Hospital

Preface

The National Cancer Center Hospital (NCCH) was established in 1962, as a hub for cancer therapy in Japan. Cooperating with patients and society, the Hospital has been providing the best medical treatment, undertaking high-quality clinical research to develop brand new medicines, and nurturing many outstanding healthcare providers, including physicians, nurses, and pharmacists in the oncology field. The NCCH has profound expertise in cancer research including drugs, devices and cell therapy from FIH to global Phase three trials, which are supported by world-class diagnosis capabilities, such as IVR, PET imaging, and by full-spec intensive care units and an ISO15189-certified laboratory. Based on the achievements in clinical research activities, the NCCH was selected as the Core Hospital for Clinical Research in August 2015. We will contribute to Japan's innovative development of medical treatments and to their dissemination across Japan, as well as around the globe.

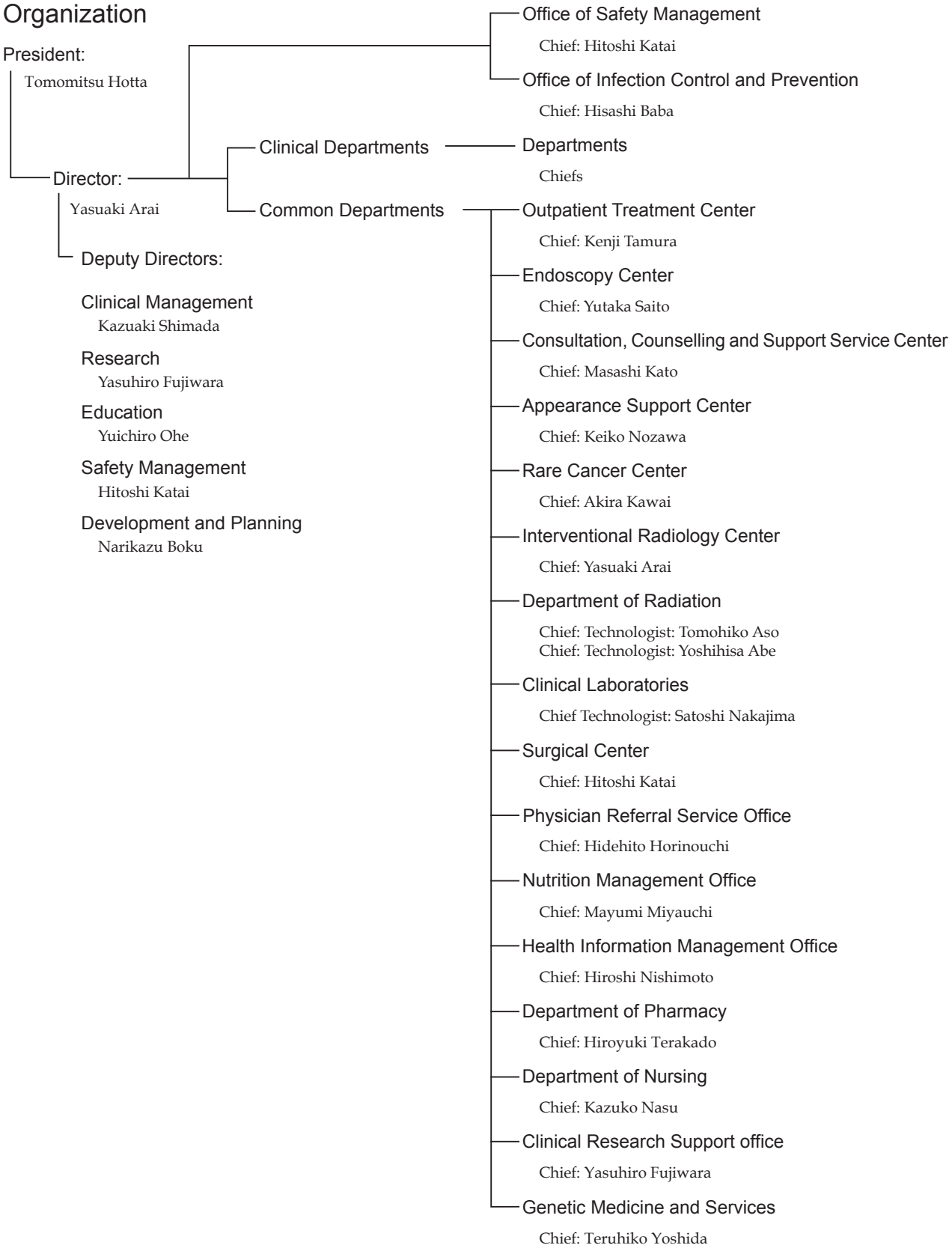
In the last year, the outpatient chemotherapy has been powered up by increasing the bedspace for chemotherapy, and the Department of Genetic Medicine and Service has been launched as common departments. These facilitate future medical practice including precision medicine and clinical research together with the CLIA-compatible NGS Lab (SCI-Lab), where clinical sequencing is conducted. In addition, we redesigned our healthcare safety system to reduce medical errors and provide safe and qualified medical treatment.

There is more to cancer patients than just being "sick." Patients may suffer from other diseases, and may have anxiety and various problems arising and affecting daily activities and employment. With the aging of the population, the number of cancer patients with comorbid diseases increases. The NCCH, a cancer-specialized facility, has been working in cooperation with Saiseikai Central Hospital and the nearby Jikei University School of Medicine since 2015 in a system in which these patients could receive secure and optimal treatment and care for cancer. Furthermore, we have provided a free-WiFi service for inpatient amenity, and the Supportive Care Development Center has been established on the 8th floor to improve the quality of life of cancer patients and to promote research of supportive care for cancer.

Over the past year, we have redesigned our system for future clinical practice and development in cancer and we appreciate your understanding and cooperation.

Toshirou Nishida, MD, PhD
Director of the Hospital
National Cancer Center Hospital

Organization



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Education
Yuichiro Ohe

Safety Management
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  Chief: Shigenobu Suzuki
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Activities of the Departments

Department of Neurosurgery and Neuro-Oncology

Yoshitaka Narita, Yasuji Miyakita, Makoto Ohno, Masamichi Takahashi, Takahiro Ogawa, Shunicihro Miki, Sakura Kuzuoka

Introduction

Patients with primary and metastatic brain tumors are treated by four neurosurgeons and three senior residents in the Department of Neurosurgery and Neuro-Oncology. A total of 327 patients were admitted and 121 craniotomies for tumor removal were carried out in 2015 including 38 gliomas, 49 brain metastases, six primary central nervous system (CNS) lymphomas, and 12 meningiomas (Table 1). The site of the craniotomy and the extent of tumor removal were visualized on the intraoperative magnetic resonance imaging (MRI) 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 magnetic resonance (MR) tractography were also used to preserve patient neurological functions. Nine awake surgeries were also performed, particularly for removal of gliomas near the speech center. Patients with malignant brain tumors were treated with postoperative radiotherapy and chemotherapy. 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 of treatment of patients with brain tumors is held with doctors of the Department of Radiation Oncology and of the Division of Brain Tumor Translational Research. Usually 15-20 patients are hospitalized and two or three of them undergo surgical treatment every week. 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 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 two years. The five-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 (BTRJ). 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 BTRJ since 1969. More than 100,000 patients have been registered and followed up. The Department of Neurosurgery and Neuro-Oncology, the 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 2005 and 2008 were collected and the report will be published in 2016 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 Brain

Tumor Translational Research, the National Cancer Center Research Institute. The determination of the methylation status of O6-methylguanine-DNA methyltransferase (MGMT) and the mutation of IDH1/2 and TERT are also carried out to predict the prognosis of patients with malignant gliomas.

Clinical trials

The Japan Clinical Oncology Group (JCOG) – Brain Tumor Study Group was organized in 2002 and a multi-institutional randomized controlled trial is performed. "A randomized controlled phase II/III study of chemoradiotherapy using nimustine hydrochloride (ACNU) versus procarbazine and ACNU for astrocytoma grade 3 and 4 (JCOG0305)" was published. "A multicenter randomized phase II trial of Interferon-beta and Temozolomide combination chemoradiotherapy for newly diagnosed glioblastomas (JCOG 0911)" and "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)" was finished.

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. "Phase III randomized Study in patients with anaplastic glioma of radiotherapy with temozolomide versus ACNU followed by temozolomide (JCOG1016)," "Phase III Study of High-dose Methotrexate and Whole Brain Radiotherapy With or Without Concomitant and Adjuvant Temozolomide in Patients with Primary CNS Lymphoma (JCGO1114)," "Randomized phase III study for unresectable WHO Grade II astrocytoma with radiotherapy alone or chemoradiotherapy with temozolomide (JCOG1303)," and "a multicenter randomized phase III study for recurrent glioblastoma comparing bevacizumab alone with dose-dense temozolomide followed by bevacizumab (JCOG1308)" are now ongoing.

Education

Our Department plays the roles of the office of the general secretary of the JCOG – Brain tumor study group and the brain tumor registry of Japan; we have conducted many clinical trials and brain tumor registries. We educate many neurosurgeons and oncologists about surgical techniques of awake craniotomy and intraoperative MRI and the effective usage and adverse effects of many chemotherapeutic agents for malignant brain tumors.

Future prospects

Malignant brain tumors, especially glioblastoma, still have worse prognosis among cancers. We always make an effort to defeat these brain cancers through various clinical works and research.

Table 1. Number of patients

	2011	2012	2013	2014	2015
Surgeries	123	132	140	128	153
Craniotomy/Biopsy	92	98	106	96	121
Glioma	35	47	39	34	38
Brain metastases	39	33	40	42	49
Meningioma	5	7	12	7	12
Lymphoma	6	4	7	5	6
Spinal tumors		2	4	1	3
Others	7	5	8	7	13
Neuroendoscope, shunt	31	34	34	32	32

List of papers published in 2015

Journal

1. Arita H, Narita Y, Matsushita Y, Fukushima S, Yoshida A, Takami H, Miyakita Y, Ohno M, Shibui S, Ichimura K. Development of a robust and sensitive pyrosequencing assay for the detection of *IDH1/2* mutations in gliomas. Brain Tumor Pathol, 32:22-30, 2015

2. Takami H, Yoshida A, Fukushima S, Arita H, Matsushita Y, Nakamura T, Ohno M, Miyakita Y, Shibui S, Narita Y, Ichimura K. Revisiting *TP53* Mutations and Immunohistochemistry-A Comparative Study in 157 Diffuse Gliomas. Brain Pathol, 25:256-265, 2015

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4. Narita Y, Shibui S, Committee of Brain Tumor Registry of Japan Supported by the Japan Neurosurgical Society. Trends and outcomes in the treatment of gliomas based on data during 2001-2004 from the Brain Tumor Registry of Japan. Neurol Med Chir (Tokyo), 55:286-295, 2015

5. Narita Y. Bevacizumab for glioblastoma. Ther Clin Risk Manag, 11:1759-1765, 2015

6. Okita Y, Narita Y, Miyahara R, Miyakita Y, Ohno M, Shibui S. Health-related quality of life in long-term survivors with Grade II gliomas: the contribution of disease recurrence and Karnofsky Performance Status. Jpn J Clin Oncol, 45:906-913, 2015

7. Arita H, Narita Y, Yoshida A, Hashimoto N, Yoshimine T, Ichimura K. *IDH1/2* mutation detection in gliomas. Brain Tumor Pathol, 32:79-89, 2015

8. Takami H, Fukushima S, Fukuoka K, Suzuki T, Yanagisawa T, Matsushita Y, Nakamura T, Arita H, Mukasa A, Saito N, Kanamori M, Kumabe T, Tominaga T, Kobayashi K, Nagane M, Iuchi T, Tamura K, Maehara T, Sugiyama K, Nakada M, Kanemura Y, Nonaka M, Yokogami K, Takeshima H, Narita Y, Shibui S, Nakazato Y, Nishikawa R, Ichimura K, Matsutani M. Human chorionic gonadotropin is expressed virtually in all intracranial germ cell tumors. J Neurooncol, 124:23-32, 2015

9. Ichimura K, Narita Y, Hawkins CE. Diffusely infiltrating astrocytomas: pathology, molecular mechanisms and markers. Acta Neuropathol, 129:789-808, 2015

10. Iwakawa R, Kohno T, Totoki Y, Shibata T, Tsuchihara K, Mimaki S, Tsuta K, Narita Y, Nishikawa R, Noguchi M, Harris CC, Robles AI, Yamaguchi R, Imoto S, Miyano S, Totsuka H, Yoshida T, Yokota J. Expression and clinical significance of genes frequently mutated in small cell lung cancers defined by whole exome/RNA sequencing. Carcinogenesis, 36:616-621, 2015

Department of Ophthalmic Oncology

Shigenobu Suzuki, Yukiko Aihara, Shuichi Sano

Introduction

Our Department is one of the rare groups specializing in ocular tumors, especially intraocular tumors. Recently, more than 70% of patients nationwide with retinoblastoma, which is the most frequent intraocular malignancy in childhood, and more than 50% of patients with choroidal melanoma, which is the most frequent primary intraocular malignancy in adults, have been referred to our department.

Routine activities

Our outpatient service is open four days a week. Every week, eight operations under general anesthesia are performed in our department. Our treatment strategies for ocular tumors are as follows:

1) Retinoblastoma

Unless the patient's family has concerns 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 intensive systemic chemotherapy are treated with dedicated support from the Department of Pediatric Oncology.

2) Choroidal melanoma

Choroidal 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 treated by radiotherapy: CyberKnife Robotic Radiosurgery in our institute or carbon ion therapy in the National Institute of Radiological Science, Research Center for Charged Particle Therapy. Choroidal 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 by excisional resection with reconstruction.

Radiotherapy using electrons is another strategy. Orbital exenteration is selected in cases of orbital invasion.

5) Conjunctival tumors

Conjunctival malignant tumors are treated by excisional resection with a safety margin combined with cryotherapy at the resection margin. Diffuse conjunctival tumors or tumors with orbital invasion are treated 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 developed in our hospital from 1987, and has been modified and performed after 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 eyes were rescued using this strategy.

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 check overlapping. This registry now covers almost all patients in Japan, 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 for a social and psychological approach for retinoblastoma patients and their families.

We are now investigating the specific marker or genetic change for eye tumors, especially retinoblastoma, choroidal melanoma, and ciliary body tumors.

We also contribute to the international registry system, as the AJCC Ophthalmic Expert Panel, to advise and reflect the Asian data in the TNM system.

Ocular adverse events caused by anti-cancer drugs used for systemic disease have been recently 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 caused by kinase inhibitor drugs, stenosis or occlusion of lacrimal drainage systems are common events caused by S-1, and cystoid macular edema (CME) caused by some drugs. We examine and follow these adverse events, with or without additional treatment, to support clinical trials, to contribute to establishing protocols, and to enlighten general ophthalmologists about these events.

Future prospects

We plan to establish the multicenter study group for eye tumors to employ clinical studies, confirm the diagnostic criteria and guidelines, and clarify the carcinogenesis for eye tumors.

Table 1. Number of patients

Retinoblastoma	53
Choroidal melanoma	26
Other intraocular tumors	39
Eyelid tumor	11
Conjunctival tumor	7
Orbital tumor	19
Ocular adnexal lymphoma	14
Other	2
Total	181

Table 2. Type of procedure

Retinoblastoma	
Selective ophthalmic arterial injection	131
Laser and/or vitreous injection	142
Ruthenium brachytherapy	14
Enucleation	10
Examination under general anesthesia	1
Choroidal melanoma	
Ruthenium brachytherapy	4
Enucleation	2
Resection of ciliary body tumor	2
Resection of eyelid tumor	7
Resection of conjunctival tumor	2
Resection of orbital tumor	14
Total	329

List of papers published in 2015

Journal

1. AJCC Ophthalmic Oncology Task Force. International Validation of the American Joint Committee on Cancer's 7th Edition Classification of Uveal Melanoma. JAMA Ophthalmol, 133:376-383, 2015

2. Goto H, Takahira M, Takahira M, Azumi A, Japanese Study Group for IgG4-Related Ophthalmic Disease. Diagnostic criteria for IgG4-related ophthalmic disease. Jpn J Ophthalmol, 59:1-7, 2015

3. Suzuki S, Aihara Y, Fujiwara M, Sano S, Kaneko A. Intravitreal injection of melphalan for intraocular retinoblastoma. Jpn J Ophthalmol, 59:164-172, 2015

4. Fujiwara T, Fujiwara M, Numoto K, Ogura K, Yoshida A, Yonemoto T, Suzuki S, Kawai A. Second primary osteosarcomas in patients with retinoblastoma. Jpn J Clin Oncol, 45:1139-1145, 2015

5. Nakamichi S, Nokihara H, Yamamoto N, Yamada Y, Fujiwara Y, Tamura Y, Wakui H, Honda K, Mizugaki H, Kitazono S, Tanabe Y, Asahina H, Yamazaki N, Suzuki S, Matsuoka M, Ogita Y, Tamura T. Phase I and pharmacokinetics/pharmacodynamics study of the MEK inhibitor RO4987655 in Japanese patients with advanced solid tumors. Invest New Drugs, 33:641-651, 2015

Department of Head and Neck Oncology

Seiichi Yoshimoto, Fumihiko Matsumoto, Kenya Kobayashi, Daisuke Maki, Masanori Teshima, Masahiko Fukazawa

Introduction

The treatment strategy for head and neck cancer is to improve survival rates while preserving the significant functions including speech, mastication, swallowing and cosmetic appearance. In order to achieve this strategy, our department has tried to select the best treatment modality and devise new surgical procedures based on clinic-pathological findings and our large database of patients with head and neck cancer.

Our department has developed and performed original surgical procedures of partial or subtotal laryngectomy for newly diagnosed and radiation-failed laryngeal cancer, partial pharyngectomy for hypopharyngeal cancer and total glossectomy for advanced tongue cancer. These surgical approaches can be performed without sacrificing the larynx. Compared with the results of conventional surgery, there are apparently fewer wound complications. Patients can resume social activities more easily when they maintain their ability to communicate vocally.

Routine activities

The Department of Head and Neck Oncology at NCCH consists of six head and neck surgeons. Many operations are performed under general and local anesthesia with or without microsurgical reconstructive surgery. In addition to radiotherapy, concurrent chemo-radiotherapy is performed with the Department of Radiation Oncology.

In 2015, 403 patients with head and neck tumor underwent surgery under local or general anesthesia: 127 and 276, respectively, including 78 patients with major ablation and reconstructive surgery. Table 1 shows the number of surgical cases with each primary site. Table 2 shows the number of each surgical procedure.

Research activities

We have been taking part in multi-institutional studies of sentinel lymph node navigation surgery for oral cavity cancer using RI and laryngopharyngeal cancer using ICG. We are also taking part in a multi-institutional study of intra-arterial chemo-radiotherapy for maxillary cancer.

Clinical trials

We are participating in a few clinical trials about immune checkpoint inhibitors.

Education

We provide plenty of educational opportunities for resident doctors, especially focusing on acquiring operative techniques. They can learn everything about perioperative management, such as physical examination, image diagnosis, informed consent, preoperative preparation and postoperative management.

Future prospects

We have recently started trans-oral resection for superficial laryngopharyngeal cancer. Trans-oral resection will be indicated for more patients. Cetuximab is used for many patients with recurrent or metastatic tumors. We will be able to get useful information about the response rate of Cetuximab for Japanese patients. The number of patients with HPV-related oropharyngeal cancer has increased. The treatment strategy for this disease should be discussed.

Table 1. Number of patients

Tongue	41
Oral cavity (without tongue)	53
Nasal and paranasal cavity	14
Nasopharynx	1
Oropharynx	50
Hypopharynx	79
Cervical esophagus	9
Larynx	30
Salivary gland	16
Thyroid	29
Parathyroid	0
Neck	57
Others	24
Total	403

Table 2. Type of procedure

Skull base (+ reconstruction)	3(3)
Maxillectomy (+ reconstruction)	16(4)
Glossectomy (+ reconstruction)	37(8)
Resection of Oral cavity (+ reconstruction)	47(18)
Nasopharyngectomy	1
Oropharyngectomy (+ reconstruction)	37(14)
Endoscopic resection of hypopharynx	7
Trans-oral resection of hypopharynx	23
Partial pharyngectomy (+ reconstruction)	7(1)
Total laryngopharyngectomy (+ reconstruction)	22(22)
Trans-oral resection of larynx	6
Partial or supracricoid laryngectomy	2
Total laryngectomy (+ reconstruction)	10(1)
Thyroidectomy (+ reconstruction)	24(1)
Parotidectomy (+ reconstruction)	12(2)
Neck dissection (+ reconstruction)	28(2)
Resection of parapharyngeal tumor	2
Voice prosthesis	12
Lymphadenectomy	68
Others (+ reconstruction)	39(2)
Total	403(78)

List of papers published in 2015

Journal

1. Murakami N, Yoshimoto S, Matsumoto F, Ueno T, Ito Y, Watanabe S, Kobayashi K, Harada K, Kitaguchi M, Sekii S, Takahashi K, Yoshio K, Inaba K, Morota M, Sumi M, Saito Y, Itami J. Severe gastrointestinal bleeding in patients with locally advanced head and neck squamous cell carcinoma treated by concurrent radiotherapy and Cetuximab. J Cancer Res Clin Oncol, 141:177-184, 2015

2. Kinjo Y, Nonaka S, Oda I, Abe S, Suzuki H, Yoshinaga S, Maki D, Yoshimoto S, Taniguchi H, Saito Y. The short-term and long-term outcomes of the endoscopic resection for the superficial pharyngeal squamous cell carcinoma. Endosc Int Open, 3:E266-E273, 2015

3. Wakisaka N, Hasegawa Y, Yoshimoto S, Miura K, Shiotani A, Yokoyama J, Sugasawa M, Moriyama-Kita M, Endo K, Yoshizaki T. Primary Tumor-Secreted Lymphangiogenic Factors Induce Pre-Metastatic Lymphvascular Niche Formation at Sentinel Lymph Nodes in Oral Squamous Cell Carcinoma. PLoS One, 10:e0144056, 2015

4. Kobayashi K, Ando M, Saito Y, Kondo K, Omura G, Shinozaki-Ushiku A, Fukayama M, Asakage T, Yamasoba T. Nerve Growth Factor Signals as Possible Pathogenic Biomarkers for Perineural Invasion in Adenoid Cystic Carcinoma. Otolaryngol Head Neck Surg, 153:218-224, 2015

Department of Plastic and Reconstructive Surgery

Shimpei Miyamoto, Masahide Fujiki, Masaki Arikawa, Yu Kagaya

Introduction

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

Routine activities

Two plastic surgeons cover reconstructive operations. Every week, five to ten reconstructive operations are performed. These reconstructive surgeries are performed in cooperation with the surgeons from other divisions of the hospital, such as Head and Neck Surgery, Breast Surgery, Orthopedic Surgery, Esophageal Surgery, and Dermatology. The number of patients who receive immediate breast reconstruction is increasing. Most patients undergo breast reconstruction with a silicone implant. Limb reconstruction after limb preservation surgery has increased.

Research activities

Multi-institutional analysis of postoperative functions after microvascular tongue reconstruction is ongoing. Also, laboratory research of flow-through flaps using a rat model is ongoing.

Table 1. Reconstructive procedures

Free flap	123
ALT	39
Jejunum	23
DIEP	13
RAMC	13
LDMC	11
TAP	8
SIEA	6
Fibula	4
Others	5
Other microsurgical procedures	11
Supercharge	1
Extremity revascularization	5
LVA	4
Others	1
Total (Microsurgery)	134
Pedicled flap	53
LD (TAP)	14(4)
Pectoralis Major	8
ALT	6
RAMC (DIEP)	5(1)
Others	20

Table 2. Breast reconstruction

Tissue expander	111
Silicone implant	56
DIEP	14
LD	5

List of papers published in 2015

Journal

1. Miyamoto S, Kayano S, Fujiki M, Kamizono K, Fukunaga Y, Sakuraba M. Flow-through divided latissimus dorsi musculocutaneous flap for large extremity defects. Ann Plast Surg, 74:199-203, 2015

2. Miyamoto S, Fukunaga Y, Fujiki M, Nakatni F, Tanzawa Y, Sakuraba M. Accompanying artery of sciatic nerve as recipient vessel for free-flap transfer: a computed tomographic angiography study and case reports. Microsurgery, 35:284-289, 2015

3. Fujiki M, Miyamoto S, Arikawa M, Sakuraba M. Combined Use of Anterolateral Thigh and Gluteal Fold Flaps for Complex Groin Reconstruction. Plast Reconstr Surg Glob Open, 3:e541, 2015

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5. Miyamoto S, Fujiki M, Sakuraba M. Clinical analysis of 33 flow-through latissimus dorsi flaps. J Plast Reconstr Aesthet Surg, 68:1425-1431, 2015

6. Fujiki M, Miyamoto S, Nakatani F, Kawai A, Sakuraba M. Rotationplasty with vascular reconstruction for prosthetic knee joint infection. Case Rep Orthop, 2015:241405, 2015

7. Miyamoto S, Fujiki M, Nakatani F, Sakisaka M, Sakuraba M. Free flow-through anterolateral thigh flap for complex knee defect including the popliteal artery. Microsurgery, 35:485-488, 2015

Department of Breast Surgery

Takayuki Kinoshita, Shin Takayama, Sota Asaga, Kenjiro Jimbo, Eriko Iwamoto, Sho Shiino

Introduction

The Breast Surgery Department deals with treatment of breast cancer through surgeries, as well as diagnosis of breast diseases and assessment of lymph nodes in the axillary and clavicular regions that are suspected of harboring metastases. The trend in surgical procedures has been changing year by year. Although breast-conserving therapy (BCT) accounted for 40% of the total surgeries in our division in 2015, BCT is on the decline in recent years. One of the reasons for such decline is increasing needs of immediate reconstruction surgery. In 2010, immediate breast reconstruction became one of the choices for patients in whom breast preservation was impossible, and a total of 130 immediate breast reconstructions were performed in 2015, comprising more than 20% of all the cases. The number of cases of immediate breast reconstruction has gradually increased year by year to match the increase in needs of patients. Sentinel lymph node (SLN) biopsies (SLNB) were performed in 83% of the cases. Following SLNB, axillary lymph node dissection (ALND) could be avoided when the SLNB was negative. One-step nucleic acid amplification (OSNA) assay, that quantitatively measures CK19 mRNA detects sentinel lymph node metastases even in molecular levels, in conjunction with this assay and conventional microscopic method, we began to be able to evaluate the SLN more precisely. Further, by comparing the OSNA results with that of conventional histological diagnosis, we try to search for the possibility of omitting axillary lymph node dissection by using two methods. Thus, we are striving continuously to meet the diverse needs of breast cancer patients.

Routine activities

Our division comprises of four staff surgeons, one chief resident, and three or four rotating residents. From 7:20 every morning, all the staff and the residents perform in-patient rounds together. The journal club and research conference are scheduled on every Tuesday morning after rounds. Weekly conferences are held on Monday and Wednesday 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 for every postoperative patient. A breast pathology/imaging conference is held on the second Wednesday of each month from 19:00 to 20:00 to discuss problems with diagnostic imaging, and with pathologically interesting cases. A conference about studies, institutional treatment guidelines and recent topics regarding breast cancer is held on the last Wednesday of each month by a multidisciplinary team. Treatment Guidelines for primary and metastatic breast cancer have been updated regularly through this multidisciplinary discussion since 2003.

Surgery

We perform surgeries from Monday to Friday; there are generally 13 to 15 cases of breast cancer in a week.

Table 1 shows the total number of patients with primary breast cancer (including breast primary sarcoma) and other breast disease. The types and number of operative procedures are shown in Table 2. The rate of mastectomy was 55% (340/614), including 130 cases of immediate reconstruction. SLNB was performed in 331 patients, and 251 patients were spared from ALND in 2014.

Research activities and Clinical trials

1) Radiofrequency ablation therapy for early breast

cancer as local therapy (RAFAELO study)

The trial of image-guided radiofrequency ablation (non-surgical therapy) has been accomplished for early-stage breast carcinomas of less than 1.0 cm in diameter (Phase I/II study; Kinoshita et al.). After years of trial, the indication has just been expanded up to 1.5 cm in diameter and this technique has been certified as an advanced medical treatment by the Ministry of Health, Labour and Welfare. Our secondary goals are to determine the size, configuration and pathological features of acute RFA treatment of breast cancers, and we have conducted clinical studies to evaluate the oncologic safety of RFA in terms of local recurrence.

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 that 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 is continuing, 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 and continued in order to slow or halt hair loss during chemotherapy.

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

This multi-center randomized trial has continued from 2012. This study compares invasive disease-free survival in patients with or without TS-1 administration together with adjuvant endocrine therapy in hormone positive and HER2 negative high recurrence risk patients.

6) Registration database system for breast cancer patients who had lymph node metastasis diagnosis by the OSNA® method (LynoLog Database)

The aim of this study is to accumulate the administrative data on cases with the OSNA method in a common database, the LynoLog Database, and to evaluate the clinical significance of intraoperative SLN metastases detected by OSNA.

7) Olaparib as adjuvant treatment in patients with germline BRCA mutated high risk HER2 negative primary breast cancer (OlympiA)

A randomized, double-blind, parallel group, placebo-controlled multi-center phase III study started in 2014. The aim of the study is to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.

Table 1. Number of patients

		2012	2013	2014	2015
Primary breast cancer (or sarcoma)		494	555	514	625
cStage	0	76	99	106	141
	Ⅰ	199	215	184	230
	Ⅱ	194	203	189	196
	Ⅲ	17	33	27	40
	Ⅳ	8	5	3	1
unknown or others		2	0	6	18

bilateral breast cancer was culculated as two cases.

Table 2. Type of procedure

	2011		2012		2013		2014		2015	
Total number of operations	577		589		618		582		679	
Total number of Primary breast cancer	526		502		560		530		625	
Mastectomy (%)	250	(48)	234	(45)	263	(47)	262	(51)	340	(55)
Breast-conserving surgery (%)	269	(51)	275	(53)	283	(51)	222	(43)	242	(40)
Radiofrequency ablation (%)	6	(1)	6	(1)	9	(2)	30	(6)	32	(5)
Axillary lymph node dissection (ALND) (%)	205	(33)	188	(15)	93	(21)	83	(20)	103	(17)
Sentinel lymph node biopsy (SLNB) (%)	402	(67)	409	(85)	347	(79)	331	(80)	501	(83)
Immediate breast reconstruction (%)	74	(14)	62	(13)	65	(12)	75	(14)	130	(20)
Secondory breast reconstruction (%)	1	0	8	(2)	5	(1)	16	(3)	11	(2)
Neoadjuvant therapy	57	(11)	45	(8)	38	(7)	36	(7)	64	(10)

Table 3. Survival (2006.1-2007.12)

		No. of patients	5-yr survival (%)
Total			92
stage	0	150	100
	Ⅰ	303	95
	Ⅱ	381	93
	Ⅲ	28	73

List of papers published in 2015

Journal

1. Jimbo K, Kinoshita T, Asaga S, Hojo T. Oncological safety of breast-conserving surgery after primary systemic chemotherapy in cT3-4 breast cancer patients. Surg Today, 45:1255-1262, 2015

2. Ono M, Tsuda H, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Kinoshita T, Fujiwara Y. Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers. Breast Cancer, 22:141-152, 2015

3. Hojo T, Masuda N, Mizutani T, Shibata T, Kinoshita T, Tamura K, Hara F, Fujisawa T, Inoue K, Saji S, Nakamura K, Fukuda H, Iwata H. Intensive vs. Standard Post-Operative Surveillance in High-Risk Breast Cancer Patients (INSPIRE): Japan Clinical Oncology Group Study JCOG1204. Jpn J Clin Oncol, 45:983-986, 2015

4. Yoshida M, Ogawa R, Yoshida H, Maeshima A, Kanai Y, Kinoshita T, Hiraoka N, Sekine S. TERT promoter mutations are frequent and show association with MED12 mutations in phyllodes tumors of the breast. Br J Cancer, 113:1244-1248, 2015

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Department of Breast and Medical Oncology

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Introduction

The Department of Breast and Medical Oncology provides the most effective treatment by the use of chemotherapy, and works on the establishment of new standard care for adult malignancies including breast cancer, gynecologic cancer, soft-tissue sarcoma, extragonadal germ cell tumors, primary unknown tumors and other rare types of solid tumors.

We envision becoming a premier medical 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 cancer patients, to develop new effective cancer treatment through clinical and translational research, and to nurture medical oncologists. An evidence-based, research-oriented and multi-disciplinary approach is the core value of our practice.

Routine activities

1) Setup

Our Department consists of eight full-time attending physicians, four chief residents (fellows), and two to three clinical residents. We also provide educational opportunities to short-term (a half year) residents. Full-time attending physicians are on duty at the outpatient clinic two to three days per week. The management of hospitalized patients is undertaken by clinical teams, which consist on attending physicians and residents. A Grand Round is scheduled every Wednesday and Friday.

2) Performance

There were 1,423 first visits of new patients including second opinions in 2016 (Table 1). Approximately two thirds of the new patients were referred from other divisions of the National Cancer Center Hospital (NCCH). About half of the new patients are breast cancer patients, but it is noteworthy that there was an approximate 30% increase in patients with adult sarcoma this year because of our work with the Rare Cancer Center. The number of outpatient who received chemotherapy delivered by our Department delivered by our division was 8,580, which accounts for 27.3% of the total number and ranks first in the number of treatments delivered at the Outpatient Treatment Center.

We have approximately 32 (range 30-40) inpatients daily. Terminally ill patients are transferred to palliative care units or in-home care clinics outside the NCCH, whereas 33 patients of our Department passed away in the NCCH in 2016. Autopsies were undertaken on five patients.

3) Conference

The one-hour briefing medical conferences are held every morning to discuss the evidenced-based care for individual patients. The phase 1 conference is held on Monday, Journal Club on Wednesday, Clinical trial conference on Thursday, and Weekend and Outpatient follow-up conference on Friday. Multidisciplinary Case Conferences with diagnostic radiologists, surgeons, and pathologists are held with members of the Department of Breast Surgery, Gynecology, Musculoskeletal Oncology and Rehabilitation, Radiation Oncology and Division of pathology once or twice (Breast) per week, respectively.

