Hospital East

Preface

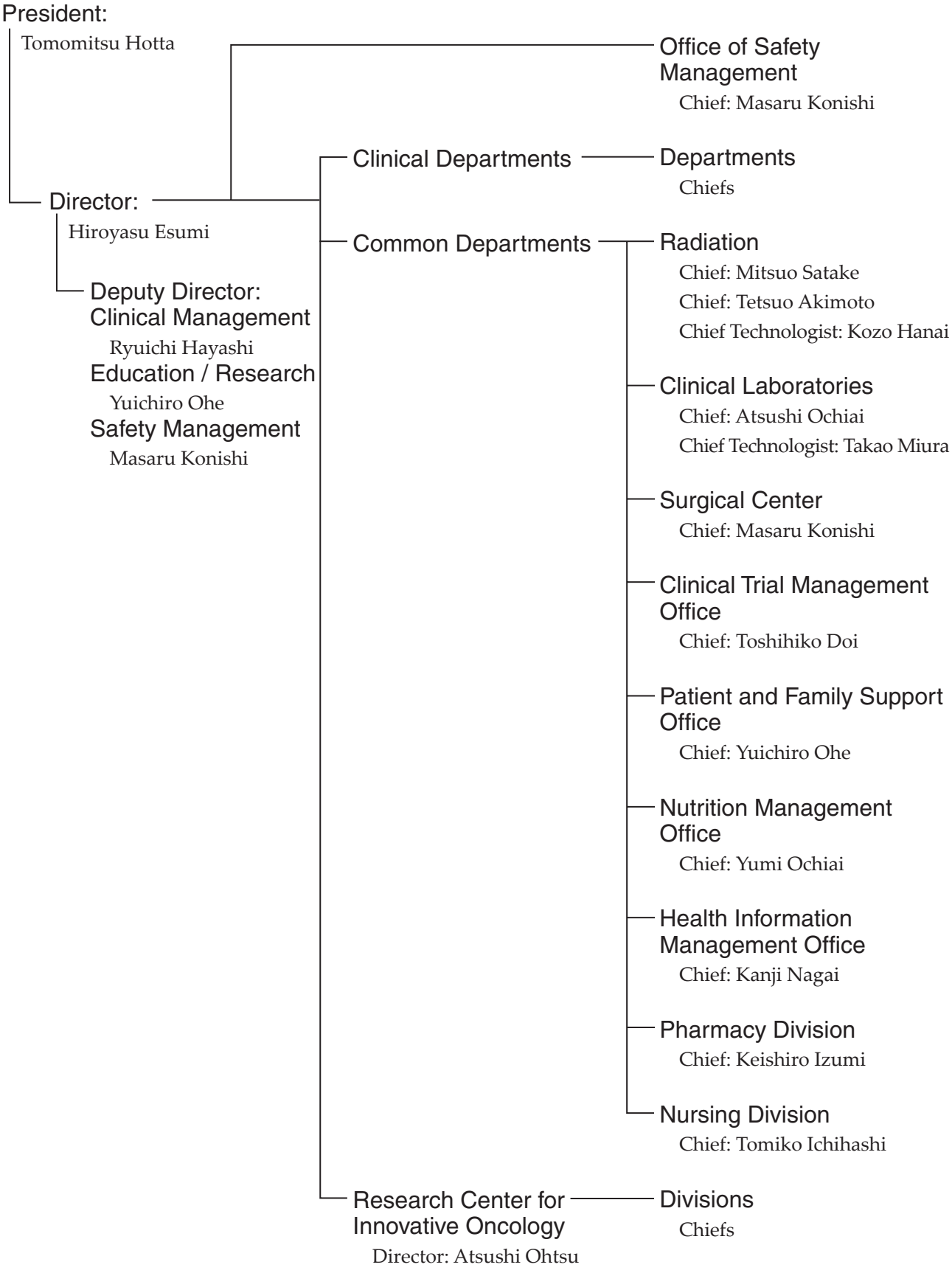
The number of patients with cancer in Japan has been steadily increasing over the last 10 years, although the age-adjusted incidence of gastric, lung, liver and cervical cancers has decreased. This has been mainly caused by the shift in the Japanese population. It is estimated that one in four people in Japan will be over 65 years old in 2015 and this country will be a super-aging society in the coming 10-20 years. Accordingly, the number of newly diagnosed cancer patients is anticipated to be almost 900,000 annually. Substantial changes in medical technology and systems for providing medical care are mandatory. The NCC Hospital East started to reorganize its activities in a timely fashion to meet these requirements by establishing the Research Center for Innovative Oncology about 10 years ago. The Research Center, together with the clinical departments of the Hospital East, is engaged in developing new cancer diagnostics, therapeutics and models of medical and care systems. Innovative endoscopy including hypoxia imaging using the differential spectrum of hemoglobin, and 3D reconstruction of endoscopic images with optical coherence tomography (OCT) technology are examples of devices developed in our Institute. New drug delivery systems using micelle technology and novel anticancer drugs based on completely new ideas, which have been developed in our Institute, are under clinical evaluation. Several investigator initiated trials, including first in human trials, have been are successfully conducted in our hospital, and others are ongoing.

In addition to the early stages of the clinical development of drugs and equipment, our activity has been extended to support the home healthcare of cancer patients that will be a keystone of the structure of the Japanese healthcare system in the coming decades. In point of fact, the number of outpatients has increased steadily every year and the number has obviously exceeded the structural limitations of our hospital outpatient clinic. Expansion of the outpatient clinic and the operating theater is now underway to fulfill the ever-increasing demand.

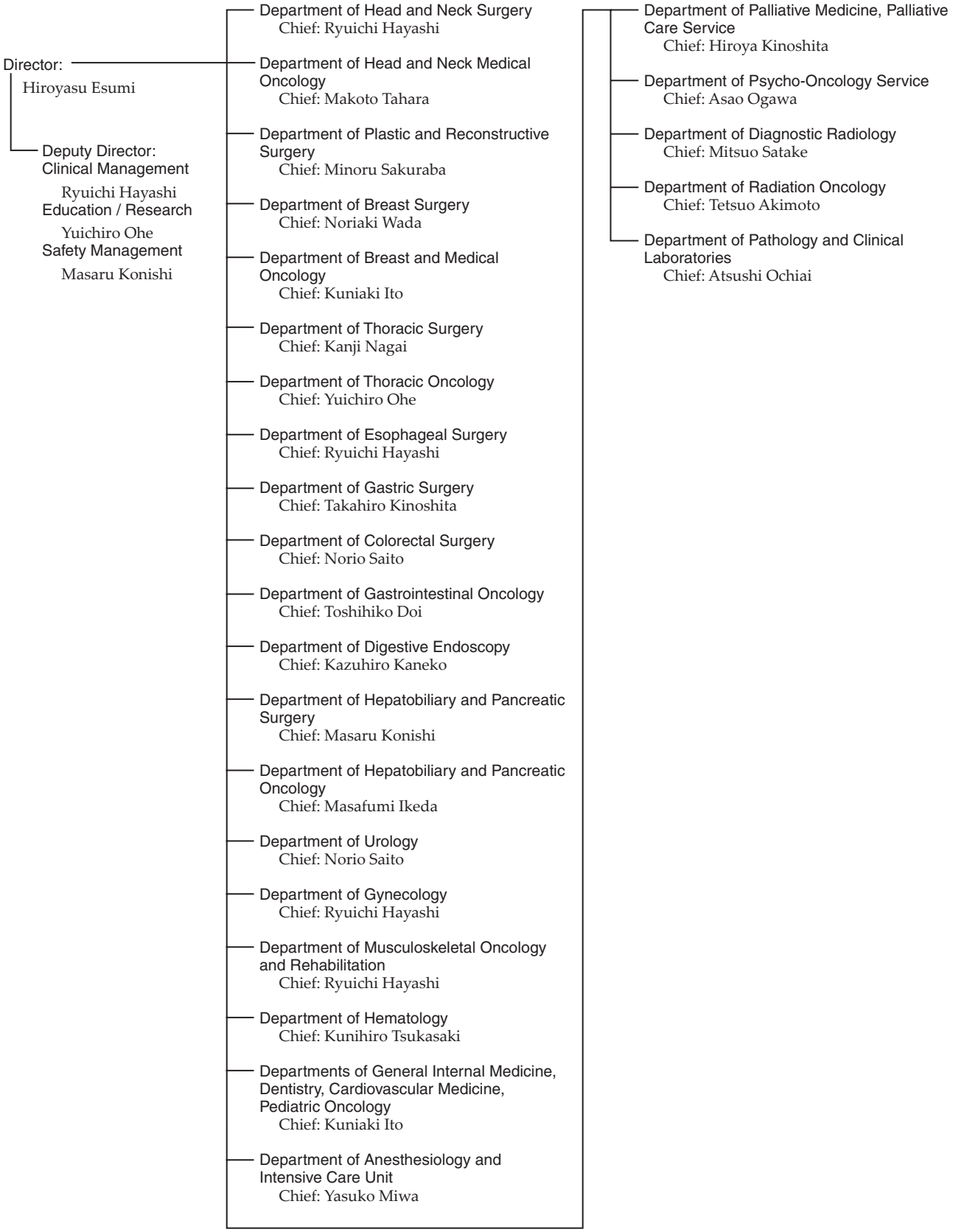
As noted above, by 2015, the 65-and-over age group will account for some 25% of the total Japanese population, and the number of people in advanced old age, above the age of 80 years, will also have grown significantly. This will make Japan a super-aging society, which is a situation that no country has ever experienced before, and we at the NCC Hospital East are already taking the requisite steps to be able to meet the unique challenges posed by such a super-aging society.

Hiroyasu Esumi M.D., Ph.D.
Director, National Cancer Center Hospital East

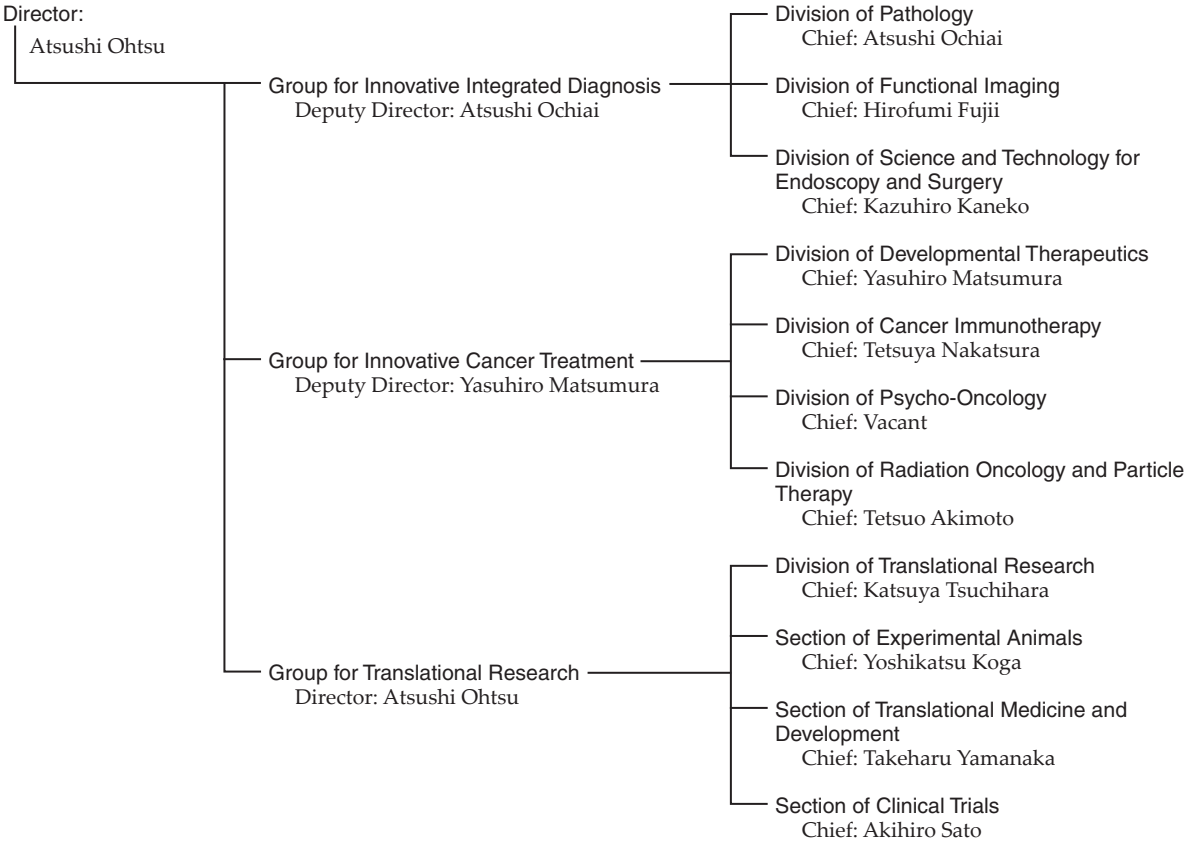
Organization



Clinical Departments



Research Center for Innovative Oncology



Activities of the Departments

Department of Head and Neck Surgery

Masakazu Miyazaki, Ryuichi Hayashi, Takeshi Shinozaki, Toshifumi Tomioka, Shinya Jinnouchi, Takao Hamamoto

