. Hashimoto K, Narita Y, Matsushita Y, Miyakita Y, Ono M, Kayama T, Shibui S. Methylation status of O6-methylguanine-DNA-methyl transferase promoter region in non-small-cell lung cancer patients with brain metastasis. Clin Transl Oncol, 14:31-35, 2012
12. Okita Y, Narita Y, Miyakita Y, Ohno M, Aihara K, Mori S, 3Kayama T, Shibui S. Reactivation of cytomegalovirus following treatment of malignant glioma with temozolomide. Int Cancer Conf J, 1:53-57, 2012

Department of Ophthalmic Oncology

Shigenobu Suzki, Yukiko Aihara

Introduction

Our Department is one of the rare groups specializing in ocular tumors, especially intraocular tumors. Recently, more than 60% of patients nationwide with retinoblastomas, which is the most frequent intraocular malignancy in childhood, and more than 50% of patients with uveal melanomas, 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 complications such as secondary glaucoma or severe hemorrhage, or if extraocular extension of the retinoblastoma is strongly suspected, we can offer the family eye-preserving treatment. Initial systemic chemotherapy and additional local therapies, called "chemoreduction therapy", comprise the main strategy. If the tumor is localized in the peripheral retina, plaque radiotherapy using ruthenium-106 is also available. Transpupillary thermotherapy or cryotherapy is also used in cases with localized small tumors. Patients with extraocular extension, recurrence or metastasis who need systemic chemotherapy are treated with dedicated support from the Department of Pediatric Oncology.

2) 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 radiotherapy is only available in our institute. Patients with much larger tumors are referred to the National Institute of Radiological Science, Research Center for Charged Particle Therapy, for carbon ion therapy. 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) 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.

4) Eyelid tumors

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

5) Conjunctival tumors

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

Research activities

One of the unique techniques in our department is local chemotherapy for retinoblastoma via selective ophthalmic artery infusion using a balloon catheter. This procedure was first developed in our hospital in 1987, and has been modified and performed until 2009 in more than 20 countries. We are planning a clinical trial on selective ophthalmic artery injection therapy for initial treatment methods.

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

The National Registry of Retinoblastoma in Japan was organized in 1975, and more than 3,000 patients are registered. We contribute to this registry as an administrator of personal data, and through checking overlapping. This registry covers almost all patients in Japan now, and provides epidemiological data.

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

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

Table 1. Number of patients

retinoblastoma	53
Choroidal melanoma	20
Other intraocular tumors	23
Eyelid tumor	9
Conjunctival tumor	9
Orbital tumor	13
Ocular adnexal lymphoma	10
Others	25
Total	162

Table 2. Type of procedure

Retinoblastoma	
Selective ophthalmic arterial injection	116
Laser and/or vitreous injection	143
Ruthenium brachytherapy	9
Enucleation	23
Examination under anesthesia (EUA)	8
Choroidal melanoma	
Ruthenium brachytherapy	7
Enucleation	3
Resection of ciliary body tumor	1
Resection of eyelid tumor	5
Resection of conjunctival tumor	5
Resection of orbital tumor	9
Others	17
Total	346

List of papers published in 2012

Journal

1. Suzuki S. A case of recurrent lacrimal gland tumor treated by orbital exenteration. Jpn J Clin Oncol, 42:560, 2012

Department of Head and Neck Surgery

Masao Asai, Sei-ichi Yoshimoto, Tsutomu Nomura, Daisuke Maki

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 vocally. We have recently started a new treatment trial of concurrent chemoradiotherapy 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 three head and neck surgeons and a chief resident. Many operations with or without major microsurgical reconstructive surgery under general and local anesthesia are performed. In addition to radiotherapy, chemo-radiotherapy for head and neck cancer have recently been performed at NCCH.

In 2012, 268 patients with head and neck cancer underwent surgery under general and local anesthesia and 52 patients had undergone major surgery with reconstructive surgery in our division. Forty seven of these patients were over 75 years old, ranging from 75 to 85. The oldest patient who was treated with microsurgical reconstructive surgery was 80 years old. There was one serious postoperative complication in 268 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 referred from other divisions have been operated on this year.

Our outpatient service is available from Monday to Friday except Wednesday, and the total annual number of newly registered patients has exceed 400. The number of new patients in 2012 was similar to 2011. 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, no standard therapy was 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 last 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 study 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 6 cases of supraglottic and glottic carcinoma and partial hypo-pharyngectomy with free jejunum in 8 cases of pyriform sinus and posterior wall hypopharyngeal carcinoma. We were able to preserve voice function in all the cases. We have been performing endoscopic mucosal resection (EMR) for small and superficial hypopharyngeal carcinomas in cooperation with the Endoscopic Division from 2006, and 24 cases were treated in 2011. The rate of voice preservation surgery in cases of hypopharyngeal cancer was very high (68%), probably the top in Japan.

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

Tongue	29
Mesopharynx	18
Hypopharynx	47
Larynx	14
Oral cavity (without tongue)	30
Nasal and paranasal cavity	10
Thyroid	16
Major salivary gland	8
Neck metastasis (primary unknown, eyelid, melanoma, etc.)	24
Others	10
Total	205

Table 2. Type of procedures

Glossectomy (partial, hemi, subtotal) [+ reconstruction]	29	[9]
Resection of mesopharyngeal tumor [+ reconstruction]	18	[5]
Total pharyngolaryngectomy (TPLE) [+ reconstruction]	15	[15]
Partial hypopharyngectomy (preserve larynx) [+ reconstruction]	8	[6]
EMR	24	
Total laryngectomy	7	
Partial laryngectomy	6	
Extended resection of larynx [+ reconstruction]	1	[1]
Resection of tumor of oral cavity [+ reconstruction]	30	[5]
Maxillectomy [+ reconstruction]	10	[2]
Thyroidectomy (hemi, total)	16	
Parotidectomy, etc. [+ reconstruction]	8	[2]
Neck dissection [+ reconstruction]	24	[2]
Neck tumor [+ reconstruction]	6	[1]
Reconstruction and plastic surgery only	3	
Tracheotomy	5	
Lymphadenectomy	48	
Others [+ reconstruction]	10	[2]
Total	268	[53]

Table 3. Operative morbidity and mortality

Major complications	1 case
(major leakage, bleeding, flap necrosis, etc.)	(0.4% in total, 1 [1.9%] in 53major surgeries)
Minor complications	12 cases (4.5%)
(high fever, infection, pneumonia, minor leakage, etc.)	
Operative death within 30 days	0 cases
Postoperative hospital death	0 cases

List of papers published in 2012

Journal

1. Yoshimoto S, Hasegawa Y, Matsuzuka T, Shiotani A, Takahashi K, Kohno N, Yoshida T, Kitano H. Sentinel node biopsy for oral and laryngopharyngeal squamous cell carcinoma: a retrospective study of 177 patients in Japan. Auris Nasus Larynx, 39:65-70, 2012

Department of Plastic and Reconstructive Surgery

Shimpei Miyamoto, Shuji Kayano, Minoru Sakuraba, Masanobu Sakisaka

Introduction

The Plastic and Reconstructive Surgery Division has mainly focused on surgical reconstruction of defects left after extirpation or excision of cancerous tissue. In our institution, reconstructive procedures using free flap transfer with microvascular anastomosis are the most important operations. In addition, several methods such as tissue transfer with a pedicled flap, local flap, skin grafting, 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 surgery. The quality of life (QOL) of the patient can be improved by good functional and morphological reconstruction.

Routine activities

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

Research activities

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

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

With the objective of addressing these four aspects, establishing a high standard 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 ongoing: 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.

Further development of reconstructive procedures in cooperation with other Divisions, such as orthopedic surgery, breast surgery and so on, is also ongoing.

Table 1. Cooperation with other divisions

Breast surgery	65
Orthopedic surgery	53
Head & Neck surgery	51
Esophageal surgery	14
HB&P surgery	4
Neurosurgery	4
Dermatology	1
Colorectal surgery	1
Gynecology	1
Total	194

Table 2. Operative Procedures

Microvascular free flap	120
DIEP	37
Jejunum	26
Anterolateral thigh	25
Latissimus Dorsi	21
Fibula bone	4
Scapula bone	2
RAMC	2
Radial Forearm	2
Other flaps	1
Other Microsurgery	19
Supercharge	6
Limb Salvage	7
Hepatic Artery	4
Others	2
Subtotal	139
Pedicled flaps	46
Latissimus Dorsi	23
PM or PMMC	8
DP	4
Other flaps	11
Other Procedures	95
Total	269

List of papers published in 2012

Journal

1. Miyamoto S, Sakuraba M, Nagamatsu S, Kayano S, Kamizono K, Hayashi R. Risk factors for gastric-tube dependence following tongue reconstruction. Ann Surg Oncol, 19:2320-2326, 2012
2. Miyamoto S, Sakuraba M, Nagamatsu S, Kamizono K, Hayashi R. Comparison of reconstruction plate and double flap for reconstruction of an extensive mandibular defect. Microsurgery, 32:452-457, 2012
3. Miyamoto S, Sakuraba M, Nagamatsu S. Inadvertent injury of critical perforator vessels during perforator flap surgery. J Reconstr Microsurg, 28:95-98, 2012
4. Kayano S, Sakuraba M, Miyamoto S, Nagamatsu S, Taji M, Umezawa H, Kimata Y. Comparison of pedicled and free anterolateral thigh flaps for reconstruction of complex defects of the abdominal wall: review of 20 consecutive cases. J Plast Reconstr Aesthet Surg, 65:1525-1529, 2012

Department of Breast Surgery

Takayuki Kinoshita, Takashi Hojo, Sota Asaga, Junko Suzuki, Eriko Iwamoto, Kenjiro Jimbo

Introduction

The Breast Surgery Division deals with treatment of breast cancer, as well as diagnosis of breast diseases and assessment of lymph nodes in the axillary and clavicular regions which are suspected harboring metastases. Although breast-conserving therapy (BCT) has accounted for 53.4% of the cases, BCT was not indicated in more than 40% of the cases even when the cancer was at an early stage. In 2010, immediate breast reconstruction became one of the choices for these patients in whom breast preservation was impossible, and a total of 62 immediate breast reconstructions were performed in 2012, comprising more than 12% of all the cases. Sentinel lymph node (SLN) biopsies (SLNB) were performed in 82.8% of the cases. Following SLNB, the axillary lymph node dissection (ALND) could be avoided when the SLNB was negative. In conjunction with the one-step nucleic acid amplification (OSNA) assay, more positive nodes including micrometastases have been detected, compared to traditional diagnosis by frozen section alone, and 25.2% of the cases after SLNB needed additional ALN dissection.

Routine activities

The Division is staffed by four staff surgeons, one chief resident, and three or four rotating residents. From 7:30 every morning, all the staff and the residents perform in patient rounds together. A journal club and research conference are scheduled on every Tuesday morning after rounds. A weekly conference is held on Wednesdays from 17:00 to 18:00 for shared discussions with surgeons, medical oncologists, radiologists, and radiology and sonography technicians. The diagnostic images of pre-operative patients are reviewed and compared to pathological reports in every postoperative patient. A breast pathology 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.

BCT usually consists of local excision of the tumor followed by postoperative irradiation of the remaining breast, and is indicated for a tumor smaller than 3 cm. Patients with multi-focal lesions or extensive micro-calcifications detected with mammography are not elegible 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 tumor sensitivity to therapeutic agents. Patients receive adjuvant chemo-endocrine therapy depending upon their prognostic and predictive factors, which include the number of lymph nodes involved, the histological grade of the tumor and secondary prognostic markers (HER2/neu, ER, PgR, and so on). Widely accepted factors that predict a response to a specific therapy are estrogen and progesterone receptors for hormone therapy and HER2 for trastuzumab. Since hormone-receptor positive patients tend to receive less chemotherapy nowadays, NAC has been decreasing and only 7.7% of all patients received neoadjuvant therapy in 2012.

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 with node-positive (Dr. Hojo) are under consideration. With the recent advance in development of an aromatase inhibitor, neoadjuvant endocrine therapy (NAET) may become the standard-bearer of tailored treatment. We have been conducting a prospective neoadjuvant endocrine study since 1998. A new protocol to evaluate the optimal duration of NAET (4M vs 6M) 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 revealed with MRI or CT.

Clinical trials

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

   A trial of image-guided radiofrequency ablation (non-surgical therapy) has been ongoing for early-stage breast carcinomas of less than 1 cm in diameter. After these years of trial, indication has just been expanded up to 1.5 cm in diameter and this technique is certified as an advanced medical treatment by Ministry of Health, Labour and Welfare.

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

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

3) Denosumab adjuvant treatment (D-CARE)

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

4) Scalp-cooling device during chemotherapy

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

5) Sentinel lymph node (SLN) biopsy

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

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

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

7) Skin care for patients receiving radiotherapy after breast conserving therapy

   This is a multi-center survey to check the frequency and degree of radiation dermatitis in order to give appropriate skin care and improve cosmetic satisfaction of the patients. Questionnaires were handed out to patients who received radiotherapy.

Table 1. Type of procedure

	2008		2009		2010		2011		2012	
Total number of operations	462		462		482		576		581	
Mastectomy (%)	197	(44.0)	209	(45.6)	213	(44.2)	250	(47.6)	234	(45.4)
Breast-conserving surgery (%)	251	(56.0)	249	(54.4)	269	(55.8)	269	(51.2)	275	(53.4)
Radiofrequency ablation (%)							6	(1.1)	6	(1.2)
Axillary lymph node dissection (ALND) (%)	100	(22.3)	89	(19.4)	136	(28.2)	205	(41.5)	188	(38.1)
Sentinel lymph node biopsy (SLNB) (%)	342	(76.3)	368	(80.3)	316	(65.6)	402	(81.4)	409	(82.8)
ALND after SLNB (%)							113	(22.9)	103	(20.9)
Immediate breast reconstruction (%)	0		0		13	(2.7)	74	(14.1)	62	(12.5)
Neoadjuvant therapy	108	(24.1)	105	(22.9)	72	(14.9)	57	(10.9)	45	(7.7)

Table 2. Number of patients

		2011	2012
Primary breast cancer		496	494
	cStage 0	100	76
	I	186	199
	II	180	194
	III	29	17
	IV	1	8
	unknown	1	2
Other malignant breast disease		1	3
Total		497	497

Table 3. Survival (2004-2005)

		No. of patients	5-yr survival (%)
stage	0	83	96.5
	I	226	98.7
	II	344	92.4
	III	65	75.3

List of papers published in 2012
Journal

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3. Kikuyama M, Takeshima H, Kinoshita T, Okochi-Takada E, Wakabayashi M, Akashi-Tanaka S, Ogawa T, Seto Y, Ushijima T. Development of a novel approach, the epigenome-based outlier approach, to identify tumor-suppressor genes silenced by aberrant DNA methylation. Cancer Lett, 322:204-212, 2012
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6. Nagao T, Kinoshita T, Hojo T, Kurihara H, Tsuda H. Sentinel lymph node biopsy using indigo carmine blue dye and the validity of '10% rule' and '4 nodes rule'. Breast, 21:455-458, 2012
7. Nagao T, Hojo T, Tanaka-Akashi S, Tsuda H, Kinoshita T. Primary leiomyosarcoma of the breast. Breast J, 18:81-82, 2012
8. Masuda N, Sagara Y, Kinoshita T, Iwata H, Nakamura S, Yanagita Y, Nishimura R, Iwase H, Kamigaki S, Takei H, Noguchi S. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. Lancet Oncol, 13:345-352, 2012
9. Zhang M, Higashi T, Nishimoto H, Kinoshita T, Sobue T. Concordance of hospital-based cancer registry data with a clinicians' database for breast cancer. J Eval Clin Pract, 18:459-464, 2012

Department of Breast and Medical Oncology

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

Introduction

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

We envision becoming a premier oncology department which leads cancer care in Japan and in the World. Our mission is to provide patient-centered, state-of-the-art medical care to individual patients suffering from cancer. 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, four chief residents (fellows) and one - three clinical residents. We also provide educational opportunities to short-term residents. Full-time attending physicians are on duty at the outpatient clinic one to three days a week. Residents, especially the first-year chief residents, are encouraged to take leadership in the clinical management of hospitalized patients. They also undertake clinical and translational research projects under the supervision of attending physicians. Three board-certified Breast Cancer Specialist Nurses help providing seamless and comprehensive care to breast cancer patients. Group-assigned pharmacists support patients receiving chemotherapy both in the ward and in the clinic.

Most of our patients are treated in an outpatient setting in cooperation with the Outpatient Treatment Center and Pharmacy Division. New patients are referred from both inside and outside the National Cancer Center Hospital (NCCH). We regularly have approximately 30 inpatients. Terminally-ill patients are transferred to palliative care units or in-home care clinics outside NCCH, whereas 41 patients of our Division passed away in NCCH in 2012. Post-operative breast cancer patients without disease recurrence have been encouraged to be referred to local breast cancer specialists participating in the Tokyo Breast Consortium network (http://breastcons.com/).

The Briefing Conference is held every morning to discuss the optimal care for individual patients. A Breast Cancer Specialist Nurse in the clinic and group-assigned pharmacists attend those conferences. Grand Rounds are scheduled every Monday, Wednesday, and Friday. A Phase I conference is held every Monday.

We are supporting the "Appearance Care Program" which encourages self-support for change of appearance due to cancer treatments. This 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. The Appearance Support Team consists of a physician, nurses, a clinical psychiatrist sub-specialized in appearance care, and a pharmacist.

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 multidisciplinary specialists to discuss recent topics in breast oncology and to develop institutional treatment guidelines. The treatment guidelines for breast cancer, both primary and metastatic, were updated in 2012.

Research activities

The goal of our research activities is to develop new therapeutic strategies for adult solid tumors based on the biology of neoplasia. A Research Conference is held every Thursday morning to discuss on-going studies. Three Clinical Research Coordinators are supporting our research activities.

In 2012, we were involved in several international first-in-human studies. We continue to put our efforts into phase I studies by enhancing team communication through in-group and intergroup Phase I conferences. For late-phase studies, 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) and others. A phase II study of CBDCA/S1 triple-negative breast cancer has recently been approved by the Institutional Review Board (IRB) and is waiting for patient accrual.

With the cooperation of Shien Lab, the Research Institute, or outside institutions, we have been conducting several translational studies that aim to discover biomarkers for patient enrichment, drug-resistance, and potential drug targets. Of note, we have published the preliminary results of our ^{64}Cu-labeled trastuzumab molecular imaging study which is being performed in cooperation with the RIKEN Center for Molecular Imaging Science. We also have recruited more than 130 patients into an observational/translational study to explore SNPS related to taxane-induced peripheral neuropathy in cooperation with the Tokyo Metropolitan Institute of Medical Science and the NCC Research Institute. We are expecting the completion of patient accrual in 2013. Other clinical studies, including the above-mentioned trials, are listed in Table 2.

In addition to clinical trials, we value cancer survivorship as a research theme in order to develop a patient-centered comprehensive care program. We have conducted several qualitative and quantitative studies focusing on patients' and physicians' perception and attitude towards fertility issues, appearance, hereditary breast and ovarian cancer, spiritual needs and end-of-life care.

List of papers published in 2012
Journal

1. Yonemori K, Hirakawa A, Ando M, Hirata T, Yunokawa M, Shimizu C, Tamura K, Fujiwara Y. Content analysis of oncology-related pharmaceutical advertising in a peer-reviewed medical journal. PLoS One, 7:e44393, 2012
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Table 1. Demographics of Patients at their 1st Visit to the Clinic of the Breast and Medical Oncology Division (Jan - Dec, 2012)

No of 1st Visits	n	%	
Total	759		
Breast	361	47.5	
GYN	136	17.9	
Cancer of primary unknown	106	14.0	
Sarcoma	78	10.3	
Others	78	10.3	
Purpose of consultation			
2nd opinion	38	5.0	
Treatment at NCCH	76	10.0	
Referrals from other hospitals	252	33.2	
Referrals from other divisions in NCCH	393	51.8	(100)
Breast surgery	243		(61.8)
GYN	68		(17.3)
Urology	19		(4.8)
Orthopedics	10		(2.5)
Others	53		(21.8)
Others	0		

Table 2. Active Clinical Trials (Jan. 2012-Dec. 2012)

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, not recruiting
		III	D-CARE	Denosumab vs placebo	Active, not recruiting
		III	APHINITY	CTx+HCN/placebo vs CTx/HCN/ pertuzumab	Active
		III	POTENT	HTx+S1 vs HTx alone	Active
	Metastatic	III	JCOG1017	Surgery vs no surgery for primary Stage IV BC	Active
		III	MARIANNE	RO5304020+/- RO4368451 vs HCN/ PTX	Active
		III	NK105	NK105 vs paclitaxel	Active
		III	ELTOP (WJOG)	lapa/capecitabine vs HCN/capecitabine	Active
		II	RO5304020	RO5304020	Active
		II	lapaHER	lapatinib/HCN	Active
		II	CBDCA/S1 for TNBC	CBDCA/S1	Active
		I/II	CAPIRI	capecitabine/CPT-11	Active
		I/II	S1/docetaxel	S1/docetaxel	Active
		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
		II	GOG268	TC+temsirolimus	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	RO5304020/RO5368451	RO5304020/RO5368451	Active
		I	AZD1208	AZD1208	Active
		I	AZD5363	AZD5363	Active
		I	PD0332991	PD0332991	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 Thoracic Surgery

Hisao Asamura, Shun-ichi Watanabe, Hiroyuki Sakurai, Kazuo Nakagawa, Takashi Makino

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 656 operations; for lung cancer in 486 patients, metastatic tumor in 89, mediastinal tumor in 17, and 64 in others.