The Monthly Breast Cancer Conference is held with the participation of multidisciplinary specialists to discuss recent topics in breast oncology and to update institutional treatment guidelines. This year, we published "Nyugan-shinnryou Application Notebook" from Nankodo based on this guideline, which reflects the consensus of the breast team on the body of evidence on breast

cancer management.

4) Coordination of care

Three board-certified Breast Cancer Specialist Nurses help provide seamless and comprehensive care to breast cancer patients. Group-assigned pharmacists support patients in the ward and in the clinic. Most patients are supported by the Consultation, Counseling and Support Service Center for coordination of care. Post-operative breast cancer patients without disease recurrence are referred to local breast cancer specialists participating in the Tokyo Breast Consortium network (http://breastcons.com/).

Research activities

Our research interest extends across a wide range of topics related to treatment and clinical program development. A lot of our research is secured by public and consignment research grants. In 2015, we conducted many research programs as the primary investigator and participated in additional research programs as the co-investigator secured by competitive public research funds. We published 29 international manuscripts. We value cancer survivorship as a research theme in order to develop a patient-centered comprehensive care program. In 2015, we published a guideline on fertility and fertility preservation for young breast cancer patients in cooperation with gynecologists and reproductive specialists. In addition, we took the lead in a multidisciplinary collaborative study group on End-of-life decision support for patients with advanced cancer.

Clinical trials

In 2015, we actively enrolled patients in phase I studies (including the first in human or global) as well as national and international phase II and III studies (Table 2). Of note, we launched a pharmacokinetic and dose-finding study of eribulin/olaparib, and a phase II study of eribulin in a neoadjuvant setting in triple negative breast cancer and phase I of Ribophorin (RPN)2 (first in human) as an investigator-initiated clinical trial (IIT in Table 2). New molecular imaging studies are launched in cooperation with research institutes. We also conducted many types of prospective cohort translational studies to find novel biomarkers.

Education

We provide rich educational opportunities to both residents and chief residents through clinical experience as well as research activities. Residents are encouraged to make presentations at local and national conferences. We vigorously support basic, clinical, or translational research conducted by postgraduate students.

Future prospects

We will continue to establish new standard treatments and propose a near-future model of clinical management of adult solid tumors, including breast cancer and gynecologic cancer. Moreover, we aim to build a comprehensive program, which includes a tumor registry, translational research, clinical trials and patient care in rare adult tumors based on our rich clinical experience. We would also like to improve the efficiency of anti-cancer drug development by coordinating basic and translational research in early-phase clinical trials.

Table 1. 1st Visiting Patients to the Department of Breast and Medical Oncology (Jan. – Dec. 2015)

No. of 1st Visits	n	%
Total	1,000	100
Breast	426	42.6
GYN	151	15.1
Cancer of primary unknown	207	20.7
Sarcoma	141	14.1
Others	75	7.5
Purpose of consultation		
Total	1,423	
2nd opinion	423	
Total No. of 1st visits	1,000	
2nd opinion as 1st visits	26	2.6
Treatment at NCCH	51	5.1
Referrals from other hospitals	286	28.6
Referrals from other divisions in the NCCH	634	63.4 (100)
Breast surgery	299	(47.2)
GYN	89	(14.0)
Urology	19	(3.0)
Orthopedics	24	(3.8)
Others	50	(7.9)
Rare Cancers Hotline	153	(24.1)
Others	3	0.3

Table 2. Active Clinical Trials (Jan. 2015-Dec. 2015)

Disease	Clinical setting	Phase	Protocol	Regimen	Status
Breast	Neo-adjuvant	II (IIT*)	Neo-Eribulin (TNBC)	Eribulin followed by FEC	Active, not recruiting
		II	Neo-Peaks	T-DM1 neoadjuvant	Active
	Follow-up	III	JCOG1204	Intensive follow-up vs. standard follow-up	Active
		II	POSITIVE	Pregnancy during hormonal therapy	Active
	Adjuvant	III	BEATRICE (TNBC)	CTx vs. CTx + Bevacizumab	Active, not recruiting
		III	ALTTO (HER2)	Lapatinib vs. HCN vs. Lapa/HCN	Active, not recruiting
		III	CREATE-X (JBCRG04)	Capecitabine vs. none post-NAC	Active, not recruiting
		III	D-CARE	Denosumab vs. placebo	Active, not recruiting
		III	APHINITY (HER2)	CTx+HCN/placebo vs. CTx/HCN/Pertuzumab	Active, not recruiting
		III	POTENT	HTx+S1 vs. HTx alone	Active, not recruiting
		III	KAITLIN (HER2)	Taxane/Trastuzumab/Pertuzumab vs. T-DM1/ Pertuzumab	Active, not recruiting
		III	OlympiA (BRCA+)	Olaparib vs. placebo	Active
			HOPE	Frozen Cap	Active
	Metastatic	III	JCOG1017	Surgery vs. no surgery for primary Stage IV BC	Active
		III	MARIANNE (HER2)	RO5304020+/- RO4368451 vs. HCN/PTX	Active, not recruiting
		III	NK105	NK105 vs. Paclitaxel	Active, not recruiting
		III	PALOMA-2 (HR+)	Letrozole +/- PD0332991	Active, not recruiting
		III	ELTOP (WJOG)	Lapa/Capecitabine vs. HCN/Capecitabine	Active, not recruiting
		III	OlympAD (BRCA+)	Olaparib vs. TPC	Active, not recruiting
		III	Monach2	Fulvestrant +/- Abemaciclib	Active, not recruiting
		III	Monach3	Letrozole +/- Abemaciclib	Active, not recruiting
		II	CAPTURE (HR+)	Paclitaxel/Bevacizumab vs. maintenance endocrine therapy	Active
		II	BEECH	AZD5363+PTX	Active, not recruiting
		II	TARGET (HR+)	Tamoxifen vs. high-dose Tamoxifen /CIP2D6	Active
		II	lapaHER (HER2)	Lapatinib/HCN	Active, not recruiting
		II	CBDCA/S1 (TNBC)	CBDCA/S1	Active
		II	KEYNOTE-086	MK3475	Active
		I/II	CAPIRI	Capecitabine/CPT-11	Active
		I/II	S1/docetaxel	S1/docetaxel	Terminated
		I/II	Lapa/eriburin (HER2)	Lapatinib/eriburin	Terminated
		I/II (*IIT)	EO (TNBC)	Eribulin/AZD2281	Active, not recruiting
		I/II	PD0332991	Letrozole +PD0332991	Active, not recruiting
		I (exp)	AZD5363 (AKT+ or PIK3CA+)	AZD5363	Active

Disease	Clinical setting	Phase	Protocol	Regimen	Status
Metastatic		I	RPN2siRNA	RPN2siRNA	Active
		I	KHK2375	KHK2375/Exemestane	Active
		PK/PD/ PGx	Eriburin PK	Eriburin	Active
		PK/ADCC	T-DM1 PK/ADCC	T-DM1	Active
		Cohort	Nursing intervention for oral chemotherapy	Oral chemotherapy	Active
Ovary	Adjuvant	III	AZD2281	Chemotherapy+/-Olaparib	Active, not recruiting
	Advanced	III	JCOG0602	Primary surgery vs. NAC	Active, not recruiting
		III	JGOG3017	TC vs. CDDP/CPT-11	Active, not recruiting
		III	GOG213	TC +/- bevacizumab	Active
		III	GOG218	TC +/- bevacizumab	Active, not recruiting
		III	AMG386	PTX+/-AMG386	Active, not recruiting
		III	GW786034	Pazopanib	Active, not recruiting
		II	MORAb-003	MORAb	Active
		II	GOG268	TC+Temsirolimus	Active, not recruiting
		II	ONO-4538	Nivolumab vs. GEM or Doxil	Active
Cervical cancer	Advanced	I	S1/CDDP	S1/CDDP chemoradiation	Active, not recruiting
		III	JCOG1311	ddTC vs TC	Active
Ovary/Endometrial/Cervical		II	Perifosine (PIK3CA+)	Perifosine	Active, not recruiting
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	AZD5363	AZD5363	Active, not recruiting
		I	PD0332991	PD0332991	Active, not recruiting
		I	Veriparib (BRCA+)	Veriparib	Active, not recruiting
		I	BAY1179470 (FGFR+)	BAY1179470	Active, not recruiting
		I	KEYNOTE-028	MK3475	Active, not recruiting
		I	GDC0032	GDC0032	Active, not recruiting
		I	Ds5573a (FIH)	Ds5573a	Active
		I	DS8201a (FIH)	DS8201a	Active
Soft tissue sarcoma		III	Olaratumab (PDGFRi)	Olaratumab + DXR	Active
		II	ET-743	ET-743	Active, not recruiting
		I	Olaratumab (PDGFRi)	Olaratumab + DXR, mono	Active, not recruiting
CIPN SNPs		TR	Paclitaxel induced peripheral neuropathy	Paclitaxel	Active, not recruiting
Molecular Imaging		TR	Cu^{64}-trastuzumab/PET	Nano-dose, radio-labeled trastuzumab as PET probe	Active
		TR	Cu^{64}- cetuximab/PET	Nano-dose, radio-labeled trastuzumab as PET probe	Active
		TR	MAS- imaging	MAS-imaging for solid tumor	Active
Liquid Biopsy		TR	CTC	CTC/breast, gynecologic (blood)	Active, not recruiting
		TR	ADCC	Quantitative ADCC (blood)	Active, not recruiting
		TR	miRNA in exosome	miRNA in exosome (blood)	Active
		TR	ctDNA	ctDNA (blood) Sequenom	Not yet recruiting
Genomic test		TR	TOP-GEAR (NGS) TOPICS-1	Genome screening for phase I	Active, not recruiting
(NGS, Sequencing at hot spots, Whole Exon Sequence)		TR	TOP-GEAR (NGS)	SCI lab	Active
		TR	HER-Antibody induced heart failure	HER-Antibody	Active
		TR	Sequencing	Methylation of promoter BRCA	Active, not recruiting
		TR	Sequencing	Methylation of promoter TERT	Active
		TR	Sequencing	AKT1P, PIK3CA	Active

*IIT; investigator-initiated clinical trial, TNBC; triple negative breast cancer, CTx; chemotherapy, HTx; hormonal therapy, HR; hormone receptor, dd; dose-dense, FIH; First in Human TR; NAC; neoadjuvant chemotherapy, translational, NGS; next generation sequence

List of papers published in 2015

Journal

1. Ono M, Tsuda H, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Kinoshita T, Fujiwara Y. Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers. Breast Cancer, 22:141-152, 2015

2. Yamamoto H, Ando M, Aogi K, Iwata H, Tamura K, Yonemori K, Shimizu C, Hara F, Takabatake D, Hattori M, Asakawa T, Fujiwara Y. Phase I and pharmacokinetic study of trastuzumab emtansine in Japanese patients with HER2-positive metastatic breast cancer. Jpn J Clin Oncol, 45:12-18, 2015

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5. Davies BR, Guan N, Logie A, Crafter C, Hanson L, Jacobs V, James N, Dudley P, Jacques K, Ladd B, D'Cruz CM, Zinda M, Lindemann J, Kodaira M, Tamura K, Jenkins EL. Tumors with AKT1E17K Mutations Are Rational Targets for Single Agent or Combination Therapy with AKT Inhibitors. Mol Cancer Ther, 14:2441-2451, 2015

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Department of Thoracic Surgery

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Introduction

The Department of Thoracic Surgery 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 Department has four attending surgeons. Attending surgeons and residents perform all of the inpatient care, operations, examinations, and outpatient care. In 2015, we performed a total of 664 operations; for lung cancer in 492 patients, metastatic tumor in 82, mediastinal tumor in 24, and others in 66.

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

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

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

Research activities

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

Minimally invasive surgery with the thoracoscope for thoracic malignancies is also an important challenge in our division. In particular, the indications and surgical techniques of video-assisted surgery for early lung cancer are of special interest because of the increased incidence of such minute tumors due to improvements in CT devices and CT screening.

Clinical trials

Due to the advent of new technologies in CT scanning, small-sized lung cancers are being found in a screening setting and also by chance. They are usually present as "ground-glass opacity (GGO)" on CT, and pathologically they are considered early adenocarcinoma. The surgical management of such GGO-type lung cancer remains undetermined in terms of the extent of pulmonary parenchymal resection and lymph node dissection. Some cases might be followed up with careful monitoring by CT, since indolent tumors are known to exist. We are seeking the appropriate way to manage these patients. A clinical trial to determine the appropriateness of limited resection for early adenocarcinoma had been planned in the Japan Clinical Oncology Group (JCOG) – Lung Cancer Study Group, and two clinical trials (a phase III trial, JCOG 0802; a phase II trial, JCOG 0804) have been conducted since the end of 2009. In addition, another phase II trial (JCOG1211), a confirmatory trial of segmentectomy for clinical T1N0 lung cancer dominant with GGO, was started in 2013. The accrual for JCOG 0804 trial has already closed. The accrual for JCOG0802 was closed in 2014. The accrual for JCOG 1211 was closed in November 2015.

As for postoperative adjuvant therapy, a phase III clinical trial to compare the effectiveness of UFT with that of TS-1 for stage IA of more than 2 cm and IB NSCLC planned in JCOG (JCOG 0707) has been conducted since 2008. This trial completed the full accrual of 960 patients in 2013. A phase III clinical trial (JCOG 1205) to compare Irinotecan/Cisplatin with Etoposide/Cisplatin for adjuvant chemotherapy of resected pulmonary high-grade neuroendocrine carcinoma was started in 2013.

Table 1. Number of patients in 2015

Primary lung cancer	492
Metastatic lung tumor	82
Mediastinal tumor	24
Pleural disease	11
Chest wall tumor	8
Benign lung nodule	28
Others	19
Total	664

Table 2. Type of procedure in 2015

Lung resection	587
Lobectomy	347
Pneumonectomy	11
Segmentectomy	101
Wedge resection	128
Tracheal resection	0
Surgery for mediastinal tumors	23
Surgery for pleural tumors	16
Surgery for chest wall tumors	8
Others	30
Total	664

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

Pathological stage (TNM-7)	No. of pts	5-yr survival (%)
IA	1,902	94.2
IB	556	83.5
IIA	320	71.7
IIB	208	64.4
IIIA	453	48.3
IIIB	82	34.9
IV	30	26.8

Operation period: 2003.1-2011.12 Total 3,551

List of papers published in 2015

Journal

1. Suzuki K, Watanabe S, Mizusawa J, Moriya Y, Yoshino I, Tsuboi M, Mizutani T, Nakamura K, Tada H, Asamura H, Japan Lung Cancer Surgical Study Group (JCOG LCSSG). Predictors of non-neoplastic lesions in lung tumours showing ground-glass opacity on thin-section computed tomography based on a multi-institutional prospective study†. Interact Cardiovasc Thorac Surg, 21:218-223, 2015

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Department of Thoracic Oncology

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Introduction

Lung cancer is the leading cause of cancer death in Japan and worldwide. The incidence of lung cancer in Japan is still increasing, especially in elderly people. The Department of Thoracic Oncology provides care for patients with primary lung cancer, mediastinal tumors, and pleural tumors. The goals of the department are to provide the highest quality treatment and establish new effective treatments against lung cancer and other thoracic malignancies through innovative clinical and translational research. To provide assistance to our patients through multidisciplinary care, the staff members of the department work closely with thoracic surgeons, radiation oncologists, pharmacists, clinical research coordinators, and psychiatrists who have expertise in these areas. The department includes seven staff physicians. Moreover, residents and trainees from other institutions have joined the Thoracic Oncology Program.

Routine activities

The staff physicians attend outpatient services for thoracic diseases, and the department has approximately 60 beds in the hospital. Inpatient care is carried out by five teams. Each team consists of one staff physician and one or two residents and/or trainee doctors. Protocol and case conferences are scheduled every Monday morning and afternoon, respectively. The journal club is scheduled on Thursday mornings.

A total of 413 new patients were admitted in 2015, and the backgrounds and initial treatments of these patients are shown in tables 1 and 2. The initial treatments were chemotherapy in 230, adjuvant chemotherapy after surgery in 44, chemoradiotherapy in 62, curative radiotherapy in 5, and supportive care including palliative radiotherapy in 49. Survival of lung cancer patients treated in 2006-2010 in our department is shown in Table 3.

Research activities

Research activities of the department can be classified into four categories: (1) multi-institutional phase III studies to establish new standard treatments against lung cancer; (2) phase I and phase II studies to evaluate new anticancer drugs, (3) pharmacokinetic and pharmacodynamic (PK/PD) studies to investigate interpatient variability, optimal administration schedules and drug-drug interactions; and (4) translational research using clinical samples from bench to bed-side or from bed-side to bench for the development of innovative treatment strategies.

Clinical trials

The department is currently conducting and participating in multi-institutional phase III studies to establish new standard treatments against lung cancer such as the Japan Clinical Oncology Group (JCOG) trials and global trials conducted by pharmaceutical companies. Three JCOG phase III studies, JCOG1201 for elderly ED-SCLC, JCOG1206 for high-grade neuroendocrine carcinoma and JCOG1210/WJOG7813L for elderly non-squamous NSCLC are ongoing. In addition to these studies, JCOG1404 (AGAIN), a phase III study for EGFR mutation positive NSCLC, was started in December. The department is also participating in a nationwide screening project of lung cancer with rare driver mutation (LC-SCRUM) and phase II studies targeting rare driver mutation. The department carried out many clinical trials using 3rd generation EGFR-TKIs, anti-PD-1Ab, and anti-PD-L1Ab.

Education

In 2015, three chief residents, 16 residents and two research residents joined the department. A monthly research conference is held to discuss clinical and translational research conducted by young doctors.

Future prospects

The recent progression of lung cancer treatment is very rapid. Driver gene alteration targeted therapy such as EGFR-TKIs and ALK inhibitors are already established as a standard treatment for lung cancer patients with EGFR mutation and ALK fusion gene. Other rare driver gene alterations such as ROS1 fusion, RET fusion, and "BRAF mutation can be good targets for treatment of lung cancer." Immunotherapy using anti-PD-1Ab has been established as a standard 2nd or 3rd line treatment for NSCLC. Anti-PD-L1Ab will also be established as a standard treatment of lung cancer in the near future. These immunotherapies could provide a durable response for some lung cancer patients. Establishment of good biomarkers to identify the patients who respond to the immunotherapy is very important.

Table 1. Number of new inpatients in 2015

Thoracic malignancies total	413
NSCLC	350
Adenocarcinoma	261
Squamous cell carcinoma	54
Others	35
SCLC	49
Mesothelioma	7
Thymic cancer	5
Thymoma	2

Table 2. Initial treatments for new inpatients with lung cancer in 2015

Chemotherapy	230
Chemoradiotherapy	62
Adjuvant chemotherapy after surgery	44
Chemoradiotherapy followed by surgery	8
Curative radiotherapy	5
Supportive care including palliative radiotherapy	49

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

Disease	Stage	Treatment	N	Survival rate (%)				
				1y	2y	3y	4y	5y
NSCLC	IIIB, IV, recurrence	chemotherapy	601	64	39	22	13	8
NSCLC	IIIA,IIIB	chemoradiotherapy	187	84	61	44	34	30
SCLC	ED	chemotherapy	133	58	23	5	5	5
SCLC	LD	chemoradiotherapy	60	87	65	38	32	28

List of papers published in 2015

Journal

1. Tsukada H, Yokoyama A, Goto K, Shinkai T, Harada M, Ando M, Shibata T, Ohe Y, Tamura T, Saijo N, Lung Cancer Study Group of the Japan Clinical Oncology Group (JCOG). Randomized controlled trial comparing docetaxel-cisplatin combination with weekly docetaxel alone in elderly patients with advanced non-small-cell lung cancer: Japan Clinical Oncology Group (JCOG) 0207†. Jpn J Clin Oncol, 45:88-95, 2015

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Department of Esophageal Surgery

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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 Department of Esophageal Surgery cooperates in particular with the Department of Gastrointestinal Medical Oncology and the Department of Radiation Oncology for preoperative chemotherapy and chemoradiotherapy and salvage surgery after definitive chemoradiotherapy, and the Department of Endoscopy for diagnosis and endoscopic resection. We also maintain close cooperation with the Department of Head and Neck Surgery for cervical esophageal carcinomas and with the Department of Gastric Surgery for adenocarcinomas in the esophagogastric junction. Patients who required a laryngectomy for resection of cervical esophageal cancer were operated on in the Department of Head and Neck Surgery. Most patients with Siewert Type III adenocarcinoma were operated on in the Department of Gastric Surgery. In our Department, squamous cell carcinomas still constitute the largest proportion of esophageal tumors, and 11 patients with adenocarcinomas of the esophagogastric junction underwent an esophagectomy in 2015.

Routine activities

The Department of Esophageal Surgery consists of three staff surgeons, one chief resident and 1-2 rotating senior residents. A multidisciplinary conference (Esophageal Tumor Board) 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. Every week, 2-3 patients with esophageal cancer undergo surgery. One hundred and four patients underwent esophagectomy including four patients with cervical esophageal cancer, three with carcinosarcoma, six with malignant melanoma, three with neuroendocrine tumors, and one with large Schwannoma. Two patients with gastric cancer after esophagectomy underwent gastric conduit resection and reconstruction. Preoperative chemotherapy was recommended for 56 patients and preoperative chemoradiotherapy was recommended for 4 patients with resectable Stage II-IV esophageal squamous cell cancer. A three-field dissection, including the whole upper mediastinum and supraclavicular area in addition to the lower mediastinum and abdomen, was performed on 72 patients as our standard procedure. Video-assisted thoracic surgery was introduced for esophagectomy as minimally invasive surgery in 44 patients. Two hospital deaths occurred due to postoperative complications including postoperative pneumonia and cardiac attack after esophagectomy.

In a paradigm shift toward organ-sparing therapy, the number of patients who receive definitive chemoradiotherapy as their primary treatment for resectable tumors is increasing. A persistent or recurrent loco-regional disease is not infrequent after definitive chemoradiotherapy. Nineteen patients underwent salvage esophagectomy after the failure of definitive chemoradiotherapy in 2015. 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. 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

A multi-institutional randomized controlled trial comparing standard preoperative chemotherapy (5FU and cisplatin), an intensive one (5FU and cisplatin plus docetaxel), and preoperative chemoradiotherapy (5FU and cisplatin plus 41.4 Gy irradiation) for Stage II-III esophageal cancer (JCOG1109) is ongoing. A new multi-institutional randomized controlled trial comparing minimally invasive esophagectomy versus open thoracic esophagectomy (JCOG1409) started registration in 2015. A Phase II trial for definitive chemoradiotherapy with or without salvage esophagectomy (JCOG0909) has finished registration. A new Phase II trial for a tri-modality strategy with docetaxel plus 5FU and cisplatin (DCF) induction chemotherapy for locally advanced unresectable esophageal cancer followed by conversion surgery for responders and chemoradiotherapy for non-responders (COSMOS) launched in 2013 and has finished registration.

Education

We accepted many surgeons from foreign countries, especially from Asia. A dramatic increase in the incidence of adenocarcinoma has been seen in Western patients. However, in Asian patients, including Japanese patients, squamous cell carcinoma remains the predominant type of esophageal cancer. Japanese strategies and surgical techniques for esophageal squamous cell carcinoma are instructive for Asian surgeons.

Table 1. Number of patients

Thoracic esophageal squamous cell carcinoma	78
Cervical esophageal squamous cell carcinoma	4
Adenocarcinoma of esophagogastric junction	11
Carcinosarcoma	3
Malignant melanoma	6
Neuroendocrine tumor	3
Large Schwannoma	1
Gastric cancer of gastric conduit after esophagectomy	2

Table 2. Type of surgical procedure

Open thoracic esophagectomy	53
Video-assisted esophagectomy	44
Transhiatal esophagectomy	1
Transhiatal esophagectomy with pharyngo-laryngectomy	3
Lower esophagectomy for esophagogastric junction cancer	5
Gastrectomy for gastric conduit cancer after esophagectomy	2
Esophageal bypass	1
Salvage lymph node dissection	7
Exploratory thoracotomy	2

List of papers published in 2015

Journal

1. Takahashi T, Yamahsita S, Matsuda Y, Kishino T, Nakajima T, Kushima R, Kato K, Igaki H, Tachimori Y, Osugi H, Nagino M, Ushijima T. *ZNF*695 methylation predicts a response of esophageal squamous cell carcinoma to definitive chemoradiotherapy. J Cancer Res Clin Oncol, 141:453-463, 2015

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6. Nozaki I, Kato K, Igaki H, Ito Y, Daiko H, Yano M, Udagawa H, Mizusawa J, Katayama H, Nakamura K, Kitagawa Y. Evaluation of safety profile of thoracoscopic esophagectomy for T1bN0M0 cancer using data from JCOG0502: a prospective multicenter study. Surg Endosc, 29:3519-3526, 2015

7. Yokota T, Ando N, Igaki H, Shinoda M, Kato K, Mizusawa J, Katayama H, Nakamura K, Fukuda H, Kitagawa Y. Prognostic Factors in Patients Receiving Neoadjuvant 5-Fluorouracil plus Cisplatin for Advanced Esophageal Cancer (JCOG9907). Oncology, 89:143-151, 2015

8. Kataoka K, Nakamura K, Mizusawa J, Fukuda H, Igaki H, Ozawa S, Hayashi K, Kato K, Kitagawa Y, Ando N. Variations in survival and perioperative complications between hospitals based on data from two phase III clinical trials for oesophageal cancer. Br J Surg, 102:1088-1096, 2015

Department of Gastric Surgery

Hitoshi Katai, Takeo Fukagawa, Shinji Morita, Hisataka Fujiwara, Takeyuki Wada, Hiroshi Moro

Introduction

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

Routine activities

The Department includes five staff surgeons, one chief resident and three or four rotating residents at any given time. Nine to eleven patients are operated upon every week. The Department shares a ward with the Departments of Hepatobiliary and Pancreatic Surgery and Oncology. 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. Adjuvant XELOX chemotherapy is applied for stage IIIC 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 to be an important function. In 2015, more than 20 surgeons from various countries visited this division for 1 week to 6 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 washings for prediction of gastric cancer recurrence is being developed. Research on the detection of small amounts of cancer cells in peripheral blood and bone marrow of gastric cancer patients is being carried out.

Clinical trials

Our Department 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. 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 completed for accrual. JCOG 1001, which is designed to evaluate the significance of bursectomy for advanced cancer, has been completed for accrual. This trial includes the evaluation of long-term survival, postoperative morbidity, and mortality. The JCOG 0912 phase III

trial to prove the non-inferiority of laparoscopic gastrectomy over its open counterpart for patients with clinical stage IA and IB gastric cancer has also been completed for accrual. The JCOG 1104 phase III trial to evaluate the optimal period of adjuvant S-1 chemotherapy for pathological stage II gastric cancer patients who underwent D2 gastrectomy is ongoing. The JCOG1301C, a randomized phase II study of systemic chemotherapy with and without trastuzumab followed by surgery in HER2 positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis, just started. JCOG1302-A is a study to evaluate the accuracy of pre-operative staging for advanced tumors and has been completed for accrual and the results were reported. A phase II study to check the feasibility of Oxaliplatin, and S-1 neoadjuvant chemotherapy for stage III disease was carried out and the results were reported. We started a new phase II trial to prove the feasibility of laparoscopic total and proximal gastrectomy for stage IA and IB gastric cancer (JCOG 1401).

Education

Education of surgical operations has been introduced for chief and rotating residents throughout the perioperative management of more than 500 gastric cancer patients.

Future prospects

D2 gastrectomy is considered the standard surgical treatment for advanced gastric cancer but multi-modality treatments combined with surgery will further improve survival rates. There are several surgical options for early gastric cancer depending on the risk of nodal metastasis. The efficacy of laparoscopic surgery for early gastric cancer is being assessed. Moreover, robotic surgery is introduced as advanced medical care services and the safety and effectiveness has currently been evaluated. These procedures will require good quality control achieved through supervision and training by experienced surgeons in high volume centers.

Table 1. Number of Patients

Adenocarcinoma	447
GIST	18
Others	39
Total	504

Table 2. Operative morbidity and mortality after gastrectomy

	Number of patients	%
Major complications (Clavien-Dindo Grade 3-4)	43	11.9
Minor complications	76	21.1
Postoperative hospital deaths	1	0.3
Total number of gastrectomy	360	

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, and line infection, etc.

Table 3. Operative Procedures

Distal gastrectomy	127
Total gastrectomy	78
Completion gastrectomy	13
Pylorus-preserving gastrectomy	32
Proximal gastrectomy	28
Pancreaticoduodenectomy	2
Wedge resection	21
Laparoscopic total gastrectomy	4
Laparoscopic distal gastrectomy	37
Laparoscopic pylorus preserving gastrectomy	39
Other (bypass, exploration, etc.)	123
Total	504

Table 4. Overall Survival Rates

Stage	No. of patients	5-yr survival
IA	1,920	94.8%
IB	396	92.6%
IIA	348	84.8%
IIB	316	78.6%
IIIA	242	64.0%
IIIB	214	57.7%
IIIC	195	38.6%
IV	644	11.9%
Total	4,275	74.2%

Stage: Japanese classification (14th ed.)
Period: 2000-2007

List of papers published in 2015

Journal

1. Sekiguchi M, Kushima R, Oda I, Suzuki H, Taniguchi H, Sekine S, Fukagawa T, Katai H. Clinical significance of a papillary adenocarcinoma component in early gastric cancer: a single-center retrospective analysis of 628 surgically resected early gastric cancers. J Gastroenterol, 50:424-434, 2015

2. Abe S, Oda I, Suzuki H, Nonaka S, Yoshinaga S, Nakajima T, Sekiguchi M, Mori G, Taniguchi H, Sekine S, Katai H, Saito Y. Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection. Endoscopy, 47:1113-1118, 2015

3. Yoda Y, Takeshima H, Niwa T, Kim JG, Ando T, Kushima R, Sugiyama T, Katai H, Noshiro H, Ushijima T. Integrated analysis of cancer-related pathways affected by genetic and epigenetic alterations in gastric cancer. Gastric Cancer, 18:65-76, 2015

4. Takeshima H, Niwa T, Takahashi T, Wakabayashi M, Yamashita S, Ando T, Inagawa Y, Taniguchi H, Katai H, Sugiyama T, Kiyono T, Ushijima T. Frequent involvement of chromatin remodeler alterations in gastric field cancerization. Cancer Lett, 357:328-338, 2015

5. Shirahige A, Suzuki H, Oda I, Sekiguchi M, Mori G, Abe S, Nonaka S, Yoshinaga S, Sekine S, Kushima R, Saito Y, Fukagawa T, Katai H. Fatal submucosal invasive gastric adenosquamous carcinoma detected at surveillance after gastric endoscopic submucosal dissection. World J Gastroenterol, 21:4385-4390, 2015

6. Hosoda F, Arai Y, Okada N, Shimizu H, Miyamoto M, Kitagawa N, Katai H, Taniguchi H, Yanagihara K, Imoto I, Inazawa J, Ohki M, Shibata T. Integrated genomic and functional analyses reveal glyoxalase I as a novel metabolic oncogene in human gastric cancer. Oncogene, 34:1196-1206, 2015

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10. Seishima R, Wada T, Tsuchihashi K, Okazaki S, Yoshikawa M, Oshima H, Oshima M, Sato T, Hasegawa H, Kitagawa Y, Goldenring JR, Saya H, Nagano O. Ink4a/Arf-Dependent Loss of Parietal Cells Induced by Oxidative Stress Promotes CD44-Dependent Gastric Tumorigenesis. Cancer Prev Res (Phila), 8:492-501, 2015

11. Katai H. Current status of a randomized controlled trial examining laparoscopic gastrectomy for gastric cancer in Japan. Asian J Endosc Surg, 8:125-129, 2015

12. Sasako M, Terashima M, Ichikawa W, Ochiai A, Kitada K, Kurahashi I, Sakuramoto S, Katai H, Sano T, Imamura H. Erratum to: Impact of the expression of thymidylate synthase and dihydropyrimidine dehydrogenase genes on survival in stage II/III gastric cancer. Gastric Cancer, 18:549, 2015

13. Umemura A, Koeda K, Sasaki A, Fujiwara H, Kimura Y, Iwaya T, Akiyama Y, Wakabayashi G. Totally laparoscopic total gastrectomy for gastric cancer: literature review and comparison of the procedure of esophagojejunostomy. Asian J Surg, 38:102-112, 2015

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17. Yamashita H, Katai H. Should adenocarcinoma of the esophagogastric junction be classified as esophageal cancer? Limited to Siewert type II, yes. Ann Surg, 261:e67, 2015

18. Abe S, Oda I, Nakajima T, Suzuki H, Nonaka S, Yoshinaga S, Sekine S, Taniguchi H, Kushima R, Iwasa S, Saito Y, Katai H. A case of local recurrence and distant metastasis following curative endoscopic submucosal dissection of early gastric cancer. Gastric Cancer, 18:188-192, 2015

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20. Fujita H, Yoshida A, Taniguchi H, Katai H, Sekine S. Adult-onset inflammatory myofibroblastic tumour of the stomach with a TFG-ROS1 fusion. Histopathology, 66:610-612, 2015

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Department of Colorectal Surgery

Yukihide Kanemitsu, Dai Shida, Shunsuke Tsukamoto, Hiroki Ochiai, Masahiro Tanaka, Gouki Morizono

Introduction

The Department of Colorectal Surgery deals with colorectal cancer and allied malignancies in the colon and rectum. Liver metastasis from colorectal cancer is treated in cooperation with the Department of Hepatobiliary and Pancreatic Surgery. Lung metastasis from colorectal cancer is also treated in cooperation with the Department of Thoracic Surgery. Although surgery is still the main treatment modality for colorectal cancer, multi-disciplinary treatments including radiotherapy and chemotherapy are important in advanced cancer. We have multi-disciplinary meetings with the Department of Gastrointestinal Oncology, Endoscopy, Radiology and Pathology and Clinical Laboratories every week, and decide treatment strategy by a multi-disciplinary team (MDT) before treatment is held.