Introduction

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

Routine activities

The current treatment policy for head and neck cancer is multimodal therapy. To effectively implement available therapeutic modalities, 4 staff surgeons at the Division work closely with plastic surgeons, radiotherapists, medical oncologists, pathologists, dentists, psycho-oncologists, nurses, and other hospital staff. To facilitate regular communication among the members of this large team, several weekly conferences are conducted. In 2012, 280 new patients were treated: 452 patients underwent surgery under general anesthesia and 31 patients under local anesthesia. 101 patients underwent major surgery with microsurgical reconstruction. The number of surgically treated high-risk patients, including elderly patients aged over 80, is currently increasing owing to the recent advances in surgical techniques and perioperative care. Technically difficult operations, such as surgical resection of advanced oropharyngeal carcinoma with immediate reconstruction and salvage surgery after chemoradiation, are also being increasingly performed. The outpatient service of the Division is available from Monday to Friday. Endoscopic, radiographic, and ultrasonic examinations are routinely performed. The dental service is also available to improve the quality of life after ablative surgery using maxillofacial prostheses, to prevent severe odontogenic infection during chemotherapy and/or radiotherapy, and to reduce local infection after major surgery for head and neck cancer.

Research activities

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

RNA and DNA were extracted from biopsy specimens of cancerous and noncancerous tissues obtained from with a laser microdissection system. The levels of expression of MMP2, LOXL2, IL7R, NTRK2, GPR161 and GPR116 were higher in the cancerous tissues than in the noncancerous tissues. The p53 mutation was found in 33% of the cancerous tissue specimens, and the frequency of mutation was almost the same as that of esophageal squamous intraepithelial neoplasia. It is suggested based on the histopathological findings that the genes identified in this study, which were highly expressed in relation to angiogenesis and induction of inflammation, participate somehow in the progression of carcinogenesis.

2. Narrow band imaging endoscopy for unknown primary tumor sites of the neck

Examinations used to search for unknown primary tumors of squamous cell carcinomas of the neck include CT, MRI, laryngoscopy, gastrointestinal endoscopy, and positron-emission tomography (PET). Narrow band imaging (NBI) endoscopy in which an optical color-separation filter is used to narrow the spectral transmittance bandwidth is also used. Twenty-eight patients in whom primary squamous cell carcinomas could not be detected with conventional white light laryngoscopy underwent NBI endoscopy and PET. Primary lesions were

Table 1. Number of new patients

Tongue	46
Oral cavity excluding tongue	48
Oropharynx	39
Hypopharynx	47
Cervical esophagus	10
Larynx	18
Nasal cavity and paranasal sinuses	8
Thyroid gland	37
Major salivary gland	17
Cancer Unknown Primary	7
Others	3
Total	280

Table 2. Type of procedure

Glossectomy	61
Resection of oral cavity	62
Oropharyngectomy	46
Hypopharyngectomy	31
Cervical esophagectomy	4
Laryngectomy	25
Resection of the nasal and/or paranasal sinuses	11
Thyroidectomy	52
Parotidectomy	20
Submandibulectomy	13
Endoscopic resection	47
Neck dissection	69
Others	11
Total	452

Table 3. Survival rates

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

n.v. : not verified

detected with NBI endoscopy in 3 patients, but no primary lesions were detected with PET. However, PET was used to detect a lower gingival cancer and a palatine tonsillar cancer. Both PET and NBI endoscopy are effective for detecting unknown primary tumors of squamous cell carcinomas of the neck.

Clinical trials

1. Multicenter study to establish the indication of paratracheal lymph node dissection for hypopharyngeal carcinoma

A retrospective study was conducted and 286 cases were enrolled in this study from 9 hospitals. Bilateral paratracheal lymph node metastasis was found in 38% of the patients with esophageal invasion, but on the other hand it was also found in 15% of the patients without esophageal invasion. Bilateral lymph node dissection and total thyroidectomy are needed for the patients with esophageal invasion, but preserving thyroid function is possible in those patients without esophageal invasion.

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

A multicenter prospective study is being conducted. The overall QOL of advanced head and neck cancer patients with EORTC-QLQ-C15-PAL, the amount of airway secretions and typical symptoms of head and neck cancer are evaluated. The planned number of cases is 100 and 80 patients have been enrolled for this study.

List of papers published in 2012

Journal

1. Shinozaki T, Hayashi R, Ebihara M, Miyazaki M, Daiko H, Saikawa M, Ebihara S. Narrow band imaging endoscopy for unknown primary tumor sites of the neck. Head Neck, 34:826-829, 2012

Department of Head and Neck Medical Oncology

Makoto Tahara, Hiroto Ishiki, Tomoko Yamazaki, Tomohiro Enokida

Introduction

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

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

Routine activities

Our division consists of two physicians, one senior resident and one resident. We manage the treatment of HNC patients who receive chemotherapy, including concurrent chemoradiotherapy, induction chemotherapy and palliative chemotherapy. An estimated 60% of HNC patients will present with locally advanced disease (stage III/IV) and require a multidisciplinary approach, including surgery, radiotherapy, and chemotherapy. Furthermore, HNC patients are at risk of injury and impairment of vital organs, including the eyes, ears, nose, mouth, pharynx, and larynx, both from the cancer itself and from the series of treatments provided to cure it. In treating patients, we therefore carefully assess both the curability of the condition and possible subsequent complications, such as swallowing dysfunction and cosmetic changes. Given the increasing complexity of the management of HNC, recommended treatment for patients who are referred to our institution is decided at weekly head and neck cancer conferences attended by a multidisciplinary team, which includes head and neck surgeons, radiation oncologists, plastic surgeons, dentists, pharmacists, and medical oncologists.

A total of 218 patients were treated in the inpatient clinic of our division from January 2012 to December (Table 1). Although induction chemotherapy is not yet standard therapy, 40 patients who had high-risk distant metastasis, including N2c or N3, or who had T4 in the nasal cavity, received induction chemotherapy followed by concurrent chemoradiotherapy.

The outpatient service of our division is available from Monday to Friday.

We carefully follow patients during and after treatment and provide palliative chemotherapy as an outpatient service.

Research activities

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

1) Development of new treatments

Based on the results of our previously reported phase I trial (Tahara M, et. al, Cancer Science 2011), a multicenter phase II trial of concurrent chemoradiotherapy with S-1 and CDDP in patients with unresectable locally advanced squamous cell carcinoma (JCOG0706) was conducted under the JCOG. Results were reported at the last ASCO meeting. Randomized trial of concurrent chemoradiotherapy with S-1 and CDDP compared with concurrent chemoradiotherapy with CDDP is now planning.

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

2) Biomarker analysis

An analysis of gene expression profiles in head and neck cancer is being carried out to determine the biomarker that can predict treatment outcomes. Recently, the existence of circulating microRNAs (miRNAs) in the blood of cancer patients has raised the possibility that miRNAs may serve as a novel diagnostic marker. Therefore, we are now conducting a prospective study to compare the miRNA expression patterns before and after disease recurrence in head and neck cancer patients.

Table 1. Number of patients

Primary site	No. of patients (N=218)
Nasal cavity	19
Nasopharynx	20
Oropharynx	28
Hypopharynx	47
Oral cavity	51
Larynx	18
Salivary	14
Thyroid	16
Primary unknown	4
Other	1

Table 2. Type of procedure

	No. of patients (N=218)
Induction chemotherapy followed by CRT	40
Definitive CRT	40
Postoperative adjuvant CRT	18
Palliative chemotherapy	23
RT	24
Hormone therapy	3
BSC	14
Others	36

Table 3. Survival rates

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

n.v. : not verified

Clinical trials

A feasibility study of the combination with docetaxel, cisplatin and 5-FU (TPF) as an induction chemotherapy for locally advanced SCCHN is ongoing.

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

To facilitate the timely approval of new drugs and eliminate the drug lag, we are also participating in the following global trials: 1) a randomized, open-label, phase III study to evaluate the efficacy and safety of oral afatinib (BIBW 2992) versus intravenous methotrexate in patients with R/M-SCCHN who have progressed after platinum-based therapy; 2) a randomized, double-blinded, placebo-controlled, phase III study to evaluate the efficacy and safety of oral afatinib (BIBW 2992) as adjuvant therapy after chemoradiotherapy in patients with primary unresected SCCHN; 3) a double-blinded, randomized phase III study evaluating the efficacy and safety of sorafenib compared to a placebo in patients with locally advanced/metastatic RAI-refractory differentiated thyroid cancer; and 4) a double-blinded, randomized phase III study evaluating the efficacy and safety of Lenvatinib(E7080) compared to a placebo in patients with locally advanced/metastatic RAI-refractory differentiated thyroid cancer.

List of papers published in 2012
Journal

1. Kiyota N, Tahara M, Okano S, Kawashima M, Matsuura K, Onozawa Y, Nibu K, Hayashi R, Yoshimura K, Ohtsu A. Phase II feasibility trial of adjuvant chemoradiotherapy with 3-weekly cisplatin for Japanese patients with post-operative high-risk squamous cell carcinoma of the head and neck. Jpn J Clin Oncol, 42:927-933, 2012

2. Okano S, Tahara M, Zenda S, Fuse N, Yoshino T, Doi T, Kawashima M, Ogino T, Hayashi R, Ohtsu A. Induction chemotherapy with docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin in patients with T4b nasal and sinonasal malignancies. Jpn J Clin Oncol, 42:691-696, 2012

Department of Plastic and Reconstructive Surgery

Minoru Sakuraba, Shogo Nagamatsu, Azusa Oshima, Masahide Fujiki, Junichi Nakao, Yutaka Fukunaga

Introduction

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

Routine activities

Five plastic surgeons cover reconstructive operations both in the National Cancer Center Hospital East (NCCH-E) in Kashiwa and the NCCH in Tokyo, and train the residents in the two hospitals. These reconstructive surgeries are performed in cooperation with the surgeons of another department of the hospital, such as Head and Neck Surgery, Breast Surgery, Orthopedic Surgery, Esophageal Surgery, Colorectal and Urological Surgery and so on. In the NCCH-E, head and neck reconstruction is the most frequently performed operation accounting for 65% of reconstructive surgical regions. In the head and neck region, the free jejunal graft and the rectus abdominis musculocutaneous flap are the most frequently used procedures. A weekly conference is held with doctors of the Department of Head and Neck surgery, Radiation Oncology, and Head and Neck Oncology. Breast reconstruction using autologous tissue transfer was employed in 2005, and since then, the patient need for breast reconstruction has continued to increase. Nineteen cases of breast reconstruction were performed in 2011, and a free deep inferior epigastric artery perforator (DIEP) flap transfer is the most frequently used procedure.

Research activities

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

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

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

Clinical trials

A clinical trial of LAT-AGN192024 eyelashes was carried out throughout 2012. LAT-AGN 192024 ophthalmic solution 0.03% was administered in patients with hypotrichosis of the eyelashes due to their anticancer drug treatment. The efficiency and safety were evaluated with a randomized and double blinded multi-institutional clinical trial. Patient registration has closed and the data are now under analysis.