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

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

For mediastinal tumors, thymic epithelial tumors are most commonly encountered for resection. In the mediastinum, where a variety of tumor histologies can arise, the treatment must be carefully determined by the cytologic/histologic diagnosis before surgery. For this purpose, CT-guided needle biopsy is replacing the formerly common biopsy under X-ray fluoroscopy. For patients with thymoma, we have already adopted video-assisted resection of the tumor. VATS resection of mediastinal tumor is indicated exclusively for small thymomas less than 4 cm in size.

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

Research activities

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

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" has been developed 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 as early adenocarcinomas. The surgical management of such GGO-type lung cancer remains undetermined in terms of the extent of pulmonary parenchymal resection and lymph node dissection. Some cases might be followed up with careful monitoring by CT, since indolent tumors are known to exist. We are seeking the appropriate way to manage these patients. A clinical trial to determine the appropriateness of limited resection for early adenocarcinomas had been planned in the Japan Clinical Oncology Group (JCOG)- Lung Cancer Study Group, and two clinical trials (a phase III trial, JCOG 0802; a phase II trial, JCOG 0804) have been conducted since the end of 2009. The accrual for JCOG 0804 trial closed last year. Fifty-eight cases have been registered for JCOG 0802 from our division.

As for postoperative adjuvant therapy, a phase III clinical trial to compare the effectiveness of UFT with that of TS-1 for stage IA more than 2 cm and IB NSCLC planned in JCOG (JCOG 0707) has been conducted since 2008. In total, 34 cases have been registered for this trial from our division.

Table 1. Number of patients

Primary lung cancer	486
Metastatic lung tumor	89
Mediastinal tumor	17
Pleural disease	12
Chest wall tumor	8
Benign lung nodule	31
Others	13
Total	656

Table 2. Type of procedure

Lung resection	606
Lobectomy	356
Pneumonectomy	12
Segmentectomy	68
Wedge resection	170
Tracheal resection	0
Surgery for mediastinal tumors	15
Surgery for pleural tumors	9
Surgery for chest wall tumors	8
Others	18
Total	656

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

List of papers published in 2012
Journal

1. Rusch VW, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, Pass H, Asamura H, Waller D, Edwards J, Weder W, Hoffmann H, van Meerbeeck JP. Initial analysis of the international association for the study of lung cancer mesothelioma database. J Thorac Oncol, 7:1631-1639, 2012
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Department of Thoracic Oncology

Tomohide Tamura, Noboru Yamamoto, Hiroshi Nokihara, Yutaka Fujiwara, Shintaro Kanda, Hidehito Horinouchi, Shinji Nakamichi, Satoru Kitazono, Hidenori Mizugaki, Shigehiro Yagishita

Introduction

Lung cancer has been the most common cause of death from cancer since 1994, and the incidence of lung cancer in Japan is still increasing in females and the elderly. The majority of lung cancer patients are diagnosed at the advanced stage, and the prognosis of these patients is poor. The standard treatments are chemoradiotherapy for locally advanced disease and platinum doublet chemotherapy for metastatic disease. Recently, several driver gene alterations such as EGFR mutation and ALK, Ros 1 or RET fusion gene, have been identified in non-small cell lung cancer. Inhibitors for these molecules show excellent response against tumors with these driver gene alterations. Optimal treatment selection based on tumor molecular analysis and biomarker analysis is a major research issue in this field.

The goals of the Department of Thoracic Oncology are to provide high quality treatment for each patient and to establish new effective treatments against lung cancer and other thoracic malignancies. The Department of Thoracic Oncology includes 6 staff physicians. A total of 3 chief residents, 9 residents, 3 short-term residents and 1 trainee joined the department during 2012.

Routine activities

The staff physicians attend outpatient services for thoracic diseases, and the division has 55-60 beds in the hospital. Inpatient care is carried out by five teams. Each team consists of one staff physician and one or two chief residents and residents.

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 328 new patients were admitted in 2012 (305 and 276 patients in 2011 and 2010, respectively). The diagnoses for these patients and initial treatments for 288 lung cancer patients are listed in Tables 1 and 2. Thirty-four percent of 182 advanced lung cancer patients receiving chemotherapy as their initial treatments participated in clinical trials. The survival outcomes of lung cancer patients treated in the Department are shown in Table 3. Thirty-four patients with miscellaneous solid tumors were admitted to, and participated in 8 phase I studies of new agents.

Research activities

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

Clinical trials

Clinical trials carried out in 2012 are shown in Table 4. More than 30 clinical trials have been carried out in the Department. Some studies were based on the JCOG Lung Cancer Study Group research program, and some were carried out under contract with pharmaceutical companies.

Table 1. Number of New Inpatients in 2012

Non-small cell lung cancer	240
Adenocarcinoma	187
Squamous cell carcinoma	36
Others	17
Small cell lung cancer	48
Mesothelioma	2
Thymic cancer	3
Thymoma	1
Others	34
Total	328

Table 2. Initial Treatments for New Inpatients with Lung Cancer in 2012

Chemotherapy	182
Chemoradiotherapy	42
Adjuvant chemotherapy following surgery	33
Preoperative chemoradiotherapy	2
Thoracic radiotherapy	4
Supportive care alone (including palliative radiotherapy)	25
Total	288

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 2012

Target disease	Stage	Phase	Treatment
NSCLC	Advanced	III	S-1 vs. DTX
NSCLC	Advanced	III	PF-00299804 vs. Erlotinib
NSCLC	Advanced	III	Erlotinib vs. Erlotinib/ARQ197
NSCLC	Advanced	III	CBDCA/PTX vs. CBDCA/PTX/AMG706
NSCLC MET+	Advanced	III	Erlotinib vs. Erlotinib/MetMAb
NSCLC	Advanced	III	Eribulin vs. Physician's choice
NSCLC	Advanced	III	Bevacizumab beyond PD
NSCLC-ALK fusion	Advanced	III	PF-02341066 vs. PEM/CDDP
NSCLC	Advanced	II	DTX+IMC1121B
NSCLC-ALK fusion	Advanced	II	PF-02341066
NSCLC-EGFR mutation	Advanced	II	Erlotinib vs. Erlotinib/Bevacizumab
NSCLC-EGFR mutation	Advanced	II	Gefitinib+PEM
NSCLC-ALK fusion	Advanced	I/II	CH5424802
NSCLC	Advanced	I	CBDCA/PTX+Ipilimumab
NSCLC	Advanced	I	CBDCA+PTX+ABT888
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	Limited	II	JCOG1101: CRT- CDDP/AMR vs. CODE
SCLC	Extensive	I/II	CPT-11 maintenance
Lung cancer	Advanced	II	CDDP short hydration
Lung cancer	Advanced	Translational	Circulating endothelial cells
Lung cancer	Advanced	PK/PK	Erlotinib
Solid tumor	Advenced	PK/PD	TS-1
Solid tumor	Advanced	I	8 New agents

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

List of papers published in 2012
Journal

1. Makihara RA, Makino Y, Yamamoto N, Yokote N, Nokihara H, Sekine I, Ohe Y, Tamura T, Yamamoto H. Gender difference in hematological toxicity among lung cancer patients receiving amrubicin monotherapy. Jpn J Clin Oncol, 42:1187-1191, 2012

2. Niho S, Ohe Y, Ishikura S, Atagi S, Yokoyama A, Ichinose Y, Okamoto H, Takeda K, Shibata T, Tamura T, Saijo N, Fukuoka M. Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: a multicenter feasibility study (JCOG 0402). Ann Oncol, 23:2253-2258, 2012

3. Horinouchi H, Sekine I, Sumi M, Ito Y, Nokihara H, Yamamoto N, Ohe Y, Tamura T. Brain metastases after definitive concurrent chemoradiotherapy in patients with stage III lung adenocarcinoma: carcinoembryonic antigen as a potential predictive factor. Cancer Sci, 103:756-759, 2012

4. Nokihara H, Yamamoto N, Yamada Y, Yamada K, Hirata T, Goto Y, Tanioka M, Ikeda Y, Tamura T. A phase I study of BMS-690514 in Japanese patients with advanced or metastatic solid tumors. Cancer Chemother Pharmacol, 70:559-565, 2012

5. Atagi S, Kawahara M, Yokoyama A, Okamoto H, Yamamoto N, Ohe Y, Sawa T, Ishikura S, Shibata T, Fukuda H, Saijo N, Tamura T. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). Lancet Oncol, 13:671-678, 2012

6. Goto Y, Sekine I, Tanioka M, Shibata T, Tanai C, Asahina H, Nokihara H, Yamamoto N, Kunitoh H, Ohe Y, Kikkawa H, Ohki E, Tamura T. Figitumumab combined with carboplatin and paclitaxel in treatment-naive Japanese patients with advanced non-small cell lung cancer. Invest New Drugs, 30:1548-1556, 2012

7. Seki Y, Yamamoto N, Tamura Y, Goto Y, Shibata T, Tanioka M, Asahina H, Nokihara H, Yamada Y, Shimamoto T, Noguchi K, Tamura T. Phase I study for ridaforolimus, an oral mTOR inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 69:1099-1105, 2012

8. Rossi A, Di Maio M, Chiodini P, Rudd RM, Okamoto H, Skarlos DV, Fruh M, Qian W, Tamura T, Samantas E, Shibata T, Perrone F, Gallo C, Gridelli C, Martelli O, Lee S-M. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol, 30:1692-1698, 2012

9. Asahina H, Tamura Y, Nokihara H, Yamamoto N, Seki Y, Shibata T, Goto Y, Tanioka M, Yamada Y, Coates A, Chiu Y-L, Li X, Pradhan R, Ansell PJ, McKeegan EM, McKee MD, Carlson DM, Tamura T. An open-label, phase 1 study evaluating safety, tolerability, and pharmacokinetics of linifanib (ABT-869) in Japanese patients with solid tumors. Cancer Chemother Pharmacol, 69:1477-1486, 2012

10. Sekine I, Sumi M, Ito Y, Horinouchi H, Nokihara H, Yamamoto N, Kunitoh H, Ohe Y, Kubota K, Tamura T. Phase I study of concurrent high-dose three-dimensional conformal radiotherapy with chemotherapy using cisplatin and vinorelbine for unresectable stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys, 82:953-959, 2012

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13. Niho S, Kunitoh H, Nokihara H, Horai T, Ichinose Y, Hida T, Yamamoto N, Kawahara M, Shinkai T, Nakagawa K, Matsui K, Negoro S, Yokoyama A, Kudoh S, Kiura K, Mori K, Okamoto H, Sakai H, Takeda K, Yokota S, Saijo N, Fukuoka M. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer, 76:362-367, 2012

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15. Morita S, Oizumi S, Minami H, Kitagawa K, Komatsu Y, Fujiwara Y, Inada M, Yuki S, Kiyota N, Mitsuma A, Sawaki M, Tanii H, Kimura J, Ando Y. Phase I dose-escalating study of panobinostat (LBH589) administered intravenously to Japanese patients with advanced solid tumors. Invest New Drugs, 30:1950-1957, 2012

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17. Tomioka H, Mukohara T, Kataoka Y, Ekyalongo RC, Funakoshi Y, Imai Y, Kiyota N, Fujiwara Y, Minami H. Inhibition of the mTOR/S6K signal is necessary to enhance fluorouracil-induced apoptosis in gastric cancer cells with HER2 amplification. Int J Oncol, 41:551-558, 2012

Department of Esophageal Surgery

Yuji Tachimori, Hiroyasu Igaki, Nobukazu Hokamura, Takayoshi Kishino

Introduction

More than 300 new patients with esophageal tumors are admitted to the National Cancer Center Hospital (NCCH) every year. The multidisciplinary treatment plans are determined by the stage of the tumor in close cooperation with other teams. The Esophageal Surgery Division cooperates with the Gastrointestinal Oncology Division and the Radiation Oncology Division particularly 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 6% in our division in 2012.

Routine activities

The Esophageal Surgery Division consists of three staff surgeons, one chief resident and 2-3 rotating senior residents. A multidisciplinary conference is held weekly in which surgeons, medical oncologists, radiation oncologists, endoscopists, radiologists, and pathologists who are involved in the treatment of esophageal diseases meet and discuss the diagnosis, staging, and treatment plans for patients with esophageal tumors. A conference for pretreatment clinical diagnosis and a pathology demonstration of resected esophageal tumors has been held irregularly this year to discuss a wide range of topics.

Every week, 2-3 patients with esophageal cancer undergo esophageal surgery. One hundred nineteen patients underwent esophagectomy including 2 patients with cervical esophageal cancer and 11 with adenocarcinoma in the esophagogastric junction, and also including two with carcinosarcoma and one with small cell carcinoma. Six of 11 adenocarcinomas arose from Barrett's epithelium. Of the 92 patients who underwent surgery as primary therapy, a curative resection was completed for 88%, significantly decreased from previous year. There was 1 hospital death due to an operative complication (1%). Preoperative chemotherapy was recommended for 52 patients and preoperative chemoradiotherapy was recommended for 2 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 21 patients, which is a decrease from the previous year and reflecting the stricter application of this method. Feasibility will be evaluated upon morbidity and survival results.

The number of patients who receive definitive chemoradiotherapy as their primary treatment for resectable tumors 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 2012. A three-field dissection is avoided for salvage esophagectomy.

Research activities

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

Clinical trials

The results of a multi-institutional randomized controlled trial (JCOG9907) confirmed preoperative chemotherapy with cisplatin and 5FU before esophagectomy as standard therapy for resectable Stage II-III esophageal cancer. A new multi-institutional randomized controlled trial comparing standard preoperative chemotherapy (5FU and cisplatin), an intensive regimen (5FU and cisplatin plus docetaxel), and preoperative chemoradiotherapy (5FU and cisplatin plus 41.4

Gy irradiation) for Stage II-III esophageal cancer (JCOG1109) has launched on December, 2012. A Phase II trial for definitive chemoradiotherapy with or without salvage esophagectomy (JCOG0909) is continuing registration. For a Stage I lesion, a multi-institutional randomized controlled comparison between surgery and definitive chemoradiotherapy for a Stage I lesion (JCOG0502) has almost finished registration.

Table 1. Type of surgery

Esophagectomy	90
Salvage esophagectomy	12
Gastric conduit cancer surgery	1
Salvage lymphadenectomy	10
Bypass surgery	3
Cervical esophagostomy	2
Exploration	1

Table 2. Type of esophagectomy

Rt. thoracotomy with 3-field	46
Rt. thoracotomy with 2-field	23
Video-assisted with 3-field	15
Video-assisted with 2-field	6
Lt. thoracotomy	1
Lt. thoraco-abodominal	3
Transhiatal	2
Cervical	4
Abdominal	4

Table 3. Survival rates after esophagectomy

Clinical stages before preoperative chemo and/or radiotherapy	No. of pts	MST (mo)	5-yr survival (%)
cStage I	171	n.v.	80.1
cStage IIA	195	86	71.1
cStage IIB	157	n.v.	72.6
cStage III	494	34	36.9
cStage IVA	42	17	21.4
cStage IVB	112	22	28.0

Operation period: 1999.1-2008.12 n.v.: not verified

List of papers published in 2012

Journal

1. Ozawa S, Tachimori Y, Baba H, Fujishiro M, Matsubara H, Numasaki H, Oyama T, Shinoda M, Takeuchi H, Teshima T, Udagawa H, Uno T, Barron JP. Comprehensive Registry of Esophageal Cancer in Japan, 2004. Esophagus, 9:75-98, 2012

Department of Gastric Surgery

Hitoshi Katai, Takeo Fukagawa, Shinji Morita, Masaki Ohashi, Yukie Yoda, Masahiro Maeda

Introduction

This Division treats not only gastric adenocarcinomas 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. Neoadjuvant chemotherapy is frequently used for patients with locally advanced tumors.

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

We consider the education of foreign surgeons is to be an important function. In 2012, 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. DNA methylation as a gastric cancer metastasis risk factor has been investigated. A mini-chip assay of peritoneal washing specimens or prediction of gastric cancer recurrence is being developed. Research on the detection of small amounts of cancer cells in the 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 on systemic chemotherapy with Docetaxel, CDDP, and S-1 followed by surgery in advanced cancer with extensive lymph node metastasis has been conducted. A phase II study has just started to check the feasibility of Oxaliplatin, and S-1 neoadjuvant chemotherapy for stage III disease.

Table 1. Number of Patients

Adenocarcinoma	413
GIST	11
Others	57
Total	481

Table 2. Operative morbidity and mortality after gastrectomy

	Number of patients	%
Major complications	55	16.1
Minor complications	77	22.5
Postoperative hospital deaths	0	0
Total	342	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	146
Total gastrectomy	90
Pylorus-preserving gastrectomy	48
Proximal gastrectomy	19
Wedge resection	10
Pancreaticoduodenectomy	1
Laparoscopic distal gastrectomy	15
Laparoscopic pylorus preserving gastrectomy	22
Laparoscopic total gastrectomy	1
Other (bypass, exploration, etc.)	129
Total	481

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

List of papers published in 2012
Journal

1. Terashima M, Kitada K, Ochiai A, Ichikawa W, Kurahashi I, Sakuramoto S, Katai H, Sano T, Imamura H, Sasako M. Impact of expression of human epidermal growth factor receptors EGFR and ERBB2 on survival in stage II/III gastric cancer. Clin Cancer Res, 18:5992-6000, 2012
2. Shigematsu Y, Niwa T, Yamashita S, Taniguchi H, Kushima R, Katai H, Ito S, Tsukamoto T, Ichinose M, Ushijima T. Identification of a DNA methylation marker that detects the presence of lymph node metastases of gastric cancers. Oncol Lett, 4:268-274, 2012
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Department of Colorectal Surgery

Yukihide Kanemitsu, Takayuki Akasu, Dai Shida, Seiichiro Yamamoto, Masashi Takawa

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, multidisciplinary 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 preoperative treatment plans for patients about to undergo surgery.

Routine activities

There are four staff surgeons, one chief resident, and four or five rotating residents. Every morning (8:00-8:30), we have a morning conference and rounds in wards 8B and 15A, B. A multidisciplinary team (MDT) meeting is held for cancer patients as a form of institutionalized communication every Tuesday morning (7:15-8:00), and a conference is held for the diagnosis of colorectal cancer: colorectal surgeons, endoscopists, and radiologists discuss the diagnosis for preoperative patients every Tuesday evening (18:30-19:30). Every Wednesday evening (17:00-18:30), a conference is held on the treatment of colorectal cancer: colorectal surgeons and medical oncologists discuss treatments for preoperative and postoperative patients. Ten to 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 trial (JCOG1006 study). Patients with advanced rectal cancers are treated with conventional surgery. Adjuvant chemotherapy is being used in stage III colorectal cancer patients in a clinical 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. To evaluate the survival benefit and safety of primary resection plus chemotherapy compared to chemotherapy alone in asymptomatic stage IV colorectal cancer with synchronous unresectable metastatic disease, a randomized controlled trial comparing resection of the primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer (JCOG1007, iPACS) is ongoing. Patients with resectable liver metastasis are treated in cooperation with the Hepatobiliary and Pancreatic Surgery Division and adjuvant chemotherapy regimens are being evaluated in a clinical trial (JCOG0603 study).

Research activities

As described in "Routine Activities", clinical trials are integrated into our routine work. 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 2012, we published 4 papers, and the results of our research in 2012 are summarized as follows.

Clinical research

To examine the technical and oncological feasibility of laparoscopic surgery for rectal cancer, we conducted a confirmatory phase II trial to evaluate laparoscopic surgery for preoperative clinical stage 0/I rectal cancer. In a prospective multicenter study of laparoscopic surgery in Japan, Lap ISR was feasible and safe for clinical stage 0/I rectal cancer

with a favorable short-term outcome.