Routine activities

There are four staff surgeons, one chief resident, and three or four rotating residents. Every morning (7:30-8:30), we have a morning conference and rounds in wards 15A and B. 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 morning (7:00-7:30), a conference is held for the treatment of colorectal cancer: colorectal surgeons discuss treatments for preoperative and postoperative patients. Ten to twelve operations are performed a week in our Department. Thus, we operate upon about 500 patients with colorectal cancers and allied diseases annually.

Research activities

Patients with advanced rectal cancers are treated with conventional surgery. Adjuvant chemotherapy is being used in stage III colorectal cancer patients in a clinical setting. Although preoperative radiotherapy is not performed routinely for advanced rectal cancer, patients with T4b rectal cancers or rectal cancers with multiple lymph node metastases are treated with preoperative chemoradiotherapy and surgery. Patients with symptoms caused by unresectable 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 primary tumor plus chemotherapy with chemotherapy alone in incurable stage IV colorectal cancer is ongoing (The Japan Clinical Oncology Group (JCOG) 1007, iPACS). Another randomized controlled trial is ongoing to evaluate the non-inferiority of overall survival of laparoscopic surgery to open surgery for palliative resection of primary tumors in incurable stage IV colorectal cancer (JCOG1107, ENCORE). Symptomatic, stage IV colorectal cancer patients with non-curable metastasis are pre-operatively randomized to either open or laparoscopic colorectal resection. Patients with resectable liver metastasis are treated in cooperation with the Department of Hepatobiliary and Pancreatic Surgery and adjuvant chemotherapy regimens are being evaluated in a clinical trial (JCOG0603 study). To confirm the superiority of perioperative chemotherapy, a randomized phase II/III trial was started in May 2015 comparing perioperative versus postoperative chemotherapy with modified infusional fluorouracil and folinic acid with oxaliplatin (mFOLFOX6) for

lower rectal cancer patients with suspected lateral pelvic node metastasis (JCOG1310).

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.

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 Department is participating in nine phase III JCOG studies.

1) 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. A total of 701 eligible patients were enrolled and recruitment is complete. Follow-up is on-going.
2) JCOG0603: A randomized study that compares adjuvant modified FOLFOX (5-FU + l-LV +Oxaliplatin) to surgery alone after hepatic resection for liver metastasis from colorectal cancer. A total of 170 patients have been enrolled and recruitment continues.
3) JCOG1006: A randomized study that compares conventional techniques to the no-touch isolation technique for clinical T3 or T4 colon cancer. A total of 570 patients have been enrolled and recruitment continues.
4) JCOG1007: A randomized controlled trial comparing resection of primary tumor plus chemotherapy with chemotherapy alone in incurable stage IV colorectal cancer is ongoing.
5) JCOG1018: Randomized phase III study of mFOLFOX7 or CAPOX plus bevacizumab versus 5-Fluorouracil/leucovorin or capecitabine plus bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer is ongoing.
6) JCOG1107: A randomized controlled trial comparing laparoscopic surgery with open surgery in palliative resection of primary tumors in incurable stage IV colorectal cancer is ongoing.
7) JCOG1310: A phase II/III randomized controlled trial comparing perioperative versus postoperative chemotherapy with mFOLFOX6 for lower rectal cancer with suspected lateral pelvic node metastasis is ongoing.
8) JCOG1410A: Japanese Observational Study to Evaluate the Accuracy of Preoperative Imaging Diagnosis for Lateral Pelvic Lymph Node Metastasis in Rectal Cancer is ongoing.
9) JCOG1506A: Prognostic or predictive biomarker study in patients who underwent surgery with/without postoperative chemotherapy for stage II/III colorectal cancer is ongoing.

Table 1. Number of patients

Operative Procedures	Number of patients	
	Open	Laparoscopic
Colectomy	111	133
High anterior resection	12	29
Low anterior resection	33	17
Abdominoperineal resection	15	1
Hartmann's operation	3	
Intersphincteric resection	10	3
Robot-assisted surgery		18
Total extirpation of large intestine	1	2
Total pelvic exenteration	5	
Total pelvic exenteration with sacrectomy	2	
Bypass	4	
Colostomy or ileostomy	53	
Local excision	1	
Other	125	

List of papers published in 2015

Journal

1. Shinto E, Takahashi K, Yamaguchi T, Hashiguchi Y, Kotake K, Itabashi M, Yasuno M, Kanemitsu Y, Nishimura G, Akagi Y, Sato T, Kato T, Matsumoto H, Hase K, Sugihara K, Study Group for Liver Metastasis projected by the Japanese Society for Cancer of the Colon and Rectum (JSCCR). Validation and modification of the Japanese classification system for liver metastases from colorectal cancer: a multi-institutional study. Ann Surg Oncol, 22:3888-3895, 2015

2. Iwasa S, Souda H, Yamazaki K, Takahari D, Miyamoto Y, Takii Y, Ikeda S, Hamaguchi T, Kanemitsu Y, Shimada Y. Safety and efficacy of adjuvant therapy with oxaliplatin, leucovorin and 5-fluorouracil after mesorectal excision with lateral pelvic lymph node dissection for stage iii lower rectal cancer. Anticancer Res, 35:1815-1819, 2015

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4. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishihara S, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Boku N, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K, Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol, 20:207-239, 2015

Department of Gastrointestinal Medical Oncology

Narikazu Boku, Tetsuya Hamaguchi, Ken Kato, Satoru Iwasa, Yoshitaka Honma, Atsuo Takashima, Natsuko Okita, Naoki Takahashi, Yusuke Sasaki, Shoko Nakamura

Introduction

The Gastrointestinal Medical Oncology Division focuses on the development of new drugs and establishment of standard chemotherapy regimens including multi-modality treatment with surgery and/or radiotherapy for advanced esophageal/gastric/colorectal cancers, gastrointestinal stromal tumor and other gastrointestinal (GI) malignancies. From this year, we have started to handle induction chemotherapy or palliative chemotherapy for head and neck cancer.

Over recent years, a new generation of molecular-target agents has been developed for colorectal cancer, and bevacizumab (BV) directs against vascular endothelial growth factor (VEGF) and changes the microenvironment of the tumor by inhibiting angiogenesis. Two other molecular target-based drugs are the anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab, which were approved in 2008 and 2010. Thereafter, for colorectal cancer, the multi-kinase inhibitor regorafenib was approved in 2013, and a new cytotoxic agent, TAS-102 (TPI/FTD), was also approved in March 2014. For gastric cancer, an anti-HER2 monoclonal antibody, trastuzumab, was approved in 2011. And new anti-VEGF agent, ramucirumab, was also approved in March 2015 for gastric cancer based on the results of two randomized controlled trials. Moreover, in recent years, the efficacy of the immune-checkpoint inhibitor has also been evaluated for GI malignancies.

In the near future, we expect to develop other novel agents for the treatment of metastatic GI cancers that inhibit intracellular signal transduction and cellular interactions. However, many unusual adverse effects and a marked increase in medical costs have led to extensive discussion on more accurate targeting of the population using biomarkers. Although the response rates of monotherapy with these molecular-targeted drugs up to now have not been so high (about 5% to 20%) when used broadly in non-selected patients, there are a few new candidate biomarkers that may be useful for identifying patients for whom these molecular-targeted drugs will be remarkably beneficial. For example, all *RAS* mutation in tumor tissue is one of the negative predictive factors in the response to cetuximab/panitumumab. Accordingly, the identification of molecular markers that can be used to predict tumor shrinkage and/or prolong prognosis will be critical for further progress in the treatment of GI malignancies.

Routine activities

The staff of the GI Medical Oncology Division consist of seven medical oncologists, three chief residents, and three or four residents. We have a daily case conference together at 5 pm and also have a weekly research conference for sharing and discussing the progress of clinical trials or translational research with each other. Intergroup meetings with each surgical division (Colorectal, Gastric, and Esophageal Surgery Divisions) and the Radiation Oncology Division are held weekly to decide optimal treatment strategies for each individual case and to discuss treatment consensus for the disease. Palliative care considering 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 2015, we treated 1,946 hospitalized patients (649 of whom were newly diagnosed). Of these patients, 90 were enrolled into protocol studies.

Research activities

An endoscopic biopsy and blood sampling before and after chemotherapy provide an excellent opportunity to study biomarkers related to therapy-induced tumor response rates, overall survival, and time to progression or recurrence. We are collecting these fresh samples from patients with gastric cancer to evaluate the correlations between gene expression profiles and patients' outcomes by using genome sequencing, microarray or real time (RT) -PCR techniques.

We have also been measuring the gene expressions of possible predictive biomarkers by using paraffin-embedded GI cancer specimens obtained from surgical resection or endoscopic biopsy, and investigated the correlation between several candidates of related to anti-cancer drug metabolism and clinical outcomes with an 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 (fibroblast growth factor) antibody or FGF kinase inhibitor for gastric cancer.

These studies are being performed in collaboration with the Center for Medical Genomics, National Cancer Center Research Institute, or other institutions.

Clinical trials

We carried out several clinical trials in collaboration with the Surgery and Radiation Oncology Divisions in our hospital and other institutions. Details of clinical trials are summarized in the Table, including JCOG (Japan Clinical Oncology Group) trials, company initiated and investigator initiated registration trials and other collaborative investigator initiated trials.

1) Colorectal and Anal Canal Cancer

In first-line treatment, the phase III PARADIGM trial, comparing FOLFOX/panitumumab with FOLFOX/BV in all RAS-wild-type population, is ongoing. We are also investigating whether SIRB regimen is non-inferior to XELOX (capecitabine/oxaliplatin) plus BV in a multicenter phase III trial (TRICOLORE), and finished patient accrual on schedule. A randomized trial to investigate the superiority of fluoropyrimidine/oxaliplatin/BV to fluoropyrimidine/BV targeted at frail or elderly patients is also ongoing (JCOG1018).

In second-line treatment, we are investigating the non-inferiority of XELIRI (capecitabine/irinotecan) to FOLFIRI (5-FU/l-LV/irinotecan), for patients whose first-line treatment with FOLFOX or XELOX plus BV failed, in a multicenter phase III trial conducted in Asian countries (AXEPT), and finished patient accrual on schedule.

As an adjuvant treatment, JCOG0910, comparing S-1 with capecitabine, finished patient recruitment in 2013 on schedule, and the result was shown in ASCO 2015. Unfortunately, it could not show the non-inferiority of S-1 to capecitabine in terms of relapse free survival. A randomized trial comparing adjuvant mFOLFOX6 with observations after complete resection of liver metastasis from colorectal cancer is ongoing (JCOG0603).

The phase II part of JCOG0903, a phase I/II trial of definitive chemoradiotherapy with S-1/MMC for locally advanced anal canal squamous cell carcinoma finished patient accrual on schedule.

2) Gastric Cancer

In first-line treatment, a pivotal phase III trial comparing S-1/CDDP (CS) to S-1/CDDP/Docetaxel (DCS), patient enrollment was finished in March 2016. A new phase III trial comparing TAS-118 (S-1 plus l-LV)/oxaliplatin with CS has started from 2015. And a phase II/III study, comparing FLTAX with 5FU alone for patients who are inappropriate for CDDP usage or oral administration of S-1 due to severe peritoneal dissemination is also ongoing.

In second-line treatment, molecular-targeted drugs for advanced gastric cancer have been investigated. For HER2 negative gastric cancer, a phase III trial which will evaluate the additive effect of nimotuzumab, anti-EGFR antibodies, combined with irinotecan in second-line chemotherapy (ENRICH) is ongoing and is targeted at patients with high expression of EGFR. Two phase III trials which evaluate the additive effect of (i) Olaparib (PARP inhibitor), (ii) BBI608 (an inhibitor targeted at cancer stem cell), combined with paclitaxel finished patient accrual. Moreover, regarding the cases

inappropriate to the ENRICH trial, a feasibility study for a combination of weekly abraxane with ramcirumab started from the end of 2015.

For HER2 positive gastric cancer, a phase III trial which evaluates the additive effect of pertuzumab with capecitabine and cisplatin plus trastuzumab in first-line treatment (JACOB) finished patient accrual. A multi-center feasibility study of S-1/oxaliplatin plus trastuzumab in first-line treatment started from early 2015. A result of the phase II/III trial comparing TDM-1, ado-trastuzumab emtansine, with paclitaxel in second-line treatment (GATSBY) was reported to fail in showing superiority to paclitaxel at the ASCO-GI 2016 meeting. And a phase III trial comparing MK-3475, anti-programed cell death 1 (PD-1) immune-checkpoint inhibitor antibody, with weekly paclitaxel (KEYNOTE-061) is also ongoing.

In salvage-line treatment, a randomized trial to investigate the efficacy of ONO-4538, anti-PD-1 immune-checkpoint inhibitor antibody, compared with best supportive care (BSC) has completed patient recruitment.

3) Esophageal Cancer

Based on the results of JCOG9907 trial, in Japan, the standard care for stage IB/II/III esophageal cancer is preoperative 5-FU plus CDDP (CF) followed by surgery. The large pivotal trial JCOG1109, which compared DCF (Docetaxel plus CF) or CF plus radiotherapy (CF-RT, 41.4Gy) regimen with standard preoperative CF in stage IB/II/III esophageal cancer, started from 2012, and is progressing on schedule. A phase II study, JCOG0909 on the efficacy of CF-RT (50.4 Gy) regimen followed by salvage surgery or endoscopic resection in stage IB/II/III esophageal cancer, finished accrual in 2014.

In first-line treatment, a phase I/II study, JCOG0807 demonstrated the promising efficacy and feasibility of bi-weekly DCF regimen. According to this precedent study, a phase III trial comparing biweekly DCF with standard CF regimen started from September 2014 in JCOG.

In second-line treatment, two randomized controlled trials to investigate the efficacy of PD-1 immune-checkpoint inhibitor are ongoing; (i) Taxan versus ONO-4538 (OPERA) and (ii) paclitaxel versus MK-3475 (KEYNOTE-181).

In salvage-line treatment, two phase II studies (i) ONO-4538, and (ii) Sym004, a mixture of two synergistic full-length anti-EGFR antibodies, which bind to two separate non-overlapping epitopes on EGFR, finished patient accrual. A feasibility study to investigate the efficacy of MK-3475 is now ongoing. A multi-center feasibility study of TAS-102 has been also started.

4) Other

For metastatic neuroendocrine carcinoma (NEC) in GI-tract or hepato-billiary-Pancreatic field, a phase III trial comparing irinotecan plus CDDP with etoposide plus CDDP as first-line treatment (JCOG1213) is progressing faster than expected. And for metastatic head and neck squamous cell carcinoma, a phase III trial comparing MEDI-4736 (PD-L1 antibody) /Tremelimumab (anti-CTLA-4 antibody), MEDI-4736, and standard chemotherapy (Docetaxel or Cetuximab or S-1) in second-line treatment (EAGLE) is also ongoing, collaborating with doctors in the Department of Head and Neck Oncology. Several clinical trials have also been conducted and eligible patients have been enrolled as shown in the Table.

Table 1. Summary of newly diagnosed patients and number of patients enrolled to clinical trial

Clinical Trials	No. of pts. enrolled
1) Esophageal cancer (No. of newly diagnost pts=216)	
neo CF vs neoDCF vs neo CF-RT JCOG1109 (phase Ⅲ)	14
CF vs biweekly-DCF JCOG1314 (phase Ⅲ)	5
S-588410 for postoperative treatment (phase Ⅲ)	0
ONO-4538 vs taxan (phase Ⅲ)	0
MK-3475 vs paclitaxel (phase Ⅲ)	0
MK-3475 (phase Ⅱ)	0
TAS-102 (IIT-phase Ⅱ)	2
BKM120 (phase Ⅱ)	0
	subtotal 21
2) Gastric cancer (No.of newly diagnost pts=162)	
CS vs DCS JCOG1013 (phase Ⅲ)	22
TAS-118+Ox vs CS SOLAR (phase Ⅲ)	1
SOX+Tmab for HER2+(phase Ⅱ)	7
CPT-11±Nimotuzmab for EGFR++pts ENRICH (phase Ⅲ)	4
FL vs FLTAX for ascites++pts JCOG1108 (phase Ⅱ/Ⅲ)	1
MK-3475 vs paclitaxel (phase Ⅲ)	3
wAbraxan+ramucirumab (phase Ⅱ)	0
ONO4538 vs BSC (phase Ⅲ)	20
	subtotal 58
3) Colorectal cancer (No.of newly diagnost pts=223)	
FOLFOX+Pmab vs FOLFOX+BV for RAS-WT PARADIGM (phase Ⅲ)	2
mFOLFOX7/CAPOX+BV vs FL/Cape+BV for eldery pts JCOG1018 (phase Ⅲ)	6
	subtotal 8
4) Others (No. of newly diagnost pts=48)	
EP vs IP for GI & HBP-NEC TOPIC-NEC JCOG1213 (phase Ⅲ)	1
MEDI-4736+Tremelimumab vs MEDI-4736 vs CTx for 2nd-line HNC EAGLE (phase Ⅲ)	1
Regorafenib for imatinib-resistanrt GIST RESET (IIT-P Ⅱ)	1
ONO-4538 for virus related cancer (phase Ⅱ)	0
	subtotal 3
Total (n=649)	Total 90

※Abbreviation: No.; number, pts; patients, neo; neoadjuvant, CF; cisplatin plus fluorouracil, DCF; docetaxel plus CF, IIT; investigator initiated trial, CS; cisplatin plus S-1, DCS; docetaxel plus CS, Ox; oxaliplatin, SOX; S-1 plus Ox, Tmab; trastuzumab, FL; fluorouracil plus leucovorin, FLTAX; FL plus paclitaxel, BSC; best supportive care, FOLFOX; leucovorin, fluorouracil plus Ox, Pmab; panitumumab, BV; bevacizumab, WT; wild type, CAPOX; capecitabine plus Ox, EP; etoposide plus cisplatin, IP; irinotecan plus cisplatin, GI; gastrointestinal, HBP; hepato-biliary-pancreatic, NEC; neuroendocrine cell carcinoma, CTx; chemotherapy, HNC; head and neck cancer, GIST; gastrointestinal stromal tumor

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Department of Endoscopy, Gastrointestinal Endoscopy Division

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Introduction

Our Endoscopy Division moved to the New Endoscopy Center from 20th January 2014 and we believe this is currently the biggest Endoscopy Center in Japan (15 Endoscopy Rooms (251.112m^2) and 136.788m^2, and Recovery Rooms on two floors of 1,949.554m^2).

The total number of nursing staff increased to 15, and three endoscopy engineers are working with us.

The Gastrointestinal Endoscopy Division has 12 staff physicians in the National Cancer Center Hospital and in the Screening Technology and Development Division, 4 chief residents, 15 residents, 4 trainees and several rotating residents.

The Bronchoscopy Division has three staff members and one resident doctor, and the total number of bronchoscopies and therapeutic procedures has been 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 disease, we routinely use the recently developed narrow-band imaging (NBI) system. A total of 12,478, 4,450, 537, 97, 250, 83 and 120 screening and/or diagnostic procedures by gastroscopy, colonoscopy, EUS, EUS-fine needle aspiration (EUS-FNA), endoscopic retrograde cholangiopancreatography (ERCP), capsule endoscopy and double balloon endoscopies, respectively, were performed in 2015 (Table 1).

Due to the increasing number of patients with superficial gastrointestinal neoplasms, the number of therapeutic endoscopy procedures is also increasing in this field. In 2015, 2,667 endoscopic resections were carried out (pharynx 9, esophagus 159, stomach 370, duodenum 25 and colon 2,104). Among these, ESD, which was developed for large en-bloc resections with a low-risk of local recurrence, was performed for 91 superficial esophageal cancers, 370 early gastric cancers and 206 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. Our colleagues originally developed these procedures and devices.

Table 1. Chronological Trend of Total Number of Diagnostic and Therapeutic Gastrointestinal Endoscopic Procedures

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015
Upper GI Endoscopy	10,910	10,909	10,174	10,644	10,810	11,193	11,314	11,481	12,478
Total Colonocopy	3.569	3,161	2,670	2,756	2,924	3,232	3,367	3,881	4,450
EUS	373	375	402	395	372	393	477	496	537
EUS-FNA	—	—	—	48	59	69	85	82	97
Therapeutic Endoscopy	1,854	1,848	1,849	1,756	1,984	2,077	2,146	2,164	3,039
Gastric EMR/ESD	24/410	19/397	36/375	23/334	23/343	361	375	340	370
Esophageal EMR/ESD	89/25	94/25	95/43	102/45	132/61	115/66	97/92	65/100	68/91
Colorectal EMR/ESD	1,212/97	1,216/97	1,177/123	1,132/120	1,210/125	1,402/133	1,398/184	1,465/194	1,898/206
Duodenal EMR	7	7	9	11	8	23	38	32	25
Pharyngeal EMR/ESD	18	7	8	9	20	24	34	23	9
Doble baloon endsocpy-Stenting. etc.						29	91	105	122
ERCP					49	104	140	175	250
Capusule endoscopy Small bowel/colon	25	30	25	22/ —	37/44	43/21	45/0	60/19	77/6
Screening canter								20,524	24,288

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.

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.

Clinical activities in GI Endoscopy (Figure 1)

Our efforts have been focused on new diagnostic and therapeutic strategies. For more accurate

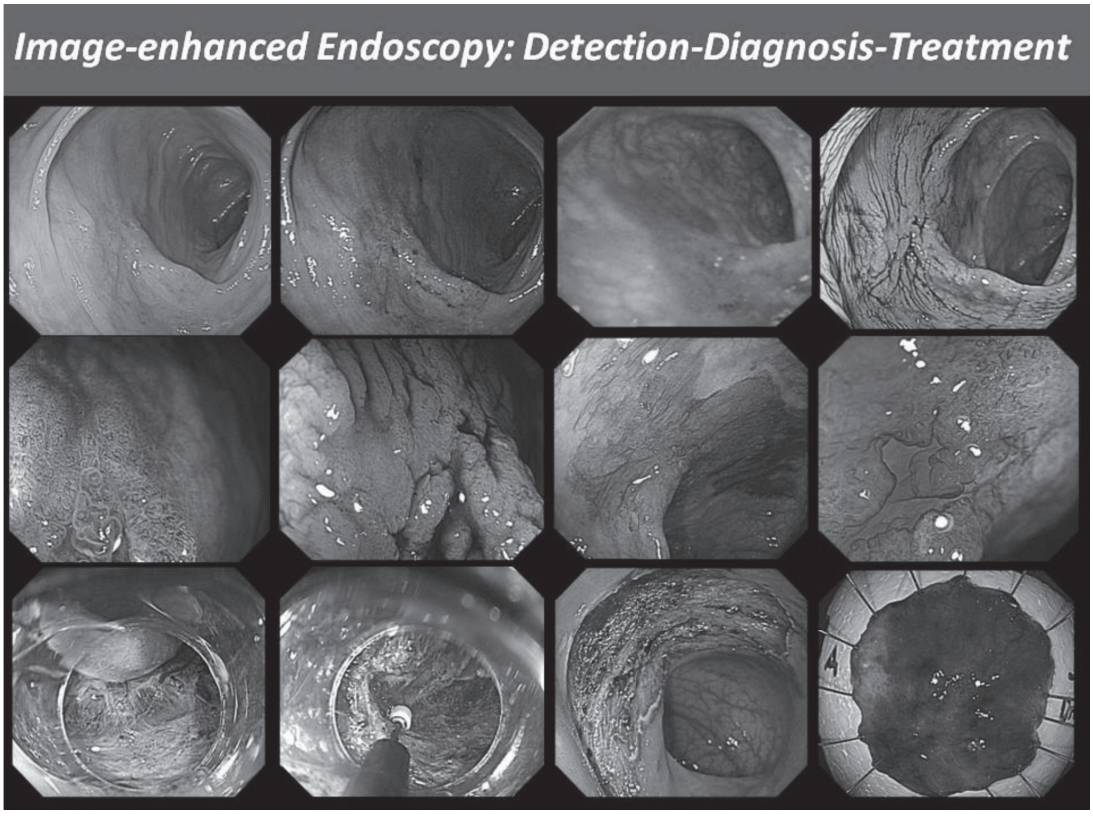

Figure 1. Endoscopic Diagnosis Using Image-enhanced Endoscopy (High-resolution Endoscopy, Narrow-band Imaging and Autofluorescence Imaging) and Endoscopic Submucosal Dissection (ESD) Procedure for Treating Early Colon Cancer

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.

Clinical trials in GI Endoscopy

We have organized several multicenter study groups in order to evaluate the efficacy and clinical impact of newly developed endoscopies and medical devices prospectively.

Esophagus

A multicenter clinical trial is under way 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 chemo-radiotherapy for clinical stage I esophageal carcinoma (JCOG 0508). In addition, we are currently enrolling our patients in two multicenter randomized controlled trials. First, a phase II/III study has been introduced to compare endoscopic balloon dilatation combined with steroids to radial incision and cutting combined with steroids for refractory anastomotic stricture after esophagectomy (JCOG1207: RICS study). Second, a phase III study is ongoing to compare oral steroid administration to local steroid injection therapy for the prevention of esophageal stricture after endoscopic submucosal dissection (JCOG1217: Steroid EESD P3).

In collaboration with TWins (Tokyo Women's Medical University), we are going to conduct a clinical trial of cell sheet-based regenerative medicine, which could reduce complications such as severe stenosis and perforation related to intensive balloon dilations. This cell sheet-base regenerative medicine is one of innovation in the gastrointestinal field and we believe that cell-based regenerative medicine would be useful to improve the quality of life of patients after esophageal ESD.

Stomach

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 (J-WEB/EGC). Our division has also cooperated as a participating institution in phase II trials of endoscopic submucosal dissection to expand the indications for early gastric cancer (JCOG 0607) (JCOG1009/1010).

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. A multicenter prospective observational study has confirmed the usefulness of the methylation level as a risk marker for metachronous gastric cancer after EMR/ESD followed by *H. pylori* eradication. Since 2015, a multicenter prospective observational study has been started to demonstrate the usefulness of the methylation level as a risk marker for gastric cancer developing after *H. pylori* eradication in healthy people. In addition, we are currently enrolling our patients in two multicenter randomized controlled trials. First, a CONNECT-G trial has been introduced to investigate the usefulness of endo-clip connecting dental floss (DFC) during gastric ESD that have a potential efficacy making a better view by traction with DFC. Second, a randomized controlled trial is ongoing to compare the second generation Narrow Band Imaging with White Light Imaging for detection of early gastric cancer (EGC Detection Trial).

Pancreas

We prospectively evaluated the efficacy and safety of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for pancreatic solid lesions in multicenters in Japan. This study was designed as a prospective cohort study conducted at the following five hospitals in Japan: National Cancer

Center Hospital, Tokyo Medical University, Aichi Cancer Center Hospital, Gifu University Hospital and Fukushima Medical University Aizu Medical Center. Two hundred and forty-nine patients were enrolled from November 2011 to June 2013. Diagnostic sensitivity of EUS-FNA in this study was 97.2%. Diagnostic specificity, accuracy, positive predictive value and negative predictive value were 88.0%, 96.2%, 100%, 81.4%, respectively. Complication after seven days was 1.6%. We could confirm the efficacy, and the safety of EUS-FNA for pancreatic solid lesions is quite satisfied.

Colorectum

RCTs concerning colorectal neoplasms are also ongoing.

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. Finally, about 4,000 patients have been enrolled in this study. This multicenter RCT is completed and analysis of data will help to develop future recommendations for surveillance guidelines in Japan after the excision of polyps including flat and depressed lesions.

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 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, five-year disease-free survival, and five-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). Considering this study result, we have just started a prospective cohort study for the possibility of chemo-radiotherapy for high-risk rectal submucosal cancer after endoscopic resections.

A nationwide cancer registry system has also been developed for early colorectal cancer treated with ESD. A five-year multicenter prospective cohort study has been ongoing using this cancer registry system since 2013. A total of 2,066 patients were enrolled to this multicenter cohort study and this should be the largest cohort study in colorectal ESD in the world.

Molecular and fluorescence Imaging and Database Study

Molecular imaging endoscopy is one of a new era for very early cancer diagnosis and detection of metastasis. We have just started a collaborative study between the Endoscopy Division, Colorectal and Gastric Surgery Division, Pathology Division, Research Institute, Tokyo University and Jikei University.

Probe-based confocal laser endomicroscopy (pCLE) allows real-time, in vivo high resolution imaging of the gastrointestinal epithelium at a cellular level. We are going to conduct a multicenter prospective study supported by the Japan Gastroenterological Endoscopy Society (JGES) to evaluate the diagnostic yield of pCLE for gastric neoplasms.

We have been collaborating with the Japan Gastroenterological Endoscopy Society (JGES) in order to build an All Japan Endoscopy Database (JED) of gastrointestinal endoscopies including not only therapeutic but also diagnostic procedures. This all Japan project is named JED and has the potential to construct the largest and most precise database of all endoscopic procedures. Japanese endoscopists are well known as most excellent endoscopists, and, therefore, from now, we can create a lot of evidence using this huge endoscopy

database.

Colon Capsule Endoscopy

We conducted a multicenter prospective study to clarify the sensitivity of colon capsule endoscopy in detecting significant lesions compared with traditional colonoscopy and to evaluate its safety and acceptability in six facilities in Japan. Our study revealed that colon capsule endoscopy with a reduced preparation regimen was safe, with a sensitivity of 94% for detecting significant lesions, including laterally spreading tumors (LSTs). Until now, there has been limited information on the accuracy of colon capsule endoscopy for flat lesions, in particular LSTs, which are contributors to the development of colorectal cancer. Therefore, we think our study is noteworthy to practice colon capsule endoscopy in the screening setting in Japan. Colon capsule endoscopy was also safe and had a high level of patient acceptability. Our study was published in 2015 in gastrointestinal endoscopy (Gastrointestinal Endoscopy 2015).

List of papers published in 2015

Journal

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Department of Endoscopy, Respiratory Endoscopy Division

Takehiro Izumo, Takaaki Tsuchida, Yuji Matsumoto

Introduction

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

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 seventy six 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.

Endobronchial stenosis patients were treated with airway stent placement, photodynamic therapy and endobronchial electrocautery ablation. Medical thoracoscopy under local anesthesia in the operation suite was performed with unknown pleural effusion or a pleural tumor.

A weekly conference with CT imaging analysis and confirmation of the pathology results was held. Furthermore, we attended all clinical conferences in the Department of Thoracic Surgery, Pathology and Clinical Laboratories and Radiation Oncology to discuss and decide upon treatment strategies.

Research activities

Endobronchial ultrasound elastography is a new technique for describing the stiffness of tissue during endobronchial ultrasound-guided transbronchial needle aspiration.

We tried to improve the accuracy of GGO (ground grass opacity), which had been impossible to visualize using a routine chest radiography or X-ray fluoroscopy. Radial endobronchial ultrasound (R-EBUS) is a useful tool for precise localization of peripheral pulmonary lesions, but there have been no detailed reports about the use of R-EBUS images for GGO. R-EBUS images of GGO were identified based on the internal structure of the lesion and classified into two groups. Blizzard showed an enlarged, diffuse hyperintense acoustic shadow. Mixed blizzard showed a combination of blizzard and some diffuse heterogeneity with several hyperechoic dots and vessels.

Clinical trials

We conducted a multicenter prospective study for evaluation of photodynamic therapy for peripheral lung cancer. A study with CT workstation is ongoing with the multicenter.

Education

A flexible bronchoscope was developed for the first time in the world in this hospital. There are many resident and overseas doctors wishing to train at our hospital. I was given the opportunity of writing papers and conference presentations for many residents. Overseas training doctors came from many countries.

Future prospects

A multicenter trial of bronchoscopic therapy for peripheral lung cancer and a new diagnostic procedure such as electromagnetic navigation bronchoscopy are expected to be carried out.

Table 1. Type of procedure and number of patients

Diagnostic bronchoscopy without X-ray	157
Diagnostic bronchoscopy under X-ray fluoroscopy	640
Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA)	185
Medical thoracoscopy	16
Therapeutic bronchoscopy	21
Total	1,019

List of papers published in 2015

Journal

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Department of Hepatobiliary and Pancreatic Surgery

Kazuaki Shimada, Minoru Esaki, Satoshi Nara, Yoji Kishi, Yoichi Miyata

Introduction

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

Routine activities

The HBP Surgery Department consists of four 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 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 mainly the patients scheduled for surgery. 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 "Research conference", which is held every three months, the progress of academic studies including clinical research and paper writing are evaluated.

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. A huge tumor or HCC with macroscopic vasculobiliary tumor thrombosis are also indicated for resection as long as sufficient hepatic function and remnant liver volume is expected. 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 curative resection followed by adjuvant chemotherapy is the standard strategy 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 and 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 perihilar cholangiocarcinoma. When necessary, portal vein and/or hepatic artery resection and reconstruction

is performed to achieve curative resection.

Laparoscopic surgery: For the liver tumors located in the peripheral site, laparoscopic lateral bisegmentectomy or partial resection is considered as a choice of treatment. Laparoscopic distal pancreatectomy is considered for slowly growing malignant tumors.

Research activities

Dr. Shimada et al. conducts one prospective randomized trial to evaluate the safety of drain tube free hepatectomy (the safety of liver surgery with No-Drain policy: a multicenter randomized controlled trial, ND-trial) and plans another multi-institutional trials to evaluate the efficacy of administrating digestive enzymes to prevent postoperative hepatic steatosis in the patients who underwent pancreaticoduodenectomy (comparison of Berizym and Pancrelipase for the effect to suppress onset of Hepatic Steatosis after Pancreaticoduodenectomy, ESOP Trial). Dr. Kishi attends an international collaboration project by EORTC (European Organisation for Research and Treatment of Cancer) and JCOG (Japan Clinical Oncology Group) as a Japanese side manager. The project is to evaluate the accuracy of Diffusion-weighted Magnetic Resonance Imaging for the assessment of diminishing colorectal liver metastases by chemotherapy, which is named "Diffusion-weighted Magnetic REsonance Imaging Assessment of Liver Metastasis, DREAM study". This trial is to be started in August 2016.

Each staff attend three to four domestic or international academic meetings per year. Residents and Chief residents also have opportunities to make a presentation with the assistance of staff surgeons.