Table1. Cooperation with other divisions

NCCH East	No. of patients
Head & Neck surgery	119
Orthopedic surgery	1
Esophageal surgery	11
Breast surgery	49
Dermatology	----
Urologic surgery	2
HB&P surgery	0
Ophthalmic surgery	----
Colorectal surgery	12
Gastric surgery	0
Thoracic surgery	2
Gynecology	----
Plastic & Reconstructive	2
Total	198

Table2. Operative Procedures

NCCH East	No. of patients
Microvascular free flap	112
Jejunum	34
RAMC or DIEP	36
Anterolateral thigh	18
Fibula bone	7
Latissimus Dorsi	1
Radial Forearm	0
Other flaps	7
Other Microsurgery	2
Supercharge	1
Nerve Graft	0
Limb Salvage	0
Hepatic Artery	0
Others	1
Subtotal	114
Pedicled flaps	28
PMMC	7
Latissimus Dorsi	8
RAMC	0
Other flaps	13
Other Procedures	57
Total	199

List of papers published in 2012
Journal

1. Sakuraba M, Miyamoto S, Nagamatsu S, Kayano S, Taji M, Kinoshita T, Kosuge T, Kimata Y. Hepatic artery reconstruction following ablative surgery for hepatobiliary and pancreatic malignancies. Eur J Surg Oncol, 38:580-585, 2012

Department of Breast Surgery

Noriaki Wada, Kimiyasu Yoneyama

Introduction

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

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

Routine activities

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

Changes in the annual number of patients with breast cancer who underwent surgery are shown in Table 1. A total of 300 patients with primary breast cancer and 23 patients with recurrence or other breast disease were operated on. Sixteen immediate breast reconstruction surgeries were included. Of the patients with primary breast cancer, 76 (25%) underwent primary systemic therapy. The types and number of operative procedures performed in 2012 are shown in Table 2. The rate of breast-conserving surgeries (including two radiofrequency ablation alone cases) was 74% (223/300). Sentinel node biopsy was performed in 226 patients, and 184 patients were spared from ALND.

Clinical and research activities (Trials)

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

   A phase II study on RFA without resection was performed for T=<1.0 cm, N0 breast cancer patients with no extensive intraductal components using a Cool-tip electrode system. Moreover, a new phase II trial of RFA for breast cancer with T =<1.5 cm is currently about to start.
2. Evaluation for the potential role of Ki67 as a biomarker for breast cancer patients.

   The Ki67 index is a marker for cell proliferation. A retrospective search of a prospectively maintained clinical breast cancer database was performed. It was concluded that the pre-therapy Ki67 index was a useful predictor for the therapeutic response to neoadjuvant chemotherapy and Ki67 post-therapy was shown to predict outcomes for patients with residual invasive disease.
3. Long term results of SLN negative patients without ALND.

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

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

Table 1. Number of primary breast cancer patients operated on during 2003-2012

Clinical stage	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Stage 0	18	14	29	34	27	23	38	39	43	28
Stage I	97	100	89	79	94	84	86	80	86	91
Stage II	104	97	94	103	87	87	122	137	112	128
Stage III	33	24	35	34	25	33	42	32	43	49
Stage IV, unknown	1	2	2	1	4	0	3	1	1	4
Total	253	237	249	251	237	227	291	289	285	300

Table 2. Types of operative procedures performed in 2012 for primary breast cancer

Type of operation	N
BT+SNB	29
BT+SNB→ALND	12
BT+ALND	32
BT alone	1
BP+SNB	153
BP+SNB→ALND	30
BP+ALND	33
BP alone	8
RFA+SNB	2
Total	300

Total mastectomy with immediate breast reconstruction was performed in 16 patients.

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

Table 3. Overall survival (OS) rate by stage
OP year: Jan 1993- Dec 2006

Clinical stage	N	5 yr. OS	10 yr. OS
Stage 0	159	99%	95%
Stage I	792	96%	93%
Stage II	1355	90%	80%
Stage III	287	68%	55%
Stage IV, unknown	30	33%	10%
Total	2623	89%	81%

Median follow up period: 98 months [0-230]

Department of Breast and Medical Oncology

Nobuaki Matsubara, Hirofumi Mukai, Kuniaki Itoh, Yoichi Naito, Ako Hosono, Masaoki Sasaki

Introduction

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

Routine activities

The major and specific target disease of the Division comprised breast cancer. Eligible patients were invited to participate in large phase II/III studies. The Division also treated cancers of the genitourinary tract, cancer of unknown primary origin, soft tissue sarcomas and gynecological cancers including uterine and ovarian cancers. For patients with diseases treated with established standard chemotherapeutic regimens, standard chemotherapy was administered in routine medical practice. Patients in whom standard chemotherapy had failed and those with cancers for which standard chemotherapy was unavailable were invited to participate in clinical studies on experimental drugs and regimens. In 2012, 597 patients with different types of cancer visited the Division for consultation. Approximately 400 patients per month received routine chemotherapy as an outpatient service by the Division. The overall inpatient care system of the Division comprises management of oncology teams, namely, a monthly rotating attending physician out of three staff physicians is responsible for all inpatient care and education of residents in oncology team. Morning case conferences on inpatient care are held on every day, and a weekly case conference on new patients visiting the clinics at the Division is held on Thursday evenings in collaboration with the Division of hematology. A weekly educational review on oncology and hematology is also conducted on Tuesday evenings. Moreover, a biweekly joint conference is held on Wednesday evenings and on Monday evenings with breast surgeons and with urologists, respectively. Morning journal clubs also meet on Mondays and Fridays at the Division in collaboration with the Division of hematology.

Research activities and clinical trials

Phase I/II studies of new anticancer agents for specific disease targets are conducted in collaboration with pharmaceutical companies. Combination phase I studies of the following anticancer agents were conducted: BIBW2992 (afatinib, an oral inhibitor of tyrosine kinases) and weekly vinorelbine for patients unresponsive to chemotherapy and those with cancers for which standard chemotherapy was unavailable, and E7389 (elibuline, a synthetic analog of Halichondrin B) and trastuzumab for patients with advanced or recurrent breast cancer in whom HER-2 was overexpressed. A phase II study of E7389 for treated patients with soft tissue sarcomas is also ongoing. Phase I studies of the following anticancer agents were conducted: cabazitaxel (a new taxane derivative) for patients with hormone refractory prostate cancer, JNJ212082 (abiraterone acetate, a CYP17 inhibitor for androgen antagonist) for patients with castration-resistant prostate cancer who have not received chemotherapeutic agents, and NK105 (paclitaxel-incorporating micellar nanoparticle formulation) for patients with advanced or metastatic cancer for which standard chemotherapy was unavailable.

In addition, many phase III studies are being conducted as follows: a randomised, open-label, phase III study on taxane based chemotherapy with lapatinib or tarastuzumab as first-line therapy for woman with HER2 positive metastatic breast cancer; a randomised placebo controlled trial of RAD001 (everolimus, mTOR inhibitor) combined with paclitaxel and trastuzumab for patients with HER-2 positive metastatic and/or locally advanced breast cancer as a primary treatment; a randomised double-blind placebo-controlled trial of neratinib (an erbB1/2/4 inhibitor) after trastuzumab in women

Table 1. Number of new patients in 2012

Breast cancer	285
Genitourinary cancers	181
Gynecological cancers	31
Cancer of unknown primary	42
Others	58
Total	597

with early-stage HER-2 overexpressed/amplified breast cancer; a randomised, open-label, phase III study on adjuvant lapatinib versus trastuzumab versus both lapatinib and trastuzumab treatment in patients with HER-2 overexpressed primary breast cancer (ALTTO: Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation); a randomised multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer (APHINITY: Adjuvant Pertuzumab and Herceptin IN Initial Therapy); a randomised phase III study on NK105 versus paclitaxel in patients with recurrent or metastatic breast cancer; and a randomised phase III study on lapatinib, trastuzumab, and both lapatinib and trastuzumab, combined with aromatase inhibitor in patients with HER-2 overexpressed breast cancer who received neo-/adjuvant therapy with trastuzumab and endocrine therapy.

List of papers published in 2012
Journal

1. Matsubara N, Itoh K, Mukai H, Nagai S. Long-term outcome of pleurodesis with OK-432 in metastatic breast cancer: a new risk model for success from an analysis of 75 cases. Int J Clin Oncol, 17:470-476, 2012
2. Yamaguchi T, Mukai H. Ki-67 index guided selection of preoperative chemotherapy for HER2-positive breast cancer: a randomized phase II trial. Jpn J Clin Oncol, 42:1211-1214, 2012
3. Ishihara M, Mukai H, Nagai S, Onozawa M, Nihei K, Shimada T, Wada N. Retrospective analysis of risk factors for central nervous system metastases in operable breast cancer: effects of biologic subtype and Ki67 overexpression on survival. Oncology, 84:135-140, 2012

Department of Thoracic Surgery

Kanji Nagai, Junji Yoshida, Tomoyuki Hishida, Keijyu Aokage, Tomohiro Haruki, Yuki Matsumura

Introduction

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

The Thoracic Surgery Division of the National Cancer Center Hospital East (NCCH-E) ranks second in Japan following the National Cancer Center Tokyo in providing surgical treatment of primary lung cancer. Since its establishment in 1992, the Division has been one of the most active leaders in the field of lung cancer in Japan. Moreover, it has been an active participant in international and national scientific venues. This year, in addition to 13 scientific papers published in English, and 2 in Japanese, the Division made 50 presentations: 8 international, 32 national, and 10 regional.

Routine activities

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

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

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

The surgical procedures of the Division have generally remained similar for the past several years, but we started to employ port-access thoracoscopic surgery more often last year. Approximately 10% of the surgeries are completed via a 3-port access, and 80% of the surgeries are thoracoscopically assisted. To date, the average postoperative hospital stays of patients in the Division have improved and have become shorter, 3 days being the shortest with a median of 7 days for cases of primary lung cancer. These shorter hospital stays are achieved with a slightly better complication rate than normal. This year, 30-day operative mortality occurred in 3 (0.9%) patients undergoing surgery for primary lung cancer.

Research activities and clinical trials

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

Table 1. Number of patients

Lung cancer	335
Metastatic lung tumor	55
Mediastinal tumor	26
Others	58
Total	474

Table 2. Type of procedure –Primary lung cancer

Pneumonectomy	18
Lobectomy	264
(Bronchoplasty)	(11)
Limited resection	45
Exploratory thoracotomy	8
Total	335

Table 3. Overall Survival rates for resected primary lung cancer(as of 2012)

Pathologic stage	Number of patients	MST(month)	5-yr survival rate(%)
IA	1115	NR	86.6
IB	459	NR	67.0
IIA	283	NR	54.3
IIB	191	42.8	44.4
IIIA	395	36.1	35.1

Surgery between 2000 and 2009, Stages according to TNM Classification 7th edition: NR:Not reached

List of papers published in 2012
Journal

1. Kawase A, Yoshida J, Ishii G, Nakao M, Aokage K, Hishida T, Nishimura M, Nagai K. Differences between squamous cell carcinoma and adenocarcinoma of the lung: are adenocarcinoma and squamous cell carcinoma prognostically equal? Jpn J Clin Oncol, 42:189-195, 2012
2. Nakao M, Hishida T, Ishii G, Yoshida J, Nishimura M, Nagai K. Malignant granular cell tumor of the posterior mediastinum with dissemination. Asian Cardiovasc Thorac Ann, 20:71-73, 2012
3. Shimada Y, Niho S, Ishii G, Hishida T, Yoshida J, Nishimura M, Yoh K, Goto K, Ohmatsu H, Ohe Y, Nagai K. Clinical features of unresectable high-grade lung neuroendocrine carcinoma diagnosed using biopsy specimens. Lung Cancer, 75:368-373, 2012
4. Matsumura Y, Ishii G, Aokage K, Kuwata T, Hishida T, Yoshida J, Nishimura M, Nagai K, Ochiai A. Morphophenotypic characteristics of intralymphatic cancer and stromal cells susceptible to lymphogenic metastasis. Cancer Sci, 103:1342-1347, 2012
5. Asai M, Akizuki N, Fujimori M, Matsui Y, Itoh K, Ikeda M, Hayashi R, Kinoshita T, Ohtsu A, Nagai K, Kinoshita H, Uchitomi Y. Psychological states and coping strategies after bereavement among spouses of cancer patients: a quantitative study in Japan. Support Care Cancer, 20:3189-3203, 2012
6. Takuwa T, Ishii G, Nagai K, Yoshida J, Nishimura M, Hishida T, Neri S, Hasegawa S, Ochiai A. Characteristic immunophenotype of solid subtype component in lung adenocarcinoma. Ann Surg Oncol, 19:3943-3952, 2012
7. Neri S, Ishii G, Taira T, Hishida T, Yoshida J, Nishimura M, Nagai K, Ochiai A. Recruitment of podoplanin positive cancer-associated fibroblasts in metastatic lymph nodes predicts poor prognosis in pathological N2 stage III lung adenocarcinoma. Ann Surg Oncol, 19:3953-3962, 2012
8. Maeda R, Ishii G, Ito M, Hishida T, Yoshida J, Nishimura M, Haga H, Nagai K, Ochiai A. Number of circulating endothelial progenitor cells and intratumoral microvessel density in non-small cell lung cancer patients: differences in angiogenic status between adenocarcinoma histologic subtypes. J Thorac Oncol, 7:503-511, 2012
9. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Influence of cigarette smoking on survival and tumor invasiveness in clinical stage IA lung adenocarcinoma. Ann Thorac Surg, 93:1626-1632, 2012
10. Nakao M, Yoshida J, Goto K, Ishii G, Kawase A, Aokage K, Hishida T, Nishimura M, Nagai K. Long-term outcomes of 50 cases of limited-resection trial for pulmonary ground-glass opacity nodules. J Thorac Oncol, 7:1563-1566, 2012
11. Matsumura Y, Hishida T, Yoshida J, Aokage K, Ishii G, Nagai K. Reasonable extent of lymph node dissection in intentional segmentectomy for small-sized peripheral non-small-cell lung cancer: from the clinicopathological findings of patients who underwent lobectomy with systematic lymph node dissection. J Thorac Oncol, 7:1691-1697, 2012
12. Kinoshita T, Yoshida J, Ishii G, Aokage K, Hishida T, Nagai K. Pulmonary metastasis from encapsulated cervical ectopic type a thymoma. Ann Thorac Surg, 94:e141-142, 2012
13. Shimada Y, Yoshida J, Hishida T, Nishimura M, Ishii G, Nagai K. Predictive factors of pathologically proven noninvasive tumor characteristics in T1aN0M0 peripheral non-small cell lung cancer. Chest, 141:1003-1009, 2012