Endoscopic submucosal dissection (ESD) is increasingly being used to resect early-stage colorectal carcinomas, despite the technical difficulties associated with the procedure. Laparoscopic-assisted colorectal surgery (LAC) is an alternative to open surgery for colorectal cancers, and ESD was recently introduced as another alternative. We compared ESD with LAC as minimally invasive treatments for early colorectal cancer. ESD was associated with a lower complication rate than LAC, with favorable en bloc and curative resection rates. The safety profile and possibility of curative treatment with colorectal ESD provide advantages for the treatment of early colorectal cancers with nul risk of lymph node metastasis.

A randomized controlled trial to confirm that the results of mesorectal excision alone are not inferior to those of mesorectal excision with lateral lymph node dissection was undertaken at 33 major hospitals in Japan. Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than mesorectal excision alone. The primary analysis will help to show whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

Clinical trials

Our division plays a central role in conducting multi-institutional clinical trials in Japan. Y. Shimada is a representative of the Colorectal Cancer Group of the Japan Clinical Oncology Group (JCOG). Our division is participating in 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.
7. JCOG1007: A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable Stage IV colorectal cancer (JCOG1007, iPACS) is ongoing.

Table 1. Number of operative procedures

Operative Procedures	Number of patients	
	Open	Laparoscopic
Colectomy	61	121
High anterior resection	3	7
Low anterior resection	54	43
Abdomino-perineal resection	20	4
Hartmann's operation	1	
Intersphincteric resection	2	10
Total extirpation of large intestine	1	1
Total pelvic exenteration	6	
Total pelvic exenteration with sacrectomy	1	
Bypass	2	
Colostomy or ileostomy	32	
Local excision	1	
Other	65	

List of papers published in 2012
Journal

1. Yamamoto S, Fujita S, Akasu T, Inada R, Moriya Y. Risk factors for anastomotic leakage after laparoscopic surgery for rectal cancer using a stapling technique. Surg Laparosc Endosc Percutan Tech, 22:239-243, 2012
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Department of Gastrointestinal Medical Oncology

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Introduction

The Gastrointestinal Medical Oncology Division is focused on the development of new drugs and standard chemotherapy regimens combined with or without surgery and radiation for advanced colorectal, gastric and esophageal cancer, gastrointestinal stromal 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. A multi-kinase inhibitor, regorafenib, will be approved for colorectal cancer in 2013. For gastric cancer, an anti-HER2 monoclonal antibody, named trastuzumab, was also approved in 2011. In the near future we expect to identify other novel agents for the treatment of metastatic GI cancers that inhibit intracellular signal transduction or cellular interactions. However, many unusual adverse effects and a marked increase in medical cost have led to extensive discussion on more accurate targeting of the population using biomarkers. Although the response rates of these molecular-targeted drugs up to now have not been high (about 10 to 20%) when used broadly in a large population of patients, there are a few new candidate biomarkers that may be useful for identifying patients for whom these molecular-targeted drugs will be effective. For example, *K-ras* mutation in tumor tissue is one of negative predictive factors for the response to cetuximab. Accordingly, the identification of molecular markers that can be used to monitor tumor shrinkage or assist prognosis will be critical for the identification of possible new targets and for tailored treatments based on patient genotype or marker expression.

Routine activities

The staff of the GI Medical Oncology Division consists of 7 medical oncologists, 1 senior resident, and 3 or 4 residents. We hold a daily case conference together at 8 am before the morning rounds. Inter-group meetings with each surgical division (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 2012, we treated 2,208 hospitalized patients (524 of whom were newly diagnosed). Of these patients, 182 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 measured the gene mutations of possible predictive biomarkers in paraffin-embedded GI cancer specimens obtained from surgical resection or endoscopic biopsy, and investigated the correlation between enzymes related to anti-cancer drug metabolism and clinical outcomes with a RT-PCR assay. Some of these results on the correlation between gene mutation profile and cancer outcomes

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

Clinical trials

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

1. Colorectal Cancer

We investigated establishing combination chemotherapy regimens based on the oral fluoropyrimidine, S-1 (S-1/oxaliplatin/BV, 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. We investigated the additive effect of ramucirumab, an anti-VEGFR2 receptor antibody, combined with FOLFIRI (5-FU/l-LV/Irinotecan) for colorectal cancer patients who failed to respond to first line treatment with FOLFOX or XELOX +bevacizumab. TAS-102, an oral novel fluoropyrimidine, was also compared to best supportive care in an international phase III trial for the salvage line of colorectal cancer patients.

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 the overseas strategies. A new adjuvant trial, JCOG0910, comparing S-1 with one of the standard regimens, capecitabine alone, started in March 2010. At the end of 2012, more than 1200 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 II part of JCOG0903, a phase I/II trial of chemoradiation with S-1/MMC for anal canal squamous carcinoma, continues to enroll patients.

2. Gastric cancer

A phase III study comparing three regimens (5-FU vs CPT-11/CDDP vs S-1) (JCOG9912) was already published in 2009. This was a pivotal study that established a new standard care protocol for advanced gastric cancer and cited the "New Japanese guidelines for diagnosis and treatment of carcinoma of the stomach", 2010 edition. A new pivotal phase III trial comparing S-1/CDDP(CS) to S-1/CDDP/Docetaxel(DCS) was started from April, 2012. 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. The AVAGAST trial which evaluated the additive effect of bevacizumab for fluoropyrimidine and cisplatin in first line treatment for metastatic gastric cancer was published in 2011.

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 has been completed, showing improved tolerability and preliminary favorable survival results.

Molecular-targeted drugs for advanced gastric cancer as well as colorectal cancer have been investigated. The result of the AVAGAST international phase III trial, showed no additive effect of bevacizumab to standard treatment. Cetuximab was also evaluated in an international phase III trial, the EXPAND trial, and the result was shown in the ASCO meeting 2012. No additive effect of cetuximab was shown, similar to the AVAGAST trial. RAD001 (an mTOR inhibitor) also showed a negative effect for gastric cancer. We have investigated some other molecular targeted drugs for example lapatinib (EGFR/HER2, a dual tyrosine kinase inhibitor), ramucirumab (anti-vascular monoclonal antibodies) or TKI258 (a receptor tyrosine-kinase inhibitor). 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

A phase III trial (JCOG0502) which compared surgery to chemoradiotherapy for stage I esophageal cancer patients started from 2006. At the end of 2012, more than 370 patients were enrolled for this study, and patient accrual was finished on January 2013.

The results of our phase III study of preoperative versus postoperative 5-FU/CDDP (FP) (JCOG9907) were reported in 2007. Preoperative FP was proven to be significantly superior to postoperative FP with regard to overall survival. Based on the results of this trial, the standard care for stage II/III esophageal cancer has been changed to preoperative FP followed by surgery. The large pivotal trial JCOG1109 which compared standard preoperative FP to a DCF regimen (FP+Docetaxel) or an FP +radiation regimen just started from December 2012. A phase II study (JCOG0909) on the FP/RT (50.4 Gy) regimen plus salvage surgery with endoscopic resection in stage IB, II or III esophageal cancer is ongoing. A phase I/II study (JCOG0807) of triplet regimen (5-FU+CDDP+Dpcetaxel) has finished the final analysis and will be presented at the ASCO meeting 2013. Nimotuzumab is one of the anti-EGFR antibodies, which has shown activity for head and neck, gastric, and lung cancer. A phase I study of 5-FU+CDDP+Radiation with Nimotuzumab was finished and showed feasibility for stage IB/II/III/IVA esophageal cancer patients. A phase II study of cancer vaccine has finished patients accrual.

4. Other

A phase I study on 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 III study on AMN107 against gastrointestinal stromal tumors has also finished. An international phase III trial using regorafenib showed positive results compared to best supportive care in salvage treatment for gastrointestinal stromal tumors. An international phase III trial, RADIANT-4, which compared RAD001 to best supportive care in neuroendocrine tumor (NET) patients, is ongoing.

Tables

Number of Patients Treated	Total no. of hospitalized pts	No. of newly diagnosed pts.	No. of pts. enrolled protocol
1) Esophageal cancer	791	171	
Stage I FP+RT vs surgery JCOG0502 (phase III)			11
Stage I EMR+5FU/CDDP+RT JCOG0508 (phase II)			1
5FU/CDDP+RT for Ce Esophageal Cancer (phase II)			1
Stage II/III EC-CRT+Salvage JCOG0909 (phase II)			9
S-488410 (phase I/II)			4
5FU/CDDP+RT +DE766 (phase I)			3
NeoCFvsNeoDCFvsNeoCF-RT JCOG1109 (phase III)			3
2) Gastric cancer	810	154	
S-1/oxaliplatin (SOX) vs S-1/cisplatin (SP) (phase III)			7
Paclitaxel ±I MC-1121B (ramucirumab/placebo) (phase III)			7
Neo S1/CDDP JCOG0501(phase III)			3
wPTX/Tmab (phase II)			1
Bevacizumab ± capecitabine/cisplatin AVAGAST (phaseIII)			1
Dovitinib (phase II)			2
AZD8931+paclitaxel (phase II)			2
S-1/cisplatin/trastuzumab (phase II)			5
S-1/CDDP(CS) vs Docetaxel+CS JCOG1013 (phase III)			29
3) Colorectal cancer	516	161	
Adjuvant Capecitabine vs S-1 JCOG0910 (phase III)			36
FOLFOX+bevacizumab vs SOX+bevacizumab (phase III)			5
Observation vs FOLFOX JCOG0603 (phase II/III)			2
Stage II/III S-1/MMC JCOG0903 (phase I/II)			3
FOLFOX or FOLFIRI/Panitumumab Paff-J (phase II)			5
FOLFIRI ± MC-1121B (ramucirumab/placebo) (phase III)			5
CapeOX+bevacizumab vs SIRB TRICOLORE (phase III)			6
TAS-102 vs BSC (phase III)			20
Elderly patients 5-FU/l-LV vs FOLFOX JCOG1018 (phase III)			1
4) Others	91	38	
AMN107 vs imatinib (GIST) (phase III)			1
Regorafenib vs BSC (GIST) (phase III)			1
RAD001 vs BSC (NET) (phase III)			2
Peptide vaccines (gastrointestinal cancer)(phase I)			12
AZD4547 (gastrointestinal cancer) (phase I) / pre screening			4/88
BYL719 (phase I)			1
Total	2208	524	187

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Department of Endoscopy, Gastrointestinal Endoscopy Division

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Introduction

The Gastrointestinal Endoscopy Division and Bronchoscopy Division were unified again and became an independent unit under the name of the Endoscopy Center from July 2012. Now our Endoscopy Division is one of the most active Endoscopy Centers for both gastrointestinal imaging and bronchoscopy in the world.

The Gastrointestinal Endoscopy Division has eight staff physicians in the National Cancer Center Hospital (NCCH), three staff physicians in the Screening Technology and Development Division, three chief residents, five residents, four trainees and several rotating residents. The Bronchoscopy Division has welcomed three additional staff and resident doctors since 2010 and the total number of bronchoscopies and therapeutic procedures has dramatically increased.

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

Routine activities in GI Endoscopy

Various diagnostic techniques including chromoendoscopy, magnifying endoscopy and endoscopic ultrasonography (EUS) are used to detect and evaluate early malignant lesions. Capsule endoscopy also has been accepted as being far less invasive. In our facility, small intestine capsule endoscopy has been performed since 2005. In order to obtain more accurate endoscopic diagnosis of gastrointestinal diseases, we routinely use the recently developed narrow-band imaging (NBI) system. A total of 11,190 (+2%), 3,231 (+8%), 392 (+5%), 69 (+6%), 41 and 16 (-43%) 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 2012.

Due to the increasing number of patients with superficial gastrointestinal neoplasms, the number of therapeutic endoscopy procedures is also increasing in this field. In 2012, 2,044 (+7%) endoscopic resections were carried out (pharynx 22 (+10%), esophagus 174 (-10%), stomach 361 (-1%) and colon 1,484 (+11%)). Among these, ESD, which was developed for large en-bloc resections with a low-risk of local recurrence, was performed for 61 (±0) superficial esophageal cancers, 330 (-4%) early gastric cancers and 125 (±0) superficial colorectal neoplasms. For colorectal ESDs and some esophageal ESDs, the newly developed ball-tip bipolar needle knife (B-knife) and IT-knife nano were used together with CO_2 insufflation. These procedures and devices were originally developed by our colleagues.

ESD achieves a higher en-bloc resection rate compared to the standard EMR technique and is less invasive than a surgical operation while EUS-FNA provides a less invasive procedure to improve diagnosis for patients with pancreatic tumors, lymph-node swelling, submucosal tumors of the GI tract, etc. As for emergency endoscopic procedures, 355 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.

Table 1. Number of Procedures

	Performed in 2012
Upper GI Endoscopy	11,190
Lower GI Endoscopy	3,231
Pharyngeal EMR/ESD	22
Esophageal EMR/ESD	113/61
Gastric EMR/ESD	31/330
Colorectal Polypectomy, EMR	1,359
Colorectal ESD	125
EUS/EUS-FNA/ERCP	392/69/41
Emergency Endoscopy	355
Capsule Endoscopy	16

Research activities in GI Endoscopy (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 conducted a trial study on an autofluorescence imaging (AFI) system. This system can identify lesions based on differences in tissue fluorescence properties and reveal gastrointestinal neoplasms that are not detectable with conventional endoscopy.

Gastric cancer is the second leading cause of cancer death worldwide. In order to improve the survival rate, early diagnosis is one of the optimal strategies, but it has been difficult to differentiate early gastric cancer from other non-neoplastic lesions using conventional WLE. We have conducted a multicenter prospective RCT and concluded that magnifying-NBI improved the diagnostic accuracy for discriminating gastric neoplasms from benign small depressed lesions. We presented this paper at a Plenary Session of the American Society for Gastrointestinal Endoscopy (ASGE) in 2011 and this study was published in *Gastroenterology* in 2012 .

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

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

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

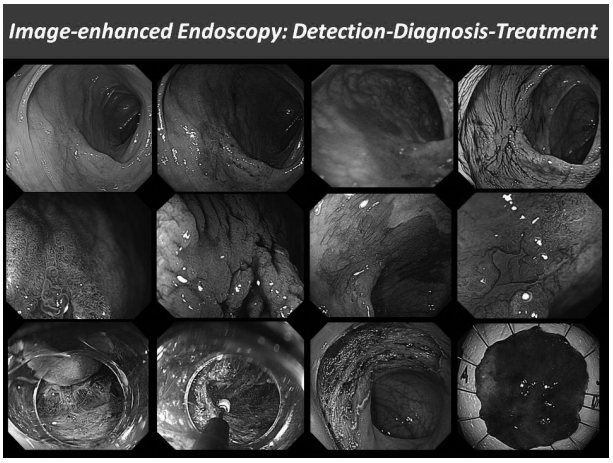

Figure 1. Endoscopic diagnosis using image-enhanced endoscopy (high-resolution endoscopy, narrow-band imaging and autofluorescence imaging) and an endoscopic submucosal dissection (ESD) procedure for treating early colon cancer

Clinical trials in GI Endoscopy

A multicenter clinical trial is already 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).

A Japanese multicenter prospective cohort study is currently being conducted on EMR/ESD for early gastric cancer using a Web registry system developed to determine short-term and long-term outcomes based on the absolute and expanded indications (J-WEB/EGC). A total of 9,599 consecutive patients with 11,156 EGCs or suspected EGCs underwent EMR/ESD at the 41 participating institutions from July 2010 to June 2012 were enrolled in the study cohort using the Web registry system and each patient will be followed up a minimum of five years. The primary endpoint is the five-year overall survival with en-bloc resection, curative resection, complication, local recurrence, distant metastasis, metachronous EGC and recurrence-free survival being secondary endpoints in addition to the successful collection of long-term outcome data on enrolled patients utilizing the survey program.

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 was scheduled to continue until 2012 and ongoing analysis of the 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.

Little is known about the long-term outcomes of patients with submucosal invasive colorectal cancer who undergo endoscopic or surgical resection. We performed a retrospective analysis of the long-term outcomes of patients treated for submucosal colon and rectal cancer. We collected data from 549 patients with submucosal colon cancer and 209 with submucosal rectal cancer who underwent endoscopic or surgical resection at 6 institutions, over a median follow-up period of 60.5 months. We assessed recurrence rates, 5-year disease free survival, and 5-year overall survival. As a result, of patients treated with only endoscopic resection, the risk for local recurrence was significantly higher in high-risk patients with submucosal rectal cancer than patients with submucosal colon cancer. The addition of surgery is therefore recommended for patients with submucosal rectal cancer with pathology features indicating a high risk of tumor progression (*Gastroenterology* 2012, Dec. e-pub ahead of print). Considering this study result, we are now planning a prospective cohort study for the possibility of chemoradiotherapy for high-risk rectal submucosal cancer after endoscopic resections.

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Journal

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Department of Endoscopy, Respiratory Endoscopy Division

Shinji Sasada, Takaaki Tsuchida, Yukiko Nakamura, Takehiro Izumo, Tomoyasu Mimori

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 conference with CT imaging analysis and confirmation of the pathology results was held. Furthermore, we attended all clinical conferences in the Surgery, Oncology, Radiology and Pathology Divisions to discuss and decide upon treatment strategies. Seven hundred and five cases of transbronchial biopsy were performed. Endobronchial ultrasonography (EBUS) is used not only to evaluate mediastinal or hilar malignant lesions but also to evaluate whether the biopsy devices can be directed to the peripheral lung lesions. One-hundred sixty two cases of EBUS-TBNA (EBUS-trans bronchial needle aspiration) were performed as a less invasive procedure to improve the diagnosis for patients with mediastinal or hilar lymph node swelling. The EBUS-GS (guide sheath) method was performed in most of the peripheral pulmonary lesions.

Nineteen endobronchial stenosis patients were treated with airway stent placement (9 cases), endobronchial electrocautery ablation (5 cases), and tracheobronchial ballooning (5 cases). Five out of 19 intervention cases underwent procedures through the rigid bronchoscope under general anesthesia in the operation suite.

Medical thoracoscopy under local anesthesia in the operation suite was performed in 31 cases with unknown pleural effusion or a pleural tumor. Seven out of 31 cases underwent an electrocautery (IT knife) pleural biopsy because of pleural thickening.

In 2012, endobronchial photodynamic therapy was introduced, and was used in the treatment of 4 cases with squamous cell carcinoma (3 early stage, 1 advanced stage).

Research activities

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

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

Clinical trials

We have started a clinical trial on detection of biomarker profiling using a small specimens obtained with bronchoscopy or thoracoscopy in patients with lung cancer.

Table 1. Type of procedure

Diagnostic bronchoscopy under X-ray fluoroscopy	551
Diagnostic bronchoscopy without X-ray fluoroscopy	195
(Transbronchial biopsy)	(705)
Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA)	162
Medical thoracoscopy	31
Airway stent placement	9
Electrocautery ablation	5
Balloon	5
Photodynamic therapy (PDT)	4
Endobronchial chemotherapy	4
Bronchial occlusion	1
Total	967

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Journal

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Department of Hepatobiliary and Pancreatic Surgery

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

Introduction

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

Routine activities

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

Operation and perioperative care

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

Conferences

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

Table 1. Number of patients

	n
Invasive pancreatic cancer	76
Other pancreatic neoplasms	24
Hepatocellular carcinoma	40
Hepatic metastases	53
Intrahepatic cholangiocarcinoma	13
Bile duct cancer	19
Gallbladder cancer	6
Duodenal cancer	15
Others	47
Total	293

Table 2. Type of procedures

	n
Hepatectomy without biliary resection	109
Hepatectomy with biliary resection	19
Right hemihepatectomy and pancreaticoduodenectomy (HPD)	1
Classical Whipple (CW)	22
Pylorus-preserving pancreaticoduodenectomy (PPPD)	45
Distal pancreatectomy	32
Appleby operation	1
Medial pancreatectomy	1
Total pancreatectomy	7
Extended cholecystectomy	8
Other resections	19
No resection	29
Total	293

Table 3. Survival rates

Invasive ductal carcinoma (2000-2009)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	11	62	62
II	7	67	67
III	80	55	41
IVa	238	37	22
IVb	107	27	16
Total	443	39	26

Hepatocellular carcinoma (2000-2009)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	37	89	73
II	158	89	82
III	227	68	54
IV	81	59	44
Total	503	74	62

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

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Department of Hepatobiliary and Pancreatic Oncology

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 multidisciplinary care given at the National Cancer Center Hospital (NCCH), we work closely with surgeons and radiologists who have special expertise in these areas. We also conduct research into the pathophysiology of hepatobiliary and pancreatic tumors and seek to develop new and more effective diagnostic methods and treatments.