Clinical trials

In addition to the abovementioned two RCTs (ND-trial and ESOP trial) and DREAM study, we attend a JCOG1202 phase III trial that evaluates the efficacy of adjuvant S-1 treatment in the patients who underwent curative surgical resection for biliary tract cancer (a phase III trial of S-1 vs. observation in patients with resected biliary tract cancer, ASCOT trial).

Education

During three to six months of the trainee period, every week, each resident attends one to two major HBP surgeries mainly as a first assistant. They also have the chance to be an operator depending on their skill. For each case, they learn how to decide the indication and type of procedure. In the operation room, the residents learn not only each step of HBP surgery, but also tips on how to help safely proceed with the surgery. The chief resident trains them in a two-year program. In the first year, they devote themselves to the management of all inpatients and attend basically every surgery. Depending on the development of their skills, they have the opportunity to be an operating surgeon for major HBP surgery. In the second year, the chief resident works on research studies and publishes several English papers. Motivated residents also have the opportunity to make presentations in academic meetings and write English papers.

Visitors from both domestic and foreign institutions are welcome anytime.

Future prospects

HBP malignancy often requires technically demanding surgical procedures, whereas the long-term prognosis so far is not satisfactory. Our most important mission is to establish more safe and feasible surgical techniques including perioperative patient management, and to promote survival outcomes by multidisciplinary approaches. Due to the recent advances of chemotherapy, we have experienced a few patients who achieved curative surgical resection for initially unresectable pancreatic cancer due to local advancement. So the feasibility of conversion therapy should be assessed prospectively. We continue making efforts to create new skills and treatment strategies.

Table 1. Type of diseases

Type of disease	n
Invasive pancreatic cancer	90
Other pancreatic neoplasm	35
Hepatocellular carcinoma	36
Colorectal liver metastases	42
Liver metastases of other than colorectal cancer	12
Intrahepatic cholangiocarcinoma	7
Other liver neoplasm	2
Perihilar bile duct cancer	18
Extrahepatic bile duct cancer	13
Gallbladder cancer	16
Benign gallbladder disease	6
Ampullary tumor	5
Duodenal tumor	11
Others	30
Total	323

Table 2. Type of procedures

Procedure	n
Hepatectomy without biliary resection (open laparotomy)	92
Hepatectomy without biliary resection (laparoscopic)	3
Hepatectomy with biliary resection	16
Hemihepatectomy and pancreaticoduodenectomy (HPD)	5
Substomach preserving pancreaticoduodenectomy (SSPPD) or Classical Whipple (PD)	26
Pylorus-preserving pancreaticoduodenectomy (PPPD)	60
Distal pancreatectomy	32
Appleby operation	1
Medial pancreatectomy	6
Total pancreatectomy*	6
Extended cholecystectomy	9
Partial resection of duodenum	6
Other resections	19
No resection**	42
Total	323

*includes total resection of remnant pancreas
**includes bypass procedure, emergency operation, or exploratory laparotomy, etc.

Table 3. Postoperative survival rates of patients with a) pancreatic invasive ductal cancer (IDC) and b) hepatocellular carcinoma (HCC)

a) IDC (2002-2011)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	16	68	68
II	21	85	64
III	135	67	56
IVa	260	41	24
IVb	141	28	18
Total	573	47	33

b) HCC (2003-2012)

Stages	n	3-year survival rate (%)	5-year survival rate (%)
I	36	91	75
II	139	89	85
III	177	77	63
IV	69	58	42
Total	421	79	69

List of papers published in 2015

Journal

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Department of Hepatobiliary and Pancreatic Oncology

Takuji Okusaka, Hideki Ueno, Chigusa Morizane, Shunsuke Kondo, Yasunari Sakamoto, Mitsuhito Sasaki

Introduction

The Department of Hepatobiliary and Pancreatic Oncology treats tumors originating from the liver, biliary system or pancreas, which include hepatocellular carcinoma (HCC), biliary tract cancer and pancreatic cancer. As part of the multi-disciplinary care given at the National Cancer Center Hospital (NCCH), we work closely with surgeons and radiologists who have 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 Department consists of five 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 three 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. Systemic or intra-arterial chemotherapeutic regimens are indicated in advanced HCC patients for whom locoregional intervention and surgery are unsuitable or unsuccessful. 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.

Case conferences are held weekly with surgeons and radiologists to determine treatment strategies for these patients. Rounds and conferences for patients admitted to the division are made by all staff oncologists and residents every morning and evening.

Research activities

We conducted a phase I study of c-Met inhibitor tivantinib in Japanese patients with advanced hepatocellular carcinoma (Okusaka, Cancer Sci; 106:611-7). In this study, patients with HCC in whom sorafenib treatment has failed were enrolled to evaluate the safety, tolerability and pharmacokinetics of oral tivantinib as a single agent. The dose was escalated separately in EM and PM, from 120 mg BID to 240 mg BID, in both capsule and tablet formulations. 120 mg BID of tivantinib is recommended among Japanese patients with HCC regardless of CYP2C19 phenotype.

A phase I trial of S-1 in combination with gemcitabine and cisplatin in patients with advanced biliary tract cancer was conducted (Shoji, Morizane, Jpn J Clin Oncol; 46:132-7. We recommend gemcitabine at 800 mg/m(2)/week, cisplatin at 25 mg/m(2)/week and S-1 at 40 mg/m(2)/day during a 21-day cycle. Dose-limiting toxicities included a Grade 3 maculopapular rash, Grade 4 thrombocytopenia and consecutive administration skips of gemcitabine and cisplatin on Day 8. Five partial responses among 17 patients were observed.

We conducted a retrospective review of 100 consecutive patients with pancreatic neuroendocrine neoplasms (NENs), which are rare tumors (Shiba, Morizane, Pancreatology; 16:99-105). The 5-year survival rates of patients with NET G1, NET G2, and NEC were 91%, 69%, and 10%, respectively. Good performance status (PS), lower stage, and histopathological grade were identified as independent favorable prognostic factors.

Clinical trials

Twenty-four clinical trials are ongoing and seven are planned, including sixteen phase I or I/II trials, eight phase II or II/III trials, and seven phase III trials such as adjuvant chemotherapy after resection versus resection alone for patients with resectable tumor, and chemotherapy with a new regimen versus standard therapy for patients with advanced tumors. Our studies are supported by the National Cancer Center Research and Development Fund (Grant No. 26-A-4), Health and Labour Sciences Research Grants (Project for Development of Innovative Research on Cancer Therapeutics -075, -080, -141) from the Japan Agency for Medical Research and Development.

Education

Our staff members are working closely with residents and chief residents to support their skill development and knowledge expansion in both clinical and research fields. We are conducting conferences daily for clinical practice and weekly for research development. The residents in our department published five papers as first authors in peer-reviewed journals in 2015, and are performing eight ongoing studies as leading researchers with assistance from staff members.

Future prospects

Our department continues providing the best and latest diagnosis, treatment and supportive care, and developing more effective methods and techniques for all patients with hepatobiliary and pancreatic cancer in this country and all over the world. Among them, conducting clinical trials with novel promising agents for this disease is considered one of the most important tasks, and establishment of cutting-edge medical treatments in this field is the most significant mission for us. To achieve our aim, we are ongoing screening for biliary cancer patients with gene-mutations in the Kanto area as the first step, and are going to expand it to a nationwide program for accrual to clinical trials for new molecular targeted agents.

Table 1. Primary tumor

	No. of pts
Pancreatic cancer	
Invasive ductal	193
Neuroendocrine	23
Others	34
Biliary tract cancer	
Extrahepatic bile duct	18
Gallbladder	22
Papilla of Vater	6
Liver cancer	
Hepatocellular	176
Intrahepatic cholangio	39

Table 2. Treatment

	No. of pts
Pancreatic cancer	
Systemic chemotherapy	242
Chemoradiotherapy	11
Adjuvant	30
Biliary tract cancer and Intrahepatic cholangio carcinoma	
Systemic chemotherapy	81
Adjuvant	3
Hepatocellular carcinoma	
Ethanol injection	8
Radiofrequency ablation	47
Transcatheter arterial (chemo)embolization	96
Intra-arterial chemotherapy	13
Systemic chemotherapy	25
Radiotherapy	19

List of papers published in 2015

Journal

1. Okusaka T, Ueno H, Ikeda M, Mitsunaga S, Ozaka M, Ishii H, Yokosuka O, Ooka Y, Yoshimoto R, Yanagihara Y, Okita K. A Phase 1 and pharmacological trial of OPB-31121, a STAT3 inhibitor, in patients with advanced hepatocellular carcinoma. Hepatol Res, 45:1283-1291, 2015

2. Honda K, Kobayashi M, Okusaka T, Rinaudo JA, Huang Y, Marsh T, Sanada M, Sasajima Y, Nakamori S, Shimahara M, Ueno T, Tsuchida A, Sata N, Ioka T, Yasunami Y, Kosuge T, Miura N, Kamita M, Sakamoto T, Shoji H, Jung G, Srivastava S, Yamada T. Plasma biomarker for detection of early stage pancreatic cancer and risk factors for pancreatic malignancy using antibodies for apolipoprotein-AII isoforms. Sci Rep, 5:15921, 2015

3. Takai E, Totoki Y, Nakamura H, Morizane C, Nara S, Hama N, Suzuki M, Furukawa E, Kato M, Hayashi H, Kohno T, Ueno H, Shimada K, Okusaka T, Nakagama H, Shibata T, Yachida S. Clinical utility of circulating tumor DNA for molecular assessment in pancreatic cancer. Sci Rep, 5:18425, 2015

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17. Murakami H, Ikeda M, Okusaka T, Inaba Y, Iguchi H, Yagawa K, Yamamoto N. A Phase I study of MEDI-575, a PDGFRα monoclonal antibody, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol, 76:631-639, 2015

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Department of Urology

Hiroyuki Fujimoto, Motokiyo Komiyama, Tomohiko Hara, Yasuo Shinoda, Aiko Maejima

Introduction

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

Routine activities

The urology team consists of four staff physicians and one chief-resident and two 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 tumors, 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.

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 neoadjuvant chemotherapy by an M-VAC/GC 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, robotic-assisted or open 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, a salvage operation is performed 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) 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 weekly CBDCA + PTX regimen has been indicated.
2) Prostate cancer: A phase II study to evaluate the efficacy of robotic-assisted laparoscopic radical prostatectomy for T1c-T3a 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. This method was introduced in robotic-assisted laparoscopic radical prostatectomy with extended lymph node dissection. To provide a more precise preoperative diagnosis, a new imaging strategy using 3.0 Tesla MRI has been developed. For DTX refractory prostate cancer, a study on a vaccine regime with IKT1 is ongoing.
3) Testicular germ cell tumors: 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/TIN regimen has completed enrollment.

Clinical trials

We are actively involved in the following mainly ongoing protocol studies:

1) A phase III study: BCG instillation for high-grade T1 bladder cancer (JCOG1019)
2) A phase III study: Anti PD-L1 antibody (ATEZOLIZUMAB) for muscle invasive bladder cancer
3) A phase II study: Robotic-assisted laparoscopic prostatectomy for low and intermediate risk prostate cancer
4) A phase II study: IKT1 for chemo-refractory prostate cancer

Table 1. Patients' statistics: Major treatment

	2011	2012	2013	2014	2015
Radical/partial nephrectomy	30	46	39	33	25
Nephroureterectomy	12	17	8	10	14
Total cystectomy	24	25	24	17	17
TURBT	140	130	117	142	127
M-VAC	50	62	45	46	76
GC	84	83	70	83	77
Radical prostatectomy	111	87 (RALP 2)	84 (RALP32)	56 (RALP 42)	67 (RALP 49)
Prostatic biopsy	175	151	128	144	138
High orchyectomy	8	6	6	5	7
Retroperitoneal lymphadenectomy	13	6	5	7	5
Chemotherapy for testicular cancer	30	35	7	3	6
Retroperitoneal tumor resection	10	18	13	32	31

List of papers published in 2015

Journal

1. Narukawa T, Hara T, Arai E, Komiyama M, Kawahara T, Kanai Y, Fujimoto H. Tumour multifocality and grade predict intravesical recurrence after nephroureterectomy in patients with upper urinary tract urothelial carcinoma without a history of bladder cancer. Jpn J Clin Oncol, 45:488-493, 2015

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3. Hara T, Fujimoto H, Sakura M, Inokuchi J, Nishiyama H, Miyazaki J, Ohyama C, Koie T, Kikuchi E, Hinotsu S, Cancer Registration Committee of the Japanese Urological Association. Prognostic factors of recurrent disease in upper urinary tract urothelial cancer after radical nephroureterectomy: Subanalysis of the multi-institutional national database of the Japanese Urological Association. Int J Urol, 22:1013-1020, 2015

4. Miyazaki J, Nishiyama H, Fujimoto H, Ohyama C, Koie T, Hinotsu S, Kikuchi E, Sakura M, Inokuchi J, Hara T, Cancer Registration Committee of the Japanese Urological Association. Impact of smoking on the age at diagnosis of upper tract urothelial carcinoma: Subanalysis of the Japanese Urological Association multi-institutional national database. Int J Urol, 22:1023-1027, 2015

Department of Gynecology

Tomoyasu Kato, Shunichi Ikeda, Mitsuya Ishikawa, Takashi Uehara

Introduction

The Department of Gynecology 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, that is, cervical, endometrial and ovarian cancer, are now on the rise in Japan.

Routine activities

1) The staff members of the Department of Gynecology comprise four gynecologic oncologists. A new staff member, Dr. Uehara, has been in our Department since October 2015. In addition, our Division includes six residents in training. Current topics in the diagnosis and treatment of gynecologic malignancies are periodically discussed after the Monday general meeting. All patients under treatment are the subjects of presentations and discussions at the weekly joint conference on Wednesdays. A clinicopathological conference is held on the fourth Tuesday of each month.
2) Treatment strategy for uterine cervical cancer: Either conization or simple total hysterectomy is the treatment of choice for persistent Cervical intraepithelial neoplasia (CIN) III, carcinoma in situ, or cervical cancer stage IA1. Patients with stages IA2 to IIB usually undergo radical hysterectomy and pelvic lymphadenectomy. Autonomic nerves during radical hysterectomy should be preserved as much as possible to prevent severe neurogenic bladder. Postoperative whole pelvic irradiation following radical hysterectomy is only considered for patients with metastasis to the pelvic nodes or parametrial tissue as confirmed by pathological examination. Furthermore, in 2011, intensity-modulated radiation therapy (IMRT) started to be employed for postoperative adjuvant radiotherapy. Thereafter, none had severe radiation enterocolitis. Radiotherapy alone or concurrent chemo-radiotherapy is given to patients at any stage. Chemotherapy is occasionally used for the treatment of distant metastasis.
3) Treatment strategy for endometrial cancer: The primary treatment choice is hysterectomy with bilateral salpingo-oophorectomy. Pelvic lymph node dissection is also performed for patients with a high risk of metastasis. Para-aortic node dissection is limited to those with biopsy-proven nodal metastasis. Postoperative adjuvant chemotherapy is performed for patients with extra-uterine disease under management of the Department of Medical Oncology.
4) 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 Neoadjuvant chemotherapy (NAC). After three of four courses of chemotherapy, an interval debulking surgery (IDS) is usually performed for three patients. Surgery alone

can offer the chance of a cure for patients with recurrence, but only when the disease is completely resectable. The type of patient number and surgical procedure are shown in Tables 1 and 2, respectively.

Research activities

1) The Japan Clinical Oncology Group (JCOG) 0806-A: This report describes a determination of indications for less invasive modified radical hysterectomy for patients with the International Federation of Gynecology and Obsterics (FIGO) stage IB1 cervical cancer. We expected that patients with <2-3% parametrial involvement and ≥95% five-year OS would be good candidates for less invasive surgery. The primary target population was patients with a tumor diameter ≤2 cm as preoperatively assessed by magnetic resonance (MR) imaging and/or cone biopsy. They had lower risk of parametrial involvement (1.9%) and more favorable five-year OS (95.8%). This population is considered a good candidate for less invasive surgery such as modified radical hysterectomy. This paper would shed new light on candidates of less invasive surgery for cervical cancer stage IB1.
2) Ascites cell block system: To investigate the diagnostic utility of the ascites cell block system (CB), 48 patients with diagnosed carcinomatous peritonitis were reviewed retrospectively between 2010 and 2014. Ascites CB sections were stained with hematoxylin and eosin (HE) and immunohistochemistry. Of the 48 patients, 32 had peritoneal cancer or ovarian cancer, three had endometrial cancers, four had breast cancers, six had digestive system malignancies, and three had peritoneal mesotheliomas. A total of seven patients (14.5%) were different between clinical diagnosis (symptom, image and tumor marker) and the diagnosis by CB. A specific immunochemistry panel was helpful for the estimation of primary lesion, especially in the diagnosis of digestive system origin.
3) Adjuvant radiotherapy for vulvar cancer stage IIIA: The groin nodes are the most important prognostic factors in squamous cell carcinoma of the vulva. Adjuvant radiotherapy is indicated for patients with node-positive disease. The most common complication is the development of lower extremity lymphedema. Lymph drainage from the vulva rarely bypasses the superficial groin nodes, and from these superficial groin nodes the disease spreads to the deep groin nodes. We regard the absence of deep groin node metastasis as a low risk for pelvic lymph node metastasis, so we have omitted adjuvant radiotherapy for patients with node metastasis limited to the superficial groin region. We showed that five patients with stage IIIA are alive without postoperative radiotherapy, even though two of the five are those with two or more positive nodes.

Clinical trials

1) A nonrandomized confirmatory trial of modified radical hysterectomy for patients with FIGO Stage Ib1 (< 2 cm) uterine cervical cancer (JCOG1101) is ongoing as planned.
2) A non-randomized verification study regarding selection of fertility-sparing surgery for patients with epithelial ovarian cancer (JCOG1203) is ongoing as planned.
3) A randomized phase II/III trial conventional paclitaxel and carboplatin versus dose-dense paclitaxel and carboplatin in stage IVB, recurrent, or persistent cervical carcinoma (JCOG 1311) has started.

Table 1. Number of patients

Primary site	number of patients
Cervix	83
Endometrium	69
Ovary/tube/peritoneum	59
Vagina	3
Vulva	8
Benign or others	38

Table 2. Type of procedure

Radical hysterectomy	33
Modified radical hysterectomy	2
TAH+/-BSO+/-omentectomy+Paraaortic lymphadenectomy	22
TAH+/-BSO+/-omentectomy+pelvic lymphadectomy	17
TAH+/-BSO+/-omentectomy+/-LAR	3
TAH+/-BSO+/- omentectomy+/-retroperitoneal lymph node biopsy	117
Total pelvic exenteration	1
Radical vulvectomy	2
Simple vulvectomy	6
Conization	20
Others	40
	263

List of papers published in 2015

Journal

1. Kato T, Takashima A, Kasamatsu T, Nakamura K, Mizusawa J, Nakanishi T, Takeshima N, Kamiura S, Onda T, Sumi T, Takano M, Nakai H, Saito T, Fujiwara K, Yokoyama M, Itamochi H, Takehara K, Yokota H, Mizunoe T, Takeda S, Sonoda K, Shiozawa T, Kawabata T, Honma S, Fukuda H, Yaegashi N, Yoshikawa H, Konishi I, Kamura T, Gynecologic Oncology Study Group of the Japan Clinical Oncology Group. Clinical tumor diameter and prognosis of patients with FIGO stage IB1 cervical cancer (JCOG0806-A). Gynecol Oncol, 137:34-39, 2015

2. Satoh T, Tsuda H, Kanato K, Nakamura K, Shibata T, Takano M, Baba T, Ishikawa M, Ushijima K, Yaegashi N, Yoshikawa H, Gynecologic Cancer Study Group of the Japan Clinical Oncology Group. A non-randomized confirmatory study regarding selection of fertility-sparing surgery for patients with epithelial ovarian cancer: Japan Clinical Oncology Group Study (JCOG1203). Jpn J Clin Oncol, 45:595-599, 2015

3. Ikeda S, Ishikawa M, Kato T. Spontaneous ureteral rupture during concurrent chemoradiotherapy in a woman with uterine cervical cancer. Gynecol Oncol Rep, 13:18-19, 2015

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7. Shimizu C, Kato T, Tamura N, Bando H, Asada Y, Mizota Y, Yamamoto S, Fujiwara Y. Perception and needs of reproductive specialists with regard to fertility preservation of young breast cancer patients. Int J Clin Oncol, 20:82-89, 2015

Department of Musculoskeletal Oncology and Rehabilitation

Hirokazu Chuuman, Akira Kawai, Fumihiko Nakatani, Yoshikazu Tanzawa, Eisuke Kobayashi, Makoto Endo, Nokitaka Setsu, Kouki Shimizu, Tomoaki Mori, Yoshihiro Araki, Masazumi Sugawara

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 Musculoskeletal Oncology 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.

Routine activities

The Musculoskeletal Oncology Division of the NCCH consists of six staff doctors, four residents and four physiotherapists, one occupational therapist and one speech therapist. Occasionally, several fellows from Japan and overseas join our group. Outpatient consultations are held every weekday. A constant number of over 25 patients are hospitalized for operation, chemotherapy or radiation therapy. Six or 10 major operations are routinely performed every week. In 2015, 410 operations were performed, including palliative operations for pathological fractures or spinal cord compression from metastatic bone and soft tissue tumors. Sarcomas in the trunk, including the 13 in the thoracic wall, 46 in the retroperitoneal space and three head and neck lesions were excised in cooperation with thoracic, general, urological or head-neck surgeons, respectively. A total of 66 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 neo-adjuvant and adjuvant chemotherapy for high-grade bone and soft tissue tumors, palliative chemotherapy for metastatic bone and soft tissue sarcomas, where necessary in collaboration with medical oncologists. We have been collaborating with pediatric oncologists for chemotherapeutic treatment of children and adolescents with sarcomas.

Research activities

Since 2004, we have been collaborating with the NCC Research Institute 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 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 with the aim of developing novel molecular targeted therapies or biomarkers.

Clinical trials

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

1) A multi-institutional phase III clinical trial of multi-drugs adjuvant chemotherapy for osteosarcomas (The Japan Clinical Oncology Group (JCOG) 0905) since 2010.
2) A multi-institutional phase 2 study of trabectedin for advanced soft tissue sarcoma since 2012.
3) A multi-institutional phase III clinical trial of multidrugs adjuvant chemotherapy for osteosarcomas (JCOG 1306) since 2014.
4) Phase Ⅱ clinical study of DXR vs. DXR + olaratumab (PDGFR α monoclonal antibody)

Education

Each resident performs 60-70 operations supervised by staff members every year, joins many domestic and international conferences and publishes several medical articles or reports during training courses. All staff members teach all clinical procedures and information related to oncological skills for bone and soft part sarcomas.

Future prospects

Our clinical divisions and translational study groups do many clinical trials of novel therapeutic innovations and promote clinical trials of novel drugs or targeted compounds for sarcomas and will continue to make focused efforts in the future.

Table 1. Number of patients (2015)

Soft tissue sarcomas	233
Bone sarcomas	38
Soft tissue tumors	216
Bone tumors	88
Metastasis consultation	159
Spinal cord tumors	6

Table 2. Type of procedure (2015)

Malignant soft tissue tumor surgery	123
Malignant bone tumor surgery	48
Soft tissue tumor excision or biopsy	114
Bone tumor excision or biopsy	59
Amputation	19
Others	26
Retroperitoneal sarcoma and tumor	46
Plastic surgery combined	66
Reconstruction with prosthesis	18
Spine surgery	4

List of papers published in 2015

Journal

1. Asano N, Yoshida A, Ogura K, Kobayashi E, Susa M, Morioka H, Iwata S, Ishii T, Hiruma T, Chuman H, Kawai A. Prognostic Value of Relevant Clinicopathologic Variables in Epithelioid Sarcoma: A Multi-Institutional Retrospective Study of 44 Patients. Ann Surg Oncol, 22:2624-2632, 2015

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13. Yoshida A, Yoshida H, Yoshida M, Mori T, Kobayashi E, Tanzawa Y, Yasugi T, Kawana K, Ishikawa M, Sugiura H, Maeda D, Fukayama M, Kawai A, Hiraoka N, Motoi T. Myoepithelioma-like Tumors of the Vulvar Region: A Distinctive Group of SMARCB1-deficient Neoplasms. Am J Surg Pathol, 39:1102-1113, 2015

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16. Yonemoto T, Hosono A, Iwata S, Kamoda H, Hagiwara Y, Fujiwara T, Kawai A, Ishii T. The prognosis of osteosarcoma occurring as second malignancy of childhood cancers may be favorable: experience of two cancer centers in Japan. Int J Clin Oncol, 20:613-616, 2015

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Department of Dermatologic Oncology

Naoya Yamazaki, Arata Tsutsumida, Akira Takahashi, Kenjiro Namikawa, Wataru Omata

Introduction

The Department of Dermatologic Oncology has consistently served as the core hospital to establish treatment strategies for malignant skin tumors since the National Cancer Center opened in 1962, with over 2000 cases of malignant melanoma treated to date; an impressive number for a hospital or research institution in Japan. Today, patients are referred here from all over Japan. Particularly noteworthy is the total of 181 patients with malignant melanoma, approximately double the number of five 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, while multi-disciplinary treatments, comprising chemotherapy, immunotherapy and radiotherapy, are also routinely carried out. This Department is also actively involved in multicenter trials for new skin cancer agents all over Japan.

Routine activities

The Department has four staff dermatologic oncologists, one chief resident and three residents. We also engage in routine outpatient activities on Wednesdays and Thursdays in the National Cancer Center East.

Our Department has a high throughput, with an average of more than 200 patients with malignant melanoma seen annually for the past four years. This follows the establishment of a national network to develop treatment for malignant skin tumors, thanks to which nivolumab, an anti-PD-1 antibody, was approved as a therapeutic agent for malignant melanoma in Japan as a world first and reflecting vigorous new drug development.

An expanded access program featuring a BRAF inhibitor, vemurafenib, was also conducted through an investigator-initiated clinical trial.

About 20 patients are hospitalized to undergo surgery, chemotherapy, or radiation therapy. In 2013, 250 operations were performed, including 118 under general anesthesia. Rounds are made and case presentations are held every morning. A Division conference is also held every Monday to discuss the therapeutic principles for outpatients and inpatients. A clinicopathological conference focusing on surgically removed skin specimens is held with pathologists once a month.

We have also treated patients with advanced cases of mucosal melanoma in the nasal cavity, genital lesions, perianal lesions and uveal melanoma, despite our original "dermatologic" specialty.

Research activities

Malignant skin tumors are mainly treated by surgery (appended table). However, in recent years, several new drugs have been rapidly developed overseas to treat malignant melanoma and our Department has been conducting numerous clinical studies and trials, with the most important listed as follows:

- A multicenter study to establish standard therapy for refractory malignancies
- A study on the establishment of an early clinical development system of drugs for rare cancers and support for research.
- Development of a system for boron neutron capture therapy (BNCT) using an accelerator installed at the hospital
- A study for developing guidelines to support the physical appearance of cancer patients
- A study on methods for assessing skin changes associated with cancer treatment and establishment of standard care
- A study on the quantitative assessment of skin disorders associated with chemotherapy using

molecular-targeted agents and skin care
- A retrospective study to clarify the outcomes of conventional treatment for cutaneous angiosarcoma of the head and neck
- A retrospective study on the outcomes of TACE therapy using cisplatin for liver metastasis from primary ocular malignant melanoma
- A phase I/II trial of combined dabrafenib and trametinib in patients with BRAF V600E or V600K mutation-positive advanced solid cancer (for phase I trials) or cutaneous malignant melanoma (for phase II trials)
- A randomized double-blind Phase III study comparing placebo and combination therapy with dabrafenib (GSK2118436) and trametinib (GSK1120212), given as postoperative adjuvant therapy for BRAF V600 mutation-positive malignant melanoma (a group at high risk of recurrence)
- A phase II, open-label, multicenter study to evaluate the efficacy and safety of avelumab (MSB0010718C) in patients with Merkel cell carcinoma
- A phase I study of repeated intratumor administration of TBI-1401 (HF10) in patients with solid tumors with superficial lesions
- A working group to prepare guidelines on "Anti-immune checkpoint therapy and combination therapy" or leaflets explaining the guidelines
- "Development of innovative cancer immunotherapy by identifying essential aspects of the tumor microenvironment associated with malignant melanoma"
- Clinical evaluation of a practical, non-invasive diagnostic tool for superficial skin tumors (hyperspectral imager)
- Practical development of therapeutic agents for refractory skin cancer using innovative molecular-targeted agents inducing cancer-specific apoptosis through an investigator-initiated clinical trial

Clinical trials

Table 2 shows our clinical trials.

Education

Currently, three resident physicians and one oncology trainee are engaged in ongoing training in routine clinical practice under skilled guidance. Conferences with the Departments of Oncology, Radiotherapy and Pathology are also regularly held. The resident physicians and the oncology trainee made a total of ten presentations at domestic academic conferences and one presentation at an international academic conference as well as publishing two papers.

Future prospects

We have devised certain measures to resolve the drug lag between Japan and Western countries in the treatment of malignant melanomas and will further promote efforts to develop effective and safe treatment strategies.

Our Department is a high-volume center in Japan for malignant melanomas and other malignant skin tumors. With the advantageous data collection associated with such a large patient base, we will reinforce our research collaboration system even more than at present, leveraging a translational research platform with the National Cancer Center Research Institute.

Table 1. Number of New Patients

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Malignant melanoma	67	68	74	97	94	79	92	75	94	88	132	228	191	206	181
Squamous cell carcinoma	27	19	24	31	36	25	25	28	36	52	27	34	40	45	42
Basal cell carcinoma	40	29	31	47	33	23	25	33	31	28	28	33	38	37	42
Sweat gland carcinoma	3	10	7	8	10	17	6	10	10	9	9	8	7	16	16
Trichilemmal carcinoma	0	1	2	0	0	1	7	0	1	0	0	1	0	1	2
Paget's disease	10	16	13	12	18	16	19	20	21	19	22	18	16	22	22
Bowen's disease	16	8	7	12	9	8	4	2	10	3	9	5	14	11	8
Dermatofibrosarcoma protuberans	2	2	3	5	3	7	3	5	10	10	10	7	13	10	2
Angiosarcoma	7	5	3	3	5	9	6	12	9	9	9	6	10	11	5
Malignant fibrous histiocytoma	0	0	1	1	1	0	1	1	3	3	1	0	1	0	2
Epithelioid sarcoma	1	1	0	0	2	1	0	1	0	0	0	0	0	0	0
Malignant lymphoma	3	10	12	12	15	7	6	15	13	16	16	15	6	11	7
Merkel cell carcinoma	-	-	-	-	2	3	2	4	3	3	8	1	1	3	7
Others	2	5	5	4	5	12	11	8	7	17	19	19	14	8	19
Total	178	175	182	232	233	208	207	204	248	257	290	375	327	381	355

Table 2. Operative Procedures (total number) in 2015

Wide local excision	156
Local excision	47
Sentinel node biopsy	45
Lymph node biopsy	9
Lymph node dissection	35
(neck)	5
(axilla)	8
(inguinal)	7
(groin)	15
(popliteal)	0
(epitrochlear)	0
Skin graft	43
Local flap	8
Free flap	2
Amputation	10
others (biopsy/debridement)	3

Table 3. New Agent Studies in 2015

Agent	Eligible Cancer Type	Trial Phase
Dabrafenib / Trametinib	Melanoma	I/II
MSB0010718C	Solid Tumors	I
ONO-4538	Melanoma	II
MEK162 / LGX818	Melanoma	III
Ipilimumab (3mg/kg)	Melanoma	II
Dabrafenib/Trametinib (COMBI-AD)	Melanoma	III
MK-3475	Melanoma	I
HVJ-E	Melanoma	I
Ipilimumab + Nivolumab	Melanoma	II
HF10	Skin Tumors	I
Avelumab	Merkel Cell Carcinoma	II

List of papers published in 2015

Journal

1. Yamazaki N, Kiyohara Y, Sugaya N, Uhara H. Phase I/II study of vemurafenib in patients with unresectable or recurrent melanoma with BRAF(V) (600) mutations. J Dermatol, 42:661-666, 2015

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Department of Hematology

Kensei Tobinai, Yukio Kobayashi, Dai Maruyama, Tatsuya Suzuki, Wataru Munakata, Suguru Fukuhara, Shinichi Makita, Nobuhiko Yamauchi, Kousuke Toyoda

Introduction

We are focusing on the diagnosis and treatment of hematological malignancies. In the past, our Department introduced several novel disease entities, including adult T-cell leukemia-lymphoma (ATL) (J Clin Oncol 2009; 27:453-9) and angioimmunoblastic T-cell lymphoma (Blood 1988; 72:1000-6). Our department is one of the leading hematology-oncology centers in the world, especially for lymphoid malignancies.

Routine activities

The number of patients with newly diagnosed hematological malignancies in the Division increased annually from 1997 to 2004, and then stabilized (Table 1). The diseases we treat are leukemia, MDS, lymphoma, and multiple myeloma. These diseases in a certain status require hematopoietic stem cell transplantation (HSCT), therefore, our Department is united with the Department of HSCT, and when necessary, HSCTs are provided by the HSCT Department. Such occasions include allogeneic HSCT against high risk AML, salvage autologous HSCT against lymphoma, and consolidative autologous HSCT against untreated multiple myeloma.

We hold a weekly case conference, where a summary of each hospitalized- or out-patient is presented. An educational cytology conference is held weekly for young doctors. Newly diagnosed lymphoma cases are presented at a weekly lymphoma case conference, where oncologists, pathologists, radiologists, and radiation oncologists discuss diagnosis and treatment plans. We also participate in weekly HSCT conferences, which deal with all HSCT cases.

In addition to patient care in the ward, our daily activities include management of hematology clinics and a diagnostic laboratory to perform bone marrow and peripheral blood microscopic examination, and flow cytometric and molecular-genetic analyses. Five staff physicians, three chief residents, and two to five rotating residents are involved in these routine 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), Flt3-ITD and so on. Our recent research has focused on indolent B-cell non-Hodgkin lymphoma (B-NHL). Clinical as well as molecular and cytogenetic analyses of ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma cases led to the discovery of a new tumor suppressor gene deleted at 6q23; we identified the A20 gene as a tumor suppressor gene in various B-cell malignancies (Nature 2009; 459:712-6). In 2015, we initiated quantitative PCR assay for detection of MyD88 gene. These genes are involved in NFκB signaling and we assume that these markers will serve as a sensitivity test when using BCR inhibitors in B-cell malignancies.