Department of Thoracic Oncology

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

Introduction

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

Routine activities

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

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

Research activities

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

Whole genome analysis of small cell cancer to detect new driver mutations and establishment of diagnosis methods for KIF5B-RET fusion gene which is a newly discovered driver gene of adenocarcinoma of the lung are under particular investigation in collaboration with the Research Center for Innovative Oncology.

Clinical trials

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

Recently, the usefulness of continuation and switch maintenance chemotherapy using pemetrexed for non-squamous non-small cell lung cancer (NSCLC) has been established. An in house feasibility study of maintenance chemotherapy of TS-1 for stage IV NSCLC is ongoing. Patients received TS-1 as a maintenance chemotherapy after 3 or 4 cycles of platinum-based 1st line chemotherapy and the target number of the patients is 78 in this study. More than two-thirds of the target number of patients have already entered in this study.

CH5424802 is a newly developed selective ALK inhibitor and very effective for ALK fusion positive NSCLC, although 4-5% of NSCLC are positive for EML4-ALK fusion protein. A phase I /II study of CH5424802 demonstrated durable response and a response rate higher than 90% without severe toxicity.

JCOG0605 is a randomized phase 3 study

Table 1. Number of patients in 2012

Lung Cancer		381
	Small cell lung cancer	68
	Adenocarcinoma	193
	Squamous cell carcinoma	69
	Large cell carcinoma	2
	NSCLC NOS	40
	Others	9
Thymic cancer		7
Thymoma		0
Malignant pleural mesothelioma		7
Primary unknown		1

Table 2. Initial treatment of lung cancer in 2012

Chemotherapy	221
Chemoradiotherapy	55
Surgery followed by chemotherapy	31
Radiotherapy	12
Palliative care	55
Others	7

Table 3. Survival of lung cancer patients treated in 2005-2009

Disease	Stage	Treatment	N	Survival rate (%)				
				1y	2y	3y	4y	5y
NSCLC	III	Chemoradiotherapy	240	78	48	37	31	23
NSCLC	IIIB-IV	Chemotherapy	832	48	26	15	8	4
SCLC	LD	Chemoradiotherapy	106	83	40	28	19	19
SCLC	ED	Chemotherapy	180	39	7	2	1	0

comparing nogitecan vs weekly cisplatin, irinotecan and etoposide for previously treated SCLC. Patient accrual of JCOG0605 has been completed this year.

JCOG1011 is a randomized phase 2 study for LD-SCLC comparing cisplatin and amrubicin with CODE regimen (weekly cisplatin, vincristine, Adriamycin, etoposide) after induction chemoradiotherapy with cisplatin and etoposide, and has started.

An investigator initiated clinical trial of vandetanib, which is inhibitor of RET, VEGFR and EGFR for KIF5B-RET fusion gene positive NSCLC is under preparation and will start soon.

List of papers published in 2012
Journal

1. Goto K, Satouchi M, Ishii G, Nishio K, Hagiwara K, Mitsudomi T, Whiteley J, Donald E, McCormack R, Todo T. An evaluation study of EGFR mutation tests utilized for non-small-cell lung cancer in the diagnostic setting. Ann Oncol, 23:2914-2919, 2012
2. Yoh K, Kubota K, Ohmatsu H, Goto K, Niho S, Ohe Y. Feasibility study of zoledronic acid plus cisplatin-docetaxel as first-line treatment for advanced non-small cell lung cancer with bone metastases. Anticancer Res, 32:4131-4135, 2012
3. Niho S, Ohe Y, Ishikura S, Atagi S, Yokoyama A, Ichinose Y, Okamoto H, Takeda K, Shibata T, Tamura T, Saijo N, Fukuoka M. Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: a multicenter feasibility study (JCOG 0402). Ann Oncol, 23:2253-2258, 2012
4. Niho S, Kunitoh H, Nokihara H, Horai T, Ichinose Y, Hida T, Yamamoto N, Kawahara M, Shinkai T, Nakagawa K, Matsui K, Negoro S, Yokoyama A, Kudoh S, Kiura K, Mori K, Okamoto H, Sakai H, Takeda K, Yokota S, Saijo N, Fukuoka M. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer, 76:362-367, 2012
5. Ito M, Niho S, Nihei K, Yoh K, Ohmatsu H, Ohe Y. Risk factors associated with fatal pulmonary hemorrhage in locally advanced non-small cell lung cancer treated with chemoradiotherapy. BMC Cancer, 12:27, 2012
6. Goto K, Ichinose Y, Ohe Y, Yamamoto N, Negoro S, Nishio K, Itoh Y, Jiang H, Duffield E, McCormack R, Saijo N, Mok T, Fukuoka M. Epidermal growth factor receptor mutation status in circulating free DNA in serum: from IPASS, a phase III study of gefitinib or carboplatin/paclitaxel in non-small cell lung cancer. J Thorac Oncol, 7:115-121, 2012
7. Kawata Y, Niki N, Ohmatsu H, Kusumoto M, Tsuchida T, Eguchi K, Kaneko M, Moriyama N. Quantitative classification based on CT histogram analysis of non-small cell lung cancer: correlation with histopathological characteristics and recurrence-free survival. Med Phys, 39:988-1000, 2012

Department of Esophageal Surgery

Hiroyuki Daiko, Takeo Fujita

Introduction

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

Routine activities

The Esophageal Surgery Division consists of 2 staff surgeons and 2 residents. An Esophageal Conference is held every Tuesday evening to discuss the diagnosis, staging, and treatment strategy for each patient and is attended by surgeons, medical oncologists, endoscopists, radiologists, radiation oncologists, and head & neck surgeons. Approximately 4 patients are operated upon every week. In 2012, 145 patients underwent esophagectomy. Transthoracic esophagectomy with extended lymph node dissection was performed on 65 nontreated cases or with neoadjuvant chemotherapy before surgery, and modified transthoracic esophagectomy was performed as a salvage procedure in 9 patients in whom other therapeutic modalities had failed. Thoracoscopic esophagectomy in the prone position with radical lymph node dissection was undertaken in 69 cases and transhiatal esophagectomy without thoracotomy was performed in 11 cases. Postoperatively, within 30 days, 1 patient died due to complications after a salvage operation.

Clinical activities

Currently, the Division is examining the role of thoracolaparoscopic esophagectomy as a minimally invasive esophagectomy comprising thoracoscopic esophagectomy and laparoscopic reconstruction. For patients without lymph node metastasis in the thoracic inlet, thoracoscopic esophagectomy in the prone position with radical lymph node dissection and laparoscopic reconstruction after esophagectomy for patients without history of laparotomy are being performed in an attempt to establish them as standard surgical procedures for esophageal cancer.

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

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

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

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

Table 1. Type of Procedure

1 stage operation	131
2 stage operation	14
Rt-Transthoracic Esophagectomy	65
Thoracoscopic Esophagectomy	69
Lt-Transthoracic Esophagectomy	0
Salvage Esophagectomy	9
Transhiatal Esophagectomy	11
Thoracoscopic enucleation for GIST	1
Emergency Operation	12
Others	8
Total	177

List of papers published in 2012
Journal

1. Daiko H, Nishimura M. A pilot study of the technical and oncologic feasibility of thoracoscopic esophagectomy with extended lymph node dissection in the prone position for clinical stage I thoracic esophageal carcinoma. Surg Endose, 26:673-680, 2012
2. Daiko H, Fujita T, Matsumura Y, Nishimura M. A new approach for posterior mediastinal tumors: thoracoscopic resection in the prone position. Asian J Endosc Surg, 5:138-140, 2012
3. Fujita T, Daiko H, Nishimura M. Early enteral nutrition reduces the rate of life-threatening complications after thoracic esophagectomy in patients with esophageal cancer. Eur Surg Res, 48:79-84, 2012
4. Hosokawa Y, Kinoshita T, Konishi M, Takahashi S, Gotohda N, Kato Y, Daiko H, Nishimura M, Katsumata K, Sugiyama Y, Kinoshita T. Clinicopathological features and prognostic factors of adenocarcinoma of the esophagogastric junction according to Siewert classification: experiences at a single institution in Japan. Ann Surg Oncol, 19:677-683, 2012

Department of Gastric Surgery

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

Introduction

Patients with gastric tumors are treated by the Gastric Surgery Division in the Upper Abdominal Surgical Oncology Group. Our group consists of six staff surgeons, three senior residents and ten resident surgeons. The gastric tumors we manage to include not only common gastric adenocarcinomas but also adenocarcinomas of the esophagogastric junction (AEG), which are increasing recently, probably due to reduction of *Helicobacter pylori* (HP)-infection rates, and gastric submucosal tumors (GIST etc.). Annually 260-300 patients are operated on either with a conventional laparotomy or laparoscopic surgery. Laparoscopic gastrectomy with radical lymph node (LN) dissection was introduced in 2010 to pursue minimal invasiveness and better quality of life (QOL) for the patients. Recent high-definition laparoscopic imaging enables more meticulous and accurate maneuvers. In 2012, about 60% of gastrectomies were performed under laparoscopy. The basis of our surgery is radical extirpation of cancer lesions, but at the same time organ functions and a better QOL should be maintained. In addition, we attempt to obtain better clinical outcomes for patients with diseases associated with dismal prognoses (scirrhous gastric cancer or with progressive lymph nodes metastasis) by surgery combined with recent advanced chemotherapy regimens, including molecular-targeting drugs (Trastuzumab).

Routine activities

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

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

Research activities and clinical trials

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

Table 1. Number of patients

Gastric cancer	284
Others (GIST etc.)	31

Table 2. Type of procedure

Open gastrectomy	92
Distal Gastrectomy	33
Pylorus-preserving Gastrectomy	1
Proximal Gastrectomy	1
Total Gastrectomy	43
Pancreaticoduodenectomy	2
Partial Gastrectomy	3
Others (bypass, exploration, etc.)	9
Laparoscopic Surgery	194
Distal Gastrectomy	117
Pylorus-preserving Gastrectomy	5
Proximal Gastrectomy	26
Total Gastrectomy	15
Partial Gastrectomy	14
Others (bypass, exploration, etc.)	17

Table 3. Survival rates of gastric cancer patients shown by stage

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

Op.year: 1995.1-2004.12
Stage: Japanese Classification (13th Ed.); Pts, patients

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

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

List of papers published in 2012

Journal

1. Kinoshita T, Gotohda N, Kato Y, Takahashi S, Konishi M, Okazumi S, Katoh R, Kinoshita T. Laparoscopic transhiatal resection for Siewert type II adenocarcinoma of the esophagogastric junction: operative technique and initial results. Surg Laparosc Endosc Percutan Tech, 22:e199-203, 2012
2. Fujita T, Gotohda N, Kato Y, Kinoshita T, Takahashi S, Konishi M, Daiko H, Nishimura M, Kuwata T, Ochiai A, Kinoshita T. Clinicopathological features of stomach cancer with invasive micropapillary component. Gastric Cancer, 15:179-187, 2012

Department of Colorectal Surgery

Norio Saito, Masanori Sugito, Masaaki Ito, Akihiro Kobayashi, Yusuke Nishizawa, Nobuhiro Sugano, Hideaki Nishigori

Introduction

The Colorectal and Pelvic Surgery Division was established 14 years ago. Its main purpose is to bring together the divisions that are composed of colorectal surgeons and urologists. Cooperation between these divisions contributes not only to the establishment of effective operative techniques but also to an oncological consensus including a consensus on the quality of life (QOL) and the various functions of patients with pelvic malignancies. New surgical procedures, such as nerve-sparing surgery, sphincter-saving surgery, bladder-sparing surgery, pouch surgery and minimally invasive surgery, are being developed to prevent postoperative dysfunctions. These new approaches will contribute to better curability and QOL among patients with pelvic malignancies.