Routine activities

The division consists of 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

A phase I and randomized phase II study with Wilms tumor 1 (WT1) peptide vaccine plus gemcitabine and cisplatin (GC) for chemo-naïve patients with unresectable or recurrent biliary tract cancer was started, because the overexpression of WT1 is seen in the majority of patients with this disease, encouraging the potential of WT1-based immunotherapy. (Okusaka et al.). The aim of this trial is to evaluate the efficacy and safety of the regimen and to determine whether the regimen should be compared with the current standard regimen, GC, in a subsequent phase III trial for patients with unresectable or recurrent biliary tract cancer. This is the first randomized trial to evaluate the use of immunotherapy in patients with advanced biliary tract cancer.

As the level of circulating endothelial cells (CECs) is known to increase in response to various cancers, we investigated the predictive potential of CEC levels and the association of these levels with the expression of proangiogenic factors in pancreatic carcinoma patients (Kondo et al.). Pancreatic carcinoma patients receiving gemcitabine chemotherapy were prospectively assigned to this study. Baseline CEC levels were markedly higher in pancreatic carcinoma patients (n = 37) than in healthy volunteers (n = 53). Moreover, these high CEC levels were associated with decreased overall survival (median, 297 days versus 143 days, $P < 0.001$) and progression-free survival (median, 150 days versus 64 days, $P = 0.008$), as well as with high vascular endothelial growth factor, interleukin (IL)-8, and IL-10 expression in the pancreatic carcinoma patients. Several chemokines and proangiogenic factors correlate with the release of CECs, and the number of CECs detected may be a useful prognostic marker in pancreatic carcinoma patients undergoing gemcitabine chemotherapy.

We reviewed the medical records of 136 patients (41 with extrapulmonary neuroendocrine carcinoma [EP-NEC] and 95 with small-cell lung carcinoma [SCLC]) who were treated using a platinum-containing regimen for advanced disease between January 2000 and October 2008 at our hospital. (Terashima T, Morizane C et al.). The primary site of the EP-NEC was the gastrointestinal tract in 18 patients (GI tract group); the liver, biliary tract or

pancreas in 16 patients (HBP group), and other sites in 7 patients ('others' group). The response rate in the SCLC patients was 77.8%, and the response rate in the EP-NEC patients was 30.8% (37.5% in the GI tract group, 12.5% in the HBP group, and 57.1% in the 'others' group). The median survival time for the SCLC patients was 13.6 months, while that for the EP-NEC patients was 9.2 months (14.9 months in the GI tract group, 7.8 months in the HBP group, and 8.9 months in the 'others' group). A multivariate analysis demonstrated that a poor performance status, liver involvement, and the treatment regimen were independent unfavorable prognostic factors.

Clinical trials

Thirty-two clinical trials are ongoing, including seven phase III trials, such as adjuvant chemotherapy versus placebo in HCC patients who had undergone hepatic resection or local ablation therapy, and adjuvant chemotherapy with a new regimen versus standard chemotherapy in pancreatic cancer patients after pancreatectomy. Two studies are collaboration trials with the Department of Diagnostic Radiology, and one with the Department of Radiation Oncology. Three trials are being conducted to evaluate cancer immunotherapy. Our studies are supported by National Cancer Center Research and Development Fund (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, No. H22-ganrinsho-ippan-015, No. H22-ganrinsho-ippan-022, No. H23-ganrinsho-ippan-006), and Health and Labour Sciences Research Grants, Clinical Research (Grant No. H21-rinshokenkyu-ippan-013, No. H23-jitsuyoka(gan)-ippan-002) from the Ministry of Health, Labour, and Welfare of Japan.

Table 1. Number of patients

	No. of pts.
Pancreatic cancer	
Invasive ductal	155
Neuroendocrine	23
Others	30
Biliary tract cancer	
Extrahepatic bile duct	9
Gallbladder	22
Papilla of Vater	5
Liver cancer	
Hepatocellular	230
Intrahepatic cholangiocarcinoma	36

Table 2. Type of procedure

	No. of pts.
Pancreatic cancer	
Systemic chemotherapy	111
Chemoradiotherapy	4
Biliary tract cancer and Intrahepatic cholangiocarcinoma	
Systemic chemotherapy	45
Hepatocellular carcinoma	
Ethanol injection	13
Radiofrequency ablation	32
Transcatheter arterial (chemo)embolization	129
Intra-arterial chemotherapy	36
Systemic chemotherapy	32
Radiotherapy	8

Table 3. Survival rates

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

List of papers published in 2012
Journal

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2. Okusaka T, Ueno H, Ikeda M, Takezako Y, Morizane C. Phase I study of TAC-101, an oral synthetic retinoid, in Japanese patients with advanced hepatocellular carcinoma. Cancer Sci, 103:1524-1530, 2012

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Department of Urology

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

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 five staff physicians and three 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 an M-VAC regimen. N+: systemic chemotherapy, radiation; sometimes urinary diversion alone. M+: chemotherapy with a M-VAC or GC regimen.
3. Prostate cancer. Organ-confined disease: active surveillance, radical prostatectomy, irradiation, or endocrine therapy. Specimen-confined disease: extended radical prostatectomy without neoadjuvant endocrine therapy, radiation therapy with endocrine therapy, or endocrine therapy alone. M1 disease: endocrine therapy and palliative radiation if necessary. For castration refractory disease, DTX chemotherapy is indicated.
4. Testicular germ cell tumor (GCT). Stage I: careful observation regardless of a pathological element. Stage II or higher: EP (etoposide + CDDP) or BEP (BLM + etoposide + CDDP) chemotherapy as the 1st line. In nonseminomatous cases, 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 malignant urological tumors.

1. Renal cell carcinoma: Improvement of the treatment outcome in metastatic renal cell carcinoma remains a major problem. A phase II and III study using a VEGFR inhibitor (AG-013766) is also in progress.
2. Urothelial cancer: The effectiveness of a phase III study to confirm the efficacy of BCG instillation for high grade T1 bladder cancer (JCOG1019) is ongoing. For metastatic disease, a phase II study using a peptide vaccine (S288310) is in progress and a weekly CBDCA + PTX regimen has been indicated.
3. Prostate cancer: A phase II study to evaluate the efficacy of robotic assisted laparoscopic radical prostatectomy for low and intermediate risk prostate cancer is ongoing. A new operative method to achieve a complete surgical margin (extended radical prostatectomy) has been developed, and its efficacy in patients with specimen-confined disease has been evaluated without neoadjuvant endocrine therapy. To provide a more precise preoperative diagnosis, a new imaging strategy using 3.0 Tesla MRI has been developed. To identify the most effective treatment for the recurrence of PSA failure after radical prostatectomy, a phase III study to evaluate the efficacy of salvage irradiation vs hormone ablation for postoperative PSA failure in T1c-T2 prostate cancer (JCOG0401) is under review. In local advanced disease, a phase III study to evaluate the survival benefit of continuous endocrine therapy after 3D conformal radiotherapy is still underway. For hormone-refractory prostate cancer, a study on a new hormonal regime with TAK700 has completed enrollment.

Table 1. Patients statistics: Major treatment

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

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 tumors, a second line TIP regimen has completed enrollment.

Clinical trials

We are actively involved in the following ongoing protocol studies;

1. A phase II & III study: AG-013766 for metastatic renal cell carcinoma
2. A phase III study: BCG instillation for high grade T1 bladder cancer (JCOG1019)
3. A phase II study: Robotic assisted laparoscopic prostatectomy for low and intermediate risk prostate cancer
4. A phase III study: Salvage radiation vs hormone ablation for postoperative PSA failure in T1c-T2 prostate cancer (JCOG0401)
5. A phase II study:TAK700 for hormone-refractory prostate cancer
6. A phase II study: TIP for CDDP-refractory metastatic germ cell tumor.

List of papers published in 2012
Journal

1. Hashimoto K, Fujimoto H, Kouno T, Koseki M, Yonemori K, Hirata T, Yunokawa M, Shimizu C, Katsumata N, Tamura K, Ando M, Takeuchi M, Nakanishi H, Komiyama M, Nakagawa T, Fujiwara Y. The incidence and management of metachronous testicular germ cell tumors in patients with extragonadal germ cell tumors. Urol Oncol, 30:319-324, 2012
2. Hara T, Komiyama M. A case of left renal cell carcinoma with massive tumor thrombus extending into the inferior vena cava. Jpn J Clin Oncol, 42:658, 2012

Department of Gynecology

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

Introduction

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

1) Treatment strategy for uterine cervical cancer. Either conization or a 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 a radical hysterectomy and pelvic lymphadenectomy. Postoperative total pelvic irradiation following a radical hysterectomy is only considered for patients with metastasis to the pelvic nodes or parametrial tissue as confirmed by pathological examination. Furthermore, in 2012, intensity-modulated radiation therapy (IMRT) was employed for postoperative adjuvant radiotherapy. Radiotherapy alone or concurrent chemo-radiotherapy is given to patients at any stage. Chemotherapy is occasionally used for the treatment of distant metastasis.
2) Treatment strategy for endometrial cancer. The primary treatment choice is a hysterectomy with bilateral salpingo-oophorectomy. Pelvic lymph node dissection is also performed for patients with a high risk of metastasis. Para-aortic node dissection is limited to those with biopsy-proven nodal metastasis. In our practice, positive peritoneal cytology is not a poor prognostic factor for patients with a well-differentiated tumor confined to the uterus, whereas postoperative adjuvant chemotherapy is performed for patients with extra-uterine disease.
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 (TC or dose dense TC). Patients with more advanced stage III and IV disease, who are unlikely to be optimally debulked, are treated with primary chemotherapy. 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, patient numbers, and survival rates are shown in Tables 1, 2, and 3.

Research activities

Serous adenocarcinoma originating from the cervix and endometrium is a rare and aggressive variant. Togami reported on the clinicopathological features of serous adenocarcinoma of the uterine cervix (1). Togami *et al.* also demonstrated that molecular biological prognostic factors, HER2 and HR, were related to RFS and/or OS in patients with

uterine papillary serous carcinoma (USPC) (2). Although UPSC is a rare tumor, it is mandatory to establish novel therapies, including chemotherapy, endocrine therapy and molecular-targeted drug therapy, based on the findings of the status of these molecular biological markers. Uehara et al analyzed the characteristics and prognosis of patients with uterine carcinosarcoma (USC) after breast cancer and hormone therapy, and concluded that a history of breast cancer and hormone therapy for breast cancer was a risk factor for developing UCS without obvious impacts on the characteristics of UCS (3). Both of these factors had statistically significant impacts on the prognosis of patients with UCS. Ikeda et al examined the correlations between the pretreatment values of four tumor markers (SCC, CEA, CA19-9, CA125) and postsurgical high-risk factors in patients with squamous cell carcinoma of the uterine cervix who underwent radical hysterectomy, and concluded that SCC, CEA, and CA19-9 ware useful for predicting the status of postsurgical high-risk factors.

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 and a phase II study on irinotecan and etoposide for patients with platinum-resistant taxan-pretreated ovarian cancer (JCOG 0503) are ongoing. A phase III trial of paclitaxel plus carboplatin (TC) versus paclitaxel plus cisplatin (TP) in stage IVB, persistent or recurrent cervical cancer was completed, and demonstrated that TC can be recommended as the new standard treatment for recurrent cervical cancer. A nonrandomized confirmatory trial of modified radical hysterectomy for patients with FIGO stage Ib1 (< 2 cm) uterine cervical cancer (JCOG1101) has been started. A phase I/II study on Heavy Ion Radiotherapy with concurrent chemotherapy for locally advanced cervical adenocarcinoma using the Heavy Ion Medical Accelerator is ongoing in Chiba (HIMAC, National Institute of Radiological Sciences).

Table 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. Number of patients

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

[a] Neoadjuvant chemotherapy

Table 3. Survival

FIGO Stage	Cervical cancer[a]		Endometrial cancer[a]		Ovarian cancer[b]	
	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

List of papers published in 2012
Journal

1. Togami S, Kasamatsu T, Sasajima Y, Onda T, Ishikawa M, Ikeda S, Kato T, Tsuda H. Serous adenocarcinoma of the uterine cervix: a clinicopathological study of 12 cases and a review of the literature. Gynecol Obstet Invest, 73:26-31, 2012
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Department of Musculoskeletal Oncology and Rehabilitation

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

Introduction

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

Clinical Practices

The musculoskeletal oncology division of NCCH consists of 5 staff doctors (Drs. Hirokazu Chuman, Akira Kawai, Fumihiko Nakatani, Yoshikazu Tanzawa and Eisuke Kobayashi), 4 residents and 2 physiotherapists, 1 occupational therapist and 1 speech therapist. Occasionally, several fellows from Japan and overseas join our group. Outpatient consults are held every weekday. A constant number of about 30 patients are hospitalized for operation, chemotherapy or radiation therapy. Five or six major operations are routinely performed every week. In 2012, 299 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 35 reconstructive operations were conducted in collaboration with plastic surgeons to achieve adequate soft tissue coverage after the resection of malignant tumors of the trunk or limb-salvage operations for sarcomas of the extremities. As a result, almost 90% of the operations were performed with a limb-sparing approach. With regard to the patients' postoperative course, we have been collaborating with a physical therapist to rehabilitate the musculoskeletal system in cancer-bearing patients.

As for chemotherapy, we have been conducting neoadjuvant and adjuvant chemotherapy for high-grade bone and soft tissue tumors, palliative chemotherapy for metastatic bone and soft tissue sarcomas, occasionally in collaboration with medical oncologists. We have been collaborating with pediatric oncologists for chemotherapeutic treatment of children and adolescents with sarcomas.

Conferences

Monday (8:00 A.M-): Post-operative case conference
Tuesday (8:00 A.M-): Pre-operative case conference
Wednesday (8:30 A.M-): Rehabilitation conference
Thursday (7:30 A.M-): Journal club/ pediatrics and adolescence case conference

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 soft tissue sarcomas. Combined with each patient's clinical information, we have been establishing novel biomarkers for prediction of patients' prognoses or effects of the chemotherapeutic agents. Using the same method, we also have been searching for new genes or proteins for the molecular-targeted

treatment approach. Since 2009, we have also been focusing on the aberrant microRNA expressions in Ewing's sarcoma and osteosarcoma in order to develop novel molecular targeted therapies

Clinical trials

We have been conducting clinical trials of image-guided surgery to improve the accuracy of operation procedures using multi-modality imaging systems including open MRI, self-mobile CT and 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 adjuvant and second-line chemotherapy for bone and soft tissue sarcomas. Three multi-institutional clinical trials are active as follows:

1. Multi-institutional phase III clinical trial of multidrugs adjuvant chemotherapy for osteosarcomas (JCOG 0905) since 2010.
2. Multi-institutional phase 3 study of trabectedin for advanced soft tissue sarcoma since 2012.
3. Multi-institutional phase II study of Eribulin (an inhibitor of microtubule dynamics) for advanced soft tissue sarcoma since 2011.

Table 1. Numbers treated in our division from 2010 -2012

Year	Benign STT	Malignant STT	Benign BT	Malignant BT	Total
2010	86	146	44	44	320
2011	57	156	41	69	323
2012	53	195	22	78	348

STT, soft tissue tumor; BT, bone tumor

[Statistics]

	Soft tissue sarcoma	Bone sarcoma	Benign bone and soft tissue Tumor	Spine or bone metastasis	Biopsy or others	Total
Surgeries performed in 2012	106	28	70	26	69	299

	Soft tissue sarcoma	Bone sarcoma	Benign bone and soft tissue tumor	Bone metastasis	Total
New patients (2012)	122	23	77	20	242

List of papers published in 2012
Journal

1. Asano N, Nakatani F. A case of hemangiopericytoma of the pelvis. Jpn J Clin Oncol, 42:1110, 2012
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Department of Dermatologic Oncology

Naoya Yamazaki, Arata Tsutsumida, Ken-jiro Namikawa, Ryota Tanaka, Wataru Omata, Hironobu Eguchi, Kohei Ooashi

Introduction

The Department of Dermatologic Oncology has consistently served as the core hospital for the establishment of treatment strategies for malignant skin tumors since the National Cancer Center opened in 1962, and over 1800 cases of malignant melanoma have been accumulated thus far; an impressive number for a hospital or research institution in Japan. Today, patients are referred from throughout Japan. In particular, the numbers of patients with malignant melanoma were two hundred twenty eight, which was approximately twice the numbers 2 years ago. Most of the patients are examined and treated for skin cancer including malignant melanoma. Surgery is the main treatment modality for skin cancer, and multi-disciplinary treatments, consisting of chemotherapy, immunotherapy, and radiotherapy, are also routinely carried out. In addition, this Department plays an active role in multicenter trials for skin cancer all over Japan.

Routine activities

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

In 2012, a total of 375 patients were examined for the first time in the dermatology department for a malignant skin tumor. The numbers of patients with malignant melanomas (228) and extramammary Paget's disease (18) were particularly large, and were approximately 10 times and 2 times, respectively, the numbers 15 years ago. There were also 6 cases of the rare cancer, angiosarcoma.

About 18 patients are hospitalized to undergo surgery, chemotherapy, or radiation therapy. In 2012, 265 operations were performed including 105 operations under general anesthesia. Rounds are made and case presentations are held every morning. A division conference is held every Monday to discuss the therapeutic principles for outpatients and inpatients. A clinicopathological conference that focuses on surgically removed skin specimens is held with pathologists once a month.

In addition to the above, we have treated patients with advanced cases of mucosal melanoma in the nasal cavity, genital lesions, perianal lesions, and uveal melanomas even though we are, from the beginning, "dermatologists ".

Research activities

Malignant melanoma

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

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

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 melanomas in Japanese, 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 are performed with the injection of technetium tin colloid, the blue dye plus fluorescence method (combination of indocyanine green and the Photodynamic Eye System). 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.

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 that with more than three lymph nodes metastases was 0 %. Therefore, SLN biopsies for extramammary Paget's disease are important in the initial surgical treatment.

Clinical trials

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

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

The clinical trials (industry-sponsored registration trials) are summarized in Table 3.
(1) We have conducted five kinds of industry-sponsored registration trials for malignant melanomas.
(2) We are carrying out some clinical trials in collaboration with the Investigational Drug Development and Hematology Divisions in our hospital.

Table 1. Number of New Patients

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

Table 2. Operative Procedures (total number)

Wide local excision	120
Local excision	78
Sentinel node biopsy	44
Lymph node biopsy	16
Lymph node dissection	32
(neck)	6
(axilla)	10
(inguinal)	12
(groin)	4
(popliteal)	0
(epitrochlear)	0
Skin graft	40
Local flap	8
Free flap	1
Amputation	14
Others (biopsy/debridement)	5

Table 3. New Agent Studies in 2011

Agent	Eligible Cancer Type	Trial Phase
ONO-4538	Melanomas	II
ONO-4538	Solid Tumors	I
MAGE-A3	Melanomas	III
BCX1777	T/NK-Cell Lymphomas	I
E7777	Peripheral/Cutaneous T Cell Lymphomas	I/II
Lenalidomide	ATL, Peripheral T Cell Lymphomas	I
KW0761	ATL,T/NK-Cell Lymphomas	II
Romidepsin	Peripheral/Cutaneous T Cell Lymphomas	I/II
Vemurafenib	Melanomas	I/II
Ipilimumab	Melanomas	II
SCH54031	Melanomas	I
Dabrafenib	Solid Tumors	I
BYL719	Solid Tumors	I
RO4987655	Solid Tumors	I
WT4869	Solid Tumors	I
AZD8931	Gastric Cancer	II
PF-00299804	Lung Cancer	III
Lenalidomide	ATL	II
SyB-1717	Radiotherapy-Induced Nausea and Vomiting	II

List of papers published in 2012
Journal

1. Oshita C, Takikawa M, Kume A, Miyata H, Ashizawa T, Iizuka A, Kiyohara Y, Yoshikawa S, Tanosaki R, Yamazaki N, Yamamoto A, Takesako K, Yamaguchi K, Akiyama Y. Dendritic cell-based vaccination in metastatic melanoma patients: phase II clinical trial. Oncol Rep, 28:1131-1138, 2012

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4. Uhara H, Yamazaki N, Takata M, Inoue Y, Sakakibara A, Nakamura Y, Suehiro K, Yamamoto A, Kamo R, Mochida K, Takenaka H, Yamashita T, Takenouchi T, Yoshikawa S, Takahashi A, Uehara J, Kawai M, Iwata H, Kadono T, Kai Y, Watanabe S, Murata S, Ikeda T, Fukamizu H, Tanaka T, Hatta N, Saida T. Applicability of radiocolloids, blue dyes and fluorescent indocyanine green to sentinel node biopsy in melanoma. J Dermatol, 39:336-338, 2012

Department of Hematology

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Introduction

The Hematology Division is united with the Hematopoietic Stem Cell Transplantation (HSCT) Division, and the research and clinical activity in the Hematology Division are devoted to the diagnosis and treatment of hematologic malignancies. In the past, our Division introduced new disease entities, including adult T-cell leukemia-lymphoma (ATL) (JCO 2009;27:453) and angioimmunoblastic T-cell lymphoma (Blood 1988;72:1000). 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 inpatient 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 and pathologists 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 cytologic examinations, flowcytometric and molecular-genetic analyses. Five staff physicians, two chief residents, and two 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 (PCR) and fluorescence in-situ hybridization (FISH) techniques for the detection of t(8;14), t(14;18), t(11;18), t(9;22), t(8;21), t(15;17), and so on. Our recent research has focused on indolent B-cell non-Hodgkin lymphoma (B-NHL). Clinical as well as molecular genetic analysis of ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma cases led to the discovery of a tumor suppressor gene deleted at 6q23; we identified the A20 gene as a new tumor suppressor gene in various B-cell malignancies (Nature 2009;459:712). We have shown that the mutations and/or deletions are common in Japanese Hodgkin lymphoma cases (Ref 5) and are now extending the study to find other mutated genes.