We have constructed a tumor sample banking system, collecting the rest of the samples taken as routine diagnostic procedures. The samples' DNA and RNAs are extracted and reserved for future use.

This year, we authored or coauthored 22 original articles related to hematological malignancies.

Clinical trials

In 2015, we conducted 41 new-agent studies, including 18 international ones (Table 2). The

number is still increasing including domestic studies. Almost all the new agents against hematological malignancies in Japan have been evaluated in our department, and a substantial number of them have been approved by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.

Various phase I and II trials are ongoing on T-cell malignancies. The agents include mogamulizumab, lenalidomide, romidepsin, pralatrexate, forodesine, darinaparsin, chidamide, and denileukin diftitox. Some of the agents are being evaluated in international studies. For indolent ATL, we are evaluating interferon-alfa and AZT, as a phase III study (JCOG1111).

With the completion of the phase I study of oligopeptide vaccine OCV-501 against WT1 protein in AML cells to keep cases in complete remission, a randomized phase II trial is ongoing to evaluate the efficacy. The agent was developed in Japan, and is the first study against hematological malignancies aiming for approval by the PMDA.

For treatment of B-cell malignancies, patient enrolment into a phase III trial for newly diagnosed, diffuse large B-cell lymphoma (DLBCL) (JCOG0601) was completed. In this trial, a dose-intense schedule of rituximab was compared with that of a standard 3-weekly regimen. We also completed patient enrolment into phase II studies of rituximab-incorporating dose-intensified chemotherapy regimens for high-risk, untreated DLBCL (JCOG0908), and untreated MCL (JCOG0406), using high-dose chemotherapy with autologous HSCT. For symptomatic multiple myeloma patients ineligible for HSCT, we are conducting a randomized phase II trial to find a more suitable combination regimen of bortezomib, melphalan and prednisolone (JCOG1105).

Education

We trained three chief residents and seven hematology residents following our residency program. We also trained five rotating medical oncology residents.

We are devoted to publication of guidelines for hematological malignancies, and act as lecturers or nominees in various hematology and oncology societies.

Future prospects

We have attracted and educated physicians in trainee programs. Many graduates from our program are actively engaged in hematology and oncology societies. We are steering JCOG and JALSG, which are major cooperative study groups for hematological malignancies in Japan. More involvement in international studies is necessary, and more cooperative studies with other departments such as the Department of Pathology and Clinical Laboratories in NCCH and Division of Hematological Malignancy in NCCRI. and Division of Hematological Malignancy in the National Cancer Center Research Institute.

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

Disease / Year	2007	2008	2009	2010	2011	2012	2013	2014	2015
Acute myelocytic leukemia (AML)	10	6	10	8	13	12	7	9	4
Acute lymphocytic leukemia (ALL)	9	8	2	2	1	1	6	3	6
Chronic myelocytic leukemia (CML)	11	3	3	2	2	2	2	3	3
Myelodysplastic syndrome (MDS)	9	8	20	9	3	3	6	3	7
Hodgkin lymphoma (HL)	11	12	7	11	16	15	13	9	13
Non-Hodgkin lymphoma (NHL)	210	208	151	185	243	172	193	151	153
Adult T-cell leukemia-lymphoma (ATL)	4	5	5	3	6	6	4	10	2
Chronic lymphocytic leukemia (CLL)	5	6	4	2	1	4	1	1	6
Multiple myeloma (MM)	8	10	12	9	10	7	8	3	10
Waldenström macroglobulinemia (WM)	2	3	1	2	2	1	0	0	2
Total	279	269	215	233	297	223	240	192	206

Table 2. Clinical trials for new agent development

Disease	Agents	Phase	Enrolled patients in 2015	Enrolled Patients in Total (2015/12/31)
CML	Nilotinib	III	0	1
	Ponatinib	I/II	0	3
	Rogosertib	I	0	1
AML, MDS	WT1 (maintenance)	I	0	4
	WT1 vaccine	II	0	0
	Volasertib	III	0	2
	ASP2215	I	2	4
	SMO inhibitor (PF-04449913)	I	3	3
ALL	Inotuzumab ozogamicin	I	0	2
	Blinatumomab	I	1	1
MM	Carfilzomib (high-dose)	I	1	2
	Carfilzomib+dexametasone vs. Bortezomib+dexametazone	III	0	1
	Weekly vs biweekly Carfilzomib	III	0	0
	Afuresertib	I	0	0
	Pomalidomide	II	0	1
T-NHL	Forodesine	I/II	0	7
	KW-0761 (ATL)	II	0	0
	Romidepsin	I/II	2	12
	Pralatrexate	I	4	7
CD30 positive PTCL	SGN-35 + CHP vs. CHOP	III	1	4
CTCL	KW-0761 vs. Vorinostat	III	0	0
CLL, B-NHL	FCR	II	1	1
	Idelalisib	Ib	0	1
	ONO-4059 (BTK-inhibitor)	I	5	6
Indolent B- NHL	Ofatumumab vs. Rituximab	III	5	46
	Obinutuzumab (GALLIUM)	III	0	16
	BR (or R-CHOP) ± ibrutinib	III	0	8
	R-CHOP ± lenalidomide	III	0	2
	Rituximab ± lenalidomide	III	2	2
	Copanlisib	Ib	1	1
	BR (or R-CHOP) ± ibrutinib	III	4	4
MCL	VcR-CAP	III	0	2
	BR ± ibrutinib	III	0	1
	Ibrutinib	II	0	4
	Ofatumumab	III	0	3
	Everolimus	III	0	1
	R-CHOP ± ibrutinib	III	5	7
HL	SGN-35	III	2	2
	ONO-4538 (nivolumab)	II	5	5
NHL, MM, CLL	Venetoclax (bcl-2 inhibitor)	I	3	4

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; MP, melphalan, prednisolone; PSL, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, PSL; R, rituximab; VcR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, PSL

Table 3. Clinical studies of Cooperative Group

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	95%	89% (5-yr)
JALSG-AML209	IV	(11-)	9	NA	NA
JALSG-APL212G	II	(14-)	1	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
JALSG-ALL 2013	II	(14-)	4	NA	NA
JALSG Ph+ALL 2013	II	(14-)	1	NA	NA
CML					
JALSG-CML 207	III	(08-10)	1	NA	NA
JALSG-CML 212	III	(12-)	4	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 / DLBCL					
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	(08-14)	57	NA	NA
JCOG 0406	III	(08-12)	3	NA	NA
JCOG 0908	III	(08-15)	20	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	(11-)	3	NA	NA
JCOG 1111	III	(13-)	6	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)	(09-)	7	NA	NA
JCOG 1105	III	(13-)	6	NA	NA

(a) The number of patients enrolled from our department; (b) As the number of enrolled patients in our department is relatively small, the % CR or OS for the entire number of 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

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Journal

1. Kamiyama Y, Kobayashi Y, Fukuhara S, Morikawa N, Munakata W, Miyagi Maeshima A, Maruyama D, Kim SW, Watanabe T, Terauchi T, Muramatsu Y, Tobinai K. Incidental detection of malignant lymphoma in subjects in a cancer surveillance programme. Br J Haematol, 169:138-142, 2015

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Department of Hematopoietic Stem Cell Transplantation

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Introduction

At the National Cancer Center Hospital, the Department of Hematopoietic Stem Cell Transplantation (HSCT) specializes in patients who undergo allogeneic or autologous HSCT. Twenty-six beds in ward 12B and an additional three 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. Yamashita, Kim, Kurosawa, Fuji, Inamoto, and Fukuda) and two chief residents (Drs. Tanaka and Ohnishi) participate in the transplant program. Children who have undergone HSCT are managed in collaboration with Dr. Ogawa, the chief of the Department of Pediatric Oncology, and the transplant team. In 2015, a total of 106 transplantations were performed at the 12B and 12A transplant units. The numbers of each type of HCST between 2011 and 2015 are shown in Table 1, and the numbers of patients according to disease type are shown in Table 2.

At the weekly conference on Monday afternoons, in collaboration with doctors of the Dopartment of Hematology, 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 24 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. In 2015, 370 patients visited our LTFU clinic. 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 reduced-intensity stem cell transplants for elderly patients. A clinical trial of post-transplant consolidation with the WT1 vaccine has been completed. We have started nationwide studies focusing on HSCT for patients with adult T-cell leukemia. Our study suggested that the use of mogamulizumab, anti-CCR4 antibody, before allogeneic HSCT significantly worsened the clinical outcome, mainly due to an increased risk of acute GVHD. We have also published a large nationwide survey of quality of life (QOL) in 576 patients with acute leukemia. In 2015, we published 27 articles in peer-reviewed international journals.

Table 1. Number of each type of HSCT

Year		2011	2012	2013	2014	2015
Allogeneic		76	72	87	93	87
Unrelated	BMT	54	46	53	52	37
	PBSCT	0	3	5	6	7
	CBT	4	8	8	9	24
Related	BMT	2	0	1	2	0
	PBSCT	16	15	20	24	19
Autologous		25	25	23	10	19
Total		101	97	110	103	106

Table 2. Number of patients who underwent HSCT in 2015

Diagnosis	Allogeneic	Autologous
Acute myeloid leukemia	29	0
Myelodysplastic syndrome	6	0
Acute lymphocytic leukemia	13	0
Malignant lymphoma (including ATL)	36	9
Multiple myeloma	0	3
Solid tumors	0	7
Others	3	0
Total	87	19

List of papers published in 2015

Journal

1. Ueda R, Fuji S, Mori S, Hiramoto N, Hashimoto H, Tanaka T, Tada K, Kobayashi Y, Morikawa N, Shinohara A, Okinaka K, Maeshima AM, Kurosawa S, Kim SW, Yamashita T, Fukuda T. Characteristics and outcomes of patients diagnosed with norovirus gastroenteritis after allogeneic hematopoietic stem cell transplantation based on immunochromatography. Int J Hematol, 102:121-128, 2015

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26. Hashimoto H, Kitano S, Ueda R, Ito A, Tada K, Fuji S, Kim SW, Yamashita T, Tomura D, Nukaya I, Mineno J, Fukuda T, Mori S, Takaue Y, Heike Y. Infusion of donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene for recurrent hematologic malignancies after allogeneic hematopoietic stem cell transplantation. Int J Hematol, 102:101-110, 2015 (Erratum in : Int J Hematol. 102:506, 2015)

27. Hashimoto H, Kitano S, Yamagata S, Miyagi Maeshima A, Ueda R, Ito A, Tada K, Fuji S, Yamashita T, Tomura D, Nukaya I, Mineno J, Fukuda T, Mori S, Takaue Y, Heike Y. Donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene: detailed immunological function following add-back after haplo-identical transplantation. Cytotherapy, 17:1820-1830, 2015

Department of Blood Transfusion and Cellular Therapy

Ryuji Tanosaki

Introduction

The missions of the Department of Blood Transfusion and Cellular Therapy are management of in-hospital transfusion and support for the hematopoietic stem cell transplantation team in respect of providing safe and secure cellular products. In common with the Department of 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 techniques, 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 one JSTMCT-accredited medical doctor and six specifically engaged medical technologists (MT) (including two JSTMCT-accredited technologists) who come to us from the Department of Pathology and Clinical Laboratories. 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, an administrative meeting is held weekly, and an all-staff meeting is held weekly in our department and once a month in the Department of Clinical Laboratories.

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. In 2015, the total units of red blood cells (RBC), platelet concentrates (PC) and fresh frozen plasma (FFP), which were used in our hospital, were 9,871, 40,225 and 4,302, respectively, with wastage rates of RCC 0.5%, PC 0.04%, FFP 0.2%, respectively. Thanks to the Tokyo Red Cross and the convenient location of our hospital, blood products are available within one hour almost every time when they are needed in an emergency.

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. All transfusion procedures are performed under a strict hemo-vigilant system that employs electronic medical records managed by the computer system at the blood transfusion service. Hematopoietic stem cells that are to be transplanted to the SCT patients, that is, grafts, are also subject to the same safety and bio-vigilant system as other blood products.

We also manage the processing, storage, and quality control of hematopoietic stem cells used for transplantation as a routine activity in collaboration with medical engineers and members of the Department of Hematopoietic Stem Cell Transplantation. We inform other SCT-team members of the optimal timing for peripheral blood stem cell harvest (PBSCH) by monitoring counts of chemotherapy/G-CSF-mobilized progenitor cells, for not only CD34-positive ($CD34^+$) cell count, but also HPC, a new enumeration marker developed in our department. The management meeting is held once a month, the members of which consist of staff from the Department of Hematopoietic Stem Cell Transplantation, Medical Engineering Section, the head of technologists, and the members of our department. 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, which facilitates and promotes inter-departmental collaboration, as mentioned above.

Since April 2015, we started a modified Cell-Free and Concentrated Ascites Reinfusion Therapy (KM-CART) for the management of patients with refractory ascites. Ascites from each patient were registered in our blood computer system with a minor modification, which could be processed in the same manner as a blood product. About 100 procedures were performed in the first year without any major problems, and almost no serious adverse events were observed in infusion to patients.

Research activities

One of the Department's research projects is to develop a new enumeration technique for hematopoietic stem cells using an automated hematology analyzer, which is designated as 'HPC', in collaboration with a medical diagnostic company. The multicenter study for evaluation of HPC with the support of JSTMCT demonstrated that there was a very strong correlation between HPC values and $CD34^+$ cell counts, and we concluded that HPC is very promising as a candidate of an alternative for $CD34^+$ cell.

Another project is to establish a nationwide infrastructure of processing and management of cellular products used for hematopoietic stem cell transplantation as a committee member of the corresponding academic societies with the support of the Ministry of Health, Labour and Welfare. In 2015, we conducted a nationwide external quality assessment of $CD34^+$ cell counts for the first time. We also published a Textbook of Cell Processing for Hematopoietic Stem Cell Transplantation. We also launched an accreditation system for Clinical Cell Therapy Specialists for the first time in Japan, and 431 medical experts were given accreditation in the first year.

Education

The chief doctor supervises the education program of the Department of Clinical Laboratories for all medical technologists. The education program consists of a monthly educational conference in which each medical technologist presents his or her research, doctors' lectures, and RCPC (twice a year) were performed. It also includes educational lectures concerning ISO 15189. We also support and facilitate academic presentations and publications by all the MT members.

List of papers published in 2015

Journal

1. Suehiro Y, Hasegawa A, Iino T, Sasada A, Watanabe N, Matsuoka M, Takamori A, Tanosaki R, Utsunomiya A, Choi I, Fukuda T, Miura O, Takaishi S, Teshima T, Akashi K, Kannagi M, Uike N, Okamura J. Clinical outcomes of a novel therapeutic vaccine with Tax peptide-pulsed dendritic cells for adult T cell leukaemia/lymphoma in a pilot study. Br J Haematol, 169:356-367, 2015

Department of Pediatric Oncology

Chitose Ogawa, Tadashi Kumamoto, Yuki Aoki, Ayumu Arakawa, Yasuhiro Fujiwara, Hiroshi Kawamoto, Ako Hosono, Naoko Yasui, Hide Kaneda

Introduction

Pediatric oncology includes a wide variety of malignancies in children and adolescents such as acute leukemia and malignant lymphoma, as well as solid tumors including osteosarcoma, soft tissue sarcoma, neuroblastoma, liver tumor and retinoblastoma. Many diseases are usually chemosensitive and curable with appropriate treatment. The common approach to these diseases is a "risk-adapted therapy" strategy considering long-term life expectancy. In the Department of Pediatric Oncology, patients with pediatric malignancies are managed by four pediatric oncologists and a pediatric surgeon. Although pediatric oncologists mainly treat and manage patients, a multidisciplinary team approach including radiation oncologists, orthopedic surgeons, ophthalmologic surgeons and others is incorporated for the treatment. To achieve treatment completion and optimal quality of hospital life for children, pediatric nurse specialists, teachers, child care staff, psychologists and psychiatrists also join our team. For young patients, educational opportunities ranging from elementary school to high school are available in the pediatric ward, where seven teachers work daily.

Routine activities

We deal with 50-80 new patients every year. Our daily activity in the pediatric outpatient clinic is to manage new patients, to treat patients with chemotherapy or blood transfusions and to provide follow-up care for patients who have completed intensive treatment. Patients receive multidisciplinary therapy, including surgical removal of tumors, radiation therapy, chemotherapy, and sometimes stem cell transplantation (SCT), as indicated.

A Pediatric Conference is held every morning, mainly to decide on individual treatment plans. The pediatric staff and trainees discuss various issues regarding pediatric inpatients on daily rounds. Inter-department conferences in cooperation with orthopedics, radiation oncology, and palliative care are individually scheduled every two weeks.

Research activities

1. For newly diagnosed patients, we participate in several multicenter studies in the Japan Children's Cancer Group (JCCG), including those by the Japan Ewing Sarcoma Study Group (JESS), the Japan Rhabdomyosarcoma Study Group (JRSG) and the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG). In addition, we also conduct our own clinical trials.
2. For relapsed patients, we are actively involved in the development of new drugs and treatments including off-label and unapproved medications.
3. For patients with veno-occlusive disease in stem cell transplantation and patients with delayed excretion of methotrexate, a phase II registration trial of defibrotide and glucarpidase are conducted.
4. For provision of a similar environment during the treatment to that of before patients' disease onset, we plan to construct a medical care system through the use of appropriate medical and social resources in their local communities.

Clinical trials

In 2015, we conducted 12 trials, including early phase trials, an international study and cooperative studies. The five trials (1, 4, 6, 7 and 12) are investigator-initiated registration-directed clinical trials conducted under the Pharmaceutical Affairs Law in Japan. Two international cooperative trials

are ongoing: in the No. 10 trial, we are collaborating with the International BFM group in Europe and in the No. 12 trial with the Children's Oncology Group in the USA.

1) A phase II trial of glucarpidase for patients who were treated with high-dose methotrexate resulting in delayed excretion.
2) A phase Ib study of 131I-metaiodobenzylguanidine (MIBG) therapy with valproic acid (VPA) for high risk or recurrent neuroblastoma
3) A phase Ib study of VPA and 13-cis-RA (isotretinoin) combination therapy for advanced and recurrent neuroblastoma.
4) A feasibility trial of ch14.18 combined with IL-2 and various colony-stimulating factors for recurrent neuroblastoma.
5) A phase I trial of immunotherapy using HLA-A2-and A24-restricted glypican-3 peptide vaccine for pediatric tumors.
6) Efficacy and safety study of defibrotide (DF) for the treatment of veno-occlusive disease (VOD).
7) Efficacy and safety study of defibrotide (DF) for the prophylaxis of veno-occlusive disease (VOD).
8) The Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) ALL-T11 and the Japan Adult Leukemia Study Group (JALSG) T-ALL-211-U ALL-T11: A Multi-Center Phase II Study in Children and Adolescents with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia
9) The Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) ALL-B12: A Multi-Center Phase II/III Study in Children with Newly Diagnosed B-cell Precursor Acute Lymphoblastic Leukemia
10) An International Study for Treatment of Standard Risk Childhood Relapsed ALL 2010 (IntReALL SR 2010): A randomized Phase III Study Conducted by the Resistant Disease Committee of the International BFM Study Group
11) A Multi-Center Seamless Phase II-III Randomized Trial of High-dose Cytarabine in Initial Induction with Evaluation of Flow-cytometry-based Minimal Residual Disease for Children with de Novo Acute Myeloid Leukemia (AML-12)
12) Treatment of Children with All Stages of Hepatoblastoma with Temsirolimus Added to High Risk Stratum Treatment: A Phase III Study

Education

We provide personnel training and education for the skills of diagnosis and management for pediatric hematological malignancies and solid tumors. Residents also learn the skills to treat not only newly diagnosed patients but also relapsed or refractory patients by global standard therapy. In addition, senior residents acquire the ability to plan studies for new agents or new therapies, which we regard as an important role of this center.

Future prospects

We promote the development of therapies for pediatric malignancies as a top priority. For this mission, we lead the planning of clinical or registration trials in cooperation with domestic and international centers as a core institution in Japan.

Our other mission is to provide individualized medicine for children with cancer. For this aim, we plan to expand the subjects in the comprehensive genetic testing project in our center to the pediatric age group. In addition, we promote clinical trials using molecular targeted agents for pediatric malignancies.

Table 1. Number of patients in 2015

Acute lymphoblastic leukemia	7
Acute myeloid leukemia	1
Non-Hodgkin lymphoma	1
Hodgkin lymphoma	1
Other hematologic malignancies	0
Neuroblastoma	7
Retinoblastoma*	7*
Osteosarcoma	8
Ewing sarcoma family tumor	10
Rhabdomyosarcoma	5
Other soft tissue tumors	7
Germ cell tumor	0
Other solid tumors	2
Total	56

* advanced cases only

Table 2. Type of procedure

Tumor resection	11	
Metastasis of Ewing sarcoma		4
Metastasis of osteosarcoma		4
Metastasis of rhabdomyosarcoma		1
Neuroblastoma		1
Other sarcoma		1
Lymph node dissection	2	
Central venous (CV) port / catheter removal	6	
Total	19	

List of papers published in 2015

Journal

1. Yoshida A, Asano N, Kawai A, Kawamoto H, Nakazawa A, Kishimoto H, Kushima R. Differential SALL4 immunoexpression in malignant rhabdoid tumours and epithelioid sarcomas. Histopathology, 66:252-261, 2015

2. Yasui N, Yoshida A, Kawamoto H, Yonemori K, Hosono A, Kawai A. Clinicopathologic analysis of spindle cell/sclerosing rhabdomyosarcoma. Pediatr Blood Cancer, 62:1011-1016, 2015

3. Ono R, Hasegawa D, Hirabayashi S, Kamiya T, Yoshida K, Yonekawa S, Ogawa C, Hosoya R, Toki T, Terui K, Ito E, Manabe A. Acute megakaryoblastic leukemia with acquired trisomy 21 and GATA1 mutations in phenotypically normal children. Eur J Pediatr, 174:525-531, 2015

4. Kato M, Manabe A, Saito AM, Koh K, Inukai T, Ogawa C, Goto H, Tsuchida M, Ohara A. Outcome of pediatric acute lymphoblastic leukemia with very late relapse: a retrospective analysis by the Tokyo Children's Cancer Study Group (TCCSG). Int J Hematol, 101:52-57, 2015

5. Mori M, Imaizumi M, Ishiwada N, Kaneko T, Goto H, Kato K, Hara J, Kosaka Y, Koike K, Kawamoto H, Maeda N, Yoshinari T, Kishino H, Takahashi K, Kawahara S, Kartsonis NA, Komada Y. Pharmacokinetics, efficacy, and safety of caspofungin in Japanese pediatric patients with invasive candidiasis and invasive aspergillosis. J Infect Chemother, 21:421-426, 2015

6. Kinuya S, Yoshinaga K, Higuchi T, Jinguji M, Kurihara H, Kawamoto H. Draft guidelines regarding appropriate use of (131)I-MIBG radiotherapy for neuroendocrine tumors : Guideline Drafting Committee for Radiotherapy with (131)I-MIBG, Committee for Nuclear Oncology and Immunology, The Japanese Society of Nuclear Medicine. Ann Nucl Med, 29:543-552, 2015

7. Yasui N, Kawamoto H, Fujiwara M, Aihara Y, Ogawa C, Hosono A, Suzuki S. High-dose chemotherapy for high-risk retinoblastoma: clinical course and outcome of 14 cases in the National Cancer Center, Japan. Bone Marrow Transplant, 50:221-224, 2015

Department of General Internal Medicine/Oncologic Emergencies

Ken Ohashi, Hisashi Baba, Keiichiro Osame, Masaaki Shoji, Takeshi Iwasa, 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 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 the NCCH. Since April 2011, we have expanded diabetes consultation services into the NCC Hospital East, improving the quality of diabetes care there.

Cardiology:

Cardiologists take charge of ECG, echocardiography, in-hospital consultation, and the 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 2,000 a year. When an emergency procedure is necessary, we consider transferring the patient to other facilities that have specialists. Recently, the number of clinical trials for cancer that require echocardiography assessment has been increasing, so we make every effort to practice tests more efficiently.

Diabetology:

We provided more than 600 diabetes consultations in 2015, which include perioperative management of diabetes and treatment of steroid-induced hyperglycemia during chemotherapy. In many cases, initiation of insulin is the treatment of choice. We also offer close follow-ups on an outpatient basis for those who have diabetes during their cancer treatment at the NCCH.

Infectious diseases:

Since August 2015, an Infectious Disease specialist has provided about 200 consultations including active interventions triggered by positive blood culture. An ID physician has been also responsible for control of healthcare-associated infections as the Chief of the Infection Control Team. Implementation of antimicrobials stewardship is the other main task of the ID physician in collaboration with pharmacists. Through these activities, we aim to provide safer and higher-quality cancer care in the NCCH.

Department of Dentistry

Takao Ueno, Wakako Yatsuoka, Kyoko Miyamoto, Hiromi Ishida, Yoko Suzuki, Chie Asano

Introduction

Oral complications are common in patients receiving chemotherapy or undergoing radiation therapy of the head and neck.

Oral complications during cancer treatment are directly linked to ingestion problems, and may even serve as a source of various infections such as aspiration pneumonia, thereby exacerbating systemic conditions, and sometimes preventing the completion of cancer treatment with negative effects on treatment prognoses.

The oral health status of patients with cancer is associated with the incidence rate and the degree of severity of oral complications. Effective oral hygiene management before initiating cancer treatment will contribute to the reduction of oral complications such as mouth sores, oral mucositis, or dental infections, and provide important support to facilitate smooth cancer treatment.

Routine activities

To prevent or reducing oral complications, we check complications during cancer treatment for oral conditions of the patients, identify the patients at risk, and start preventive measures before cancer therapy begins.

Our routine activities for cancer patients is below:

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

Education

The lecture and the practice concerning oral health care were regularly held for nurses and residents.

Future prospects

Making a new system that strengthens collaboration with the nurse ~ An emphasis on preventive dental intervention, carried out screening of the oral cavity problem.

Contribute to medicine and dentistry collaboration in cancer care hospitals in the region.

Number of patients

The number of total patients：9,100
The number of new patients: 1,189

List of papers published in 2015

Book

1. Ueno T, Yurikusa T. 3. Oral health and lifestyle-related diseases, noncommunicable diseases (NCDs) 3) Cancer – Role of oral care in cancer treatment –. In: The current evidence of dental care and oral health for achieving healthy longevity in an aging society 2015, Japan, Japan Dental Assosiation, pp 86-108, 2015

2. Ueno T, Yurikusa T. 9. Effects of dental care 1) Effects of oral care on postoperative recovery period and state (including multidisciplinary cooperation) – Role of oral care in perioperative complications in surgery –. In: The current evidence of dental care and oral health for achieving healthy longevity in an aging society 2015, Japan, Japan Dental Assosiation, pp 236-244, 2015

Department of Anesthesia and Intensive Care

Tetsufumi Sato, Yoko Kinoshita, Minako Arai, Junya Matsumi, Nobuko Yokokawa, Seiji Shiraishi, Rie Suzuki, Mari Shibata, Yosuke Kawaguchi, Maria Ikegami, Ryota Tsukui, Miyako Nagaya, Kanae Tsutsumi, Fumiko Seto, Kazumasa Hiroi, Sayo Iwasaki, Kihoko Ichikawa, Yutaro Asagoe, Rutesara Kyuragi

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 eight beds and provides care for all specialties including general medical and general surgical cases. There are over 500 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 seven staff anesthetists who are involved in critical care, education and research. Our Department provides perioperative care to the all patients who require general anesthesia and spinal analgesia. Our operation theater performs approximately 4,500 surgical procedures per year, which include neurosurgical, orthopedic, plastics, ophthalmologic, gynecologic, urologic, and general surgery (Table 1, 2). 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 Consulting Clinic, which runs every weekday. Many staff also have other clinical appointments including attending the ICU (the eight-bed Medical/Surgical Unit) and providing acute pain management. Some members of the department are actively involved in research at 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, supported by two certificated intensivists and a trainee. There are eight operational ICU beds and over 650 admissions annually (Table 3). The ICU is also responsible for resuscitation services within the hospital.

Clinical trials

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

Table 1. Cases for anesthetic management

	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
Department of Neurosurgery and Neuro-Oncology	7	11	17	9	8	17	13	12	10	10	12	12
Department of Ophthalmic Oncology	26	24	30	20	26	24	32	26	28	32	28	32
Department of Head and Neck Oncology	17	23	22	21	17	21	27	22	24	23	26	22
Department of Plastic and Reconstructive Surgery	10	8	9	6	3	7	10	10	11	9	10	14
Department of Breast Surgery	43	41	53	46	41	57	58	48	44	50	48	42
Department of Breast and Medical Oncology	0	0	0	0	0	0	0	0	1	0	0	0
Department of Thoracic Surgery	53	52	55	51	43	64	68	53	46	50	57	56
Department of Esophageal Surgery	9	11	10	12	11	12	12	13	9	9	11	10
Department of Gastric Surgery	35	42	39	39	39	43	48	50	41	39	36	38
Department of Colorectal Surgery	43	44	44	41	33	46	49	48	54	44	39	41
Department of Gastrointestinal Medical Oncology	0	1	0	0	0	0	0	0	0	0	0	0
Department of Endoscopy, Gastrointestinal Endoscopy Division	7	6	10	7	6	5	4	6	8	4	5	7
Department of Hepatobiliary and Pancreatic Surgery	26	23	24	26	23	28	25	25	21	24	22	23
Department of Urology	22	25	29	26	27	30	35	31	28	27	29	30
Department of Gynecology	23	21	25	24	23	25	24	24	18	24	21	21
Department of Musculoskeletal Oncology and Rehabilitation	24	21	31	33	19	29	25	27	28	25	21	32
Department of Dermatologic Oncology	12	10	10	11	7	14	13	8	10	8	6	8
Department of Hematopoietic Stem Cell Transplantation	3	4	2	3	2	4	4	2	2	2	4	3
Department of Pediatric Oncology	2	0	1	2	0	2	1	2	0	0	0	0
Department of Anesthesia and Intensive Care	0	0	0	1	0	0	1	0	0	0	0	0
Department of Diagnostic Radiology	0	0	0	0	0	0	0	0	1	0	1	0
Department of Radiation Oncology	2	2	2	3	2	3	4	6	2	2	5	5
Total	364	369	413	381	330	431	453	413	386	382	381	396

Table 2. Type of procedures

	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
General Anesthesia	164	182	206	197	157	220	226	212	195	188	199	213
General Anesthesia + Epidural Anesthesia	193	179	165	171	161	171	169	159	143	157	147	141
Spinal Anesthesia + Epidural Anesthesia	0	0	0	0	0	0	0	0	0	0	0	0
Epidural Anesthesia	0	1	0	0	0	0	0	0	0	0	1	1
Spinal Anesthesia	1	2	42	6	6	40	57	41	47	37	32	41
Others	6	5	0	7	6	0	1	1	1	0	2	0
Total	364	369	413	381	330	431	453	413	386	382	381	396

Table 3. Number of cases, Deaths in ICU and ICU mortality

ICU Admission	No. of Cases	Deaths in ICU	ICU mortality
Department of Hepatobiliary and Pancreatic Surgery	160	2	1.30%
Department of Esophageal Surgery	120	1	0.80%
Department of Neurosurgery and Neuro-Oncology	114	0	0.00%
Department of Head and Neck Oncology	78	1	1.20%
Department of Gastric Surgery	41	0	0.00%
Department of Colorectal Surgery	39	0	0.00%
Department of Musculoskeletal Oncology and Rehabilitation	37	0	0.00%
Department of Hematopoietic Stem Cell Transplantation	24	4	16.70%
Department of Thoracic Surgery	18	1	5.60%
Department of Urology	11	0	0.00%
Department of Hematology	7	1	14.30%
Department of Breast and Medical Oncology	7	0	0.00%
Department of Endoscopy, Respiratory Endoscopy Division	6	2	33.30%
Department of Radiation Oncology	6	0	0.00%
Department of Gastrointestinal Medical Oncology	5	1	0.20%
Department of Hepatobiliary and Pancreatic Oncology	4	0	0.00%
Department of Dermatologic Oncology	4	0	0.00%
Department of Gynecology	3	0	0.00%
Department of Pediatric Oncology	1	0	0.00%
Total	685	13	

List of papers published in 2015

Journal

1. Nonaka S, Kawaguchi Y, Oda I, Nakamura J, Sato C, Kinjo Y, Abe S, Suzuki H, Yoshinaga S, Sato T, Saito Y. Safety and effectiveness of propofol-based monitored anesthesia care without intubation during endoscopic submucosal dissection for early gastric and esophageal cancers. Dig Endosc, 27:665-673, 2015

Department of Palliative Medicine

Eriko Satomi, Kaoru Nishijima, Daisuke Kiuchi

Introduction

The palliative care service started with a palliative care team of multidisciplinary professionals (palliative care specialists, psycho-oncologists, certified nurses, pharmacists, psychologists, Hospital Play Staff, an acupuncturist) in the National Cancer Center Hospital (NCCH) in 1999 and the Department of Palliative Care and Psychooncology was established in 2010 with the reorganization of the NCCH. In 2013, the Department of Palliative Medicine started. We provide palliative care to patients and families as members of the palliative care team with leading doctors, nurses and other professionals to create an individualized palliative care plan. Our goals are:

-Relieve pain and other physical symptoms
-Focus patients' emotional and spiritual concerns, and those of their caregivers
-Coordinate patients' care
-Improve the quality of life of patients with cancer
-Advanced care planning

Routine activities

Our missions are:

-Manage cancer-related pain and other symptoms
-Collaborate with other medical professionals and establish care plans
-Support patients' decision making and advanced care planning
-Teach basic skills in supportive and palliative medicine to resident doctors
-Research about new treatment for supportive and palliative medicine

1) For hospitalized patients

We work as a palliative care team and provide consulting and follow-up services to hospitalized patients throughout the NCCH. A consultation request is made by a physician (doctor in charge) or the medical staff. We provide support to the primary team. We follow up about 25 to 30 patients every day.