Routine activities

The Colorectal and Pelvic Surgery Division comprises 7 consultants (5 colorectal surgeons and 2 urologists) and 10 residents. The outpatient clinic is open 5 days a week. More than 350 new patients with colorectal carcinomas and more than 150 new patients with other pelvic malignancies visited this Division during the last year. Treatment plans are discussed at a weekly conference on GI malignancies and at another weekly conference on pelvic malignancies. Many treatment modalities, such as local excision with or without adjuvant chemo- or radiotherapy and other minimally invasive forms of surgery using laparoscopy, have been introduced for the treatment of patients in the early stages of cancer. Laparoscopy-assisted operations (Lap-Ops) with wider lymphadenectomy of up to more than D2 are also increasingly being performed in patients with advanced colorectal carcinomas. Abdominoperineal resection (APR) has, in the past, been the standard surgery in patients with very low rectal cancer; however, partial anal sphincter preserving surgery such as intersphincteric resection (ISR) has been performed in about 350 patients with very low rectal tumors and has resulted in cure, preservation of anal function, and a better QOL.

Research activities

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

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

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

Clinical trials

Other clinical trials are also in progress as follows.

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

Table 1. Number of patients (2012.1-2012.12)

Colorectal cases			Other cases		Total
Colon	Rectum	Sub-total	Gastro-intestinal	Others	
148	180	328	5	112	445

Table 2. Type of procedure
Operative Procedures (2012.1-2012.12)

Colon N=148 Laparoscopic (LAP) : 119, Open : 29		
Sigmoidectomy	41	(LAP:36)
Right (hemi) colectomy	43	(LAP:36)
Ileocecal resection	20	(LAP:19)
Limited colectomy	27	(LAP:23)
Hartmann procedure	0	
High anterior resection	0	
Low anterior resection	3	(LAP:1)
Left (hemi) colectomy	4	(LAP:3)
Stoma	0	
Other	10	

Rectum N=180 Laparoscopic (LAP) :103, Open : 93		
Low anterior resection	71	(LAP:50)
*Abdominoanal resection(AAR)	50	(LAP:22)
High anterior resection	17	(LAP:11)
Abdominoperineal resection (APR)	18	
Hartmann procedure	4	
Local excision	4	
Total pelvic exenteration	2	
Stoma	7	
Others	7	

* Conventional coloanal anastomosis:5
Partial intersphincteric resection (ISR) :17
Subtotal ISR:23
Total ISR:4
Partial external sphincter resection (ESR):1

Table 3. Survival rates

Stage	Colon			Rectum		
	No. of pts	5-yr survival (%)		No. of pts	5-yr survival (%)	
		overall	cancer specific		Overall	cancer specific
Stage 0	7	100	100	10	100	100
Stage I	155	96	100	119	94.9	99.1
Stage II	239	91.8	95.5	158	84.6	89.9
Stage III	158	83.9	87.5	132	81.3	83.4
Stage IIIb	50	66.1	66.1	89	60.8	63.6
Stage IV	133	21.1	22.5	77	25.3	25.7

Op:1999.1-2005.12

List of papers published in 2012
Journal

1. Nishizawa Y, Kobayashi A, Saito N, Nagai K, Sugito M, Ito M, Nishizawa Y. Surgical management of small bowel metastases from primary carcinoma of the lung. Surg Today, 42:233-237, 2012
2. Nishigori H, Ito M, Nishizawa Y, Koyama A, Koda T, Nakajima K, Minagawa N, Nishizawa Y, Kobayashi A, Sugito M, Saito N. Postoperative chylous ascites after colorectal cancer surgery. Surg Today, 42:724-728, 2012
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Department of Gastrointestinal Oncology

Toshihiko Doi, Takayuki Yoshino, Nozomu Fuse, Takashi Kojima, Kohei Shitara

Introduction

In 2012, approximately 500 patients were treated by 5 medical oncologists and 5 residents in the Gastrointestinal (GI) Oncology Division, which focuses on the use of chemotherapy with or without radiation for the treatment of GI malignancies.

Routine activities

Inter-Divisional tumor board conferences with the Surgical/Radiation Oncology Divisions are held regularly to review and direct treatment for each patient or to discuss treatment strategies. Chemotherapy on an outpatient basis for probable candidates was managed passively, approximately 1361 patients are hospitalized under normal circumstances and the hospital stay with chemotherapy or palliative therapy was short. Our activities for each type of GI cancer in 2012 are shown in Table 1 (Number), Table 2 (Treatment), and Table 3 (efficacy). In clinical trials, both 62 sponsored initiated trials which consisted of 31 phase I trials including first-in-human, first-in-class drugs in a global fashion and 31 phase2/3 global trials to approve investigational new drugs (INDs) were conducted.

Research activities

Phase I

Our Division has focused more on the early stage clinical development of investigational agents. Over 100 patients have been registered in phase I trials annually. We organize a weekly phase I trials meeting to share the updated information and to allocate patients to adequate phase I trials. Several results of phase I trials, such as studies on a cMET+VEGFR-2 inhibitor (golvatinib, E7050), an angiopoietin-1/2 antagonist (trebananib, AMG 386), an IGF-1R inhibitor (ganitumab, AMG 479) and a histone deacetylase inhibitor (vorinostat) for GI cancer, were presented at international meetings and published. Recently, the number of first-in-human trials and trials around the same time as Western countries is increasing. Our retrospective analysis of 368 patients treated in 47 phase I trials in the recent 3 years showed that the frequency of severe adverse events in these early 14 phase I trials were not higher than that of other 34 phase I trials conducting after completion of phase I trials in Western countries (3.3% vs. 8.5%).

Esophageal Cancer (EC)

The result of a multicenter phase II trial of neo-adjuvant chemo radiotherapy (CRT) in stage II or III EC was presented at the ASCO-GI meeting, 2012. A multicenter phase II trial of combined treatment with endoscopic mucosal resection and chemoradiotherapy for clinical Stage I EC (JCOG0508) has been completed. The enrollment in of a multicenter phase II trial of S-488410 (vaccination with multiple peptides) in stage IV EC has been completed.

Gastric Cancer (GC)

The results of a global randomized phase III trial comparing everolimus to placebo (GRANITE) was presented at the 2012 Gastrointestinal Cancers Symposium and the results of a global randomized phase III trial comparing capecitabine plus cisplatin (XP) with cetuximab to XP (EXPAND) was presented at the ESMO 2012 Congress. They failed to show any survival benefit for everolimus and cetuximab in GC patients. We investigated the relationship between serum HER2 levels and the histologic HER2 status in patients with advanced/recurrent gastric cancer and presented the results at the 2012 Gastrointestinal Cancers Symposium.

Colorectal Cancer (CRC)

Based on our promising results from a randomized phase II trial comparing TAS-102 with BSC (best supportive care) published in *Lancet Oncology*, an international phase III trial, called the *RECOUSE* trial, to confirm the clinical benefit of TAS-102 is ongoing as a company-sponsored trial. We reported the results of the *CORRECT* trial to show the clinical benefit of regorafenib published in *the Lancet*, which has just been approved by the US FDA and will be approved in Japan soon. We have developed a consortium of 7 cancer centers to collect more than 100 strictly selected archived samples as the first-step in the trial called the BREAC trial (*Biomarker Research for Anti-EGFR Monoclonal Antibodies by Comprehensive Cancer*

Genomics), from colorectal cancer patients who had received anti-EGFR therapy; the selection of more than 50 super-responder and non-responder cases. We have started whole exon mutation analyses to find the specific gene candidates potentially related to the efficacy of anti-EGFR therapy. As the second step to validate the specific gene candidates, we will investigate the association between the specific gene candidates and the efficacy for another consecutive 250 colorectal cancer patients who had received anti-EGFR therapy. Our BREAC trial is built upon a "disruptive paradigm" that brings together the best attributes of both academia and industry by creating cross-functional professional teams working in a goal-oriented, milestone-driven manner to convert knowledge into tests, devices, drugs and policies that can benefit patients as quickly as possible.

Clinical trials (describing only ongoing disease-specific trials)

Esophageal Cancer (EC)

A multicenter phase III trial comparing surgery with CRT concurrent with 5-FU and cisplatin in stage I EC (JCOG0502) and a multicenter phase II trial of chemo radiotherapy (CRT) in stage II or III EC (JCOG0909) are ongoing. A multicenter phase II trial of adjuvant chemotherapy with IMF-001 (vaccination with multiple peptides) in stage II/III EC is going as investigator initiated trial.

Gastric Cancer (GC)

In a phase II trial of TAS-102, which was the first investigator-initiated trial using an unapproved agent for us, a multicenter global phase II/III trial comparing trastuzumab emtansine to taxane in HER2-positive GC patients (GATSBY) and a multicenter phase III trial comparing docetaxel with cisplatin plus S-1 (DCS) to cisplatin plus S-1 (CS; JCOG 1013), a multicenter phase II trial comparing 12 months of S-1 to 6 months of S-1 as an adjuvant chemotherapy (JCOG 1104), a multicenter phase II trial of AUY922 and trastuzumab in HER2-positive GC patients, and a multicenter phase II trial of dovitinib in scirrhous GC patients, enrollment has been opened.

The enrollment for a multicenter global phase III trial comparing paclitaxel plus ramucirumab to paclitaxel plus placebo (RAINBOW), a multicenter phase II trial of cetuximab with CS, a multicenter randomized phase II trial of S-1 plus leucovorin (SL), oxaliplatin with SL and CS has been completed and the follow-up is ongoing. The enrollment for a multicenter phase II trial of neoadjuvant chemotherapy with DCS (JCOG 1002) is ongoing. The follow-up of a multicenter phase III trial (G-SOX) comparing S-1 plus oxaliplatin to CS is ongoing.

Colorectal Cancer (CRC)

An international randomized phase III trial comparing ramucirumab with a placebo in combination with FOLFIRI in the second-line setting is ongoing. Similarly, an international phase III trial called the *RECOUSE* trial, to confirm the clinical benefit of TAS-102 with a placebo in a salvage setting is ongoing. We have conducted a randomized, multicenter, phase III study called the *ACHIEVE* trial, to compare 6 months of either mFOLFOX6 or XELOX with 3 months of the same regimen as adjuvant chemotherapy in patients with completely resected stage III colon cancer, together with 6 other nations' collaborative groups in the US, UK/Australia, Italy, Greece and France. We also have conducted a confirmatory study, called the *SUNRISE* trial, on an Onco*type* DX Colon Cancer assay to assess the relationship between continuous recurrence score and the likelihood of recurrence in patients with resected stage II and stage III colon cancer. In order to achieve personalized medicine, we are conducting an *Analysis of Biopsy samples for Cancer genomics* called *ABC* study, using target sequencing from pre-treatment biopsy samples for advanced solid tumors including CRCs.