From January 2012 to December 2012, we authored or coauthored 21 original articles concerning hematologic malignancies. Among them, discussions concerning the origin of epithelial tumors developing after allogeneic HSCT contributed to our understanding of the stem cells of solid tumors (Ref 6).

Clinical trials

In 2012, we conducted 32 new-agent studies, including 9 international studies, and 7 cooperative group studies (Tables 2 and 3). The numbers are still increasing including domestic ones. Almost all the new agents that are developed against hematologic malignancies in Japan have been evaluated in our

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	2012
Acute myelocytic leukemia (AML)	12	18	10	8	8	9	8	9	10	6	10	8	13	12
Acute lymphocytic leukemia (ALL)	6	3	8	3	2	1	2	4	9	8	2	2	1	1
Chronic myelocytic leukemia (CML)	15	9	24	11	7	5	6	10	11	3	3	2	2	2
Myelodysplastic syndrome (MDS)	9	9	8	5	6	5	3	3	9	8	20	9	3	3
Hodgkin lymphoma (HL)	10	10	14	15	16	9	13	21	11	12	7	11	16	15
Non-Hodgkin lymphoma (NHL)	133	204	215	268	291	299	278	265	210	208	151	185	243	172
Adult T-cell leukemia-lymphoma (ATL)	3	4	5	4	5	4	6	6	4	5	5	3	6	6
Chronic lymphocytic leukemia (CLL)	1	2	3	3	2	4	5	4	5	6	4	2	1	4
Multiple myeloma (MM)	7	7	8	6	9	19	14	9	8	10	12	9	10	7
Waldenström macroglobulinemia (WM)	3	1	1	1	1	1	0	0	2	3	1	2	2	1
Total	199	267	295	324	347	356	335	331	279	269	215	233	297	223

Division, and many of them have been approved by the Ministry of Health, Labour and Welfare (MHLW).

For ATL, based on the published results of a phase III study, JCOG9801 (JCO 2007;25:5458) and a phase I study on mogamulizumab, a humanized anti-CCR4 (CC chemokine receptor 4) antibody (JCO 2010;28:1591), we completed patient enrolment to a randomized phase II study comparing the intensified chemotherapy regimen (mLSG15) with or without mogamulizumab. We have conducted a pivotal phase II study on mogamulizumab monotherapy against relapsed ATL (Ref 15), and the agent was approved by the MHLW in March 2012. The agent is now being applied to treat other types of T-cell malignancies, and has shown promising activity against peripheral T-cell lymphoma (ASH 2012, #795).

A phase I study of oligopeptide vaccine OCV-501 against WT1 protein in AML cells to maintain cases in complete remission, is continuing. The agent was developed in Japan, and the study is the first vaccine study against hematologic malignancies aiming at approval by the MHLW.

For treatment of B-cell malignancies, a phase III trial for newly diagnosed diffuse large B-cell lymphoma (JCOG0601) is ongoing. In that trial, a dose-intense schedule of rituximab is being compared with that of a standard 3-week regimen, in combination with the administration of Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisolone (CHOP regimen).

In June 2012, we completed patient enrolment into a phase II study on a rituximab-incorporating dose-intensified chemotherapy with autologous HSCT for untreated mantle cell lymphoma (JCOG0406).

Table 2. Clinical trials for new agent development

Disease	Agents	Phase	Enrolled Patients in 2012	Enrolled Patients in Total
CML	Nilotinib	III	0	1
	Bosutinib	I/II	1	3
	Ponatinib	I	1	1
MDS	Panobinostat + Azacitidine	Ib	0	0
	Rigosertib	I	0	0
AML	WT1 vaccine	I	2	3
	WT1 (maintenance)	I	2	2
	Volasertib (BI6727)	I	1	1
ALL	Inotuzumab ozogamicin (CMC-544)	I	0	0
MM	Bendamustine + PSL	II	1	1
	Carfilzomib	I	2	3
	Siltuximab	I	1	1
	Anti-BAFF Ab (LY2127399)	I	0	0
	Perifosine	I	0	0
	Pomalidomide	I	0	0
	Lenalidomide	II	0	0
PTCL	Forodesine	I	0	2
	Mogamulizumab (KW-0761)	II	0	2
	Romidepsin	I/II	6	6
	Denileukin diftitox (E7777)	I	1	2
	Darinaparsin	I	1	1
	Lenalidomide	II	1	1
CD30+ lymphoma	Brentuximab vedotin (SGN-35)	I	6	7
B-CLL	Ofatumumab + Chlorambucil	I/II	0	0
FL	Obinutuzumab (GA101)	III	8	11
	Inotuzumab ozogamicin + R-CVP	I	0	8
	Everolimus (RAD001)	I	4	4
	Ofatumumab vs. Rituximab	III	17	27
	Ofatumumab +/- Bendamustine	III	2	2
	Rituximab + Bendamustine	II	6	6
	Forodesine	I	0	2
MCL	R-CHP +/- Bortezomib	III	0	2
DLBCL	Enzastaurin	III	0	7
	Ofatumumab	III	1	1
	Everolimus	III	0	1
	Inotuzumab ozogamicin	III	4	7
B-NHL	Ibrutinib (PCI-32765)	I	1	1
ML	Alisertib (MLN8237)	I	3	3
	Vorinostat (SAHA)	I	10	10
AML, ML, MM	OPB-51602	I	0	1

PTCL, peripheral T-cell lymphoma; FL, follicular lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; ML, malignant lymphoma; MM, multiple myeloma; MP, melphalan, prednisolone; PSL, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, PSL; R, rituximab; CHP, cyclophosphamide, doxorubicin, PSL

To develop new effective treatments for B-cell malignancies, we have investigated an anti-CD22 antibody drug conjugate (inotuzumab ozogamicin) (Ref 14), as well as new generation anti-CD20 antibodies (Ref 3). In addition, we initiated a phase I study on the Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765), which has shown significant efficacy against various B-cell malignancies.

For CD30-expressing lymphomas such as Hodgkin lymphoma and anaplastic large cell lymphoma, we have been conducting a phase I/II study on brentuximab vedotin (SGN-35), an anti-CD30 antibody drug conjugate, which has shown remarkable efficacy against relapsed or refractory patients.

Table 3. Cooperative group studies

Disease / Protocol	Phase	Year	No. of pts (a)	%CR (b)	OS (b)
AML					
JALSG-AML 97	III	(98-01)	15	79%	47% (5-yr)
JALSG-AML 201	III	(02-06)	13	78%	57% (5-yr)
JALSG-APL 97	III	(98-02)	2	95%	86% (4-yr)
JALSG-APL 204	III	(04-11)	2	94.50%	89.1% (5-yr)
JALSG-AML209	IV	(11-)	9	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-)	36	NA	NA
JCOG 0406	III	(08-)	5	NA	NA
JCOG 0908	III	(10-)	11	NA	NA
Indolent B-cell lymphoma					
JCOG 0203	II/III	(02-07)	52	77%	88% (6-yr)
Adult T-cell leukemia-lymphoma					
JCOG 9303	II	(94-97)	6	36%	31% (2-yr)
JCOG 9801	III	(98-03)	6	33%	19% (3-yr)
JCOG 0907	II	(10-)	0	NA	NA
Nasal NK/T-lymphoma					
JCOG 0211-DI	I/II	(03-07)	8	77%	78% (2-yr)
Multiple myeloma					
JCOG 9301	III	(93-98)	10	50% (d)	50% (4-yr)
JCOG 0112	III	(02-05)	9	46% (d)	63% (2-yr)
JCOG 0904	II(c)	(10-)	5	NA	NA

(a) the number of patients enrolled from our division; (b) As the number of enrolled patients in our division is relatively small, the %CR or OS for the entire enrolled patients in the JCOG or JALSG trials is shown here.

(c) randomized phase II study

(d) CR + PR rate. Abbreviations: JCOG, Japan Clinical Oncology Group; JALSG, Japan Adult Leukemia Study Group; LSG, Lymphoma Study Group; OS, overall survival; NA, not available

List of papers published in 2012
Journal

1. Tsukasaki K, Tobinai K. Clinical Trials and Treatment of ATL. Leuk Res Treatment, 2012:101754, 2012
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Department of Hematopoietic Stem Cell Transplantation

Takahiro Fukuda, Yuji Heike, Takuya Yamashita, Sung-Won Kim, Saiko Kurosawa, Shigeo Fuji

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, which are 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, Fuji, and Fukuda) and 2 chief residents (Drs. Hayashi and Ito) participate in the transplant program. Children who have undergone HSCT are managed in collaboration with Dr. Makimoto, the Chief of the Pediatric Oncology Division, and transplant team. In 2012, a total of 97 transplantations were performed at the 12B and 12A transplant units. The numbers of each type of HCST and those who underwent HSCT between 2008 and 2012 are shown in Tables 1 and 2, respectively. At the weekly conference on Monday afternoons, in collaboration with doctors of the Hematology Divisions, about 30 hospitalized HSCT patients and those who have been referred for HSCT, are reviewed for clinical management and a decision regarding their eligibility for HSCT. The transplant unit is staffed by 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 the principal investigators for Government-supported grant projects. Dr. Heike has organized a cell processing facility on the adjoining 12^{th} floor and a facility on the 11^{th} floor specializing in gene therapy in compliance with good manufacturing procedures (GMP). One clinical trial of gene therapy using the HSV-TK suicide gene for T-cell add-back following haploidentical HSCT is ongoing. A clinical trial of post-transplant consolidation with the WT1 vaccine is also ongoing. We have been working on expansion of the indication of drugs used for the treatment of GVHD and infections. In May 2011, foscarnet, an anti-viral agent, was approved for cytomegalovirus infection after HSCT in Japan. In the Division, 11 clinical trials are ongoing, and 11 trials have completed patient accrual. A nationwide large survey of quality of life (QOL) was conducted for patients with acute leukemia who received chemotherapy or HSCT. In 2012, we have published 19 articles in peer-reviewed international journals and 8 manuscripts have been accepted for E-pub before print or are in press for publication.

Table 1. Number of each type of HSCT

	Year	2008	2009	2010	2011	2012
Allogeneic		77	93	90	76	72
Unrelated	Bone marrow transplantation	48	59	60	54	46
	Peripheral blood stem cell transplantation	1	0	0	0	3
	Cord blood transplantation	1	5	1	4	8
Related	Bone marrow transplantation	5	2	5	2	0
	Peripheral blood stem cell transplantation	22	27	24	16	15
Autologous		8	18	19	25	25
Total		85	111	109	101	97

Table 2. Number of patients who underwent HSCT between 2008 and 2012

Diagnosis	Allogeneic	Autologous
Acute myeloid leukemia	165	1
Myelodysplastic syndrome	32	0
Acute lymphocytic leukemia	58	0
Malignant Lymphoma (including ATL)	143	56
Multiple Myeloma	0	20
Solid tumors	2	18
Others	8	0
Total	408	95

List of papers published in 2012
Journal

1. Tada K, Kim SW, Asakura Y, Hiramoto N, Yakushijin K, Kurosawa S, Tajima K, Mori S, Heike Y, Tanosaki R, Maeshima AM, Taniguchi H, Furuta K, Kagami Y, Matsuno Y, Tobinai K, Takaue Y, Fukuda T. Comparison of outcomes after allogeneic hematopoietic stem cell transplantation in patients with follicular lymphoma, diffuse large B-cell lymphoma associated with follicular lymphoma, or de novo diffuse large B-cell lymphoma. Am J Hematol, 87:770-775, 2012
2. Hatanaka K, Fuji S, Ikegame K, Kato R, Wake A, Hidaka M, Ito T, Inoue M, Nagatoshi Y, Takami A, Uike N, Sakamaki H, Yabe H, Morishima Y, Suzuki R, Atsuta Y, Fukuda T. Low incidences of acute and chronic graft-versus-host disease after unrelated bone marrow transplantation with low-dose anti-T lymphocyte globulin. Int J Hematol, 96:773-780, 2012
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5. Ishida T, Hishizawa M, Kato K, Tanosaki R, Fukuda T, Taniguchi S, Eto T, Takatsuka Y, Miyazaki Y, Moriuchi Y, Hidaka M, Akashi K, Uike N, Sakamaki H, Morishima Y, Suzuki R, Nishiyama T, Utsunomiya A. Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study. Blood, 120:1734-1741, 2012
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9. Fuji S, Nakamura F, Hatanaka K, Taniguchi S, Sato M, Mori S, Sakamaki H, Yabe H, Miyamoto T, Kanamori H, Ueda Y, Kawa K, Kato K, Suzuki R, Atsuta Y, Tamaki T, Kanda Y. Peripheral blood as a preferable source of stem cells for salvage transplantation in patients with graft failure after cord blood transplantation: a retrospective analysis of the registry data of the Japanese Society for Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant, 18:1407-1414, 2012
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Department of Blood Transfusion and Cellular Therapy

Ryuji Tanosaki

Introduction

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

Routine activities

Currently, our staff members consist of 1 JSTMCT-accredited medical doctor and 4 specifically-engaged medical technologists (including 1 JSTMCT-accredited technologist) who come to us from the Department of Pathology and Clinical Laboratories consisting of 49 full-time and 9 part-time medical technologists and 4 assistants. Most activities in our department are undertaken in collaboration with the Department of Pathology and Clinical Laboratories. The Transfusion Medicine Committee is held every month, the members of which consist of the deputy director in charge of safety management, chief doctors of this department and clinical departments of surgery and internal medicine, chief of Department of Pharmacy, vice-chief of the Nursing Division, and a secretary. An administrative meeting is also held weekly, the attendees consisting of two chief doctors and three head doctors of this Department and the Department of Pathology and Clinical Laboratories, and the head and vice-head medical technologists. An all-staff meeting is held once a month.

As an in-hospital transfusion service section, we purchase blood products, which are required and ordered by clinicians, from the Red Cross, and examine and confirm the ABO blood type, and provide them for clinical use without any delay. Last year, the total units of red cell concentrates (RCC), platelet concentrates (PC) and fresh frozen plasma (FFP), which were consumed in our hospital, were 8793, 32445 and 4212, respectively. We employ the Type & Screen and computer cross-match system, but special attention is paid to blood typing, because about 100 cases of hematopoietic stem cell transplantation (SCT) are performed in our hospital every year including many ABO-mismatched donor-recipient pairs. To avoid any mistake of transfusions going to the incorrect recipients, we have established a firm safety system; a check sheet in which the appropriate or permissive ABO-blood types for the particular patient are described is always placed on the bedside of each patient undergoing allogeneic SCT and the attending doctor, nurses, and the patient double check this list with each other on every occasion of blood transfusion. When ordering blood products, protection is in place to prevent changing of the ABO-blood type, and some special process is required before any blood product of a type other than the patient's original blood type can be ordered. The unique computer program of the transfusion service section also protects inappropriate blood-type orders. The blood transfusion service also uses a check and identify system for those patients who need ABO-mismatched blood product. Bar codes are used to match the patient and his or her designated blood product at each process during transfusion.

About 90% of platelet concentrates (PC) are consumed by hematology-oncology patients. Once an order for PC is made, the blood transfusion service staff checks the patient's morning platelet counts, and, when it is 20,000/μL or more, the staff calls and asks the attending physician if the order is really necessary. In a review we previously performed, we revealed that the platelet counts were below 20,000/μL in more than 80% of patients who underwent PC transfusion in our hospital. In 2012, the wastage of total blood products was 0.6%; RCC 1.6%, PC 0.2%, FFP 1.1%. Thanks to the Tokyo Red Cross and the convenient location of our hospital, blood products are available within 1 hour almost every time when

they are needed in an emergency.

All transfusion procedures in our hospital are performed under a strict hemo-vigilant system which employs electronic medical records managed by the computer system at the blood transfusion service. Any adverse events must be recorded by the attending nurse at 5 min, 20 min, and at the end of transfusion and these data are gathered in the computer at the blood transfusion service. Adverse events are observed associated with transfusions, especially in the case of PC (about 5%). Reduction of supernatant from a PC pack is performed in patients who have experienced repetitive or severe transfusion-associated reactions. Severe adverse events must be reported to the Red Cross and to the Ministry of Health, Labour and Welfare of Japan, and a further analysis of the causative agents is then performed by the Red Cross laboratory.

The chief doctor is also involved in the management of transplant patients both as inpatients and in the outpatient clinic as a staff member of the hematopoietic stem cell transplantation team. He attends a daily morning round, a weekly transplantation conference, a weekend check-out meeting, and a weekly journal club. These activities facilitate and promote inter-departmental collaboration.

List of papers published in 2012

Journal

1. Kanda J, Hishizawa M, Utsunomiya A, Taniguchi S, Eto T, Moriuchi Y, Tanosaki R, Kawano F, Miyazaki Y, Masuda M, Nagafuji K, Hara M, Takanashi M, Kai S, Atsuta Y, Suzuki R, Kawase T, Matsuo K, Nagamura-Inoue T, Kato S, Sakamaki H, Morishima Y, Okamura J, Ichinohe T, Uchiyama T. Impact of graft-versus-host disease on outcomes after allogeneic hematopoietic cell transplantation for adult T-cell leukemia: a retrospective cohort study. Blood, 119:2141-2148, 2012

Research activities and clinical trials

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

The chief doctor also contributes to transplantation activities, especially for adult T-cell leukemia-lymphoma in collaboration with the Department of Hematopoietic Stem Cell Transplantation with the support of a grant for an Anti-Cancer Project from the Ministry of Health, Labour and Welfare of Japan, and as a member of the National Marrow Bank.

Department of Pediatric Oncology

Atsushi Makimoto, Hiroshi Kawamoto, Chika Tanaka, Yuko Araki, Hide Kaneda

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 pediatricians, two pediatric surgeons and one resident. This division handles about 60 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 a "risk-adapted therapy" method 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 Division's 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, the DC is managing 5 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.

Table 1. Number of patients

Diagnosis	Newly diagnosed	Pretreated
Rhabdomyosarcoma	5	3
Ewing sarcoma family	4	1
Osteosarcoma	2	2
Neuroblastoma	1	1
Retinoblastoma*	2	3
Germ cell tumor	2	0
Hepatoblastoma	1	2
Other solid tumors	15	4
Acute lymphoblastic leukemia	3	0
Acute myeloid leukemia	1	0
Non-Hodgkin lymphoma	2	0
Other hematologic diseases	1	0
Total	39	16

*; extended case only

(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 or unapproved drugs. One of the objectives of the following trials is gathering data on, and assessing the safety and efficacy data of, such off-label or unapproved drugs. The two trials (4 and 5 below) are investigator-initiated registration-directed clinical trials conducted under the Pharmaceutical Affairs Law.

(1) A phase I-II trial of the combination of topotecan and ifosfamide for recurrent pediatric solid tumors.
(2) A randomized phase II study on two 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) A phase I trial of immunotherapy using HLA-A2- and A24-restricted glypican-3 peptide vaccine for pediatric tumors.
(4) Phase II trial of glucarpidase for patients who were treated with high-dose methotrexate resulting in slow excretion.
(5) A feasibility trial of ch14.18 combined with IL-2 and various colony-stimulating factors for recurrent neuroblastomas.

List of papers published in 2012

Journal

1. Yamamoto Y, Makimoto A. A case of stage IV neuroblastoma treated with aggressive surgery following intensive neoadjuvant chemotherapy with autologous stem cell transplantation. Jpn J Clin Oncol, 42:359, 2012

Department of General Internal Medicine

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

Introduction

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

Routine activities

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

Cardiology:

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

Diabetology:

We have provided more than 400 diabetes consultations in 2012, which include perioperative management of diabetes, treatment of steroid-induced hyperglycemia during chemotherapy, and so on. In many cases, initiation of insulin is the treatment of choice. We also offer close follow-up on an outpatient basis for those who have diabetes during their cancer treatment at NCCH.