2) For outpatients

Our outpatient clinic for palliative medicine is open from Monday through Friday. It is possible for us to see patients on demand.

Research activities

We have just started the group J-SUPPORT (Japanese Supportive, Palliative and Psychosocial Oncology Group) for clinical trials in supportive and palliative care.

Clinical trials

JORTC-PAL08, PASQoL, PHASE-R (Olanzapine for nausea and vomiting: observational study), etc.

Education

We have two training courses for doctors who will be palliative care specialists and for residents to learn primary palliative care. All the surgical and medical oncologist residents in the NCCH need knowledge and skill about primary supportive and palliative care in oncology. They participate in our team for 4 weeks and undergo on-the-job training for palliative medicine. This includes an opportunity to attend home hospice rounds in cooperation with Chuo-ku medical association. A total of 20 residents finished the 4-week palliative medicine course in 2015. On the three-month course for palliative care specialists, two participants enrolled. They learned specialist palliative care in oncology including physical, psychosocial and spiritual supportive care during anti-cancer therapy, end-of-life care, support for decision making and advanced care planning.

Table 1. Number of patients

Cases	476	
Male/female	227	127
Age	53.9 (SD16.1)	

Table 2. Clinical stage

Ⅰ	9
Ⅱ	15
Ⅲ	20
Ⅳ	146
recurrence	224
others	26
unknown	36

Table 3. Primary site of cancer

brain, eyes	3
head and neck	8
esophagus	20
stomach	35
colorectal	58
hepatobiliary	5
pancreas	4
lung	20
breast	73
uterus, ovary	37
prostate	22
kidney, adrenal gland	2
thyroid	7
blood	3
bone	38
skin	3
soft tissue, methotelioma	49
unknown origin	46
others	13

Table 4. Symptoms

pain	402
breathlessness	108
nausea/vomiting	118
fatigue	65

List of papers published in 2015

Journal

1. Inoue I, Higashi T, Iwamoto M, Heiney SP, Tamaki T, Osawa K, Inoue M, Shiraishi K, Kojima R, Matoba M. A national profile of the impact of parental cancer on their children in Japan. Cancer Epidemiol, 39:838-841, 2015

Department of Psycho-Oncology

Ken Shimizu, Rika Nakahara, Yoshio Oshima, Masashi Kato, Saho Wada, Chikako Dotani, Hironobu Inoguchi, Saran Yoshida, Mariko Kobayashi, Chisato Kobayashi, Mae Endo

Introduction

The Department of Psycho-Oncology was reestablished in September 1995, together with the establishment of the Psycho-Oncology Division, the National Cancer Center Research Institute East (reorganized to the Division of Psycho-Oncology, Research Center for Innovative Oncology in 2005). One of the most important clinical activities of the department 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.

Routine activities

The Department of Psycho-Oncology consists of four full-time staff psychiatrists, three full-time staff psychotherapists and three part-time psychotherapists. The Department provides two major services; a clinic for outpatients (five 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 department has played an active role as a member of the palliative care team. There is a palliative care team meeting with other members of the team every Tuesday. Additionally, a multicenter joint clinical teleconference to discuss difficult cases is held biweekly on Thursday evenings with staff members from six cancer center hospitals and four university hospitals.

In 2015, a total of 1,032 patients were referred for psychiatric consultation (Table 1). The mean age was 52.3 years old and 21.8% percent of the referrals were outpatients. A total of 463 (44.9%) of all the referred patients were males (Table 1). The most common cancer referrals were patients with hematological and breast cancer (11.4%), followed by sarcoma (10.7%), colorectal cancer (10.2%), and lung cancer (9.4%). The most common psychiatric diagnosis that is based on the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) was adjustment disorders (25.5%), followed by delirium (20.9%), and major depressive disorder (11.1%), while 20.9% of the referrals had no psychiatric diagnosis. The three common mental disorders (delirium, adjustment disorders, and major depressive disorder) were responsible for half of the psychological problems.

Research activities

We are now developing the psychosocial intervention for allogenic hematopoietic stem cell transplant survivors, the purpose of which is to improve the quality of life. This year, we have planned an observational study to decide the intervention components.

We also explored the contents of "post-traumatic growth" in Japanese cancer patients. Post-traumatic growth is a positive dimension of patients' psychological change in the aftermath of trauma. Little is known about the process in Japanese cancer patients, and this result will provide precious information to develop interventions to support patients' psychological adaptation after cancer diagnosis.

Table 1. Psychiatric Consultation Data in 2015 (n=1,032)

	n	%
Age (years)	52.3	
Male	463	44.9
Inpatients	808	78.2
Top 5 cancers by site		
Hematological	118	11.4
Breast	118	11.4
Sarcoma	110	10.7
Colorectal	105	10.2
Lung	97	9.4
Psychiatric diagnoses		
Adjustment disorders	263	25.5
Delirium	216	20.9
Major depressive disorder	115	11.1
Others	222	21.5
No diagnosis	216	20.9

List of papers published in 2015

Journal

1. Wada S, Shimizu K, Inoguchi H, Shimoda H, Yoshiuchi K, Akechi T, Uchida M, Ogawa A, Fujisawa D, Inoue S, Uchitomi Y, Matsushima E. The Association Between Depressive Symptoms and Age in Cancer Patients: A Multicenter Cross-Sectional Study. J Pain Symptom Manage, 50:768-777, 2015

2. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Ogawa A, Fujisawa D, Sone T, Yoshiuchi K, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Personality traits and coping styles explain anxiety in lung cancer patients to a greater extent than other factors. Jpn J Clin Oncol, 45:456-463, 2015

Department of Diagnostic Radiology

Yasuaki Arai, Yasunori Mizuguchi, Gen Iinuma, Miyuki Sone, Hiroaki Kurihara, Nachiko Uchiyama, Hirokazu Watanabe, Minoru Machida, Mari Kikuchi, Tomoko Manabe, Mototaka Miyake, Syunsuke Sugawara, Hideaki Kobayashi, Koji Tomita

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. The Center for Interventional Radiology, launched in 2014, continues to provide various IR treatments for patients referred from other hospitals or clinics as well as patients at our hospital. We seek individuals with outstanding leadership capabilities, proven academic and administrative experience, the vision to build and sustain programs at the forefront of imaging research, and a commitment to clinical experience.

Table 1. Routine activities

Modality	Number of examinations
1 CT :	46,375
2 MRI :	8,665
3 IR :	5,591
4 RI :	4,597
5 Ultrasound :	16,062
6 Radiograph :	68,386
7 Gastrointestinal study :	1,972

Research activities

CT colonography (CTC) has been successfully introduced as an effective option for preoperative staging and colorectal screening in our center. Nearly 2,000 patients and/or candidates were examined with this modality in 2013. For the preparation of screening CTC, electronic cleansing with fecal barium tagging and automated CO_2 gas insufflation systems have been established in the formal National Cancer Center (NCC) collaboration studies with the associated companies. Furthermore, we are now developing computer-aided detection (CAD) for colorectal lesions, especially for flat lesions. The main purpose of our CTC research work is to conduct a multi-center trial to establish evidence regarding fully digitalized CTC for a colorectal screening system in Japan.

With use of one positron emission tomography (PET)/MRI scanner and three PET/CT scanners, molecular imaging of multi tracers consisting of [18F] FDG, [18F] FBPA, [11C] choline, [11C] methionine and [64Cu]-DOTA-antibody 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 has been conducted in 22 cancer patients this year. [11C]-choline and [11C]-methionine PET examinations have been scheduled routinely for two days per week. As for [64Cu]-DOTA-antibody PET imaging, [64Cu]-DOTA-trastuzumab PET has been conducted in HER-2 positive breast cancer patients. Respiratory-gated PET was evaluated to reduce breathing-induced artifacts using a four-dimensional PET protocol. It provided better localization and quantification of tumors around the lower thorax to the upper abdomen. For cancer treatment, internal radiotherapy was carried out in 20 thyroid cancer patients with use of radioactive iodine (I-131) chloride.

In accordance with the achievement of collaborative research with the associated company since 2009, Digital breast tomosynthesis (DBT) has been introduced as an effective routine option for preoperative evaluation since March 2014. Up to December 2015, 1,067 patients were examined.

A multicenter study has started to establish the CT classification of lung adenocarcinomas corresponding to the new International Association for the Study of Lung Cancer, American Thoracic Society and European Respiratory Society (IASLC/ATS/ERS) pathological classification and to build

the database of small adenocarcinomas. Digital Imaging and Communications in Medicine (DICOM) data of resected lung cancers from each institute have been accumulated and evaluated 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 data.

Image guided preoperative Breast Marking using ultrasound alone or combined with mammography has been performed for partial mastectomy cases in which it is difficult to determine the spread of disease. This technique makes it possible to resect abnormal lesions more precisely and helps to prevent both re-operation and local recurrence. A total of 85 cases were handled from January 2015 to December 2015.

We investigate the correlation between the image findings and clinical course of ovarian clear cell carcinoma.

Clinical trials

A major departmental research theme is establishing evidence for interventional radiology procedures. We have led a multi-institutional cooperative study group of interventional radiology (JIVROSG: Japan Interventional Radiology in Oncology Study Group) since 2002 as a steering organization of 95 participating domestic institutions. In this study group, we are investigating the efficacy of palliative interventional radiology in randomized controlled trials (RCTs) to compare it with other therapies. These palliative RCTs include: 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); and a phase III study evaluating the efficacy of stenting for superior vena cava/inferior vena cava (SVC/IVC) syndrome (JIVROSG-0807). JIVROSG-0807 and JIVROSG-0805 completed patient enrollment in 2013 and 2014, respectively. A feasibility study of Epirubicin-eluting-bead Embolization for Hepatocellular Carcinoma (JIVROSG-1301) also completed patient enrollment in 2014. Other ongoing clinical trials are a phase II study evaluating the efficacy of arterial infusion chemotherapy and radiotherapy for unresectable maxillary carcinoma (JIVROSG-0808), a phase II trial of palliative intra-arterial epirubicin/5FU therapy for patients with chemotherapy-refractory locally advanced or metastatic breast cancer (JIVROSG-1107 RESAIC-II) and a phase II study evaluating the efficacy and safety of n-butyl-2-cyanoacrylate (NBCA) in embolization (JIVROSG-0802). A phase I/II study of radiofrequency ablation (RFA) for pelvic malignant tumors (JIVROSG-0204) was stopped in 2014 due to the insufficient number and speed of patient enrollment.

Education

The clinical education and training of young radiologists is an important part of our department's activities. During 2015, six residents and one short-term resident were trained by our department. Educational opportunities were also provided to six overseas physicians from Malaysia, Taiwan, and India. We have several clinical or educational conferences. A daily clinical interventional radiology (IVR) case conference, a weekly educational case conference on diagnostic radiology, and a monthly IVR research conference, are held.

Future prospects

The Department of Radiology strives for excellence in clinical care, education, and research. Our goal is to provide outstanding patient-centered radiology services and to establish evidence in this area. Future challenges include promoting the active role of the Center for Interventional Radiology and facilitating imaging as biomarkers for personalized cancer treatments such as molecular-targeted agents, immunoagents, and boron neutron capture therapy.

List of papers published in 2015

Journal

1. Kono Y, Shimizu Y, Wakatsuki Y, Yasui N, Aso T, Kawamoto H, Kurihara H. Letter to the editor. Radiat Prot Dosimetry, 163:533-534, 2015

2. Mori M, Tsunoda H, Takamoto Y, Murai M, Kikuchi M, Honda S, Suzuki K, Yamauchi H. MRI and ultrasound evaluation of invasive lobular carcinoma of the breast after primary systemic therapy. Breast Cancer, 22:356-365, 2015

3. Yang Y, Suzuki K, Abe E, Li C, Uno M, Akiyama F, Yamauchi H, Kikuchi M, Ohde S, Deshpande G, Shibahara Y, Nakamura Y, Sasano H. The significance of combined CK5/6 and p63 immunohistochemistry in predicting the risks of subsequent carcinoma development in intraductal papilloma of the breast. Pathol Int, 65:81-88, 2015

4. Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, Watanabe H, Wu YL, Zielinski M, Ball D, Rami-Porta R, International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Board Members, and Participating Institutions. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol, 10:1675-1684, 2015

5. Horikawa M, Miyayama S, Irie T, Kaji T, Arai Y. Development of Conventional Transarterial Chemoembolization for Hepatocellular Carcinomas in Japan: Historical, Strategic, and Technical Review. AJR Am J Roentgenol, 205:764-773, 2015

6. Hiraki T, Koizumi J, Arai Y, Sakurai Y, Kumada H, Nambu Y, Hori S. Transcatheter arterial embolization of hypervascular tumors with HepaSphere: prospective multicenter open label clinical trial of microspheres in Japan. Jpn J Radiol, 33:479-486, 2015

7. Sofue K, Arai Y, Takeuchi Y, Tsurusaki M, Sakamoto N, Sugimura K. Ultrasonography-guided central venous port placement with subclavian vein access in pediatric oncology patients. J Pediatr Surg, 50:1707-1710, 2015

8. Inaba Y, Yamaura H, Sato Y, Kato M, Kawada H, Murata S, Hasegawa T, Arai Y. Side-Hole Catheter Placement with Fixation and Embolization in Common Hepatic Artery for Hepatic Arterial Infusion Chemotherapy (Modified CHA-Coil Method) for Patients with Celiac Artery Stenosis or Occlusion. Cardiovasc Intervent Radiol, 38:1621-1626, 2015

9. Arai Y, Aoyama T, Inaba Y, Okabe H, Ihaya T, Kichikawa K, Ohashi Y, Sakamoto J, Oba K, Saji S. Phase II study on hepatic arterial infusion chemotherapy using percutaneous catheter placement techniques for liver metastases from colorectal cancer (JFMC28 study). Asia Pac J Clin Oncol, 11:41-48, 2015

10. Sone M, Nakajima Y, Woodhams R, Shioyama Y, Tsurusaki M, Hiraki T, Yoshimatsu M, Hyodoh H, Kubo T, Takeda S, Minakami H. Interventional radiology for critical hemorrhage in obstetrics: Japanese Society of Interventional Radiology (JSIR) procedural guidelines. Jpn J Radiol, 33:233-240, 2015

11. Yoshimoto M, Kurihara H, Fujii H. Theragnostic imaging using radiolabeled antibodies and tyrosine kinase inhibitors. ScientificWorldJournal, 2015:842101, 2015

12. Morita S, Onaya H, Kishi Y, Hiraoka N, Arai Y. Multiple Intraglandular Metastases in a Patient with Invasive Ductal Carcinoma of the Pancreas. Intern Med, 54:1753-1756, 2015

13. Kurihara H, Hamada A, Yoshida M, Shimma S, Hashimoto J, Yonemori K, Tani H, Miyakita Y, Kanayama Y, Wada Y, Kodaira M, Yunokawa M, Yamamoto H, Shimizu C, Takahashi K, Watanabe Y, Fujiwara Y, Tamura K. ^{64}Cu-DOTA-trastuzumab PET imaging and HER2 specificity of brain metastases in HER2-positive breast cancer patients. EJNMMI Res, 5:8, 2015

14. Kinuya S, Yoshinaga K, Higuchi T, Jinguji M, Kurihara H, Kawamoto H. Draft guidelines regarding appropriate use of (131)I-MIBG radiotherapy for neuroendocrine tumors : Guideline Drafting Committee for Radiotherapy with (131)I-MIBG, Committee for Nuclear Oncology and Immunology, The Japanese Society of Nuclear Medicine. Ann Nucl Med, 29:543-552, 2015

Book

1. Sone M, Arai Y. Section B. Coils and Plugs - 5. Gelfoam. In: Marcelo G, Riccardo L, Gary PS (eds), Embolization Therapy: Principles and Clinical Applications, Netherland, Wolters Kluwer, 2015

2. Arai Y. Section D. Liquid Agents - 9. Glue. In: Marcelo G, Riccardo L, Gary PS (eds), Embolization Therapy: Principles and Clinical Applications, Netherland, Wolters Kluwer, 2015

Department of Radiation Oncology

Jun Itami, Yoshinori Ito, Hiroshi Igaki, Naoya Murakami, Koichi Inaba, Kana Takahashi, Rei Umezawa, Shuhei Sekii, Mayuka Kitaguchi, Ken Harada, Hiroyuki Okamoto, Shie Nishioka, Akihisa Wakita, Satoshi Nakamura

Introduction

The role of the Department is to provide state-of-the-art radiation therapy to all 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. A linear accelerator for hospital-based boron neutron capture therapy (BNCT) was installed in the new facility and an epithermal neutron beam could be obtained in August 2015 and the neutron facility passed the governmental inspection for radiation leakage. The Department is now fully involved in the development of BNCT. Through the assistance of the management of the center, the number of medical physicists was increased to four.

Routine activities

The Department of Radiation Oncology of the National Cancer Center Hospital is one of the biggest radiation oncology departments in Japan. Five linear accelerators, CyberKnife, one X-ray simulator, three XCT-simulators, and 15 treatment planning computers are working together through on-line networks to provide state-of-the-art precision external beam radiation therapy. In addition to the conventional X-ray and electron therapies, stereotactic irradiations of brain and body tumors and intensity-modulated radiation therapy (IMRT) are performed routinely. Stereotactic brain irradiation is performed with CyberKnife 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 in linear accelerators or CyberKnife. Four of the five linear accelerators have on-board kilovoltage CT imagers, which help to precisely align patient and tumor coordinates. 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. Gold marker fiducials have been implanted to improve geometric precision of radiation field reproducibility.

Brachytherapy is also intensively performed to improve local control and many patients are referred from all over Japan. For brachytherapy, the following modalities are being employed: an Ir-192 high dose rate (HDR) afterloading system including 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 Department is the only institution in Tokyo where HDR interstitial as well as intracavitary irradiations can be performed. HDR interstitial radiation is used mainly in gynecological, genitourinary, and head and neck tumors. Additionally, there are two 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 shortened fractionation regimen for various malignancies, especially for breast cancer and vocal cord cancer; 3) image-guided HDR and LDR brachytherapy for genitourinary and gynecologic cancers; 4) hypofractionated stereotactic irradiation of brain and body tumors; 5) adaptive radiation therapy in accordance with the intratherapeutic tumor and normal tissue change; and 6) development of an accelerator-based BNCT system.

Clinical trials

Brain tumors: A multicenter phase II/III trial on interferon-beta and temozolomide combination therapy for newly diagnosed glioblastomas.

Metastatic brain tumor: Phase II trial of hippocampal sparing IMRT

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 non-verified lung tumors.

Pediatrics: Phase II clinical trial on multimodality therapy in localized Ewing sarcomas and related tumors (The Japan Ewing Sarcoma Study Group (JESS 04)).

Head and neck cancers: Various JCOG (The Japan Clinical Oncology Group) studies including IMRT for nasopharyngeal and oropharyngeal cancers

Breast cancer: Phase II trial of SAVI applicator HDR brachytherapy after partial mastectomy.

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

Cervical cancer: Phase I/II trial of hybrid brachytherapy of cervical cancer

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

Development of an Adaptive Radiation Therapy System

Education

Five residents are trained in all fields of radiation oncology except particle beam therapy. Seminars about biology, physics, and clinical radiation oncology are regularly held in the evenings.

Future prospects

With the introduction of BNCT, new manpower will be required and research perspectives will be greatly widened. Additionally, installment of an MRI-Cobalt system is planned.

Table 1.

Year	No. of Patients 2014	2015
1) New patients referred to the Department	1,458	1,640
2) All patients undergoing radiation therapy	2,063	2,646
External Beam Radiation Therapy (EBRT)		
1) New patients undergoing EBRT	1,383	1,567
2) All patients undergoing EBRT	1,976	2,546
Brachytherapy (BT) and Radionuclide Therapy		
1) All patients undergoing intracavitary radiation	40	32
2) All patients undergoing interstitial radiation	78	101
3) All patients undergoing prostate permanent seed implantation	15	14
4) All patients undergoing I-131 therapy for thyroid cancer	22	6
5) All patients undergoing Sr-89 therapy for bone metastasis	2	4
Other Special Radiation Therapy		
1) All patients undergoing total body irradiation	68	56
2) All patients undergoing stereotactic brain radiation	247	426
3) All patients undergoing stereotactic body radiation	49	96
4) All patients undergoing intensity modulated radiation therapy	246	310
No. of New Patients according to the Primary Site		
1) CNS	48	56
2) Head and Neck	142	142
3) Esophagus	117	124
4) Intrathoracic	258	350
4)-a) Lung	136	305
5) Breast	296	332
6) Liver/Bile Duct/Pancreas	88	95
7) Digestive Tracts	252	277
8) GYN	80	74
9) GU	138	157
9)-a) Prostate	102	91
10) Hematopoietic/Lymphatic	88	95
11) Cutaneous/Bone/Soft Tissue	110	111
12) Other Malignancies	0	0
13) Benign	2	6
14) Children Less than 15 Years Old	19	24
Radiation Therapy of Brain or Bone Metastasis		
1) Brain metastasis	266	562
2) Bone metastasis	159	456

List of papers published in 2015

Journal

1. Murakami N, Yoshimoto S, Matsumoto F, Ueno T, Ito Y, Watanabe S, Kobayashi K, Harada K, Kitaguchi M, Sekii S, Takahashi K, Yoshio K, Inaba K, Morota M, Sumi M, Saito Y, Itami J. Severe gastrointestinal bleeding in patients with locally advanced head and neck squamous cell carcinoma treated by concurrent radiotherapy and Cetuximab. J Cancer Res Clin Oncol, 141:177-184, 2015

2. Satoh T, Dokiya T, Yamanaka H, Saito S, Ishiyama H, Itami J, Shibuya H, Nakano T, Shigematsu N, Aoki M, Egawa S, Hashimoto M, Nishimura T, Yorozu A. Postmortem radiation safety and issues pertaining to permanent prostate seed implantation in Japan. Brachytherapy, 14:136-141, 2015

3. Miyashita M, Kawakami S, Kato D, Yamashita H, Igaki H, Nakano K, Kuroda Y, Nakagawa K. The importance of good death components among cancer patients, the general population, oncologists, and oncology nurses in Japan: patients prefer ”fighting against cancer”. Support Care Cancer, 23:103-110, 2015

4. Murakami N, Kobayashi K, Nakamura S, Wakita A, Okamoto H, Tsuchida K, Kashihara T, Harada K, Yamada M, Sekii S, Takahashi K, Umezawa R, Inaba K, Ito Y, Igaki H, Itami J. A total EQD2 greater than 85 Gy for trachea and main bronchus D2cc being associated with severe late complications after definitive endobronchial brachytherapy. J Contemp Brachytherapy, 7:363-368, 2015

5. Murakami N, Okamoto H, Isohashi F, Murofushi K, Ohno T, Yoshida D, Saito M, Inaba K, Ito Y, Toita T, Itami J. A surveillance study of intensity-modulated radiation therapy for postoperative cervical cancer in Japan. J Radiat Res, 56:735-741, 2015

6. Kobayashi K, Murakami N, Wakita A, Nakamura S, Okamoto H, Umezawa R, Takahashi K, Inaba K, Igaki H, Ito Y, Shigematsu N, Itami J. Dosimetric variations due to interfraction organ deformation in cervical cancer brachytherapy. Radiother Oncol, 117:555-558, 2015

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8. Otani Y, Nose T, Dokiya T, Saeki T, Kumazaki Y, Asahi S, Tsukiyama I, Fukuda I, Sekine H, Shikama N, Takahashi T, Yoshida K, Kotsuma T, Masuda N, Yoden E, Nakashima K, Matsumura T, Nakagawa S, Tachiiri S, Moriguchi Y, Itami J, Oguchi M. A Japanese prospective multi-institutional feasibility study on accelerated partial breast irradiation using interstitial brachytherapy: treatment planning and quality assurance. Radiat Oncol, 10:126, 2015

Department of Pathology and Clinical Laboratories

Atsushi Ochiai, Nobuyoshi Hiraoka, Koji Tsuta, Shigeki Sekine, Koh Furuta, Noriko Motoi, Akiko Maeshima, Taisuke Mori, Hirokazu Taniguchi, Reiko Watanabe, Masayuki Yoshida, Akihiko Yoshida, Hiroshi Yoshida, Aoi Sukeda, Kuniko Sunami, Yae Kanai, Eri Arai, Shintaro Fukushima, Yuko Sasajima, Junko Itoh, Taiki Hashimoto, Koko Mitsuma, Michiko Sugiyama

Introduction

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

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. The laboratories in this Division have acquired the accreditation of ISO 15189, which certifies the quality and competence of a medical laboratory with regard to quality management and techniques, developed by the International Organization for Standardization's Technical Committee 212 (ISO/TC 212). In order to start a genome medicine where gene mutation profiles occurring in cancer tissues can contribute to select treatment options, a new genetic analyzing laboratory was established for performing comprehensive gene mutation analysis to clinical cancer samples using new-generation-sequencers under accreditation of semi- Clinical Laboratory Improvement Amendments (CLIA). The staff of the Clinical Laboratories Division will continuously work to improve the quality and quantity of laboratory services.

Routine activities

Pathology Division: In 2015, a total of 17 board-certified pathologists, four residents and 13 medical technologists, including nine 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. 16 pathologists working exclusively in the NCCH also shared management of the division. We provided a total of 23,720 histological diagnoses consisting of 23,720 biopsy specimens, including 2,102 intraoperative frozen sections, and 4,060 surgically resected specimens, a total of cytopathological diagnoses of 12,026 patients, including 446 for intraoperative diagnosis, and a total of 31 autopsies. We also provided a total of 222 pathological diagnoses for an outpatient clinic for pathology consultation (second opinion).

Clinical Laboratories Division: 52 full-time and nine part-time medical technologists, two photographers and five 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 NCCH, and in the sections of phlebotomy and physiological examination in the RCCPS. The sections of 1) to 5) are to be supervised by Drs. Koh Furuta and Kuniko Sunami, 6) and 7) by

Dr. Ryuji Tanozaki (Transfusion Therapy), 8) by Dr. Yasunori Mizuguchi (Diagnostic Radiology), Drs. Masaaki Shoji and Takeshi Iwasa (General Internal Medicine), and Dr. Eriko Iwamoto (Breast Surgery), and 9) by doctors in the Pathology Division. The bacteriology staff are members of the Infection Control Team and participate in infection management activities. The actual number of laboratory tests performed in this division in 2015 is shown in Table 2.

Research activities

1. Hepato-biliary pancreatic pathology

Tumor-infiltrating $CD8^+$ T cells, lower ratios of BTLA/CD8 and Cbl-b/CD8 were unfavorable prognosticators in gallbladder cancer patients. It was suggested that upregulation of BTLA in cancer tissues is involved in inhibition of antitumor immunity. We identified a significant subgroup of HER2-positive gallbladder cancer cases (16.6 %), for whom a clinical trial with anti-HER2 therapy might be considered.

2. Gastrointestinal pathology

We demonstrated the frequent presence of activating *GNAS* and *KRAS* mutations in heterotopic gastric-type mucosa in the duodenum, suggesting that these lesions are precursors to adenocarcinomas with a gastric epithelial phenotype. The common presence of *APC* mutations in pyloric gland adenomas was revealed by a genetic analysis of familial adenomatous polyposis-associated cases. A detailed histological analysis revealed highly prevalent lymphovascular invasion even in minute rectal carcinoids; this observation raises a question regarding its significance as a risk factor for metastasis.

3. Hematopathology

We reported clinicopathological characteristics of follicular lymphoma with peripheral blood involvement, lymphomas in the upper aerodigestive tract, and classical Hodgkin lymphoma of the elderly. We also reported pitfalls of flow cytometry for B-cell non-Hodgkin lymphomas.

4. Thoracic pathology

Clinicopathological analysis was made on HER2-mutated non-small cell carcinomas. Adenocarcinomas with cavitary changes were characterized. Ciliated muconodular papillary tumors were studied in a series of 10 cases. Myocardial sleeve tissues incidentally identified in lung resection specimens were analyzed. The utility of AR and GATA3 immunostaining in diagnostic settings was validated. A case of concurrent thymoma, thymic carcinoma, and lymphoblastic lymphoma was reported.

5. Bone and soft tissue pathology

Unusual superficial SMARCB1-deficient ER-positive tumors were characterized in a series of nine cases and they were proposed to constitute a potentially new nosologic entity "myoepithelioma-like tumors of the vulvar region" (MELTVR). Spindle cell/sclerosing rhabdomyosarcomas were clinicopathologically analyzed in 16 cases. Prognostic factors of epithelioid sarcomas were identified in a multi-institutional series of 44 cases.

6. Breast pathology

The frequent presence of *MED12* mutations among the phyllodes tumors of the breast was found regardless of the tumor grade. We found also that *TERT* promoter mutations were frequent in phyllodes tumors but rare in fibroadenomas. We proposed that intraductal papillomas on core biopsy could be upgraded to carcinomas on subsequent excisional biopsy regardless of the presence of atypical features.

7. Gynecological pathology

Immune contexture and PD-L1 expression status of uterine cervical adenocarcinoma have been reported. We have made case reports of an unusual recurrence pattern of uterine carcinosarcoma and uterine metastasis from duodenal adenocarcinoma.

8. Head and Neck/Ophthalmic pathology

We reported that in persistent severe chronic graft versus host disease (cGvHD) that underwent bone marrow transplantation there was the risk of oral squamous cell carcinoma development in long-term follow-up cases. We published the first case on primary intraocular synovial sarcoma.

9. Clinical Laboratories

An in-hospital bio-bank has been maintained for use by various researchers, and more than 650,000 post-clinical-test blood samples have been stored at -20 °C as of the end of 2015. Three sections of hematology, biochemistry and endocrinology, immunology and tumor markers, participated in

the external quality control program endorsed by the Japanese Society of Laboratory Medicine. Some medical technologists made interesting findings in their routine practice and made presentations at several domestic medical assemblies. In the molecular diagnostic section, mutation analyses of *EGFR*, *KRAS*, *NRAS*, and *BRAF* were provided as routine tests. At the cytogenetics section, 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 and maintained. These two sections provided data not only for clinical practices but also for research activities of doctors in the NCCH and/or the NCCRI.

Table 1. Numbers of histopathological and cytopathological specimens diagnosed and autopsies performed in the Pathology Division in 2015

Field	Histopathological Specimens	Cytopathological Specimens	Autopsies
Neurosurgery	290	48	2
Head and Neck	1,154	258	0
Breast	3,086	588	5
Respiratory organs	2,563	2,248	12
Gastrointestinal tracts	8,942	839	3
Hepatobiliary and Pancreas	805	638	3
Urology	858	2,795	0
Gynecology	1,397	3,886	0
Orthopedics	697	24	2
Dermatology	531	28	0
Hematology	1,639	366	3
Radiation Oncology	220	189	1
Others	305	117	0
Research Center for Cancer Prediction and Screening	1,233	2	0
Total	23,720	12,026	31

Table 2. Number of laboratory tests examined in the Clinical Laboratories Division in 2015

Section	Number
General laboratory medicine	544,154
Hematology	1,377,066
Biochemistry	3,264,652
Endocrinology, immunology, and tumor markers	409,377
Bacteriology	47,034
Physiology	102,574
Genetic diagnostics	35,470
Total	5,780,327

List of papers published in 2015

Journal

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Department of Experimental Therapeutics

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Introduction

In April 2015, the affiliation of the Department of Experimental Therapeutics was changed from the National Cancer Center (NCC) - the Exploratory Oncology Research & Clinical Trial Center (EPOC) to the NCC-Hospital. The goal of our Department is to perform initial clinical evaluation of promising new anti-cancer compounds emerging from the laboratory in phase I trials. The staff of this Department consists of specialists from various oncology fields (that is, thoracic oncology, breast & medical oncology, gastro-intestinal oncology, hepato-biliary & pancreatic oncology, and immune-oncology).

Routine activities

This Department plays an important role in new anti-cancer drug development in Japan as well as in Asia. The top priority is to conduct First-In-Human (FIH) trials, and we also perform phase I trials for solid tumors (that is, all comers). Recently, we have joined the global phase I trial to accelerate new drug development in Japan. Web- or tele-conferences are held with the EU and US sites, and we discuss patient enrollment as well as further developmental strategy. Routine web-conferences are also held between NCC-Hospital (Tokyo) and NCC-East Hospital (Chiba) every Friday morning, and we share information about adverse events, patient enrollment and refer candidates to each other to accelerate enrollment.

Research activities

The elucidation of the proof of concept is essential in new anti-cancer drug development especially in early phases, so we conduct several translational research (TR) projects in collaboration with the adjoining research institute. Comprehensive genomic analyses, named TOP-GEAR-studies, are ongoing to facilitate patient enrollment for new molecular targeted drugs under investigation. Also, we conduct the TR with the pharmaceutical industry to discover new targets for anti-immune therapy using human tissue (tumor and normal tissue) samples.

Clinical trials

In 2015, 20 phase I trials including 8 FIH trials were conducted (Table 1).