Table 1. Number of patients

Tumor Type	Number of new patients	Number of hospitalized patients
Esophageal	219	128
Gastric	246	118
Colorectal	395	47
Other type of tumors	80	13
Total	940	306

Table 2. Treatment

Tumor Type	Treatment	Number of patients
Esophageal Cancer	Chemotherapy (include CRT*)	130
Gastric Cancer	Chemotherapy	158
Colorectal Cancer	Chemotherapy	218

*chemoradiation

Table 3. Survival of patients who received standard chemotherapy

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

List of papers published in 2012
Journal

1. Doi T, Ohtsu A, Yoshino T, Boku N, Onozawa Y, Fukutomi A, Hironaka S, Koizumi W, Sasaki T. Phase I study of TAS-102 treatment in Japanese patients with advanced solid tumours. Br J Cancer, 107:429-434, 2012
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3. Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, Tsuji A, Yamaguchi K, Muro K, Sugimoto N, Tsuji Y, Moriwaki T, Esaki T, Hamada C, Tanase T, Ohtsu A. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol, 13:993-1001, 2012
4. Yoshino T, Yamazaki K, Hamaguchi T, Shimada Y, Kato K, Yasui H, Boku N, Lechuga MJ, Hirohashi T, Shibata A, Hashigaki S, Li Y, Ohtsu A. Phase I study of sunitinib plus modified FOLFOX6 in Japanese patients with treatment-naive colorectal cancer. Anticancer Res, 32:973-979, 2012
5. Bando H, Yoshino T, Yuki S, Shinozaki E, Nishina T, Kadowaki S, Yamazaki K, Kajiura S, Tsuchihara K, Fujii S, Yamanaka T, Ohtsu A. Clinical outcome of Japanese metastatic colorectal cancer patients harbouring the KRAS p.G13D mutation treated with cetuximab + irinotecan. Jpn J Clin Oncol, 42:1146-1151, 2012
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Department of Digestive Endoscopy

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Introduction

The Digestive Endoscopy Division covers the fields of the gastrointestinal (GI) tract and head and neck regions. In 2012, a total of 11,815 examinations were performed. A narrow band imaging (NBI) system using the LUCERA spectrum (Olympus Optical Co., Ltd.) has been included for routine examination in 6 endoscopy rooms since September 2009. Furthermore, endoscopic treatments such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), percutaneous endoscopic gastrostomy (PEG), endoscopic balloon dilation (EBD), radial incision and cutting (RIC), and photodynamic therapy (PDT) have been performed.

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

Routine activities

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

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

Research activities

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

Table 1. Number of Patients Examined in 2008-2012

Section	2008	2009	2010	2011	2012
Upper gastrointestinal endoscopy	5154	5545	5720	6350	6647
Endoscopic ultrasonography	110	86	78	70	54
Endoscopic mucosal resection (esophagus)	111	130	145	181	168
Endoscopic mucosal resection (stomach)	196	231	211	205	215
Endoscopic balloon dilation	1073	866	613	644	711
Percutaneous endoscopic gastrostomy	146	173	218	215	171
Photodynamic therapy (esophagus)	36	23	47	48	39
Colonoscopy	2071	2027	2250	1550	2302
Polypectomy/EMR	731	791	744	800	912
Narrow Band Imaging (head and neck)	193	194	147	95	106
Endoscopic mucosal resection (head and neck)	31	21	41	41	46

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

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

In contrast, developing research into novel endoscopy systems is being performed. Hypoxia imaging is applied in the detection of neoplastic lesions of the head and neck and alimentary tracts, with blue visualized images. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and nanoparticles of a rare earth, doped yttrium oxide. This system is capable of penetrating through the intestinal wall and obtaining images. Furthermore, molecular imaging endoscopy for the use of this system with an InGaAs CCD imaging system has been developed, since nanoparticles of rare earth act as fluorescent agents. With a low-temperature atmospheric pressure plasma system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnosis system using photosensitizing agents, such as hypericin and 5ALA, has been constructed. Moreover, research is ongoing into the development of a new electrosurgical knife as an endoscopic device, which will be used in ESD for esophageal and gastric cancer.

Clinical trials

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

Table 2. Endoscopic procedures in 2012

		2011	2012
Esophagus	EMR	100	89
	ESD	45	79
Stomach	EMR	9	3
	ESD	202	212
Colon and rectum	EMR*	744	834
	ESD	17	78
Head and neck	EMR	6	7
	ESD	35	33

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

List of papers published in 2012
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Department of Hepatobiliary and Pancreatic Surgery

Masaru Konishi, Shinichiro Takahashi, Takahiro Kinoshita, Hidehito Sibasaki, Naoto Gotohda, Yuichiro Kato, Motokazu Sugimoto, Takahiro Toda, Kenji Sakai, Eiji Higaki

Introduction

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

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

Routine activities

In the National Cancer Center Hospital East (NCCH-E), surgeons in the Upper Abdominal Surgical Oncology Group operate on all patients with gastric, hepatobiliary and pancreatic cancer. Our group is composed of 6 attending surgeons, 3 chief residents, and 4–6 residents. The outpatient clinic is open 5 days a week. Staff meetings are held 3 times a week during which treatment strategies from the medical and surgical points of view are discussed. A case conference on imaging diagnosis is conducted every Tuesday in cooperation with radiologists and medical oncologists, and a pathology conference is held every month with pathologists. In 2012, 209 patients with hepatobiliary and pancreatic diseases underwent surgical treatment at our Division.

Research activities and clinical trials

1) Pancreatic cancer

JASPAC-01 is a randomized phase III trial to compare orally administered S-1 with intravenous gemcitabine as adjuvant chemotherapy for patients with curatively resected pancreatic cancer. Three hundred and fifty-eight patients have been enrolled. The results of the primary endpoint will be opened in 2013.

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

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

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

Pancreatic fistula represent a major complication after pancreatoduodenectomy (PD). Mortality after PD is mostly due to pancreatic fistula formation. We are engaged in exploratory studies to investigate the innovative techniques or management for reducing pancreatic fistula formation after PD. Furthermore, perfusion CT analysis is underway to quantify the preoperative risk of the formation of pancreatic fistulae.

2) Biliary tract cancer

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

JCOG1202 is a phase III study to compare S-1 with surgery alone as adjuvant chemotherapy for patients with curatively resected extrahepatic bile duct cancer. This study is now under preparation.

Table 1. Number of patients

Invasive pancreatic cancer	33
Other pancreatic neoplasms	19
Hepatocellular carcinoma	30
Hepatic metastases	63
Intrahepatic cholangiocarcinoma	5
Bile duct cancer	24
Gallbladder cancer	6

Table 2. Type of procedure

Pancreaticoduodenectomy	53
Distal pancreatectomy	11
Total pancreatectomy	4
Laparoscopic distal pancreatectomy	4
Hepatectomy with biliary reconstruction	4
Hepatectomy without biliary reconstruction	74
Laparoscopic hepatectomy	22
Other procedures	37
Total	209

Table 3. Survival rates

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

3) Hepatocellular carcinoma

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

Recruitment in a phase II trial on adjuvant immunotherapy with Glypican-3, and in a phase III trial on adjuvant chemoprevention with Peretionin for HCC patients following curative local treatment is on-going.

4) Liver metastasis from colorectal cancer

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

5) Immune-enhancing enteral diet (IED)

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

List of papers published in 2012
Journal

1. Konishi M. Adjuvant chemotherapy for resectable biliary tract cancer: current status and future direction. J Hepatobiliary Pancreat Sci, 19:301-305, 2012
2. Shirakawa H, Kinoshita T, Gotohda N, Takahashi S, Nakagohri T, Konishi M. Compliance with and effects of preoperative immunonutrition in patients undergoing pancreaticoduodenectomy. J Hepatobiliary Pancreat Sci, 19:249-258, 2012
3. Kato Y, Konishi M, Kinoshita T, Takahashi S, Gotohda N, Kinoshita T. Intraductal oncocytic papillary neoplasm of the extrahepatic bile duct: report of a case. Surg Today, 42:1240-1243, 2012
4. Gotohda N, Konishi M, Takahashi S, Kinoshita T, Kato Y, Kinoshita T. Surgical outcome of liver transection by the crush-clamping technique combined with Harmonic FOCUS. World J Surg, 36:2156-2160, 2012

Department of Hepatobiliary and Pancreatic Oncology

Masafumi Ikeda, Shuichi Mitsunaga, Satoshi Shimizu, Izumi Ohno, Hideaki Takahashi

Introduction

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

Routine activities

Our Division is composed of 5 staff oncologists and 2 residents, with 35-45 beds in the hospital and we conduct clinical rounds for admitted patients every morning and evening. Most new patients with unresectable hepatobiliary and pancreatic tumors are hospitalized for tumor diagnosis and treatment. Individual patient treatment strategies are discussed in weekly tumor board conferences attended by medical oncologists, surgeons, radiologists, radiation oncologists, and pharmacologists.

Furthermore, we are also responsible for all abdominal ultrasonographic examinations at our hospital, as well as ultrasound-guided biopsies of abdominal masses, particularly those in the liver and pancreas, performed for pathological diagnosis. Recently, endoscopic ultrasonographic examinations or endoscopic ultrasound-guided fine needle aspiration have also begun to be frequently performed for biliary and pancreatic tumors. Furthermore, endoscopic or percutaneous transhepatic biliary drainage and stenting are performed for obstructive jaundice.

Research activities

A medical team, "Team Nexavar", composed of medical oncologists, pharmacologists and nurses, provides supportive care for the toxicities of sorafenib. The results of our medical team are superior in terms of the percentage of cases discontinuing treatment on account of adverse events, including the hand-foot syndrome, as compared to previous reports, and the significance of team medication has been clarified. The predictive factors of tumor response and survival, the usefulness of urea-containing ointments for the prevention of hand-foot syndrome and the efficacy and safety for Child Pugh B cases have been also investigated in advanced hepatocellular carcinoma (HCC) patients treated with sorafenib.

Pancreatic cancer

Arctigenin, which is contained in abundance in the seeds of Arctium lappa, exerts favorable antitumor activity by attenuating the tolerance of cancer cells to glucose starvation, as demonstrated in mouse xenograft models. A phase I trial was conducted to investigate the recommended dose of this agent in patients with gemcitabine-resistant metastatic pancreatic cancer, and favorable clinical responses were obtained. A multicenter phase II trial is being planned to evaluate the efficacy and safety of this substance.

For advanced pancreatic cancer, the current research focus is investigation of the mechanism of cancer cachexia to facilitate development of innovative therapies. Our data indicate that the causes of cachexia are 'Neural invasion' and 'Inflammation'. We have shown that neural invasion induces cachexia via astrocytic activation of the neural route, termed neuroinflammation, in patients with pancreatic cancer. In addition, we have investigated the impact of tumor-associated macrophages on invasive ductal carcinoma of the pancreatic head, the clinical significance of des-acyl ghrelin levels as a predictor of gastrointestinal toxicities, and the symptomatic changes to predict disease control by chemotherapy.

Hepatitis B viral (HBV) reactivation following chemotherapy

HBV reactivation has often been reported in patients undergoing chemotherapy for the treatment of malignant disease. Prospective studies to clarify the present status of HBV reactivation following chemotherapy for solid tumors are being conducted.

Clinical trials

Forty one clinical trials (sponsored: 26 trials, investigator-initiated: 15 trials) are ongoing, and 11 clinical trials (sponsored: 6 trials, investigator-initiated: 6 trials) are being planned for the upcoming year.

Table 1. Number of patients

Hepatocellular carcinoma	119
Biliary tract cancer	
Intrahepatic cholangiocarcinoma	20
Extrahepatic cholangiocarcinoma	8
Gallbladder cancer	23
Papilla of vater carcinoma	2
Pancreatic cancer	
Locally advanced disease	56
Metastatic disease	116
Other	25
Total	369

Table 2. Type of procedure

	Number of patients
Hepatocellular carcinoma	
Radiofrequency ablation	87
Transarterial chemoembolization	192
Intra-arterial chemotherapy	59
Systemic chemotherapy	70
Proton beam radiotherapy	13
Biliary tract cancer	
Systemic chemotherapy	55
Radiotherapy	4
Pancreatic cancer	
Systemic chemotherapy	239
Chemoradiotherapy	13
Total	732

Table 3. Survival rates

Diagnosis			
Hepatocellular carcinoma	No. of pts	MST(mo)	2-yr survival(%)
Radiofrequency ablation	191	57.2	83.0
Transcatheter arterial chemoembolization	292	22.7	46.9
Intra-arterial chemotherapy	75	6.5	21.9
Systemic chemotherapy	16	4.7	0
Period:	1992/11-2005/12		
Biliary tract cancer	No. of pts	MST(mo)	2-yr survival(%)
Systemic chemotherapy	385	6.5	7.2%
Period:	1992/11-2012/12		
Pancreatic cancer	No. of pts	MST(mo)	1-yr survival(%)
Locally advanced disease	115	8.9	35.9
Metastatic disease	833	6.9	26.1
Period:	1992/11-2012/12		

Hepatocellular carcinoma

To elucidate the survival benefit of intra-arterial chemotherapy, a randomized controlled trial comparing the combined administration of sorafenib with intra-arterial cisplatin with sorafenib alone for highly advanced HCC is underway.