Infectious diseases:

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

Nephrology:

To reply to consultations from NCCH cancer specialists is the main work (213 consultations per year in 2012). The details of consultations are as follows: assessment and treatment of acute kidney injury (AKI), management of chronic kidney disease (CKD) (including assessment of the optimal drug dose for CKD patients), treatment of electrolyte imbalance (hyponatremia, hypernatremia, hyperkalemia, hypokalemia, hypercalcemia, hypocalcemia, hypomagnesemia), assessment of polyuria (diabetes insipidus, salt wasting syndrome [SWS], diabetes mellitus and so on), assessment of edema, management of hypertension (including refractory hypertension, like renovascular hypertension), assessment and treatment of nephrotic syndrome especially after the hematopoietic stem cell transplantation, and so on. In case of the necessity for further evaluation of a patient, we work in cooperation with the Department of Internal Medicine, Keio University Hospital. An apparatus for hemodialysis was acquired in October, 2012, so that hemodialysis patients have been able to receive cancer treatment at NCCH.

Research activities

The evaluation of hyponatremia in cancer patients was performed. The article under the title of "Hyponatremia in cancer patients " was published in *The Japanese Journal of Nephrology*.

Department of Dentistry

Takao Ueno

Introduction

Oral complications are common in cancer patients, especially those receiving chemotherapy or undergoing radiation therapy of the head and neck. Various oral complications in cancer patients can disturb eating and the deglutition of the patient and thus cause a hypoalimentation state and dehydration, while also leading to the onset of infections such as aspiration-related pneumonia.

The Division of Dentistry provides oral hearth care for cancer patients in cooperation with various medical departments in order to reduce the risk of complications. It is necessary for dentists and dental hygienists to support a patient to allow for the successful performance of appropriate cancer treatment. To prevent and treat oral complications associated with 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.

Furthermore, in 2008 the Division established a medical cooperation system to provide dental treatment to cancer patients at local dental clinics in cooperation with the Japan Dental Association. Dentists attended a lecture on the basic knowledge necessary for treatment of cancer patients, and such participating dental clinics were then registered as "cancer cooperation dental clinics". This cooperation is divided into three phases, with three different lectures depending on the stage of the cooperation.

There were 2,019 "cancer cooperation dental clinics" in stage 1, and 1,494 people in stage 2, as of December 2012. The first stage of the cooperation was started at the end of January, 2011, and 570 patients had consulted by the end of December 2012. The second stage of the cooperation was started in March 2012, and 32 patients were introduced to dental clinics within the medical cooperation system. The medical-dental cooperative system for cancer patients is now expected to spread throughout Japan in the future. A local dentist that becomes a member of the cancer treatment team will thus be provided with support to "maintain the function of the oral cavity " in cancer patients.

Routine activities

1) Management of oral complications associated with high-dose chemotherapy and/or stem cell transplantation before treatment begins
2) Prevention and treatment of oral complications during chemotherapy and/or radiation therapy
3) Perioperative dental management for the prevention of postoperative pneumonia with oral, pharyngeal and esophageal surgery
4) Making prostheses for restoration of postoperative facial defects
5) Prevention and treatment of bisphosphonate-associated osteonecrosis
6) Establishing the cooperative system between medical departments and dental clinics 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 the medical-dental cooperative system are under study.
2) A prospective study about the onset frequency of pneumonia after operations for esophageal cancer
3) A prospective study on the taste disorder in the stomach cancer adjuvant postoperative treatment

Table1. Number of patients

	Number of patients
Dental check up and oral health care before operation (Introduction to the cooperation dental clinic)	338 (246)
Dental check up and oral care before chemotherapy	81
Dental check up and oral care before stem cell transplant	78
Dental check up and oral care before Radiation therapy to the head and neck cancer	54
Oral care and treatment of oral complications (mucositis or oral infection) During canter therapy	188
Dental treatment relevant to bisphosphonate or denosumab	168
General dental treatment, others	115
Total	1026

Department of Genetic Counseling

Teruhiko Yoshida, Kokichi Sugano

Introduction

Most of the common diseases arise through a complex interplay among life style/ environmental factors, genetic predisposition and aging. Cancer is among such multi-factorial diseases, and nowadays, as many as half of the Japanese population develop some form of malignancy during their life time. Although it is no longer rare to have some relatives with cancer, most of the cases are considered polygenic and have no obvious family history (such as 3 or more patients with the same or related cancer types within the 2nd-degree relatives). 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 Genetic Counseling Division in a daily practice is to provide cancer genetic counseling in a broad sense, and we respond to 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 active participation of a nurse with an interest and training in clinical genetics is critical for the counseling sessions. Genetic risk for the possible hereditary cancer syndromes will be assessed for each client, based on a family history, age at diagnosis, type and pattern of cancer development such as multiple primaries, other accompanying signs and symptoms. The availability of a genetic testing session will be then explained, if applicable, with careful consideration of risk, benefit and limitation. Both pre- and post-genetic test counseling is essential to make the genetic testing useful to the clients and their family members in the long run. A flowchart of the outpatient clinic genetic counseling process is shown in Figure 1.

Research activities

Genetic diagnosis in the Division has been performed in close collaboration with the Division of Genetics of the National Cancer Center Research Institute, especially in the genetic testing for hereditary retinoblastoma, familial adenomatous

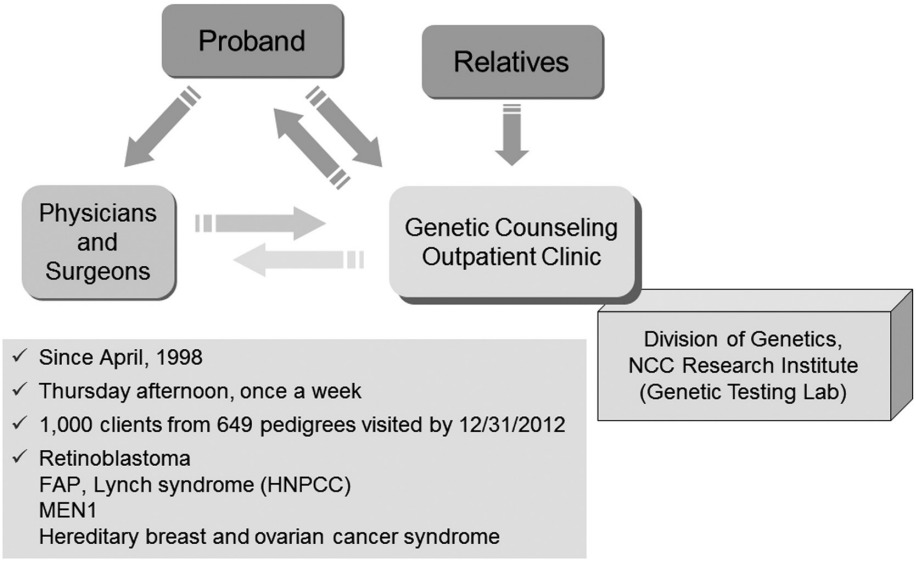

Figure 1. An outline of genetic counseling clinic at NCC hospital

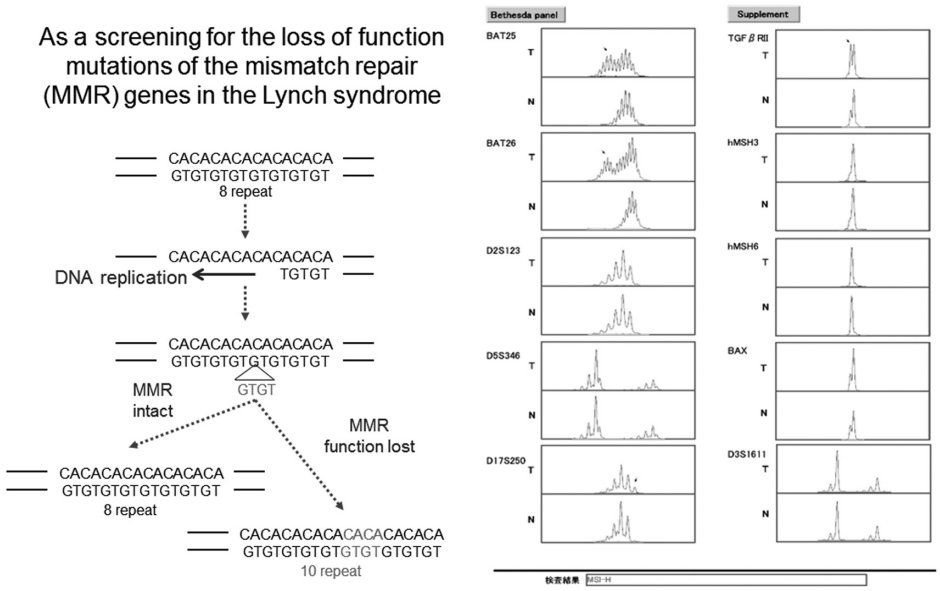

Figure 2. Principle of MSI and an example of the MSI test report at the NCC hospital.

Table 1. Number of patients

	Proband	Relative	Total
Lynch syndrome (Hereditary Non-Polyposis Colon Cancer; HNPCC)	17	10	27
Familial Adenomatous Polyposis (FAP)	2	8	10
Retinoblastoma	8	7	15
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	20	6	26
MEN I (Multiple Endocrine Neoplasia Type I)	0	0	0
Other diseases	12	1	13
Counseling only	0	0	0
Total	59	32	91

polyposis and Lynch syndrome. In 2012, the genetic testing was included as a part of the Core Facility activity of the Research Institute and has been continued by the staff of the Division of Genetics. For Lynch syndrome, microsatellite instability (MSI) testing has been performed on formalin-fixed paraffin-embedded histological sections as an initial screening of the candidates for the sequencing analyses of the mismatch repair (MMR) genes. The MSI test is now covered by the health insurance system in Japan, but immunohistochemical detection of the loss of an MMR protein expression has been shown to be as sensitive and specific as the MSI test. A collaborative study supported by the National Cancer Center Research and Development Fund and led by the doctors in the Gastrointestinal Endoscopy Division and Department of Pathology and Clinical Laboratories is now underway to compare MSI and MMR immunohistochemistry and to find the optimum criteria to identify those patients in whom the Lynch syndrome screenings are recommended.

List of papers published in 2012

Publication list of the Genetic Counseling Division is included in that of the Division of Genetics, National Cancer Center Research Institute.

Clinical trials

No clinical trial was performed in 2012.

Department of Anesthesia and Intensive Care

Tetsufumi Sato, Yoko Kinoshita, Tsukasa Satake, Nobuko Yokokawa, Rie Suzuki, Minako Arai, Moritoki Egi, Yosuke Kawaguchi, Shinji Sugita, Yuya Uyama, Jun Hozumi, Takayuki Sugai, Takuya Oohata

Introduction

Our Department provides anesthesia and intensive care. Anesthetic services are provided for 15 main operating theatres and sessions in endoscopy. There are about 4,000 operations per year. The Intensive Care Unit has 8 beds and provides care for all specialties including general medical and general surgical cases. There are over 400 admissions annually and the ICU is also responsible for resuscitation services within the hospital.

Routine activities

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

Our ICU is certificated by the Japanese Society of Intensive Care Medicine. It provides care for all specialties including general medical, general surgical and neurosurgical cases. It is managed as a closed-system ICU, supported by two certificated intensivists and a trainee. There are 8 operational ICU beds and over 400 admissions annually (41.4 patients per month) (Figure 1). The length of stay in the ICU is 3.9 days on average (Figure 2). The ICU is also responsible for resuscitation services within the hospital.

A weekly conference is held with all anesthesiologists and Intensives for updating the current world standard of acute medicine. A weekly lecture is also held for education of intensive care nurses. Occasionally, a mortality and morbidity conference is held with doctors of other departments.

Clinical trials

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

Table 1. Case for anesthetic management

Thoracic surgery	604
Breast surgery	484
Gastric surgery	464
Colon surgery	443
Urologic surgery	354
Ophthalmologic surgery	301
Orthopedic surgery	286
Hepato-Biliary-Pancreatic surgery	245
Gynecologic surgery	205
Esophageal surgery	139
Head-neck surgery	122
Neuro-surgery	117
Skin surgery	101
Plastics surgery	82
Other	86
Total	4033

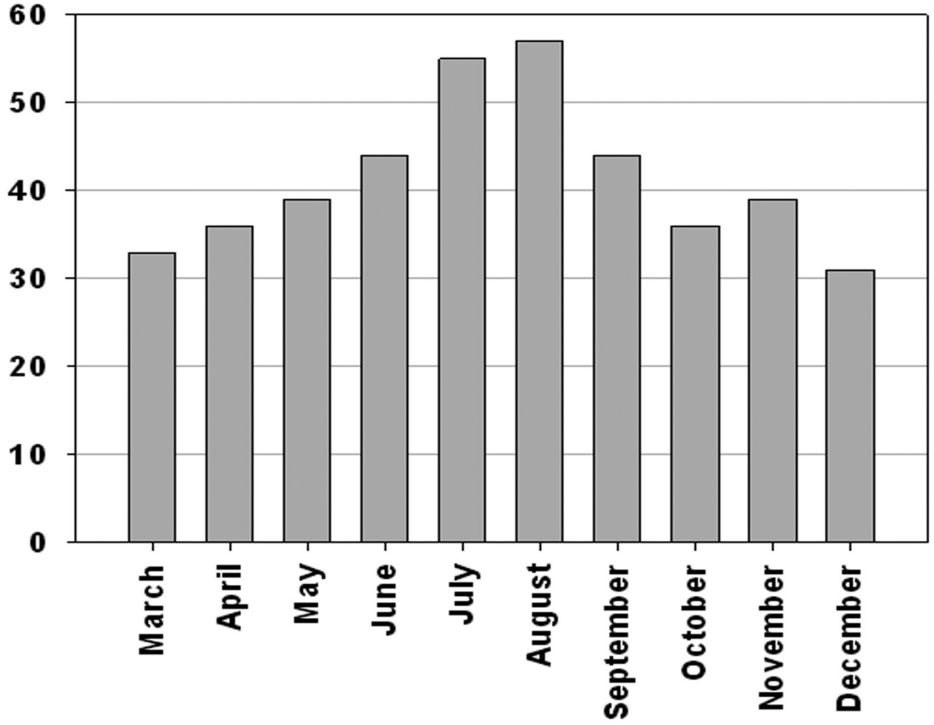

Figure 1. Number of patients admitted to the ICU.

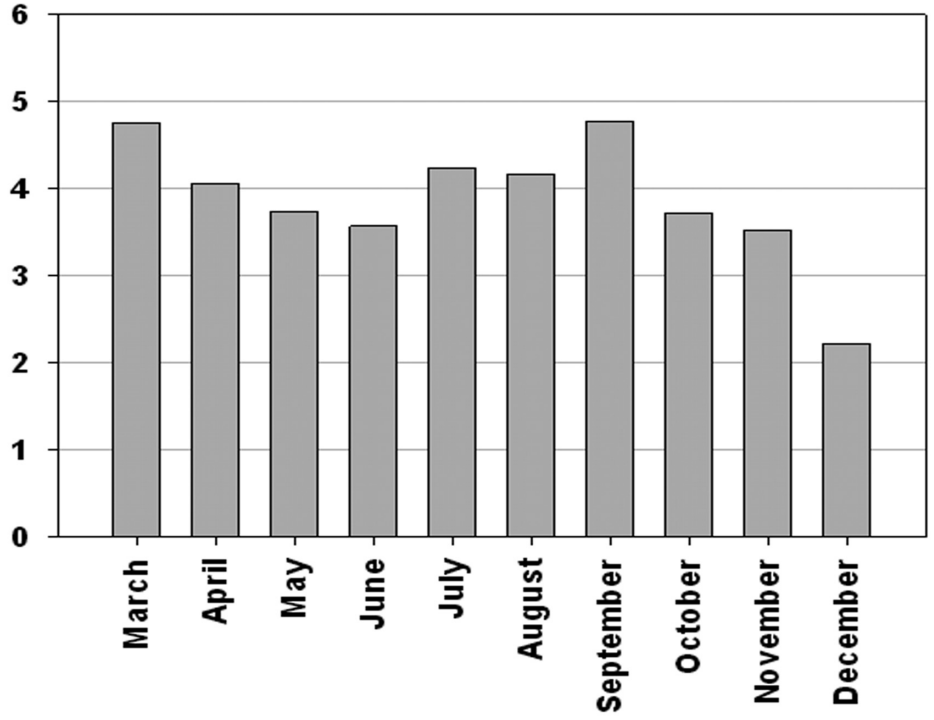

Figure 2. Length of stay in the ICU

Department of Palliative Care

Motohiro Matoba, Osamu Saito, Chio Shuto, Hironori Mawatari

Introduction

It was in June, 1999, when a palliative care team was established as a multi-disciplinary team, and the Department of Palliative Care and Psycho-Oncology was established in April, 2010, with the reorganization of the National Cancer Center Hospital (NCCH). The team provides palliative care to attenuate the total pain of cancer patients and their families. 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, child care 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 instill 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 a day. In the outpatient department, we treat approximately 20 patients per week. Besides conventional drug therapy, we perform various neuronal blockades, place emphasis on mental support for the patient and their families and sometimes refer the patients to the Division of Psycho-Oncology, Department of Orthopedic Surgery, Department of Pediatric Oncology and Department of Diagnostic Radiology to attain better symptom management. For the purpose of equilibration of palliative medicine, bimonthly conferences are held, and consequently coordination with the community palliative care in the vicinity is strengthened.

Education for residents

With regard to their clinical education and training, all the residents of the NCCH are required to train with our team for 1 month, within which a one-week home hospice course is mandatory. In total, 26 residents trained with our team during 2012. The course is whole-person-care oriented. The home hospice course offers an opportunity to understand the role of various occupations other than doctors, such as visiting nurses and care managers.

Research activities

In particular, our division has focused on basic to clinical, and clinical to basic translational interactive collaboration with the Division of Cancer Pathophysiology in National Cancer Center Research Institute.

Our collaborative studies are focused on the aspect of the improvement of pain treatment for severe and intolerable cancer pain. One is abdominal pain of patients with peritoneal carcinomatosis, most of which are refractory to morphine. In collaboration with the Division of Cancer Pathophysiology, we demonstrated that abdominal pain associated with peritoneal carcinomatosis is accompanied by decreased expression of the m-opioid receptors (ref). Second is pain induced by oral mucositis of cancer patients receiving radiation and/or anticancer drugs. In such cancer patients, to date no appropriate analgesic has been found which does not affect the senses of taste and food texture. Our division is developing such an innovative and unique analgesic. With experiments using a cell culture system and an animal mucositis model, we found that cell membrane-impermeable local anesthetic QX-572 could be a candidate. Based on the preclinical studies, we are going to try a Phase I/II study with oral mucositis patients.

In addition, establishment of a pain management monitoring system and improving opioid consumption has started at Aomori Prefectural Central Hospital. Also, construction is underway of a supporting system for children and their families whose father/mother is suffering and dying from advanced cancer.