Table 1. Number of patients

No.	Target of agents	FIH	Tumors	Enrollment in 2015	Status
1	PD-L1		Solid tumors	5	Ongoing
2	FGFR	○	Solid tumors	10	Ongoing
3	B7-H3	○	Solid tumors	5	Ongoing
4	FGFR	○	Solid tumors	2	Ongoing
5	MDM2		Solid tumors	5	Closed
6	PI3K		Solid tumors	6	Closed
7	Hedgehog		Solid tumors	3	Closed
8	PD-1		Solid tumors	1	Closed
9	FGFR		Solid tumors	1	Closed
10	PDGFR		Solid tumors	18	Closed
11	MDM2	○	Solid tumors	3	Ongoing
12	mTOR		Solid tumors	12	Ongoing
13	HSP90	○	Solid tumors	11	Ongoing
14	MET+VEGFR	○	Solid tumors	3	Ongoing
15	CTLA-4		Solid tumors	8	Ongoing
16	AKT		Solid tumors	4	Ongoing
17	HER2	○	Solid tumors	3	Ongoing
18	PD-1+CCR4	○	Solid tumors	13	Ongoing
19	PI3K & mTOR		Solid tumors	3	Ongoing
20	Chk-1		Solid tumors	4	Ongoing

FIH: first in human trial

List of papers published in 2015

Journal

1. Ono M, Tsuda H, Yunokawa M, Yonemori K, Shimizu C, Tamura K, Kinoshita T, Fujiwara Y. Prognostic impact of Ki-67 labeling indices with 3 different cutoff values, histological grade, and nuclear grade in hormone-receptor-positive, HER2-negative, node-negative invasive breast cancers. Breast Cancer, 22:141-152, 2015

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Office of Infection Control and Prevention

Hisashi Baba, Noriko Wada, Keiichi Koido, Michi Shouji, Midori Ohkubo

Introduction

The mission of the Office of Infection Control and Prevention is to control healthcare-associated infections during a variety of cancer care including highly advanced cancer treatments. The Office consists of an Infectious Disease specialist (physician), a Certified Nurse in Infection Control, a Board-certified Pharmacist in Infection Control, an Infection Control Microbiological Technologist, and an office clerk. We execute our tasks in collaboration with the Infection Control Team, which consists of cross-sectional members from various areas throughout our hospital. We also collaborate with "link nurses" to facilitate appropriate infection control practice in each ward.

Routine activities

- Advice about the control and prevention of healthcare-associated infections, problematic pathogens including multidrug-resistant bacteria, and occupational infections.
- Supporting for physicians on appropriate diagnosis and treatments of infectious disease.
- Implementation of antimicrobials stewardship based on data from our hospital and clinical evidence.
- Monitoring of environmental maintenance and compliance with the manual of infection control practice in weekly ward rounds.
- Surveillance of healthcare-associated infections and drug-resistant bacteria.
- Staff education on various infection control practices including up-to-date evidence.
- Checking for immunization status of staff and vaccination for staff with insufficient protective immunity.
- Advice on building and refurbishment projects in terms of infection control aspect.
- Planning conferences among regional small and medium-sized hospitals to promote improvement of infection control in each hospital.

Research activities

- Effective education of infection control practice, especially medical device management.
- Appropriate dosing of antimicrobial drugs in cancer patients.
- Ideal system of infection control for cancer centers in Japanese medical care system.
- Virulence factors of *Bacillus cereus* isolated from an outbreak of bacteremia.

Future prospects

Our final goal is to establish an ideal and feasible model of an infection control system for cancer centers in Japan.

Outpatient Treatment Center

Kenji Tamura, Hiroshi Nokihara, Hidehito Horinouchi, Shunsuke Kondo, Satoru Iwasa, Chitose Ogawa, Yasuji Miyakita, Natsuko Okita, Atsuko Kitano, Mayumi Tsukagoshi, Mihoko Asanabe, Hiroe Ohara, Akiko Takeda, Tomonobu Otsuka, Hironobu Hashimoto, Toru Akagi, Satoshi Nakajima

Introduction

The Outpatient Treatment Center deals with all kinds of cancer patients who have received chemotherapies. Our mission is to provide safe, comfortable and high-quality chemotherapies. Several groups collaborate to ensure the best chemotherapies, consisting of medical oncologists, nurses, pharmacists, medical social workers (MSW) and clinical research coordinators (CRCs). Our visions are 1) To provide evidence-based medicine (EBM), and development of novel anti-cancer drugs. 2) To provide safe and efficient treatments, and management of adverse events. 3) To create a comfortable environment, and to maintain the quality of life of the patients.

Routine activities

1) Setup

Our Division consists of one director (doctor), another 11 medical doctors, one nurse manager, two deputy nurse managers, one deputy drug director, one chief pharmacist, one dispensing chief, one chief engineer, Dept. Clinical Laboratory, 15 nurses, three pharmacists, and two to three reception staff.

2) Performance

We established a second Outpatient Treatment Center in the beginning of 2015. There are 30 beds in the first Outpatient Treatment Center and 26 in the second Outpatient Treatment Center (a total of 56). We also have six beds for general infusions or blood transfusions.

In 2015, the Outpatient Treatment Center supported 31,861 patients who received anticancer drugs (Table 1). The breakdown by department was Breast and Medical Oncology (n=11,997), Gastrointestinal Medical Oncology (n=6,928), Hepatobiliary and Pancreatic Oncology (n=3,642), Hematology (n=2,912), Thoracic Oncology (n=2,870), and other departments (n=3,733). Clinical trials for unapproved drugs increased to around 240 cases per month. General infusions, general intramuscular or subcutaneous injections, blood transfusions, bone marrow puncture, lumbar puncture, intraperitoneal or chest drainage, and blood gas analyses were conducted in the center.

3) Staff meeting

The monthly staff meeting is held on the second Tuesday, 16:30-17:30, every month with the participation of physicians and nurses who are main members of the center. The steering committee is held on the third Thursday of every month.

4) Hot line and conference

We have a telephone consultation service (Hot line) for outpatients who have received chemotherapies. A case conference dedicated to the Hot line is held monthly on a Tuesday with the participation of multidisciplinary specialists, including medical oncologists, nurses, and pharmacists.

5) Research activities

- Treatment of platinum-containing regime in outpatient style.
- Efficacy of frozen globe against nail toxicities by docetaxel.
- Protection of allergic reaction by Oxaliplatin in outpatients.
- Management of skin toxicities as an adverse event of molecular-targeted drugs.
- Cosmetic support for female cancer patients
- Support for continuing working for outpatients.
- Telephone hot line for emergencies for outpatients who receive chemotherapy.

・Monitoring adverse events of immuno checkpoint inhibitors.

6) Publication

1) Kondo S, Shiba S, Udagawa R, Ryushima Y, Yano M, Uehara T, Asanabe M, Tamura K, Hashimoto J. Assessment of adverse events via a telephone consultation service for cancer patients receiving ambulatory chemotherapy. BMC Res Notes. BMC Res Notes. 2015 Jul 26; 8:315. doi:

Education

We provide educational opportunities for multidisciplinary specialists, including medical oncologists, nurses, and pharmacists. We also provide an educational program directed outside the hospital for medical oncologists, nurses, pharmacists and MSW in specially designed hospitals for cancer treatment in each prefecture.

Future prospects

We are planning to undertake more activities in the second Outpatient Treatment Center, and continue to propose a model for more clinical trials in an outpatient style. We aim to shorten waiting times, undertake the smooth administration of novel molecular targeted drugs for outpatients, put into practice multidisciplinary care, and create a comfortable environment for cancer patients who received chemotherapy in the Outpatient Treatment Center.

Table 1. Cumulative total number of patients who received anticancer drugs by intravenous administration

Department	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Total
Breast and Medical Oncology	937	951	991	979	918	999	1,074	939	998	1,052	1,027	1,132	11,997
Gastrointestinal Medical Oncology	600	549	565	612	569	550	624	547	544	537	543	688	6,928
Hepatobiliary and Pancreatic Oncology	292	283	282	315	289	277	342	304	304	298	327	329	3,642
Hematology	202	174	228	233	217	232	231	238	237	248	218	233	2,691
Thoracic Oncology	179	161	205	214	219	226	273	271	238	248	306	330	2,870
Others	322	213	319	325	346	316	321	314	325	298	316	318	3,733
Total	2,532	2,331	2,590	2,678	2,558	2,600	2,865	2,613	2,646	2,681	2,737	3,030	31,861

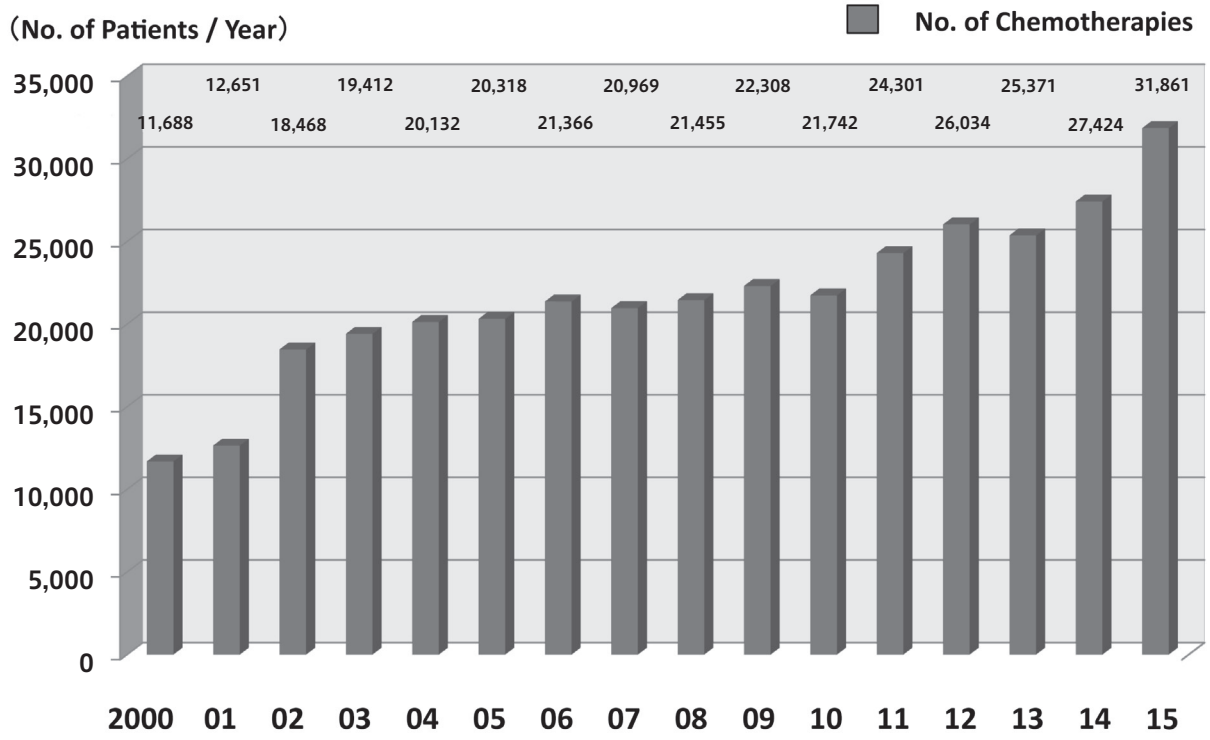

Figure 1. Total number of patients who received chemotherapy in Outpatients Treatment Center

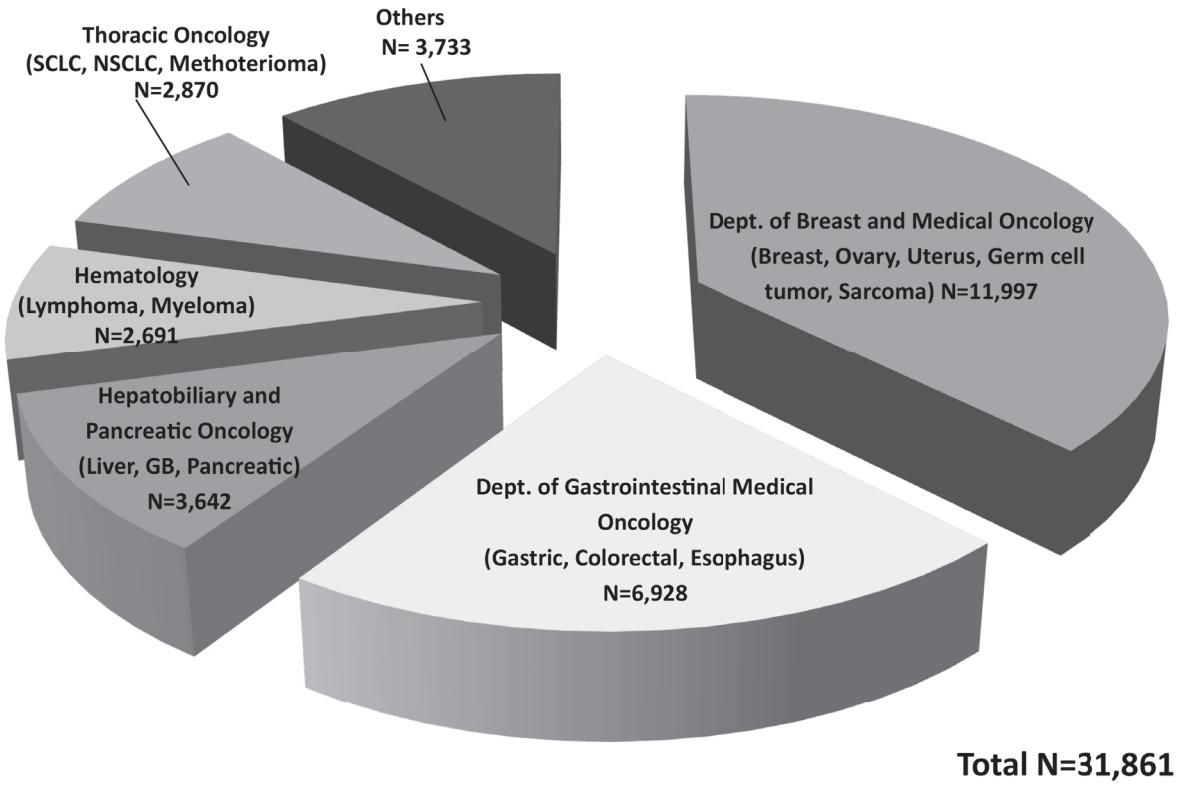

Figure 2. Proportion of cancer types in patients who received chemotherapy in Outpatients Treatment Center

List of papers published in 2015

Journal

1. Kondo S, Shiba S, Udagawa R, Ryushima Y, Yano M, Uehara T, Asanabe M, Tamura K, Hashimoto J. Assessment of adverse events via a telephone consultation service for cancer patients receiving ambulatory chemotherapy. BMC Res Notes, 8:315, 2015

Consultation, Counseling and Support Service Center

Masaki Kato, Kayoko Miyata, Natsuko Moroi, Rieko Shimizu, Naoko Goto, Mariko Tsuchiya, Miho Koitabashi, Megumi Ohsuga, Mariko Shimizu, Yumiko Fujimaki, Tomoko Asayama, Hyeon Ok Kim, Emi Takeuchi

Introduction

The Consultation, Counseling and Support Service Center provides psychosocial support services for people with cancer and their families. Staff, referred to as "Cancer Counseling and Support Specialists," were qualified as medical social workers, nurses and clinical psychologists. We make extensive efforts to solve patients' problems.

Routine activities

1) Consultation, Counseling and Support Services
   (1) Face-to-face counseling
   (2) Telephone counseling

Both face-to-face and telephone counseling are available for not only cancer patients but also their families and any people concerned with cancer. Any inquiries related to cancer such as cancer treatment and financial, social and psychological issues are accepted. We also make efforts to support special cases such as job seeking and infertility issues. Although we have tackled work-related issues so far, they are one of the major issues facing patients. Since 2013, we have cooperated with a "Hello Work Navigator," a job-finding advisor, and Social Insurance Labor Consultants to help cancer patients find new jobs and provide professional advice regarding managing cancer treatment and work. Moreover, we have prepared for the launch of a service for young adult patients who are concerned with impact of cancer treatment on fertility.

2) Activities accompanying Consultation, Counseling and Support Services
   (1) Holding group programs for patients and their families
   (2) Working on an interdisciplinary team with other medical staff
   (3) Coordinating care and patient pathways

We hold the following support groups and programs for the patients and their families

- The class for pancreatic cancer and biliary tract cancer
- The class for women before undergoing breast cancer surgery
- The support class for job seekers

We work with an interdisciplinary team with physicians, nurses and medical staff to improve or sustain patient's quality of life as much as possible. Also, in order to coordinate patient care and patient pathways, we arrange social resources and contact with other hospitals and institutions.

3) Cooperation activities with other regional hospitals and institutions
   (1) Information sharing with regional hospitals and institutions
   (2) Managing the medical institution database

4) Activities related to volunteers of the NCCH
5) Activities related to NCCH committees
6) Activities related to the education of NCCH staff
7) Administration of the patient library

Research activities

Research into young adult patients' concerns related to infertility has been conducted.

Education

We lecture and act as facilitators in seminars for education of Cancer Counseling and Support Specialists.

Future prospects

We practice high-quality cancer counseling and support, develop models and disseminate the results for the whole county.

Table 1. Number of cases (January 2015-December 2015)

1 Total	13,519
2 New cases	7,335
New cases from NCCH	3,608
New cases from other hospitals	3,727

Appearance Support Center

Keiko Nozawa, Naoya Yamazaki (Joint appointment in the Department of Onco-Dermatology), Chikako Shimizu (Joint appointment in the Department of Breast and Medical Oncology), Masahide Fujiki (Joint appointment in the Department of Plastic Surgery), Shoko Toma, Kazuko Aoki, Atsuko Ito, Eriko Takahashi

Introduction

The Appearance Support Center aims to support patients to be able to 'live in society' and to 'live as a human' through clinical research and educational practices regarding patients' physical appearance.

Clinical activities

Our team consists of two clinical psychologists (one full-time and one part-time) specialized in cosmetics, and they consult both in- and out-patients as well as their families for questions and concerns regarding physical appearance. Examples of issues are side effects of chemotherapy and radiotherapy on skin, nails, and hair, scarring and epithesis from surgeries, and breast surgery. In order to expand our practice beyond solely consultation, we are currently developing a new team in collaboration with a dermatologist, plastic surgeon, medical oncologist, pharmacist, and nurses.

The outpatient space is open to the public from Monday to Thursday between 12 am and 1 pm during which patients can try on different products and consult staff. Despite limited hours for security reasons, we had 894 users from January to December. Additionally, we conduct a patient support program titled "Cosmetic Information" every Tuesday and Thursday from 2 pm. Its main aim is to provide information to patients through group sessions. We had 99 sessions in which 438 patients participated. 40 men participated in "Men's Consultation Day" held on the fourth Wednesday of every month from 1 to 3 pm. In addition, we offered long-term inpatients a special program at the transplantation ward four times this year, and a total of 17 men and women participated.

As for individual consultations for new patients, there were a total of 1,696 consultations offered to 250 in- and out- patients. Patients' main concerns were coping strategies with specific symptoms. Following last year, consultations including seeking stress relief increased as patients with pediatric cancer increased. There were also consultations of concerns over significant life events such as the coming-of-age ceremony, weddings, and questions regarding mortuary makeup.

Research activities

Our center conducts research actively due to the lack of evidence regarding physical appearance. Current research projects are: the establishment of guidelines for support of cancer patients' appearance problems, the development of assessments and care methods for dermatological changes due to cancer treatment, the examination of distress by changes in physical appearance in male cancer patients and support by information provision, and the development of a program for an educational workshop on appearance care of cancer patients for cosmeticians.

Research outcomes

We instructed patients for treatments and care of side effects on physical appearance and developed a guideline that should guide medical staff (provisional). We also found that it was possible to evaluate skin symptoms by a device prior to grading by eyes. In addition, we investigated the effects of an appearance-related group program, and reported at the Annual Meeting of Japan Society of Clinical Oncology.

Education

In order to support medical staff to practice appearance care, "The Educational Workshop Regarding Appearance Care for Cancer Patients" was held three times in a year (237 participants) for medical staff working at designated regional cancer centers and hospitals. Additionally, we welcomed visitors of our hospital and held a special educational workshop to offer the same program conducted at Kobe University Hospital. We also held "The Educational Workshop on Appearance Care of Cancer Patients for Cosmeticians" once a year (30 participants).

Future prospects

We anticipate the emergence of patient needs of support for physical appearance as the variety of treatment drugs increases, longer-survival rates increase, and so on. Although responding to all patient needs is difficult as fulltime workers are scarce, we hope to expand human resources and develop this emerging field based on research.

Conferences

Sponsor: The Appearance Support Center (Center Hospital)
Conference title: The Educational Workshop on Appearance Care of Cancer Patients for Medical Staff: Basic course
Date: November 8th - December 20th, 2015
Location (prefecture): Tokyo

Sponsor: The Appearance Support Center (Center Hospital)
Conference title: The Educational Workshop on Appearance Care of Cancer Patients for Medical Staff: Advanced course
Date: October 11th, 2015
Location (prefecture): Tokyo

Sponsor: The Appearance Support Center (Center Hospital)
Conference title: The Educational Workshop on Appearance Care of Cancer Patients for Cosmeticians
Date: January 31st, 2016
Location (prefecture): Tokyo

List of papers published in 2015

Journal

1. Nozawa K, Ichimura M, Oshima A, Tokunaga E, Masuda N, Kitano A, Fukuuchi A, Shinji O. The present state and perception of young women with breast cancer towards breast reconstructive surgery. Int J Clin Oncol, 20:324-331, 2015

Rare Cancer Center

(NCCH) Akira Kawai, Yoshitaka Narita, Shigenobu Suzuki, Seiichi Yoshimoto, Kan Yonemori, Mayu Yunokawa, Makoto Kodaira, Tatsunori Shimoi, Yasushi Goto, Yoshitaka Honma, Chigusa Morizane, Motokiyo Komiyama, Tomoyasu Kato, Hirokazu Chuuman, Yoshikazu Tanzawa, Eisuke Kobayashi, Makoto Endo, Naoya Yamazaki, Arata Tsutsumida, Akira Takahashi, Kenjiro Namikawa, Wataru Munakata, Chitose Ogawa, Ayumu Arakawa, Miyuki Sone, Shunsuke Sugawara, Hiroshi Igaki, Kana Takahashi, Akihiko Yoshida, Noboru Yamamoto, Shunsuke Kondo, Koichi Ichimura, Tadashi Kondo, Takahiro Higashi, Takuro Sakurai, Makiko Murase, Yoko Katoh, Natumi Takeuchi,
(NCCHE) Naoto Gotohda, Tetsuo Akimoto, Fumihiko Nakatani, Ako Hosono, Toshihiko Doi, Yoichi Naito, Junya Ueno

Introduction

The Rare Cancer Center was launched in December 2013 and officially opened in June 2014 as a multidisciplinary team to take measures against the innate problems associated with rare cancers. Based on discussions, rare cancers are defined as those with an incidence < 6/100,000/year. Although each rare cancer is rare by itself, when the numbers of each rare cancer are combined, they correspond to up to 15% of all new cancer diagnoses. Information on rare cancers is scarce. Rare cancers are often inadequately diagnosed and treated in relation both to lack of knowledge and clinical expertise. Patients with rare cancers face great difficulty in having their diseases treated adequately.

Activities

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

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

I) Establishing a vital network of diagnosis and treatment for rare cancers in the NCC Hospital and Hospital East.
II) Reviewing the problems associated with rare cancers in Japan and making proposals and taking up the issues as medical professionals.

To enable the Center to play its role, a total of 45 doctors, nurses and researchers dealing with rare cancers have joined as members of the Center. Each staff member of the Rare Cancer Center provides specialized, high-quality medical care to patients with rare cancers in cooperation with his/her Department staff.

The Rare Cancer Center provides consultation to the patients and relatives with rare cancers on the telephone (Rare Cancer Hotline). The number of telephone call was 3,006 cases in 2015. (Figure 1) The Center also provides comprehensive, scientifically based, up-to-date unbiased information about rare cancers to all patients, families and health professionals fighting against rare cancers via its website (Rare Cancer Center Homepage). The Rare Cancer Center organized the 1st International Cancer Research Symposium "Rare Cancers: Seeking Ideal Medical Care" on February 12 to 13, 2015. Also, staff of the Rare Cancer Center served as members of the committee on rare cancers (March to August, 2015) set up by Ministry of Health, Labour and Welfare.

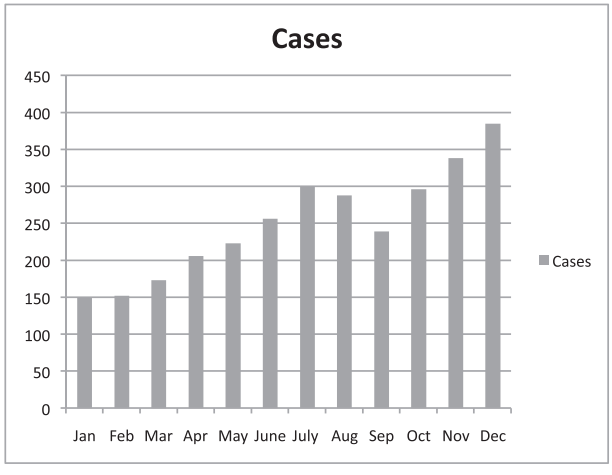

Figure 1. The Number of telephone calls to the Rare Cancer Hotline in 2015

List of papers published in 2015

Journal

1. Tahara M, Kiyota N, Mizusawa J, Nakamura K, Hayashi R, Akimoto T, Hasegawa Y, Iwae S, Monden N, Matsuura K, Fujii H, Onozawa Y, Homma A, Kubota A, Fukuda H, Fujii M. Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). Cancer Sci, 106:726-733, 2015

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Book

1. Sone M, Arai Y. Section B. Coils and Plugs - 5. Gelfoam. In: Marcelo G, Riccardo L, Gary PS (eds), Embolization Therapy: Principles and Clinical Applications, Netherland, Wolters Kluwer, 2015

Department of Radiation (Diagnosis)

Tomohiko Aso, Kanyu Ihara, Yuzuru Kouno, Takamasa Hirai, Noriko Nishikawa, Naoya Ikeno, Hirobumi Nagasawa, Jun Takita, Naotoshi Atoda, Chieko Nagashima, Akira Inagaki, Hideaki Kitamura, Mayumi Kitagawa, Akiko Nagoshi, Kiyoyuki Kodama, Masahiro Suzuki, Takeshi Murano, Junko Sonehara, Naoki Shimada, Toshimitsu Utsuno, Kenta Hiroi, Jun Torii, Eiko Taguchi, Midori Nagata, Mari Sakaguchi, Yusuke Miyamoto, Takumi Iwase, Yuji Jibiki, Yuya Kanai, Nao Ozaki, Gyoko To, Yuto Tanaka, Ryo Kawana, Yusuke Wakatsuki, Yuhei Shimizu, Aika Ozaki, Seiya Sato, Akira Yoshida, Syunichi Usui, Yuto Kakuta, Hiroyuki Saegusa, Tomomi Saito, Masae Fujisawa, Syuuji Teraoka, Syouta Kuribayashi

Introduction

The Department of Radiological Diagnosis has a wide range of radiological modalities, including interventional radiology (IR), general X-ray, computed tomography (CT), magnetic resonance imaging (MRI), mammography, ultrasound, and nuclear medicine (NM). This year we installed positron emission tomography (PET)-magnetic resonance imaging (MRI) to provide improved clinical information.

In order to meet increasing clinical needs, we put a considerable effort into education and training for the staff. Serving as a teaching hospital, we accept not only domestic but also oversees students, visitors, and trainees.

Routine activities

1) General X-ray

We have successfully reduced radiation exposure and installed real-time imaging by installing two wireless unlinked flat panel detector (FPD) systems. We provide qualified medical images, sharing patient information and the purpose of examination among the radiological technologists (RTs) before they take X-rays. The amount of mammography is also on the increase and inspection frames have been doubled, resulting in the patients' waiting time being reduced. RTs routinely take part in preoperative and pathological conferences. Ultrasonic mammography has been performed by RTs.

2) Computed Tomography (CT)

The number of examinations is on the increase.

We have performed a joint study with Toshiba medical systems. We gave many presentations and lectures on image quality assessment and clinical application of super high-definition CT both inside and outside Japan.

We gave some lectures to radiological technologists on the acquisition and reconstruction technique of CT for cancer patients at a skill improvement intensive seminar supported by the Ministry of Education, Culture, Sports, Science and Technology.

We have improved three dimensional (3D)-CT image displays that resulted in new stereography technology, which enables observers to see the object in three dimensions (3D) without any aids.

In the quality control (QC) activity scope, hand disinfection and glove procedures have been thoroughly installed as a measure against hospital acquired infection.

3) Magnetic Resonance Imaging (MRI)

The number of MRI cases amounted to over 8,500 this year. We have made a considerable effort to meet this increasing clinical demand. Since PET/MRI was installed and started working in October, we have offered technical support to the Nuclear Medicine section.

4) Interventional Radiology (IR)

We made some presentations on the education program for RTs and how we should be in this department at international conferences. We had discussions with nurses and RTs from Korea and Singapore. We made a survey on incomplete medical billing in cooperation with the accounting section and fed back the results. We started making bed-side explanations to the examinee before IR, resulting in improving their understanding and consent for such procedure.

5) Fluoroscopy

We perform various kinds of X-ray examinations including plain lung CT, CT colonography and conventional fluoroscopies. The number of plain lung CT and CT colonography (CTC) cases are on the increase. This trend owes to patient-friendly procedures especially in the case of CTC.

We accept RTs from other institutions for technical training on CTC, which contributes to disseminating and improving this technique.

6) Endoscopy

The number of endoscopies is on the increase according to the increasing clinical demand. We undertook joint research on improving 2D and 3D fluorography.

7) Nuclear Medicine

PET-MRI has been installed and the clinical significance of PET has been disseminated. New single photon emission computed tomography (SPECT) examination "somatostatin receptor scintigraphy" will be performed in 2016 for the first time in our institution.

The number of PET cases in 2015 was about 4,300 and that of SPECT was about 1,800.

Education

We train the staff and plan job rotation effectively using our own education and achievement program.

Our staff regularly attend various training sessions supported by the Ministry of Health, Labour and Welfare, the National Hospital Organization and so on.

The staff also attend clinical department conferences (for example, breast surgery and urology) sharing lots of information.

We accept not only domestic but also oversees students.

List of papers published in 2015

Journal

1. Kitamura H, Kono Y, Murano T, Hiroi K, Ihara K, Aso T, Inoue K, Fukushi M. Estimation of radioactivity in single-photon emission computed tomography for sentinel lymph node biopsy in a torso phantom study. Nucl Med Commun, 36:646-650, 2015

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Department of Radiation (Oncology)

Yoshihisa Abe, Tooru Kato, Ako Aikawa, Masashi Ito, Minoru Hamada, Yosihiro Shibata, Yuya Suzuki, Tatsuya Mogaki, Emi Sakamoto, Toshiyoshi Katahira, Satoshi Nakajima, Yuuki Miura, Daisuke Fujiyama, Manabu Kimura, Kenta Hashimoto, Takuya Nakagawa, Rie Ishikawa, Shuuhei Kamikaji

Routine and research activities

1) Our Department installed a new Linear Accelerator (LINAC) and CyberKnife system last year and analyzed their operating efficiency. As a result, our Department effectively utilized those systems.
2) Our Department was able to perform on all the patients who needed Total Body Irradiation (TBI) treatment before bone marrow transplants.
3) Our Department performed the treatment with five LINACs, and also has seen stable operation with the new LINAC with various energy levels. Thus, high-precision treatment could be performed efficiently. No treatments were interrupted because they could be carried out among these LINACs.
4) Two years have passed since the installation of CyberKnife. Our Department had 20 new patients and an introduction rate of 20% per month on average. Stereotactic Radio Surgery (SRS) using real-time tracking capabilities has started.
5) A facility inspection by an administrative agency has been completed to allow the installation of a hospital-based accelerator Boron Neutron Capture Therapy (BNCT) system.

Research results

Our Department developed and assessed an automatic tumor identification system on CT imaging for BNCT.

Education

1) Our Department systematically rotated the staff and educated them effectively using our education program.
2) Our Department accepted many visitors and trainees from all around Japan.
3) Our Department accepted students from the Department of Radiological Science, Graduate School of International University of Health and Welfare.
4) Our Department accepted not only domestic but also overseas students studying radiological technology.

Future prospects

1) Our Department aims at the early start of BNCT by installing a LINAC system and its peripheral equipment specifically designed for this purpose.
2) Our Department contributes to immediate pharmaceutical approval of the BNCT system, and to disseminating the system worldwide.
3) Sixteen years have passed since installing the first LINAC system. Our Department plans to smoothly renew the LINAC system.

Clinical Laboratories

Satoshi Nakajima, Shigeyuki Hasuo, Masahiro Uchikawa, Susumu Wakai, Naoshi Sasaki, Motoi Miyakoshi, Koji Ono, Hiroshi Yamakawa, Ryuzaburo Ohtake, Akashi Koseki, Yoji Hashimoto, Yasuo Shibuki, Hiroki Kakishima, Tomohiro Nakatani, Michi Shoji, Tsutomu Watanabe, Rie Matsuo, Yukie Nakajima, Sachiko Kobayashi, Katsuhide Ikeda, Kazuya Tokita, Satoe Miyaki, Kumiko Nagasaki, Noriko Takahashi, Mizuho Fujima, Daisuke Asahina, Tomoe Ito, Midori Hashimoto, Kaori Ueki, Fumie Watanabe, Akino Chiba, Takako Takada, Kyoko Osanai, Yuko Adegawa, Ruriko Miyake, Asuka Matsunaga, Hiroshi Chigira, Go Sato, Sakiko Yoshimura, Yuu Aruga, Saori Kobayashi, Kaori Yamaguchi, Ryoko Uegaki, Kensyo Kashiwaya, Saori Nakabayashi, Shingo Nakajima, Hideya Matsubayashi, Saeko Shirahama, Akiko Takayanagi, Mei Fukuhara, Kumi Ohashi, Momoko Kitou, Moemi Kasane, Kazuki Ito, Haruki Sasaki, Asuka Takaku, Keiko Arai, Yuri Kurosawa, Megumi Masuda, Yoshiko Shibata, Naomi Fujiki, Ritsuko Tohyama, Chieko Nozawa, Kozaburo Endou, Keiko Mizukoshi, Kiyoaki Nomoto, Masahiko Ushigome, Minami Takahashi, Sachiko Katayama, Shigeru Tamura, Megumi Miura

Routine activities / Research activities

The services of the Clinical Laboratories are organized into five sections: in vitro diagnostics (routine tests, hematology, biochemistry, immunity and serology, bacteriology, and genetic diagnosis), transfusion and cell therapy testing, blood collection, physiological examination, and histopathology. The Clinical Laboratories have obtained accreditation under ISO 15189, the international standards for quality management and technical competence in medical laboratories, after successful completion of the second surveillance stage. The In Vitro Diagnosis Section has undertaken a complete renewal of hematology and coagulation test systems to improve its ability for timely provision of accurate test results. The Transfusion and Cell Therapy Testing Section is using KM-CART (novel cell-free and concentrated reinfusion therapy) for the management of patients with refractory ascites. It also has renewed the fully automated pre-transfusion testing system, achieving better safety in the management of blood products. The Histopathology Section has been reinforced with the introduction of an automatic thin section machine in response to the increase in the number of specimens, and is preparing it for full-scale operation. The Physiological Examination Section has been experiencing increases in electrocardiography and echocardiography in clinical trials and ultrasonography of lower extremities for the close assessment of deep vein thrombosis. In response, the Section has been refurbished with the renewal of the electrocardiography filing system and respiratory function test equipment, as well as the expansion of circulatory function tests. The Genetic Diagnosis Section has opened the Sysmex Cancer Innovation Laboratory (SCI-Lab), which performs exhaustive gene analysis using the next-generation sequencer (NGS) in collaboration with Sysmex. The total number of laboratory tests in 2015 was 5,780,327, recording a 7% increase from the previous year. In particular, genetic diagnosis tests and physiological examination increased by 9% and 10%, respectively (Tables 1 and 2). The Clinical Laboratories are also cooperating in the promotion of academy-industry-government joint research, clinical trials, and biobank projects.