Among sponsored trials, the enrollments for some phase III trials of brivanib vs. placebo in combination with TACE, of brivanib vs. sorafenib as a first-line chemotherapy, and of brivanib vs. placebo, S-1 vs. placebo, everolimus vs. placebo as second-line chemotherapy have already been completed. Some phase III trials of peretinoin vs. placebo in the adjuvant setting after resection or ablation, and of orantinib vs. placebo in combination with TACE are underway. Two randomized phase II trials comparing dovitinib vs. sorafenib as a first-line chemotherapy, and GC33 vs. placebo in the second-line setting are also underway. Enrollments for phase I trials of an ALK-1 inhibitor (PF-03446962) and a PDGFR-α antagonist (MEDI-575) have been completed, and phase I trials of nintedanib, pimasertib, a STAT3 inhibitor (OPB-31121), a c-MET inhibitor (ARQ197) and a peptide vaccine including glypican-3, etc. (ONO-7268MX1) are ongoing.

Biliary tract cancer

A phase I investigators-initiated trial of combined gemcitabine, cisplatin and S-1 therapy is ongoing to determine the recommended doses for subsequent trials. The role of adjuvant therapy in resectable biliary tract cancer is still uncertain, and no recommended standard exists. A randomized trial comparing adjuvant S-1 with observation is being planned to determine whether adjuvant chemotherapy with S-1 might improves the outcomes of patients with resected biliary tract cancer.

Pancreatic cancer

A multicenter phase II trial of neoadjuvant S-1 and concurrent radiotherapy for borderline resectable pancreatic cancer (JASPAC05), and a randomized phase II trial of S-1 and concurrent radiotherapy with versus without induction chemotherapy for locally advanced pancreatic cancer (JCOG1106) are ongoing. As sponsored trials, enrollments for a phase III trial of gemcitabine and an IGF-1R antagonist (AMG479) with gemcitabine and a placebo for untreated metastatic pancreatic cancer have been completed. In this trial, the number of enrolled cases was the highest in the world. As for Japanese multicenter trials, a phase II trial of FOLFIRINOX has been completed, while enrollments for a phase III trial of a peptide vaccine (OCV-C01) and a phase II trial of gemcitabine and nab-paclitaxel are now ongoing.

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2. Kudo M, Tateishi R, Yamashita T, Ikeda M, Furuse J, Ikeda K, Kokudo N, Izumi N, Matsui O. Current status of hepatocellular carcinoma treatment in Japan: case study and discussion-voting system. Clin Drug Investig, 32 Suppl 2:37-51, 2012
3. Imoto A, Mitsunaga S, Inagaki M, Aoyagi K, Sasaki H, Ikeda M, Nakachi K, Higuchi K, Ochiai A. Neural invasion induces cachexia via astrocytic activation of neural route in pancreatic cancer. Int J Cancer, 131:2795-2807, 2012
4. Yoshikawa K, Mitsunaga S, Kinoshita T, Konishi M, Takahashi S, Gotohda N, Kato Y, Aizawa M, Ochiai A. Impact of tumor-associated macrophages on invasive ductal carcinoma of the pancreas head. Cancer Sci, 103:2012-2020, 2012

Department of Urology

Yasuyuki Sakai, Yoshinobu Komai

Introduction

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

Routine activities

Outpatient activities: An outpatient clinic is open 2 days a week as a Urology Department. Flexible cystoscopy, abdominal ultrasonography, retrograde pyelography and some prostate biopsies are performed in the outpatient clinic. Superficial bladder cancer (G3, cis, or recurrent tumor) after TUR-Bt is treated by instillation of BCG into the bladder. Advanced urogenital cancers including stage D2 prostate cancer are referred to the medical oncology division for chemotherapy or hormone therapy. Extrinsic obstructions of the upper urinary tract that directly result from invasion of an adjacent malignancy or peritoneal metastasis are also treated. In most cases, internal stenting is better tolerated than percutaneous nephrostomy. Thirty-seven patients newly received ureteral stents and 15 underwent nephrostomy for obstructive uropathy.

Inpatient activities: A daily conference is held with doctors of the Department of Pelvic Surgery on diagnosis and treatment of the patients with colorectal and urological cancer. We performed 38 combination surgeries with colorectal surgeons. In the Department of Urology, 104 general anaesthesia surgeries, 78 spinal anesthesia surgeries and 56 prostate biopsies were performed.

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

Research activities

Minimum incision endoscopic surgery was introduced from 2011, the surgery is a gasless, single-port access, cost-effective, and minimally invasive surgery. We intend to make this operation more sophisticated in coordination with the Department of Urology, Tokyo Medical and Dental University. For those patients (intermediate and high-risk groups) who desired preservation of sexual function, bilateral sural nerve grafting was performed for the recovery of sexual function. Sural nerve interposition grafting was performed in 46 patients from 2004, and they were followed up for 1 year. Overall, 10 men (22.2%) had return of erectile activity (partial erection). Total pelvic exenteration (TPE) is the standard procedure for locally advanced rectal cancer involving the prostate and seminal vesicles. We evaluated the feasibility of bladder-sparing surgery as an alternative to TPE. We performed concomitant prostatectomy and cysto-urethral anastomosis.

Table 1. Number of patients

Renal cell carcinoma	33
Upper urinary tract urothelial cell carcinoma	19
Bladder cancer	48
Prostate cancer	28
Testicular cancer	9

Table 2. Type of procedure

Radical nephrectomy	17
Partial nephrectomy	16
Nephroureterectomy	19
Radical cystectomy	15
TURBT	68
Radical prostatectomy	28

Table 3. Survival rates

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

List of papers published in 2012
Journal

1. Waseda Y, Komai Y, Yano A, Fujii Y, Noguchi N, Kihara K. Pathological complete response and two-year disease-free survival in a primary gastric choriocarcinoma patient with advanced liver metastases treated with germ cell tumor-based chemotherapy: a case report. Jpn J Clin Oncol, 42:1197-1201, 2012

Department of Musculoskeletal Oncology and Rehabilitation

Umio Yamaguchi, Takuro Sakurai

Introduction

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

Routine activities

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

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

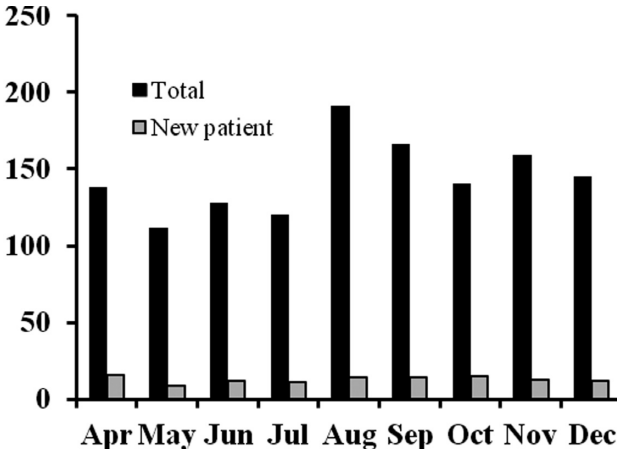

Figure 1. Number of patients treated at the outpatient clinic (2012).

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

Clinical department	2011	2012
Hematology oncology	29	39
Thoracic oncology	24	35
Thoracic surgery	18	29
Head and neck oncology	12	21
Gastrointestinal oncology	12	21
Esophageal surgery	18	19
Musculoskeletal oncology	2	17
Palliative medicine	9	15
Colorectinal surgery	8	13
Hepatobiliary and pancreatic oncology	7	12
Others	7	24
Total	146	245

Department of Hematology

Kunihiro Tsukasaki, Masahiko Nezu, Kuniaki Itoh, Hiromi Yuasa

Introduction

The Department of Hematology works in cooperation with the Department of Breast and Medical Oncology. The staff physicians of both Departments collaborate regarding outpatient care and education of residents as a medical oncology team. The staff physicians and residents of this Department carry out clinical and research activities related to the multi-disciplinary treatment of patients with hematological malignancies which consist of more than 100 disease entities under the WHO classification (version 2008). Our Department focuses on early and late phases of clinical trials in collaboration with the Research Center for Innovative Oncology and Japan Clinical Oncology Group (JCOG), respectively, especially studies on lymphoid malignancies.

Routine activities

The number of patients with newly diagnosed hematologic malignancies in our Department is increasing, and approximately 220 patients with newly diagnosed hematological malignancies including non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, macroglobulinemia, acute leukemia, myelodysplastic syndrome and chronic leukemia were cared this year (Table 1). The Department is currently providing routine chemotherapy as an outpatient service to an increasing number of relatively aged patients with hematological malignancies. All patients undergoing intensive chemotherapy and autologous peripheral blood hematopoietic stem cell transplantation (APBSCT) (Table 2) are managed in laminar airflow rooms in the designated ward on the eighth floor. Besides managing patients, the Department also provides consultation on hematological abnormalities detected in the Department of Clinical Laboratories. A morning case conference on inpatient care of our Department is held from Monday to Friday, and a weekly case conference on new patients visiting the clinics at our Department and Breast and the Medical Oncology Department is held on Thursday evenings. A weekly conference, including an educational review on hematology, is conducted on Tuesday evenings. On Wednesday evenings, a weekly joint conference on lymphoid malignancies with expert pathologists and an educational cytology conference are held. A joint morning journal club for both or Department of ours and the Breast and Medical Oncology Department is held on Mondays and Fridays.

Research activities

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

Clinical trials

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

Table 1. Number of patients

Non-Hodgkin's lymphoma	153
Hodgkin's lymphoma	6
Multiple myeloma	15
Acute leukemia	6
Chronic leukemia	3
Others	32
Total	215

Table 2. Type of procedure

PBSCT for non-Hodgkin's lymphoma in relapse	3
PBSCT for myeloma in remission	2
Total	5

a phase II trial comparing rituximab-high-CHOP/CHASER followed by high dose LEED with autologous peripheral blood hematopoietic stem cell transplantation in patients with newly diagnosed mantle cell lymphoma (JCOG0406); a randomized phase II trial comparing dexamethasone with bortezomib or thalidomide in patients with relapsed/refractory multiple myeloma in relapse (JCOG0904); and a phase II study of mLSG15 chemotherapy followed by allo-HSCT, comparing the results with historical controls in JCOG9801 to evaluate the promising efficacy of allo-HSCT, possibly associated with a graft-versus-ATL effect, especially in view of a comparison with intensive chemotherapy. A phase III study evaluating the efficacy of the combination of interferon-alpha (IFN) and zidovudine (AZT) as compared to watchful-waiting for indolent ATL is to be initiated (JCOG PC908) under a highly advanced medical technology assessment system because IFN and AZT are not covered for ATL by the National Health Insurance in Japan.

List of papers published in 2012

Journal

1. Tsukasaki K, Tobinai K, Hotta T, Shimoyama M. Lymphoma study group of JCOG. Jpn J Clin Oncol, 42:85-95, 2012
2. Yamaguchi M, Tobinai K, Oguchi M, Ishizuka N, Kobayashi Y, Isobe Y, Ishizawa K, Maseki N, Itoh K, Usui N, Wasada I, Kinoshita T, Hotta T, Tsukasaki K, Oshimi K. Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211. J Clin Oncol, 30:4044-4046, 2012
3. Kagami Y, Itoh K, Tobinai K, Fukuda H, Mukai K, Chou T, Mikuni C, Kinoshita T, Fukushima N, Kiyama Y, Suzuki T, Sasaki T, Watanabe Y, Tsukasaki K, Hotta T, Shimoyama M, Ogura M. Phase II study of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) therapy for newly diagnosed patients with low- and low-intermediate risk, aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG9508. Int J Hematol, 96:74-83, 2012
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Department of Pediatric Oncology

Ako Hosono, Kuniaki Itoh

Introduction

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

Routine activities

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

Research activities and clinical trials

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

Two clinical trials described below are currently active.

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

One pediatric clinical trial using a cocktail of three peptide vaccines is about to start as an investigator-initiated registration-directed clinical trial.

List of papers published in 2012
Journal

1. Kanegane H, Yang X, Zhao M, Yamato K, Inoue M, Hamamoto K, Kobayashi C, Hosono A, Ito Y, Nakazawa Y, Terui K, Kogawa K, Ishii E, Sumazaki R, Miyawaki T. Clinical features and outcome of X-linked lymphoproliferative syndrome type 1 (SAP deficiency) in Japan identified by the combination of flow cytometric assay and genetic analysis. Pediatr Allergy Immunol, 23:488-493, 2012

Department of Anesthesiology and Intensive Care Unit

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

Introduction

The Department of Anesthesiology and Intensive Care Unit (ICU) consists of 5 staff members, including 4 JSA (Japan Society of Anesthesiologists) board certified anesthesiologists and 3 rotating residents. Each year, we provide more than 2,000 anesthesia services in 8 operating rooms and over 1200 patients are admitted to the ICU. A large number of operations in the head and neck surgery division and procedures involving a thoracotomy for lung and esophageal cancer are one of the features of this hospital. Accordingly a special anesthesia induction method for difficult airway and use of the one-lung ventilation technique are often necessary for anesthesiologists.