Table 1. Number of patients

Lung cancer	37
Sarcoma	30
Breast cancer	26
Rectal cancer	23
Esophageal cancer	20
Primary unknown cancer	20
Bladder cancer	18
Uterine cancer	16
Leukemia	14
Gastric cancer	11
Skin cancer	11
Pancreatic cancer	9
Malignant melanoma	9
Renal cancer	8
Prostate cancer	8
Malignant lymphoma	7
Colon cancer	6
Head and Neck cancer	6
Urethral cancer	6
Bile duct cancer	5
Multiple myeloma	4
Liver cancer	4
Malignant mesothelioma	3
Others	27
Total	328

Table 2. Type of procedure

Adjustment of non-opioid analgesics	118
Commencement of opioid analgesics	61
Adjustment of opioid analgesics	104
Opioid rotation	51
Adjustment of adjuvant analgesics	41
Nerve block	2
Management of side effect of analgesics	80
Others	23

List of papers published in 2012
Journal

1. Saito O, Akagi T, Tatsuno M, Miura K, Shuto C, Kudo N, Murakami S, Matoba M. A small amount of katamine with oxycodone induced an acute hyperactive delirium due to voriconazole, a CYP3A4 inhibitor, in a case of multiple myeloma with cancer pain. Palliat Care Res, 7:506-509, 2012
2. Shuto C. Activation of in-hospital palliative care – from the palliative care team approach. Symptom Management in Cancer Patients, 23:151-157, 2012
3. Suzuki M, Narita M, Hasegawa M, Furuta S, Kawamata T, Ashikawa M, Miyano K, Yanagihara K, Chiwaki F, Ochiya T, Suzuki T, Matoba M, Sasaki H, Uezono Y. Sensation of abdominal pain induced by peritoneal carcinomatosis is accompanied by changes in the expression of substance P and mu-opioid receptors in the spinal cord of mice. Anesthesiology, 117:847-856, 2012
4. Suzuki M, Narita M, Ashikawa M, Furuta S, Matoba M, Sasaki H, Yanagihara K, Terawaki K, Suzuki T, Uezono Y. Changes in the melanocortin receptors in the hypothalamus of a rat model of cancer cachexia. Synapse, 66:747-751, 2012
5. Higashi T, Yoshimoto T, Matoba M. Prevalence of analgesic prescriptions among patients with cancer in Japan: an analysis of health insurance claims data. Glob J Health Sci, 4:197-203, 2012
6. Yamaguchi T, Narita M, Morita T, Kizawa Y, Matoba M. Recent developments in the management of cancer pain in Japan: education, clinical guidelines and basic research. Jpn J Clin Oncol, 42:1120-1127, 2012
7. Kokubun H, Ebinuma K, Matoba M, Takayanagi R, Yamada Y, Yago K. Population pharmacokinetics of transdermal fentanyl in patients with cancer-related pain. J Pain Palliat Care Pharmacother, 26:98-104, 2012
8. Akiyama M, Takebayashi T, Morita T, Miyashita M, Hirai K, Matoba M, Akizuki N, Shirahige Y, Yamagishi A, Eguchi K. Knowledge, beliefs, and concerns about opioids, palliative care, and homecare of advanced cancer patients: a nationwide survey in Japan. Support Care Cancer, 20:923-931, 2012
9. Torigoe K, Nakahara K, Rahmadi M, Yoshizawa K, Horiuchi H, Hirayama S, Imai S, Kuzumaki N, Itoh T, Yamashita A, Shakunaga K, Yamasaki M, Nagase H, Matoba M, Suzuki T, Narita M. Usefulness of olanzapine as an adjunct to opioid treatment and for the treatment of neuropathic pain. Anesthesiology, 116:159-169, 2012
10. Morita T, Miyashita M, Yamagishi A, Akizuki N, Kizawa Y, Shirahige Y, Akiyama M, Hirai K, Matoba M, Yamada M, Matsumoto T, Yamaguchi T, Eguchi K. A region-based palliative care intervention trial using the mixed-method approach: Japan OPTIM study. BMC Palliat Care, 11:2, 2012

Department of Psycho-Oncology

Ken Shimizu, Yoshio Oshima, Masashi Kato, Tomomi Takahashi

Introduction

The Psycho-Oncology Division was reestablished in September 1995, together with the 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 the 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 members.

Routine activities

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

A range of psychiatric diagnosis is based on the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) shown in the Table. In 2012, a total of 757 patients were referred for psychiatric consultation. The mean age was 52.8 years old and 16.6% percent of the referrals were outpatients. Three-hundred and sixty (47.6%) of the total number of referred patients were males. The most common psychiatric diagnosis was Adjustment Disorders (20.5%), followed by Delirium (19.6%), and major depression (8.7%), while 17.4% 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 (14.9%), followed by lung cancer (8.7%), stomach cancer (8.7%), esophageal cancer (7.5%) and breast cancer (6.9%).

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 planned protocols are also discussed. Important relevant articles from international medical journals are reviewed together with the members of the Psycho-Oncology Division of the 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 its feasibility and usefulness.

Table 1. Patient demographics

Patients	Total number	757	
	Age	52.8 years	
	Male	360	47.6%
	Inpatients	631	83.4%

Table 2. Number of cancers by site

Cancer site	Lung	66	8.7%
	Breast	52	6.9%
	Hematological	113	14.9%
	Esophageal	57	7.5%
	Stomach	66	8.7%

Table 3. Breakdown of diagnoses

Diagnosis	Adustment Disorders	155	20.5%
	Delirium	148	19.6%
	Major Depression	66	8.7%
	No Diagnosis.	132	17.4%

List of papers published in 2012
Journal

1. Asai M, Akizuki N, Fujimori M, Matsui Y, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Psychological states and coping strategies after bereavement among spouses of cancer patients: a quantitative study in Japan. Support Care Cancer, 20:3189-3203, 2012
2. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Yamada Y, Fujimori M, Ogawa A, Fujisawa D, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Clinical biopsychosocial risk factors for depression in lung cancer patients: a comprehensive analysis using data from the Lung Cancer Database Project. Ann Oncol, 23:1973-1979, 2012
3. Ogawa A, Nouno J, Shirai Y, Shibayama O, Kondo K, Yokoo M, Takei H, Koga H, Fujisawa D, Shimizu K, Uchitomi Y. Availability of psychiatric consultation-liaison services as an integral component of palliative care programs at Japanese cancer hospitals. Jpn J Clin Oncol, 42:42-52, 2012

Department of Diagnostic Radiology

Yasuaki Arai, Masahiko Kusumoto, Yoshito Takeuchi, Kenichi Takayasu, Yasunori Mizuguchi, Gen Iinuma, Miyuki Sone, Hiroaki Kurihara, Hirokazu Watanabe, Tomoko Manabe, Kentaro Shibamoto, Mototaka Miyake, Shunsuke Sugawara, Hirotaka Tomimatu, Hiroaki Onaya

Introduction

The Department of Diagnostic Radiology provides a wide range of modalities, including interventional radiology (IR), general radiology, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, mammography and nuclear medicine. We seek individuals with outstanding leadership capabilities, proven academic and administrative experiences, 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	38,683
2	MRI	7,721
3	IR	3,606
4	RI	4,347
5	Ultrasound	13,165
6	Radiograph	78,561
7	Gastrointestinal study	2,071

Research activities

CT colonography (CTC) has been covered by medical insurance for a diagnostic tool in colorectal diagnosis since last year. In our center, CTC has been successfully introduced into the colorectal screening program, and 1200 candidates have been examined since 2010. Electronic cleansing with fecal barium tagging and CO2 gas insufflation systems have been developed for effective CTC preparation in formal NCC collaboration studies with the associated companies. Furthermore, we are now planning a multi-center trial to establish an evidence of CTC for colorectal screening system in Japan.

Small hypovascular hepatocellular carcinoma (HCC) is frequently found but the biological behavior still remains unclear. The 4,474 patients who met solitary HCC <=3cm, histopathologically proven and Child Pugh A or B were studied. Of them, 802 (18%) were hypovascular. Logistic regression analysis revealed five independent predictors for hypovascular HCC; tumor size <1.5 cm, alpha-fetoprotein <200 ng/ml, des-γ-carboxy prothrombin < 40 mAU/ml, well differentiated grade, and positivity for hepatitis C virus antibody. These results could help in determining a diagnostic and treatment algorithm for small hypovascular HCC.

To clarify the characteristics of ovarian endometrial tumors of borderline malignancy, MR imaging findings and histopathological findings were correlated. The relationship between extracapsular extension of prostate cancer and ADC values was evaluated using 3.0 T MR imaging.

To establish the CT classification of lung adenocarcinoma corresponding to the new IASLC/ATS/ERS pathological classification and to build the database of small adenocarcinomas with both volumetric thin-section CT images and continuous histological sections, a multicenter study has started in collaboration with the Japanese Society of Thoracic Radiology.

The Japan Response Evaluation Criteria in Solid Tumors (RECIST) working group has developed a tumor response evaluation computer system, which is capable of semiautomatic RECIST evaluation and is compliant with DICOM (Digital Imaging and Communications in Medicine) data. Moreover, two tumor response evaluation criteria, RECIST version 1.1 and modified RECIST for hepatocellular carcinoma (HCC) treated using transcatheter arterial chemoembolization (TACE), were compared. From the viewpoint of the high inter- and intra-observer reproducibility, we concluded that the modified RECIST approach was more suitable for tumor response criteria in clinical trials of TACE for HCC.

A multi tracer consisting of [18F]FDG, [18F]FBPA, anti-[18F]FACBC, [11C]choline, [11C]methionine and [64Cu]DOTA-antibody PET imaging has been studied for cancer patients to improve the sensitivity and specificity of detecting tumor sites or tumor characteristics. [18F]FDG dynamic PET sampling with Patrak-plot analysis allows us to calculate the glucose metabolic rate of the tumor site. [18F]FBPA PET/CT, known as an evaluator for BNCT, has been conducted in 25 cancer patients in this year. Anti-[18F]FACBC PET/CT has been carried out in prostate cancer patients as a phase II clinical trial. [11C]choline and [11C]methionine PET/CT examinations have been performed routinely one

day per week. As for [64Cu]DOTA-antibody PET imaging, [64Cu]DOTA-trastuzumab PET/CT has been conducted in HER-2 positive breast cancer patients. Furthermore, [64Cu]DOTA-cetuximab, an anti-EGFR-1 imaging agent, has been synthesized successfully in the hospital and we are waiting for the institutional review board (IRB) approval for clinical use. 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.

Clinical trials

In addition to a number of company-oriented clinical trials, investigator-oriented clinical trials on interventional radiology are ongoing at NCC. We led a multi-institutional cooperative study group of interventional radiology (JIVROSG: Japan Interventional Radiology in Oncology Study Group) as the flagship hospital and recruited patients for 8 ongoing trials: a phase I/II study of RFA for intrapelvic malignant tumors (JIVROSG-0204); 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 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 stenosis (JIVROSG-0806); a phase III study evaluating the efficacy of stenting for SVC/IVC syndrome (JIVROSG-0807) and a phase II study evaluating the efficacy of arterial infusion chemotherapy and radiotherapy for unresectable maxillary carcinoma (JIVROSG-0808).

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Journal

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5. Sato Y, Inaba Y, Yamaura H, Takaki H, Arai Y. Malignant inferior vena cava syndrome and congestive hepatic failure treated by venous stent placement. J Vasc Interv Radiol, 23:1377-1380, 2012
6. Sofue K, Tateishi U, Tsurusaki M, Arai Y, Yamazaki N, Sugimura K. MR imaging of hepatic metastasis in patients with malignant melanoma: evaluation of suspected lesions screened at contrast-enhanced CT. Eur J Radiol, 81:714-718, 2012
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Department of Radiation Oncology

Jun Itami, Minako Sumi, Yoshinori Ito, Hiroshi Mayahara, Madoka Morota, Naoya Murakami, Koichi Inaba, Kotaro Yoshio

Introduction

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

Routine activities

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

Brachytherapy is also performed very intensively to obtain local control and many patients are referred to our Department from all over Japan. For brachytherapy the following modalities are being employed, an Ir-192 high dose rate (HDR) afterloading system including a dedicated CT simulator and fluoroscopy, an I-125 seed implantation system, and other low dose rate (LDR) brachytherapy systems using Au grains, Ir-thin wires, and ruthenium eye plaques. The number of patients undergoing HDR brachytherapy continued to rise constantly 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 and choroidal melanomas. LDR interstitial implants are carried out by radiation oncologists using Au-198 grains and Ir-192 thin wires for the management of head and neck tumors and gynecological malignancies.

Research activities

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

The Division staff is 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: 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: Phase II clinical trial on multimodality therapy in localized Ewing sarcomas and related tumors (JESS 04).

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

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

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

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

Development of an Adaptive Radiation Therapy System

Table 1. Number of Radiation Treatment Plans

Primary Sites	No. of All Treatment Plans					
	2007	2008	2009	2010	2011	**2012**
Head & neck	111	115	95	128	166	**158**
Brain	90	117	99	113	97	**77**
Lung	357	397	431	429	348	**430**
Breast	523	549	452	487	503	**485**
Esophagus	276	220	213	265	237	**268**
Stomach	30	34	29	25	15	**35**
Colorectal	101	86	78	66	119	**113**
Pancreas and hepatobiliary	60	38	48	69	68	**64**
Gynecological	154*	255	331	274	328	**418**
Genitourinary	118	128	159	192	169	**172**
Bone & soft tissue	64	75	69	103	92	**86**
Skin	19	16	26	58	71	**58**
Pediatric	25	22	32	25	66	**49**
Hematological	145	137	220	159	157	**202**
Other	35	47	52	19	14	**39**
Total	2108	2236	2334	2412	2450	**2654**

*: No. of Cases

Table 2. Purpose of Radiation Therapy

	No. of All Treated Patients					
	2007	2008	2009	2010	2011	**2012**
No. of Treatment Plans	2108	2236	2334	2412	2450	**2654**
Curative Intent	1393	1535	1500	1587	1662	**1858**
Palliative Treatment	715	701	834	825	788	**796**
Curative/Palliative	1.95	2.19	1.80	1.92	2.11	**2.33**
New Patients	1234	1181	1210	1277	1288	**1271**

Table 3. Special Radiation Therapy

	No. of Treated Patients			
	2009	2010	2011	**2012**
IORT	0	0	1	**0**
TBI	38	41	52	**51**
SRT-Brain	6	3	2	**6**
SRT-Body	20	33	45	**37**
IMRT-Brain	1	7	11	**12**
IMRT-H&N	27	34	45	**62**
IMRT-Thorax	0	1	3	**6**
IMRT-Gyne	0	6	14	**23**
IMRT-Prostate	47	46	55	**56**
IMRT-Others	7	11	9	**13**
Intracavitary RT 192Ir-HDR	41	50	49	**40**
Intracavitary RT 192Ir-LDR	0	0	0	**0**
Interstitial RT 192Ir-HDR	22	6	25	**37**
Interstitial RT 192Ir-LDR	0	0	0	**1**
Interstitial RT 198Au-LDR	6	6	4	**7**
Interstitial RT 125I-LDR	16	26	16	**28**
Interstitial RT 106Ru-LDR	7	10	13	**23**
Non-Sealed Radionuclide Therapy 89Sr	3	5	12	**4**
Non-Sealed Radionuclide Therapy 131I	1	14	21	**24**

IORT; intraoperative radiotherapy
TBI; total body irradiation

List of papers published in 2012
Journal

1. Mayahara H, Ito Y, Morizane C, Ueno H, Okusaka T, Kondo S, Murakami N, Morota M, Sumi M, Itami J. Salvage chemoradiotherapy after primary chemotherapy for locally advanced pancreatic cancer: a single-institution retrospective analysis. BMC Cancer, 12:609, 2012
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Department of Pathology

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

Introduction

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

Routine activities

In 2012, a total of 14 board-certified pathologists, 7 residents and 11 medical technologists, including 11 cytotechnologists, cooperatively performed routine histological and cytopathological diagnosis of specimens obtained from patients at the National Cancer Center Hospital (NCCH) and the Research Center for Cancer Prevention and Screening (RCCPS), and education of the residents. Seven pathologists working exclusively in the NCCH also shared management of the division. Another 7 pathologists were concurrently on the staff of NCC Research Institute (NCCRI). In September, in parallel with Clinical Laboratories Division, this Pathology Division obtained certification of ISO15189.

1. Surgical pathology

A total of 19,834 histological diagnoses were provided consisting of 16,085 biopsy specimens including 1,913 intraoperative frozen sections and 3,749 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 1,006 sentinel lymph nodes n the intraoperative assessment of metastasis.

2. Cytopathology

Cytopathological diagnoses were provided for a total of 11,335 patients including 404 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-four 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. Outpatient clinic for pathology consultation (second opinion)

To the 191 patients, we provided histopathological/cytopathological diagnosis as a second opinion.

5. 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, NCC East, and trimonthly multi-institutional pathology TV conferences.

Research activities

1. Gastrointestinal pathology

Clinicopathological and molecular characteristics of premalignant lesions and initial carcinomas of the stomach and colon were studied.

The histological status of gastritis surrounding carcinomas at the esophagogastric junction was studied.

2. Hematopathology

Prognostic factors in patients with diffuse large B-cell lymphomas treated with rituximab-containing chemotherapy were studied.

3. Pulmonary and mediastinal pathology

The clinical significance of c-Met, phosphor-Met expressions, MET gene copy alterations, cathepsin D expression, and metastasis limited to segmental and/or subsegmental lymph nodes were studied in lung adenocarcinoma. Molecular alterations were examined in thymomas and thymic carcinomas. Development of the assay system to detect rearrangements of ALK, ROS, and RET by fluorescence in situ hybridization and immunohistochemistry is ongoing in collaboration with the NCCRI and other divisions in NCCH.

4. Soft tissue pathology

MDM2 and CDK4 co-expression was shown to be correlated with dedifferentiated-type osteosarcoma. NKX2.2 expression was shown to be a marker for Ewing's sarcoma.

5. Neuropathology

A case of unclassified high-grade glioma with polar spongioblastoma pattern was reported.

6. Breast and gynecological pathology

The intensity of tumor-infiltrating lymphocytes was shown to be a significant predictive factor of the response to neoadjuvant chemotherapy in triple-negative breast cancer. The gene protein assay, in which both HER2 protein expression and gene amplification are seen simultaneously, was developed and applied to breast cancer specimens.

7. Digital pathology

We continued the establishment of digital pathology and intelligence database system in collaboration with a Japanese company using a high-speed, high-resolution, and high-fidelity scanner and PlayStation™-based viewers.

8. Quality assessment and central pathology review

A study of nationwide external quality assessment with regard to immunohistochemistry of hormone receptors and HER2 was conducted in collaboration with the Japanese Society of Pathology. A central pathology review in clinical trials was performed for cancers of various organs.

Table 1. Numbers of Histopathological Specimens Diagnosed in the Pathology Division in 2012

Field	Number of specimens
	Total
Gastrointestinal tracts	8105
Breast	2384
Respiratory organs	2063
Gynecology	1267
Hematology	1032
Urology	894
Hepatobiliary and pancreas	670
Head and neck	635
Dermatology	596
Orthopedics	518
Others	1182
Research Center for Cancer Prevention and Screening	488
Total	19834

Table 2. Numbers of Cytopathological Specimens Diagnosed in the Pathology Division in 2012

Field	Number of specimens
	Total
Gynecology	4034
Urology	2988
Respiratory organs	1863
Gastrointestinal tracts	733
Breast	435
Hepatobiliary and pancreas	426
Radiation oncology	188
Head and neck	177
Hematology	116
Others	375
Research Center for Cancer Prevention and Screening	812
Total	12147

Table 3. Numbers of Autopsies Performed in the Pathology Section in 2012

Department/Division	Number
Thoracic Oncology	9
Hematology and Hematopoietic Stem Cell Transplantation	7
Breast and Medical Oncology	5
Gastrointestinal Oncology	3
Neurosurgery	3
Hepatobiliary and Pancreatic Oncology	2
Radiation Oncology	2
Dermatology	1
Thoracic Surgery	1
Urology	1
Total	34

List of papers published in 2012
Journal

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. Multicenter study for optimal categorization of extramural tumor deposits for colorectal cancer staging. Ann Surg, 255:739-746, 2012
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13. Tsuta K, Wistuba II, Moran CA. Differential expression of somatostatin receptors 1-5 in neuroendocrine carcinoma of the lung. Pathol Res Pract, 208:470-474, 2012
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15. Yoshida A, Ushiku T, Motoi T, Beppu Y, Fukayama M, Tsuda H, Shibata T. MDM2 and CDK4 immunohistochemical coexpression in high-grade osteosarcoma: correlation with a dedifferentiated subtype. Am J Surg Pathol, 36:423-431, 2012
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Book

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Department of Clinical Laboratories

Hitoshi Tsuda, Koh Furuta, Takao Miura

Introduction

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

Routine activities

Forty-nine full-time and 9 part-time medical technologists, and 4 assistants provide services. These staff work in the sections of 1) general laboratory medicine and hematology; 2) biochemistry; 3) endocrinology, immunology, and tumor markers; 4) bacteriology; 5) genetic diagnostics, 6) transfusion, 7) phlebotomy, 8) physiological examination, and 9) pathology in the National Cancer Center Hospital (NCCH); and in the sections of phlebotomy and physiological examination in the Research Center for Cancer Prevention and Screening (RCCPS). The sections of 1) to 5) are to be supervised by Dr. Koh Furuta. The pathology section staff are supervised by the doctors in the Pathology Division, and the transfusion and phlebotomy staff are supervised by a doctor of the Department of Transfusion Therapy. In addition, the physiological examination staff are directly supervised by Dr. Yasunori Mizuguchi, Department of Diagnostic Radiology, and Dr. Masaaki Shoji and Dr. Takeshi Iwasa, the General Internal Medicine Division. The bacteriology staff are members of the Infection Control Team (ICT) and participate in the activities of infection management in collaboration with the staff physicians.

An administrative meeting is held weekly, attending members of which consist of two chief doctors and three head doctors of this Department and the Department of Transfusion Therapy, and the head and vice-head medical technologists. The quality control meeting is regularly held twice a month, and an all-staff meeting is held once a month. The division also participates in several domestic and international programs for inter-laboratory standardization and external quality control including the College of American Pathologists (CAP) Survey. The actual number of laboratory tests performed in this Division in 2012 is shown in Table 1.

Research activities

An in-hospital bio-bank, which was established in 2002, has been maintained for use by various researchers, and more than 700,000 post clinical test blood samples have been cryo-preserved at -20 °C as of the end of 2012.