Research achievement

The Clinical Laboratories are working actively toward the improvement of accuracy and standardization in genetic diagnosis.

Education

The Clinical Laboratories conducted a revision of their original system for accreditation in blood collection, which has been in place since the previous year. The system is being continued with the elongation of the period of training and enrichment of technical training, including

education in reception for blood collection, handling of specimens, response to mechanical problems, and dealing with patients. Young technologists are assigned to specialist sections after mastering the basics of laboratory work in the In Vitro Diagnostics Section. A workshop focusing on ISO 15189 was held to ensure the adherence to the quality management system under ISO. Because reinforcement of individual sections is essential to the improvement of the Clinical Laboratories as a whole, monthly study meetings were held and personnel were encouraged to participate in and give presentations at external seminars and academic conferences. As a new initiative, the Clinical Laboratories launched an internship program with universities, aiming to promote the appeal of medical laboratory work.

Future prospects

The Clinical Laboratories intend to construct a system in which medical laboratory technologists play a part in the services of SCI-Lab and participate in the development of advanced medical techniques. In the Microbiology Section, we intend to shorten the time to reporting of test results through the use of a mass spectrometer mainly in blood culture tests, where immediacy is demanded. In ultrasound tests, we intend to establish a system to evaluate the cardiotoxicity of anticancer agents. In response to the increasing number of patients, we strive to shorten waiting time with an emphasis on TAT (turnaround time) from blood collection to analysis and the reporting of results.

Table 1. Trends in the total number of laboratory tests

Item	Number in 2014	Number in 2015
Routine tests	507,051	544,154
Hematology	1,308,384	1,377,066
Biochemistry	2,999,388	3,264,652
Immunity and serology	368,436	409,377
Microbiology	49,126	47,034
Physiological function tests	93,522	102,574
Histopathology	34,352	35,470
Total	5,360,259	5,780,327
Tests for research purpose	192,563	190,551
Commissioned tests	23,355	28,713

Table 2. Trends in the number of genetic diagnosis tests

Item	Number in 2014	Number in 2015
Nucleic acid identification of hematopoietic neoplasm	330	352
HER2 gene (FISH)	180	242
Malignant soft tissue neoplasm (FISH)	41	35
EGFR	261	264
Total	812	893

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 18 surgical oncology groups, nurses, and medical-technical staff with support staff from Department of Pathology and Clinical Laboratories.

Routine activities

During 2015, the Surgical Center supported 5,294 surgical cases and 4,738 general anesthesia surgical cases, a 12.6% increase in the general anesthesia cases over 2014. 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, and are occasionally performed in the Surgical Center. Over the years, minimally invasive procedures have increased remarkably. Endobronchial brachytherapy under general anesthesia in lung cancer, endoscopic resection under general anesthesia in GI cancer are also unique treatments and are carried out in the Surgical Center.

The Da Vinci robotic surgical system has been introduced to provide less invasive surgery for the patients for not only prostate cancer but also rectal cancer.

The post-anesthesia care unit has been a part of the Surgical Center this year.

The multidisciplinary meeting started in 2014. The multidisciplinary team includes medical doctors, nurses, and ME, and meet to plan the best surgical pathways during operations.

The Surgical Center staff work as part of a multidisciplinary team active in planning the best utilization of operating rooms. Scheduling, equipment usage, and staffing in the 16 operating suites were evaluated to establish an optimal work flow, streamline room turnover, and improve start times.

A medical device nurse, who is engaged in equipment usage, has been assigned.

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	364	396	422	385	330	433	453	413	385	382	379	396	4,738
Others	31	48	39	57	33	46	44	43	48	48	53	66	556
Total	395	444	461	442	363	479	497	456	433	430	432	462	5,294

Table 2. Number of general anesthesia cases

	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
Neurosurgery	7	11	19	8	8	17	13	12	10	10	11	12	138
Ophthalmology	26	24	30	23	26	24	32	26	28	32	28	32	331
Head and Neck Surgery	17	23	26	24	17	21	27	22	24	23	26	22	272
Breast Surgery	44	41	53	47	41	57	58	48	44	50	48	42	573
Thoracic Surgery	53	52	56	49	43	64	68	53	46	50	57	56	647
Esophageal Surgery	9	11	10	12	11	12	12	13	9	9	11	10	129
Gastric Surgery	35	42	39	41	39	43	48	50	41	39	36	38	491
Colorectal Surgery	43	44	44	42	33	46	49	48	54	44	39	41	527
Hepatobiliary and Pancreatic Surgery	26	23	24	28	23	28	25	25	21	24	22	23	292
Gynecology	23	21	25	23	23	25	24	24	18	24	22	21	273
Urology	22	25	30	28	27	32	35	31	28	27	28	30	343
Dermatology	12	10	11	10	7	14	13	8	10	8	6	8	117
Orthopedic Surgery	24	21	31	30	19	29	25	27	28	25	21	32	312
Plastic and Reconstructive Surgery	9	8	9	5	3	7	10	10	11	9	10	14	105
Endoscopy	7	7	10	7	6	5	4	6	8	4	4	7	75
Radiation Oncology	2	2	2	3	2	3	4	6	2	2	5	5	38
Transplantation	3	4	2	3	2	4	4	2	2	2	4	3	35
Pediatric Surgery	2	0	1	2	0	2	1	2	0	0	0	0	10
Total	364	369	422	385	330	433	452	413	384	382	378	396	4,708

Physician Referral Service Office

Hidehito Horinouchi, Makiko Murase, Maya Ozawa, Hisako Tanaka, Keiko Tsutsumi, Fumiko Onishi

Introduction

The physician referral service office was established as an independent section directly under the director of the hospital. The mission of this Office is to provide appropriate access to best cancer practice for more patients and their physicians. To help cancer patients with various needs to visit the National Cancer Center Hospital, the physician referral service office consists of a physician, a nurse, a medical social worker and one clerk. This office also corresponds with inquiries for patients' medical records from their physician. Another important activity is to record and analyze the information concerning patients' referral to the National Cancer Center Hospital.

Routine activities

1) Physician referral service
   Through strong collaboration with the reservation center, this office helps patients and their physicians promptly select the proper doctor.
2) Inquiry for patients' medical record
   We receive and correspond with inquiries for medical records from physicians who see patients from our hospital.
3) Relationship with affiliated hospitals and clinics
   We send reminders to patients' physicians at the time of patients' first visits to our hospital. To maintain our relationships, we hold regular meetings and invite physicians from affiliated hospitals and clinics.
4) Record and analysis of clinical information
   The information of all patients and their physicians is appropriately recorded in order to analyze and apply for next strategies for a better service.
5) Corporation with intramural departments and staff

To provide best practice, we make a considerable effort to collaborate with intramural departments, sections and staff.

Future prospects

The physician referral service office will continuously support patients, physicians and other medical staff for better cancer treatment and care.

Table 1. Routine activities of Physician Referral Service Office

	Referral reply letters	Medical record inquiries	FAX service	Reservation support
January	764	85	60	19
February	763	95	59	12
March	858	118	77	35
April	854	105	49	33
May	798	111	69	40
June	870	130	84	30
July	966	147	50	51
August	892	126	75	29
September	756	142	67	41
October	968	150	70	45
November	948	165	72	47
December	962	138	75	44
Total	10,399	1,512	807	426

Nutrition Management Office

Mayumi Miyauchi, Tomoko Suzuki, Hiroko Abe, Noriko Aoki, Saki Hoshino, Moe Nishio, Ayumi Makita, Maki Miura, Naomi Togashi

Introduction

In 2015, I placed emphasis on NST（Nutrition Support Team）activities. As for the number of interventions, the number increased 1.5 times. As a novel measure, I participated in the AYA (Adolescence and Young Adult) support team. The significance of the involvement of prandial activities to AYA was understood and the NST involvement number increased. In accordance with the amendment of the Overview of Dietary Reference Intake for Japanese (2015), I reexamined the patient's prandial standards. I participated in the creation of the guidelines as a committee member at the Japan Pancreas Society's pancreatic-carcinoma guideline meeting.

Routine activities

The therapeutic diet, which is provided as part of nutritional therapy, accounted for 441,164 meals. We also provided 1,432 dietary consultations. The NST accepted 931 patients, and consultations averaged 78 cases per month. It was 1.5 times greater than the number for the previous year. (Table 1)

Research activities

We created the assessment sheet corresponding to the prandial activities that we are performing through collaboration, and announced this to the Japan Society of Metabolism and Clinical Nutrition.

In addition, we are conducting research on nutrition and the diet management environment of cancer patients thanks to a cancer survivorship research grant from the Foundation for Promotion of Cancer Research.

I conducted the factual survey of the taste disorder in a stomach-cancer postoperative auxiliary treatment as a cancer research and development.

We participated in a seminar and symposium on cancer survivorship, holding such things as open classes, and performed the educational activities in the region.

The study meetings in 2015 were as follows:

1) The Nutritional Management Workshop for cancer patients marked its 34th anniversary, and "Nutrition past, present and future" was delivered as the President's lecture in Tokyo.
2) Cooperation to provide the meal courses for cancer prevention targeting the general public and cancer nutritional management courses held by the university (in Miyagi, Yamanashi and Tokyo)
3) Research initiatives

① Fact-finding for taste disorders
② Prospective observational study on the long-term follow-up system in a single facility after allogeneic hematopoietic stem cell transplantation
③ Cancer survivorship study

Education

In the field of human resources development, we have a strong commitment to education and training and conducted 10 university courses for registered dietitians within the university. By strengthening our cooperation with universities, our aim is to enhance future research activities through the development of human resources.

Future prospects

We aim to provide effective nutritional management and nutrition counseling services, to achieve improved treatment outcomes, as well as enhance vital prognosis and patient's QOL. In

addition, we try to cultivate human resources who are expected to become the core of the NST, which is involved in nutritional clinical research.

Table 1. Number of NST consultations in 2015

Clinical Departments	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sept	Oct	Nov	Dec	Total
Esophageal Surgery		1	1	2		4	4	2	4	2	3	6	29
Head and Neck Surgery	5	6	12	7	3	7	5	6	6	8	9	11	85
Gastrointestinal Medical Oncology	9	20	9	14	16	13	18	21	12	17	9	18	176
Hematopoietic Stem Cell Transplantation	11	10	8	13	11	10	13	8	11	13	14	7	129
Thoracic Oncology	5	16	10	16	10	11	18	13	17	9	15	15	155
Thoracic Surgery			1	4			1	3	1	1	1	1	13
Hepatobiliary and Pancreatic Oncology	11	5	8	5	7	5	3	4	3	8	3	7	69
Hepatobiliary and Pancreatic Surgery	9	6	3	7	8	8	7	8	6	18	18	17	115
Breast Oncology and Medical Oncology	3	2	3	3	3	1		3	3	5	9	11	46
Gynecology	1		2	2	3	1	1		2		4	3	19
Neurosurgery and Neuro-Oncology								1					1
Gastric Surgery	16	20	15	11	23	29	24	24	18	17	25	18	240
Colorectal Surgery	10	14	11	9	9	16	12	12	4	12	11	10	130
Urology	2	1	2	2	2	4	4	6	4	4	2	7	40
Pediatric Oncology		1			1			1		1			4
Musculoskeletal Oncology	1			2	1	4	5	3	6	9	4	4	39
Dermatologic Oncology		1		2	3	2	6	4	3	1		2	24
Hematology	5	4	2	5	1	5	2	3	4	7	5	3	46
Radiation Oncology	3	4	2	5	4	7	2	9	2	3	4	12	57
Diagnostic Radiology				1						1	1		3
Breast Surgery													0
Gastrointestinal Endoscopy						2		1	1	1			5
Respiratory Endoscopy													0
Plastic and Reconstructive Surgery			1										1
Experimental Therapeutics				1		1	1		1		1	1	6
Total	91	111	90	111	105	130	126	132	108	137	138	153	1,432
												mean	119

Health Information Management Office

Hiroshi Nishimoto, Mieko Furumoto, Shinobu Fukuoka, Yukiko Sekimizu, Masami Kakimoto, Marika Nozuki, Chie Ogura, Hisayo Nishizawa

Introduction

The Health Information Management Office was established in April 2011. We took over several duties from the Cancer Information Service and Surveillance Division. One of them was the medical record administration, and the others are the auditing activity for discharge summary and the National Cancer Center Hospital Cancer Registry (NCCH-CR), which is executed as a hospital-based cancer registry. Some statistical activities for the NCCH and prognostic investigation were taken over by the Medical Affairs Office, but since the main initiatives of the NCCH are activities against cancer, we will expand our role as the major statistics office of the NCCH.

Routine activities

1) Medical Record Administration

We perform the management of the patients' database based on their medical records. Their clinical data, such as examination, surgery, and outcomes are summarized and indexed.

2) Auditing Discharge Summary (quantitative inspection)

Data on discharge summaries should be entered by the attending physician. We inspected and checked about 16,000 summaries and where required, gave advice regarding correct input.

3) NCCH Cancer Registry (Hospital-based Cancer Registry)

The office has continuously managed the NCCH-CR since 2004, handling more than 5,000 records per year（Table 1）. We have provided our data to the Japanese Institutional Cancer Database that is handled by the Center for Cancer Control and Information Services of the NCC.

Future prospects

We have developed and tested software for medical record administration and cancer registry, "Hos-CanR", collaborating with the Surveillance Division of the NCC. We will effectively perform our duties using this integrated information system.

Table 1. Cancer Patients Data from the NCCH-CR

Year of Diagnosis	Number of New Cancer Cases
2010	5,440
2011	5,446
2012	5,543
2013	5,669

Department of Pharmacy

Hiroyuki Terakado

Introduction

The Department of 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 Department 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 Department. As 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, while the Pharmacy provides outpatients with guidance in the proper use of opioids and anti-cancer agents. The Department also places pharmacists in every hospital ward to provide a medication reconciliation service for inpatients, with a view to enhancing the quality of chemotherapy as well as to ease the burden of doctors and nurses.

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 that provides drug information. The medicine-package information, instructions and explanations, which are easy to understand for 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 that makes it possible to check the dose as well as the interval of chemotherapy. The Department has a robot that prepares injection preparations without human assistance.

Research activities

Since an important mission of the Department 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 Department 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 three-year postgraduate pharmacist residency training in clinical oncology. In the first year, the program attaches the most importance to the technical aspects of cancer care. In the second year, through required rotations in a variety of focused hematology/oncology services, the resident will refine his/her clinical problem-solving skills in cancer management and patient education, as well as provide pharmaceutical care to ambulatory care patients and participate in an oncology-focused Drug Information Program. In the third year, residents participate in specialized pharmaco-clinical practice and research activities, which may be tailored to the resident's goals. The hospital also provides a two-year chief residency program in which post-residency trainees may develop their clinical research capabilities to a higher level. Moreover, there are 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 in 2015

1) Oral and topical preparations	
Prepared in the hospital pharmacy	149,234
Inpatients	137,476
Outpatients	11,758
Taken to outside pharmacies	104,190
(% of prescriptions filled outside)	89.9
2) Injections	
Inpatients	392,801
Outpatients	46,075

Table 2. Amounts of Drugs Consumed in 2015

	(including sales tax)	(%)
Total	6,397,942	100.0
Internal Medicines	549,116	8.6
External	48,465	0.8
Injection	4,876,590	76.2
Narcotics	132,865	2.1
Blood	435,756	6.8
X-ray Imaging	226,539	3.5
RI	71,852	1.1
Others	56,754	0.9

Unit: 1,000 yen

Table 3. Aseptic Preparation of Injectable Drugs in 2015

Anticancer Drugs	64,742
Others	43,391

Table 4. House Preparations in 2015

Sterilized	86
Non-sterilized	109

Table 5. Investigational Drugs

Newly Registered	79
Ongoing Study	179
Total	258

List of papers published in 2015

Journal

1. Motonaga M, Yamamoto N, Makino Y, Ando-Makihara R, Ohe Y, Takano M, Hayashi Y. Phase I dose-finding and pharmacokinetic study of docetaxel and gefitinib in patients with advanced or metastatic non-small-cell lung cancer: evaluation of drug-drug interaction. Cancer Chemother Pharmacol, 76:713-721, 2015

Department of Nursing

Kazuko Nasu

Introduction

The Department of Nursing 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 Department is to develop and improve the quality of cancer nursing as well as to contribute to the appropriate management of the hospital. The Department is also expected to foster nursing staff to achieve the best cancer nursing.

Routine activities

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

We adopted the two-shift nursing system in 13 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 numerous patient education programs produced by Certified Nurse Specialists and Certified Nurses. We have five patient education programs and consultation services, three outpatient clinics run by nurses, and a support program for patients and their families. Many patients and families have participated in the educational program for self-care and survivorship in their daily life.

Research activities

We presented 19 studies on nursing at annual conferences in 2015. 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 in their nursing research based on their clinical questions. We are making efforts to improve the quality of nursing research through support from some physicians and statisticians. We expect our nurses from the NCCH to move and develop cancer nursing to even higher levels of proficiency and expertise.

Education

1) Assist and support new nurses

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

2) Development of knowledge and skills for cancer nursing

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

We have 11 specialized nurse training courses: Cancer chemotherapy nursing I and II; Palliative

care nursing I and II; Lymphedema care; Wound and skin care; Dysphagia nursing; Radiation therapy and IVR nursing; Support for discharge and home care coordination nursing; and nursing research. A total of 189 nurses have participated, all of whom have over four years' nursing experience. Many nurses want to participate in the courses. Through evaluation of the results 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, 11 certified nurse specialists and 32 certified nurses are working at the NCCH. They represent the role model for cancer nursing practice in both 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. The number of support meetings and consultations for patient's decision making by physician and CNS/CN was 1,162 cases, and the number of support meetings and consultations for psychosocial problems by CNS/CN was 1,758 cases in 2015.

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, and respiratory support, 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 education and coordination for ethical issues in a clinical setting. They support and empower not only patients and families, but also nursing staff.

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

Clinical Research Support office

Yasuhiro Fujiwara

- **Clinical Trial Coordination (& Support) Office:**
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Introduction

In 2015, the Research Coordination Division and the Research Promotion Division of the Center for Research Administration and Support (CRAS), the Clinical Trial Coordination (& Support) Office and Biobank and the Translational Research Support section of the National Cancer Center Hospital (NCCH) were reorganized into the Clinical Research Support Division of the NCCH. The Clinical Research Support Office supports clinical research conducted under the leadership of investigators in the Hospital. Supporting activities include protocol writing, central/local data management, statistical design and analysis, in-house/on-site monitoring, audits, patient recruitment, and other coordinating jobs.

Activities and future prospects of each section

・Clinical Trial Coordination (& Support) Office：

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 28 CRCs (clinical research coordinators) are supporting these trials. The number of industry-sponsored registration trials is increasing year by year, and we supported 270 registration-directed clinical trials including 20 physician-initiated registration-directed clinical trials in 2015 (Table 1). The number of 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 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. Supported Trials in Clinical Trial Coordination (& Support) Office in 2015

Phase	Ongoing	New (since 2015)	Total
I	56	30	86
I/II	15	3	18
II	31	17	48
II/III	1	0	1
III	64	20	84
POS	9	1	10
Medical device	2	1	3
In-vitro diagnostics	0	0	0
IITs	12	8	20
Total	190	80	270

POS: post marketing study
IITs: physician-initiated registration-directed clinical trials

・Clinical Trial Management Section

The Clinical Trial Management Section has five functions: i) Multi-institutional trial support, ii) Investigational new drug (IND) trial management, iii) Biostatistics, iv) Safety management, and v) Pharmaceutical affairs consultation. One of the strengths of the NCCH is implementing various types of clinical trials covering both early phase trials including first-in-human trials and late phase multi-institutional trials. The IND trial management function is responsible for comprehensive study coordination and site visit monitoring in early phase trials. The multi-institutional trial support function works as the JCOG Operations Office, which engages in protocol development, manuscript drafting, study coordination, etc., for late phase trials. The section is also responsible for coordination of the study planning consultation meeting and the concept review committee meeting. As a future direction, the section will reinforce the support function for various types of clinical trials including advanced medical care systems.

・Data Management Section

The section is responsible for central data management and in-house study monitoring in the investigator-initiated clinical trials for cancer therapeutic development. The Section consists of 3 teams: (1) Data managers in JCOG Data Center, (2) In-house research team, (3) Pediatric research team. The JCOG Data Center mostly supports late development multi-modality multi-institutional phase II or phase III trials for adult cancer. The in-house research team supports early phase adult cancer trials mainly for drug development including registration trials. The pediatric research team supports mainly registration trials for pediatric cancer.

The section is introducing a web-based electronic data capturing (EDC) system and is promoting standardization of all aspects of data management, such as data format, case report forms and monitoring reports for increasing data integrity and cost effectiveness of day-to-day work.

・Biobank and Translational Research Support Section

The Biobank and Translational Research Support Section has routinely obtained informed consent to participate as an NCCBB donor from patients who consult with the NCCH for the first time. Clinical research coordinators in this section coordinate translational research in several ways, such as assistance of registration for clinical trials, logistics of pathological specimens, data collection for case report forms and coordination between sections.

We explained the purpose of NCCBB to 5,991 patients from May 2015 to January 2016, and received consent for blood collection and research use of their surplus samples for research from 5,371 patients (89.7% consent rate). The patient load with our assistance in filling in the preliminary-diagnosis card and so on was 6,337.

We support 6 biomarker trials, and for registered patients (pts), 62 pts for BT-SCRUM, 74 pts for TOP-GEAR study, 14 pts for liver amino acid trial, 45 pts for GI-SCREEN_CRC, 42 pts for GI-SCREEN_nonCRC and 16 pts for DEF trial.

List of papers published in 2015

Journal

1. Kataoka K, Aoyama I, Mizusawa J, Eba J, Minashi K, Yano T, Tanaka M, Hanaoka N, Katayama H, Takizawa K, Fukuda H, Muto M, Gastrointestinal Endoscopy Study Group (GIESG) of the Japan Clinical Oncology Group. A randomized controlled Phase II/III study comparing endoscopic balloon dilation combined with steroid injection versus radial incision and cutting combined with steroid injection for refractory anastomotic stricture after esophagectomy: Japan Clinical Oncology Group Study JCOG1207. Jpn J Clin Oncol, 45:385-389, 2015
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7. Etoh T, Inomata M, Watanabe M, Konishi F, Kawamura Y, Ueda Y, Toujigamori M, Shiroshita H, Katayama H, Kitano S. Success rate of informed consent acquisition and factors influencing participation in a multicenter randomized controlled trial of laparoscopic versus open surgery for stage II/III colon cancer in Japan (JCOG0404). Asian J Endosc Surg, 8:419-423, 2015

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9. Homma A, Nakamura K, Matsuura K, Mizusawa J, Onimaru R, Fukuda H, Fujii M. Dose-finding and efficacy confirmation trial of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer (JCOG1212, RADPLAT-MSC). Jpn J Clin Oncol, 45:119-122, 2015

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Genetic Medicine and Services

Teruhiko Yoshida, Narikazu Boku, Takayuki Kinoshita, Shimizu Chikako, Mitsuya Ishikawa, Takeshi Nakajima, Shigenobu Suzuki, Tadashi Kumamoto, Shigeki Sekine, Taisuke Mori, Nobuyoshi Hiraoka, Kuniko Sunami, Takahisa Matsuda, Hiromi Sakamoto, Hitoshi Zenbutsu, Mineko Ushiama, Takashi Kohno, Mamoru Kato, Hitoshi Ichikawa, Kokichi Sugano

Introduction

It has been estimated that roughly 5% of all cancer cases are caused by a highly penetrant monogenic mutation. Major causative genes for most hereditary cancer syndromes were identified in the 1990s, and since then, genetic diagnosis has been considered as a part of standard medical care in oncology clinics. The National Cancer Center Hospital (NCCH) launched the Outpatient Genetic Counseling Clinic in 1998 as a part of collaboration with the Research Institute, especially the Fundamental Innovative Oncology Core (FIOC). However, cancer medical genetics still has a number of issues to be addressed as shown in Figure 1, which is again shown this year with some modifications from the previous year, because it has been the basic set of the agenda of the Department of Genetic Medicine and Services (GeMS).

Routine activities

As shown on the National Cancer Center Hospital (NCCH) Web site the aim and mission of the clinical service of the Outpatient Genetic Counseling Clinic, which is the main routine clinical activity of the Department, are:

1) to provide consultation and appropriate medical and genetic information (that is, genetic counseling) to anyone who has a worry related to heredity cancer.
2) to provide genetic testing when appropriate.
3) to support early diagnosis and treatment based on family history and/or genetic test results.

In 2015, 173 patients and their relatives from 121 families visited the Clinic. In total, 1,414 clients from 955 families have visited the Clinic since its inception in 1998.

Research activities

Although at least one causative gene has been identified for each of the major hereditary cancer syndromes, overall sensitivity of the current genetic tests is far from 100% and may be around 70-80%, even for the cases that meet clinical and/or screening criteria for hereditary cancer syndromes. The false negative cases may include both inadequate technical sensitivity of the current genetic test methods on the established causative genes (allelic heterogeneity) and also yet-identified genes representing locus heterogeneity. There has been great expectation that the introduction of next generation sequencers (NGS) would change the situation. The staff of the Department of GeMS have established a new Common Protocol to perform NGS-based germline clinical sequencing for patients with negative test results by conventional genetic tests, who would represent a part of the Undiagnosed Disease Patients in the oncology field. The Common Protocol has been adopted by other hospitals and institutions in a long-standing multi-institute collaborative research group based on the National Cancer Center Research and Development Fund and its predecessor. In addition to whole exome sequencing (WES), a multi-gene panel has been developed based on Agilent SureSelect technology.

Clinical trials

The Outpatient Genetic Counseling Clinic has participated in a prospective clinical study to optimize BRCA1/2 genetic tests and a clinical trial of a PARP inhibitor for patients with ovarian or breast cancer, and both are directed by the departments of Breast and Medical Oncology and Breast Surgery.

Education

The Department has accepted attendees for outpatient genetic counseling, so that they could be eligible to take the examination for clinical geneticists and certified genetic counselors acknowledged by the Japanese Society of Human Genetics and the Japanese Society of Genetic Counseling. In 2015, eight doctors were registered as trainees for clinical geneticists in the education committee of clinical geneticists.

Future prospects

The Department of GeMS was launched in November 2015. Although this section reports on the routine clinical activity of the Department and clinical research associated directly with the Outpatient Genetic Counseling Clinic, the scope and mission of the Department extends beyond hereditary cancer syndromes and includes support of the genomic biomarker-driven personalized cancer treatments offered by other clinical departments (Figure 2). The core technology of the new discipline, also known as a precision medicine, is next-generation sequencers, which would bring massive amounts of genomic data to cancer diagnosis, treatment and prevention. The crux of this emerging opportunity is how to convert the sequence data to clinically valid and useful knowledge, which could include incidental or secondary findings. The Department of GeMS is expected to support other departments in the era of genomic medicine.

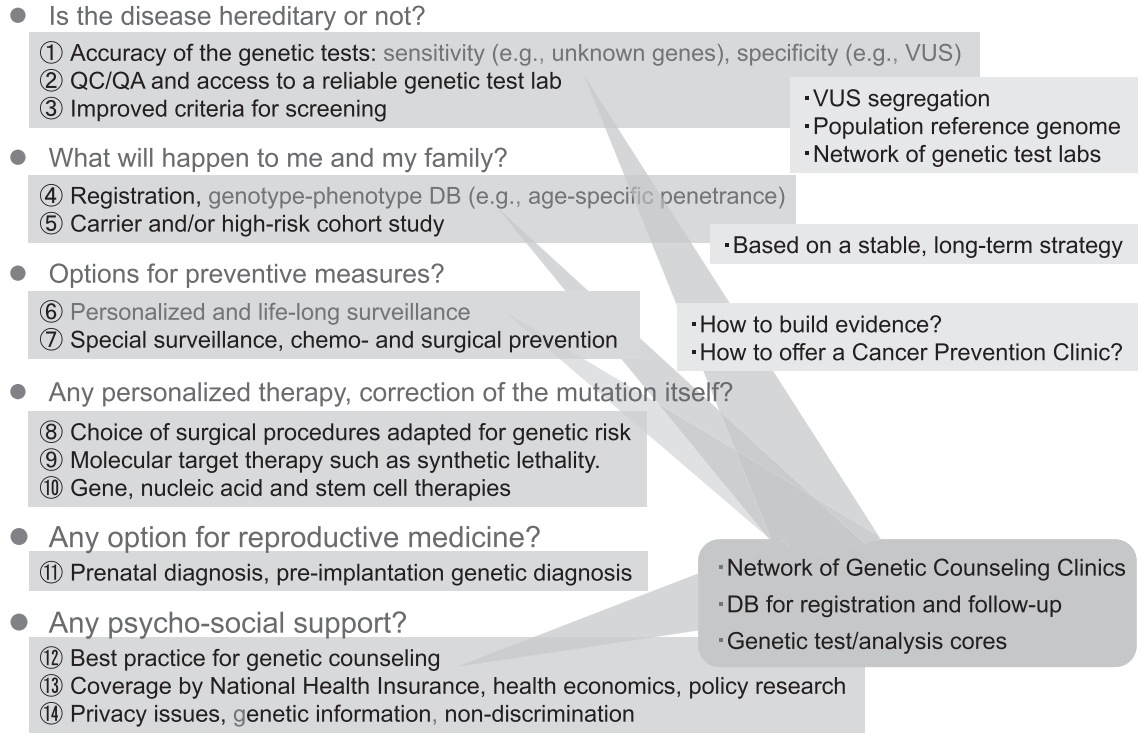

Figure 1. Major Questions of Patients and Families with Hereditary Cancer Syndromes

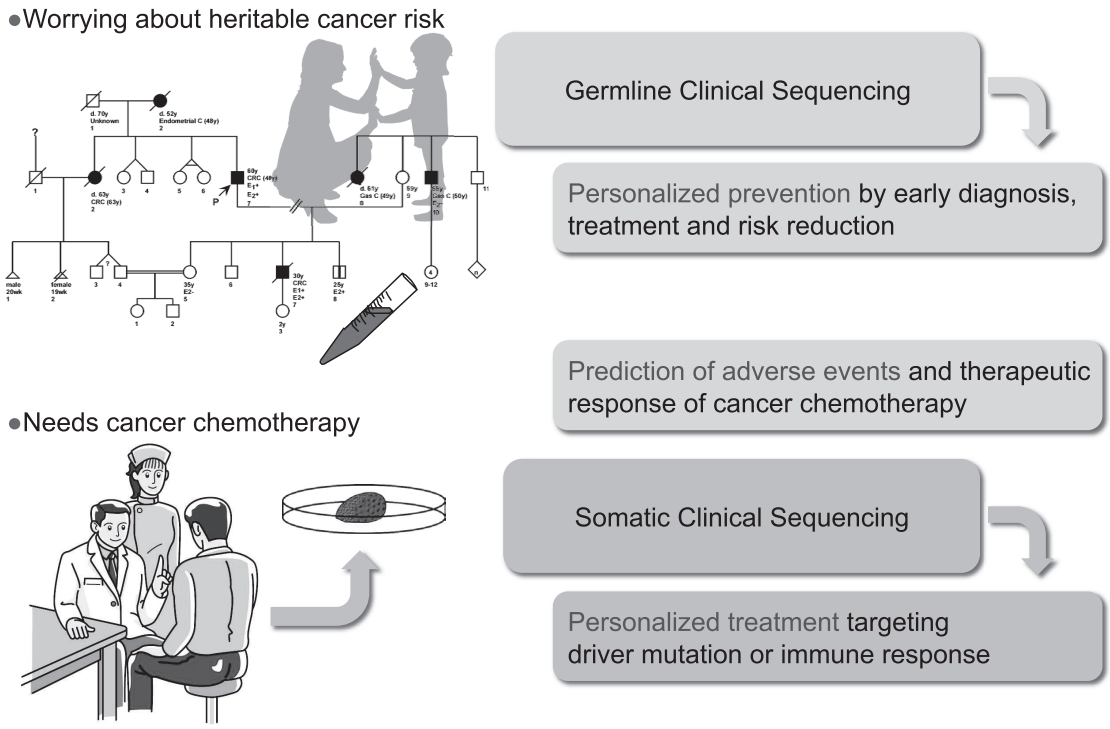

Figure 2. Patients and Families Faced With GeMS

Table 1. Number of patients

	Proband	Relative	Total
Lynch Syndrome (Hereditary Non-Polyposis Colon Cancer; HNPCC)	23	15	38
Familial Adenomatous Polyposis (FAP)	5	9	14
Retinoblastoma	15	11	26
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	66	9	75
Other diseases	7	8	15
Counseling only	5	0	5
Total	121	52	173

List of papers published in 2015

Journal

1. Hashimoto T, Ogawa R, Matsubara A, Taniguchi H, Sugano K, Ushiama M, Yoshida T, Kanai Y, Sekine S. Familial adenomatous polyposis-associated and sporadic pyloric gland adenomas of the upper gastrointestinal tract share common genetic features. Histopathology, 67:689-698, 2015

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