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

Using the Metafer system (an automated image analysis-assisted fluorescence in situ hybridization [FISH] system), the technique to evaluate the FISH imaging of HER2 gene amplification was established. Furthermore, using the Metafer system, we tried to establish a method to evaluate FISH images of ALK-rearranged, ROS-rearranged, and RET-rearranged lung cancers.

The molecular pathology laboratory has been set up, FISH of epidermal growth factor receptor (EGFR) in stomach cancer was performed, and data are under acquisition. Many case reports with important ultrasound findings were presented in scientific meetings by the staff of the physiology section.

Under the education committee in the ISO15189 scheme, a monthly seminar by the staff was started from this year for the purpose of promoting research activity in the Division.

Table 1. Number of laboratory tests examined in the Clinical Laboratories Division (2012)

Section	Number
General laboratory medicine	499,152
Hematology	1,296,880
Biochemistry	2,851,195
Endocrinology, immunology and tumor markers	353,591
Bacteriology	52,305
Physiology	83,158
Genetic diagnostics	760
Total	5,137,041

List of papers published in 2012

Journal

1. Furuta K, Matsuhita K, Goto Y, Miyagi Y, Sawabe M, Shirakashi R, Takeuchi T, Masui T, Aoki I, Nakagawara A. An attempt to establish a network of bioresource facilities in Japan. Biopreserv Biobank, 10: 6, 2012
2. Wakai S, Yokozawa K, Nakamura A, Adegawa Y, Furuta K. Long term storage of fluorescent in situ hybridization (FISH) slides. Biopreserv Biobank, 10: 23, 2012
3. Wakai S, Yokozawa K, Nakamura S, Miura T, Furuta K, Tanosaki R, Tsuda H. HER2 amplification testing using automated image analysis-assisted fluorescence in situ hybridization. Jpn J Med Technol, 61:562-566, 2012

Consultation, Counseling and Support Service Center

Masashi Kato, Yukiko Higuchi, Mariko Suda, Ryuta Suyama, Natsuko Moroi, Kayoko Miyata, Noriko Saito, Kyoko Shima, Yuko Ogo, Keiko Nozawa, Tomoko Takayama, Chikako Yamaki, Maiko Fujimori, Eri Hirayama, Miyako Momiyama

Introduction

The staff members called "Cancer Counseling and Support Specialists" work mainly at the Consultation, Counseling and Support Service Center of the National Cancer Center Hospital (NCCH). The staff cope with various problems of cancer patients and their families with the ultimate aim of helping patients feel relieved and to help them receive medical care. By putting ourselves in the patients' position, we can make real efforts to solve their problems.

Routine activities

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

We provide consultation, counseling and support to help the cancer patients, their families and ordinary citizens solve their psychosocial problems through various social work skills, social recourses and cancer information. We also counsel on the telephone in the hope that patients can see the benefit of the information in the books and websites, and make use of this information by themselves.

By August 2012, we also provided consultation for the clients of the "Kanja-Hikkei Support Center" by means of the booklets published by the Cancer Control and Information Services (CIS). Since September 2012, the operation of the "Kanja-Hikkei Support Center" was transferred to the CIS section.

2 Activities accompanying Consultation, Counseling and Support Services
  (1) Administration of a group program for patients and their families
  (2) Cooperation inside the hospital
  (3) Cooperation with other hospitals and institutions

We hold the following support groups and programs for the patients and their families
- The pancreatic cancer and biliary tract cancer class
- The class for women before undergoing breast cancer surgery
- The support group for families of brain tumor patients
- The support group for families of pancreatic cancer and biliary tract cancer patients
- CLIMB (Children's Lives Include Moments of Bravery) Support Program
- 1st year anniversary program of the support group for families of brain tumor patients

In the hospital, we discuss the patients with the doctors and medical staff. We are participating in the medical meetings of five specialties.

We cooperate with other hospitals and institutions so that cancer patients can live with as high a quality of life as possible. We rearranged community services where required and helped patients to change hospitals.

3 Activities of cooperation with other regional hospitals and institutions
  (1) Support for holding information exchange meetings with regional hospitals and institutions
  (2) Administration of database on information about regional hospitals and institutions

4 Activities related to volunteers of the NCCH

5 Activities related to NCCH committees

6 Activities related to the education of NCCH staff

7 Others
  (1) Administration of the patient library

Research activities

We analyze information and opinions obtained by counseling. In addition, we develop effective procedures regarding counseling and support for cancer patients and their families.

1. Yukiko H, Kayoko M. New support class to understand changes in body image for women with breast cancer. In The 20th Annual Meeting of the Japanese Breast Cancer Society in Kumamoto city Japan. June 28-30, 2012.

2. Yukiko H, Ryuta S, Kayoko M. The background about the consultation about the treatment choice in a consultation, counseling and support service center. In The Japan Society of Clinical Oncology in Pacifico Yokohama, Kanagawa Japan. October 25-27, 2012.

3. Yukiko H, Mariko S, Natsuko M. Psychosocial support for family members of a malignant brain tumor patient by support group. In The 30th Annual Meeting of the Japan Society for Neuro-Oncology in Grand Prince Hotel Hiroshima, Hiroshima Japan. November 25-27, 2012.

4. Yukiko H, Kayoko M, Natsuko M, Mizuho Information and Research Institute. 2012 Entrustment Project of Ministry of Health, Labour and Welfare. Development of assistance procedure for the compatibility of medical care and occupational life: Occupational cancer and other malignant neoplasms.

Table 1. The number of cases

1	Total	9,201 (Per month: 767)
2	New cases	5,368
	New cases from NCCH	2,138
	New cases from Other hospitals	3,230

Table 2. Achievements of support groups and programs

		Number of times meetings were held	Number of participants
1	The pancreatic cancer and biliary tract cancer cundergoinglass	46	207 (Patients: 131, Families: 76)
2	The class for women before receiving breast cancer surgery	11	61 (Patient: 50, Families: 11)
3	The support group for families of brain tumor patients	12	50 (Spouses: 28, Children: 12, Parents: 1, Siblings: 9)
4	The support group for families of pancreatic cancer and biliary tract cancer	1	11
5	CLIMB (Children's Lives Include Moments of Bravery) Support Program	2	3
6	1st year anniversary program of the support group for families of brain tumor patients	1	72 (Families: 50, Medical personnel: 16, Mass media: 6)

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. Plastic Surgery and Pediatric Surgery Groups have newly joined this year.

Routine activities

During 2012, the Surgical Center supported more than 4,700 surgical cases and more than 4,100 general anesthesia surgical cases, a 4.8% increase in the number of cases and a 4.9% increase in the general anesthesia cases over 2011. 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 Da Vinci robotic surgical system has been introduced to provide less invasive surgery to the patients.

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 50 foreign doctors have visited our surgical center.

Table 1. Total number of operations

	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Anesthesia													
General	132	147	125	129	143	131	133	165	129	134	133	129	1630
General and epidural	201	227	222	179	201	188	205	207	208	244	209	211	2502
Epidural and lumbar	0	0	0	2	0	1	0	1	1	3	0	1	9
Epidural and lumbar	0	0	0	0	0	0	1	0	0	1	1	1	4
Lumbar	17	15	14	8	11	15	12	7	5	4	7	4	119
Local	31	40	32	38	34	39	53	40	27	49	31	36	456
Others	0	1	0	0	1	0	0	0	33	5	6	8	27
Total	381	430	393	356	390	374	404	420	382	440	387	390	4747

Table 2. Number of general anesthesia cases

	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Neurosurgery	10	12	11	13	11	6	9	14	9	7	8	12	122
Ophthalmology	26	29	26	26	26	32	27	25	26	29	26	21	319
Head & Neck Surgery	12	14	13	13	16	18	17	22	16	13	16	12	182
Breast Surgery	43	40	37	29	29	39	44	55	43	43	44	47	501
Thoracic Surgery	51	53	56	48	48	51	51	50	60	68	52	59	657
Esophageal Surgery	11	11	13	11	11	11	16	13	11	14	8	13	141
Gastric Surgery	37	37	45	30	30	40	46	43	44	51	33	41	482
Colorectal Surgery	43	60	38	32	32	27	28	34	39	45	44	35	464
Hepatobiliary & Pancreatic Surgery	19	27	23	23	23	23	18	22	17	23	25	24	267
Gynecology	15	20	20	17	17	13	17	20	18	19	19	11	207
Urology	20	18	27	21	21	16	20	24	21	27	20	21	251
Dermatology	9	9	5	9	9	8	10	7	7	10	12	12	108
Orthopedic Surgery	21	26	17	27	27	21	19	25	16	19	18	20	262
Others	16	18	16	9	9	14	16	18	10	10	17	12	169
Total	333	330	347	308	308	319	338	372	337	378	342	340	4132

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 4 divisions (the Clinical Trial Coordination Division, the Physician-initiated Registration-directed Clinical Trials Support Division, Clinical Trial Site Management 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 as well as the physician-initiated registration directed clinical trials. 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 192 registration-directed clinical trials including 6 physician-initiated registration directed clinical trials in 2012 (Table 1). The Clinical Data Management Division supports 17 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 the National Cancer Center Hospital (NCCH), all members of this Office will work together to contribute to reinforcing the clinical research capabilities of the NCCH and to making this Office a valuable unit for all members of our hospital.

Table 1. Registration-directed Clinical Trials including Investigator-initiated Registration-directed Clinical Trials

Department	Eligible Cancer Type	Trial Phase	number of trials
Department of Neurosurgery and Neuro-Oncology			2
	Glioma	Phase III	1
	Glioblastoma	Phase III	1
Department of Breast Surgery			1
	Breast cancer	Phase III	1
Department of Breast and Medical Oncology			26
	Breast cancer	Phase I	1
		Phase I/II	1
		Phase II	3
		Phase III	7
		Post-marketing	1
	Ovarian cancer and others	Phase I	1
		Phase II	2
		Phase III	2
	Cervical cancer	Phase III	1
	Uterine corpus cancer	Phase II	1
	Endometrial cancer	Phase II	1
	Solid tumors	Phase I	3
	Malignant tumor	Phase I/II	1
		Post-marketing	1
Department of Thoracic Surgery			1
	Lung cancer	Phase III	1
Department of Thoracic Oncology			33
	Solid tumors	Phase I	12
	Lung cancer	Phase I	3
		Phase I/II	2
		Phase II	4
		Phase III	8
		Post-marketing	4

Department of Colorectal Surgery			1
	Colon cancer	medical device	1
Department of Gastrointestinal Medical Oncology Division			24
	Colon cancer	Phase I/II	1
		Phase III	3
		Post-marketing	1
	Gastric cancer	Phase II	3
		Phase III	6
	Esophageal cancer	Phase I	1
		Phase I/II	2
		Phase II	1
	GIST	Phase III	2
	Neuroendocrine tumor	Phase III	1
	Solid tumors	Phase I	3
Department of Endoscopy			1
	Colon cancer	medical device	1
Department of Hepatobiliary and Pancreatic Oncology			28
	Hepatocellular cancer	Phase I	4
		Phase I/II	3
		Phase II	1
		Phase III	8
	Pancreatic cancer	Phase I/II	1
		Phase II	3
		Phase III	2
	Pancreatic endocrine tumors	Phase II	1
		Phase III	1
	Neuroendocrine tumor	Phase I/II	1
		In vitro diagnostic	1
	Solid tumors	Phase I	2
Department of Urology			8
	Renal cell cancer	Phase II	2
		Phase III	1
	Prostatic cancer	Phase I/II	2
		Phase II	1
		Phase III	2
Department of Orthopedic Surgery			5
	Soft tissue sarcoma	Phase II	3
		Phase III	1
	Soft tissue tumors, Bone tumors	Phase II	1
Department of Dermatologic Oncology			5
	Malignant melanoma	Phase I	1
		Phase I/II	1
		Phase II	2
		Phase III	1
Department of Hematology Division			47
	Malignant lymphoma	Phase I	10
		Phase I/II	2
		Phase II	6
		Phase III	9
	Leukemia	Phase I	3
		Phase I/II	3
		Phase II	1
		Phase III	2
	Multiple myeloma	Phase I	4
		Phase I/II	1
		Phase II	2
	MDS	Phase I	2
	Hematopoietic organ tumor	Phase I	2
Department of Hematopoietic Stem Cell Transplantation			2
	Allogenic stem cell transplant	Phase I	1
	GVHD	PhaseII/III	1
Department of Pediatric Oncology			4
	Nausea/Vomiting	Phase III	1
	Candidiasis, Aspergillosis	Phase II	1
	Malignant tumor	Phase I	1
		Phase II	1
Department of Diagnostic Radiology			3
	Hepatocellular cancer	Phase III	2
	Hypervascular cancer	medical device	1
Department of Radiation Oncology			1
	Nausea/Vomiting	Phase II	1
Total			192

As of December 2012

Nutrition Management Office

Setsuko Kuwahara, Masahiro Sunaga, Hiroki Matsubara, Hiroko Takashima, Yasuko Muramatsu, Noriko Aoki

Introduction

2012 was a year for enhancing the organization of the Nutritional Management Office. We organized our resources so as to enhance the activity of the Nutrition Support Team (NST) to promote patient support through having and more than one specialized and full-time service in the NST, and we were happy to obtain approval for the inclusion of two registered dietitians.

Our research project was to promote the continuation of last year's research plan "Towards the development of supportive therapy, to improve taste disorders" During cancer treatment, many patients have experienced a decrease in appetite and QOL, and it is believed that improving their appetite could improve successful treatment rates.

Other activity. Six 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 their post-surgical status following, for example, esophageal surgery and hepatobiliary-pancreatic surgery.

In addition, we have also supported treatment which focuses on the provision of meal planning. In the August 2012 survey, 50% of the total patient are using individual comments meal.

Routine activities

Dietary meals totaled 435,209 in 2012, and we gave nutrition-related dietary advice to 1,992 persons. There have been 809 requests for consultation to the NST, 67 per month on average, and this aspect of the Office has shown strong growth by 35% annually. (Table 1)

We created a booklet "Tips for meals in troubled times"and sent out 200,000 copies to cancer facilities nationwide. This was done in cooperation with the Foundation for Cancer Research, and the booklet has been utilized by many patients and medical staff . At the same time, we also focused on food service.

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. 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) In Kobe, we have held 31 study groups on nutritional management in cancer patients, with educational lectures and research reports as the contents of the program.
2) The Hospital Group for Disease Prevention Study Group of Japan, under the slogan "A Beneficial 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, Saitama , Nagano, Yamanashi, Osaka)
4) Research project
   ① Survey of dysgeusia
   ② Studies on nutrition in the surgical treatment of esophageal cancer
   ③ Perioperative nutritional assessment after pancreaticoduodenectomy

Future prospects

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

Table 1. Number of NST consultations in 2012

Clinical Departments	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sept	Oct	Nov	Dec	Total
Esophageal Surgery	1	6	1	2	3	2	6	3	3		3	6	36
Head and Neck Surgery				1	4	3	5	3	1	1	7	2	27
Gastrointestinal Medical Oncology	9	7	12	23	14	15	17	16	10	21	24	18	186
Hematopoietic Stem Cell Transplantation	9	8	11	9	14	9	16	12	13	14	14	7	136
Thoracic Oncology	2	3	4	1	3		4	2	5	3	6	4	37
Thoracic Surgery		1			6	2		2		1		2	14
Hepatobiliary and Pancreatic Oncology	2	4	2	1	4	3	5	4	2	6	3	2	38
Hepatobiliary and Pancreatic Surgery	2	4	1	3		4		1	2	2	4	6	29
Breast Oncology and Medical Oncology	6	7	4	9	7	16	5	3	12	6	13	4	92
Gynecology	3	2	2	2	4	1	1	2	1	5		3	26
Neurosurgery and Neuro-Oncology			1	1		1			1				4
Gastric Surgery	1	2	3	1		2	1	4	3	10	6	12	45
Colorectal Surgery		1			2	3	3	8	5	2	1	1	26
Urology	4	3	3	2	1	2	3	2	6	3	1	1	31
Pediatric Oncology		1	1		2	2	1		1			1	9
Orthopedic Surgery								2	1	1		2	6
Dermatologic Oncology	1	1	2		1	1	4	2	2	2		1	17
Hematology	1	2	2	1	3	4	2	4	1		6	6	32
Radiation Oncology	1		4	2		1	1	1		2	1	1	14
Diagnostic Radiology							1				1		2
Breast Surgery					1								1
Respiratory Endoscopy									1				1
Total	42	52	53	58	69	71	75	71	70	79	90	79	809
												mean	67

Department of Pharmacy

Yoshikazu Hayashi

Introduction

The Pharmacy stores and dispenses drugs, prepares injections (including aseptic mixtures), collects and disseminates drug information and provides patients with guidance regarding the proper use of drugs. Its services have improved toward 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 for patients has been widely acknowledged. Clinical pharmacists visit inpatients and give advice on taking medicine, focusing especially on pain control with opioids, and participate in the palliative-care support team. The Pharmacy also provides outpatients with guidance on 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, instructions and explanations, which are easy to understand by patients, for the proper use of drugs, such as those regarding efficacy and effectiveness, precautions, and guidance concerning symptoms at the early stage of adverse reactions, are automatically printed out for patients when a prescription is ordered.

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

Research activities

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

Information services

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

Education and Training

The National Cancer Center Hospital offers a three-year postgraduate pharmacist residency in clinical oncology. In the first year, the program attaches the most importance to technical aspects of cancer care. In the second year, through required rotations in a variety of focused hematology/oncology services, the resident refines 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 2011	FY 2010
1) Oral and topical preparations		
Prepared in the hospital pharmacy	136,594	141,536
Inpatients	123,594	128,566
Outpatients	13,000	12,970
Taken to outside pharmacies	67,346	66,080
(% of prescription filled outside)	83.8	83.6
2) Injections		
Inpatients	268,631	289,568
Outpatients	36,372	34,697

Table2. Amounts of Drugs Consumed

	FY 2011 (including sales tax)	(%)	FY 2010 (including sales tax)	(%)
Total	4,663,916	100.0	4,564,239	100.0
Internal medicines	398,595	8.5	407,375	8.9
External	50,001	1.1	33,747	0.7
Injection	3,352,939	71.9	3,129,818	68.6
Narcotics	166,877	3.6	154,469	3.4
Blood	357,681	7.7	430,021	9.4
X-ray imaging	240,041	5.1	249,640	5.5
RI	58,537	1.3	108,945	2.4
Others	39,245	0.8	50,223	1.1

Unit:1000 yen

Table 3. Aseptic Preparation of Injectable Drugs

	FY 2011	FY 2010
Anticancer Drugs	35,154	49,552
Others	32,489	32,112

Table 4. House Preparations

	FY 2011	FY 2010
Sterilized	108	103
Non-sterilized	172	138

Table 5. Investigational Drugs

	FY 2011	FY 2010
Newly registered	41	46
Ongoing study	123	109
Total	164	155

List of papers published in 2012

Journal

1. Makino Y, Yamamoto N, Sato H, Ando R, Goto Y, Tanai C, Asahina H, Nokihara H, Sekine I, Kunitoh H, Ohe Y, Sugiyama E, Yokote N, Tamura T, Yamamoto H. Pharmacokinetic and pharmacodynamic study on amrubicin and amrubicinol in Japanese patients with lung cancer. Cancer Chemother Pharmacol, 69:861-869, 2012
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Department of Nursing

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Introduction

The Nursing Division bears responsibility for team healthcare at the National Cancer Center Hospital (NCCH), the core institution for national cancer treatment and control in Japan. The responsibility of the 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.

Routine activities

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 Division is working to provide safe and reliable nursing in response to advances in medicine with a conscientious approach and responsibility as a nurse in the NCCH.

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

We are accepting and meeting the challenge to provide many patient education programs produced by Certified Nurse Specialists and Certified Nurses. We have 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 stage required for actual cancer care by carrying out practical nursing training. During the first month, we provided training courses on basic nursing skills for new nurses. New nurses learn about clinical nursing practices by shadowing a senior nurse for the first one month. We ensure that new nurses can work in a non-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 developing and improving 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 10 specialized nurse training courses: Cancer chemotherapy nursing I and II; Clinical trial nursing; Palliative care nursing I and II; Lymphedema care; Wound and skin care; Pressure ulcer care; Dysphagia nursing; and Radiotherapy and IVR nursing. A total of 212 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, 8 certified nurse specialists and 27 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 the educational program by giving lectures and practice training for the curricula of Certified Nurse Specialists or Certified Nurses.

Research activities

We presented 13 studies on nursing at some annual conferences in 2012. Last 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 are making effort to improve the quality of nursing research through getting support from some physicians and statisticians. We expect our nurses from the NCCH to create and develop cancer nursing to even higher levels of proficiency and expertise.