Currently, our ICU admits mainly postsurgical patients that have undergone major abdominal, thoracic and complex surgical procedures, as well as patients who have suffered from serious preoperative complications. Increasingly complex procedures are being performed on more seriously ill patients with coronary disease, chronic obstructive pulmonary disease (COPD), neurological disorders and so on. Accordingly, the ICU needs to play a more and more important role in postsurgical care for such patients.

The goals of The Department of Anesthesiology and Intensive Care Unit are to provide anesthetic and perioperative care to patients, with their safety being the highest priority.

Routine activities

Five staff members (4 full-time and one visiting anesthesiologists) and 9 part-time anesthesiologists cover 8 operating rooms. A preanesthesia case presentation is held every morning to examine the case of the day and discuss the anesthesia strategy for patients with various complications. A Journal club is also held once a week. We provided 2,542 anesthesia services in 2012 and annual number of patients admitted to the ICU was 1412.

Research activities

Dr. Miwa presented "A Combination of treatments between Kampo Medicine and Neuronal Blockade for Post-herpetic Neuralgia" at the 15th World Congress of Pain Clinicians of WSPC (The World Society of Pain Clinicians) and "The exploitation of a transdermal system (TDS) of ketamine: a pharmacokinetic assessment" at the 14th World Congress on Pain of IASP (International Association for the Study of Pain).

Table 1. Number of Anesthesia Cases

Type of Surgery	2008	2009	2010	2011	2012
Head and Neck	458	474	515	424	454
Thoracic	472	503	488	466	473
Esophageal	-	-	137	126	182
Gastric, Hepatobiliary, Pancreatic	508	566	542	-	-
Hepatobiliary and Pancreatic	-	-	-	269	231
Gastric	-	-	-	286	308
Colorectal	453	418	491	426	453
Urologic	59	79	88	78	107
Orthopedic	-	-	-	-	22
Breast	233	282	297	291	309
Plastic and Reconstructive	-	-	-	-	3
Total	2183	2322	2558	2366	2542

Table 2. Number of Patients Admitted to the ICU

	2008	2009	2010	2011	2012
Number of Patients	1163	1167	1435	1228	1412

Department of Palliative Medicine, Palliative Care Service

Hiroya Kinoshita, Yoshihisa Matsumoto, Mieko Fukui, Kazuaki Hiraga

Introduction

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

Routine activities

1. Palliative care unit

This unit is the main designated inpatient setting unit for palliative care in the Toukatu-Hokubu region. Before 2007, the registry system for admittance was adopted wherein patients were admitted in the order of their application. This system was abolished because patients with severe symptoms had to wait for a long time before being admitted. In line with this, criteria for admitting patients were changed to ensure optimal use of limited resources and provide appropriate care to patients with severe physical symptoms and psychological problems. The waiting time for admission and the mortality rate in this unit were reduced to approximately 5 days and approximately 70%, respectively.

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

2. Outpatient clinic

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

Research activities

The Department is actively studying the construction of a regional palliative care model prepared for large scale disasters and a feasibility study on early palliative care. In addition, the Department participates in the Outreach Palliative care Trial of Integrated regional Model (OPTIM), which is an intervention study for the purpose of dispersing palliative care in four typical regions in Japan.

Clinical trials

A late phase II study on S-297995 for opioid-induced constipation is ongoing.

Table1. New referrals to the outpatient clinic (n=385, January - December 2012)

		N (%)
Age	Mean ± SD (median, range) (yr)	67.8±11.4 (70, 13-91)
Gender	(male/female)	220/165
Survivors or receiving anticancer therapy		78 (20.3)
Cancer site	Lung	108 (28.1)
	Breast	41 (10.6)
	Head and Neck	37 (9.6)
	Colorectal	34 (8.8)
	Pancreas	28 (7.3)
	Stomach	24 (6.2)
	Kidney/Bladder	20 (5.2)
	Others	93 (24.2)

Table2. Admission to the palliative care unit (n=363, January - December 2012)

		N (%)
Age	Mean ± SD (median, range) (yr)	67.1±10.6 (67, 36-92)
Gender	(male/female)	223/140
Cancer site	Lung	107 (29.5)
	Colorectal	43 (11.8)
	Pancreas	33 (9.1)
	Stomach	31 (8.5)
	Head and Neck	29 (8.0)
	Breast	28 (7.7)
	Esophagus	12 (3.3)
	Others	80 (22.0)
Waiting time for admission	Mean ± SD (median, range) (days)	4.1±5.0 (2, 0-32)

Department of Psycho-Oncology Service

Asao Ogawa, Daisuke Fujisawa, Hiroyuki Takei, Kensuke Higa, Tomohiko Mitsutsuka, Junko Ueda, Harumi Koga

Introduction

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

Routine activities

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

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

Research activities and clinical trials

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

Table1. Psychiatric consultation data (n=1111; January-December, 2012)

Section		N (%)
Age	Mean ± SD (median, range) (yr)	65.8±11.7 (67, 23-93)
Gender	(male/female)	670 (60.3%) / 441 (39.7%)
Inpatient / Outpatient		741 (66.7%) / 370 (33.3%)
Cancer patient / Family member		1066 (95.9%) / 45 (4.1%)
Cancer site	Lung	231 (20.8%)
	Head and Neck	198 (17.8%)
	Colon	114 (10.3%)
Stage	Recurrent or metastatic	767 (69.0%)
PS	0/1, 2/3, 4	378 (34.0%) / 465 (41.9%) / 268(24.1%)
Pain	Present	241 (21.7%)
Psychiatric diagnosis	Delirium	312 (28.1%)
	Adjustment disorders	109 (9.8%)
	Major depression	54 (4.9%)
	Dementia	86 (7.7%)
	No diagnosis	247 (22.2%)

List of papers published in 2012
Journal

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2. Kato TA, Tateno M, Shinfuku N, Fujisawa D, Teo AR, Sartorius N, Akiyama T, Ishida T, Choi TY, Balhara YP, Matsumoto R, Umene-Nakano W, Fujimura Y, Wand A, Chang JP, Chang RY, Shadloo B, Ahmed HU, Lerthattasilp T, Kanba S. Does the 'hikikomori' syndrome of social withdrawal exist outside Japan? A preliminary international investigation. Soc Psychiatry Psychiatr Epidemiol, 47:1061-1075, 2012
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4. Inoue T, Honda M, Kawamura K, Tsuchiya K, Suzuki T, Ito K, Matsubara R, Shinohara K, Ishikane T, Sasaki K, Boku S, Fujisawa D, Ono Y, Koyama T. Sertraline treatment of patients with major depressive disorder who failed initial treatment with paroxetine or fluvoxamine. Prog Neuropsychopharmacol Biol Psychiatry, 38:223-227, 2012
5. Ito M, Nakajima S, Fujisawa D, Miyashita M, Kim Y, Shear MK, Ghesquiere A, Wall MM. Brief measure for screening complicated grief: reliability and discriminant validity. PLoS One, 7:e31209, 2012
6. Ogawa A, Nouno J, Shirai Y, Shibayama O, Kondo K, Yokoo M, Takei H, Koga H, Fujisawa D, Shimizu K, Uchitomi Y. Availability of psychiatric consultation-liaison services as an integral component of palliative care programs at Japanese cancer hospitals. Jpn J Clin Oncol, 42:42-52, 2012
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8. Takeuchi M, Takeuchi H, Fujisawa D, Miyajima K, Yoshimura K, Hashiguchi S, Ozawa S, Ando N, Shirahase J, Kitagawa Y, Mimura M. Incidence and risk factors of postoperative delirium in patients with esophageal cancer. Ann Surg Oncol, 19:3963-3970, 2012
9. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Yamada Y, Fujimori M, Ogawa A, Fujisawa D, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Clinical biopsychosocial risk factors for depression in lung cancer patients: a comprehensive analysis using data from the Lung Cancer Database Project. Ann Oncol, 23:1973-1979, 2012

Supportive Care Team

Hiroya Kinoshita, Asao Ogawa, Daisuke Fujisawa, Yoshihisa Matsumoto, Hiroyuki Takei, Yoichiro Higashi, Tomofumi Miura, Kensuke Higa, Yasuhiro Hirano, Junko Nouno, Harumi Koga, Yuko Tanaka, Chiyuki Terada, Kumi Nakamura, Yasuhiko Ichida, Shinya Motonaga, Asuka Iwamoto, Aya Matsumaru, Hatoe Sakamoto

Introduction

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

Routine activities

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

Research activities and clinical trials

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

Table1. Supportive Care Team consultation data (n = 936; January-December, 2012)

		N (%)
Age	Mean ± SD (range) (yr)	66.1 ± 11.7 (23-93)
Gender	(male/female)	619 (66%) / 317 (34%)
Service	Palliative care/ Psycho-oncology	195 / 741
Cancer site	Lung	235 (25%)
	Head and Neck	177 (19%)
	Colon	100 (11%)
	Stomach	78 (8%)
	Esophagus	73 (8%)
	Pancreas	71 (8%)
Stage	I / II / III / IV	93 (10%) / 68 (7%) / 98 (10%) / 398 (43%)
	/ recurrence / unknown / others	/ 217 (23%) / 23 (2%) / 38 (4%)
Performance status	0/ 1/ 2/ 3/ 4	173 (19%) / 166 (18%) / 218 (23%) / 245 (26%) / 134 (14%)
Physical symptoms	Pain	367 (39%)
(moderate - severe)	Appetite loss	241 (26%)
	Fatigue	135 (14%)
	Respiratory distress	129 (14%)
Psychiatric diagnosis	Delirium	292 (39%)
(primary diagnosis)	Adjustment disorders	33 (4%)
	Dementia	49 (7%)
	Major Depressive Disorder	24 (3%)
Outcome	Discharge/ Hospital transfer	607 (65%) / 55 (6%)

List of papers published in 2012
Journal

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

Department of Diagnostic Radiology

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

Introduction

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

Routine activities

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

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

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

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

Research activities and clinical trials

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

(1) Development of new Nuclear Medicine tracers

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

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

(2) Development of new CT technology

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

Dual-energy CT images reveals tumor invasion within the cartilage as red color-coded areas of the iodine distribution, resulting in contrast enhancement between the tumor and non-calcified cartilage.

Table1. Number of Cases Examined

	2008	2009	2010	2011	2012
Plain X-ray examination	33,913	33,841	34,330	35,032	39,128
Mammography (MMG)	2,272	2,388	2,595	2,434	2,380
Fluoroscopic Imaging (GI-series, etc.)	3,387	3,781	3,478	3,903	4,029
CT	18,014	19,543	21,128	21,967	24,101
MRI	5,053	5,723	5,830	5,708	5,619
RI	1,693	1,718	1,676	1,582	1,586
PET	1,585	1,670	2,048	2,239	2,284
Angiography	766	711	728	656	742
Total	66,683	69,375	71,813	73,521	79,869

Preliminary evidence suggests that dual-energy CT can decrease the overestimation of laryngeal cartilage invasion. This is particularly important for treatment strategy decisions, especially when function-preserving therapy is being considered.

(3) Construction of a cancer image reference database

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

List of papers published in 2012

Journal

1. Kuno H, Onaya H, Iwata R, Kobayashi T, Fujii S, Hayashi R, Otani K, Ojiri H, Yamanaka T, Satake M. Evaluation of cartilage invasion by laryngeal and hypopharyngeal squamous cell carcinoma with dual-energy CT. Radiology, 265:488-496, 2012

Department of Radiation Oncology

Tetsuo Akimoto, Mitsuhiko Kawashima, Sadatomo Zenda, Masakatsu Onozawa, Satoko Arahira, Masamichi Toshima, Atsushi Motegi

Introduction

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

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

Routine activities

At present, the staff of the Radiation Oncology Division consists of 7 consultant physicians (radiation oncologists), 15 radiation technologists, 3 medical physicists, 1 nurse, and 1 clerk. We have more than 1,000 thousand new cases for conventional RT and 200 new patients for proton beam therapy every in every year. The quality assurance of both conventional RT and PBT is performed by medical physicists and radiation technologists, and a conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. RT and PBT are routinely based on three-dimensional radiation therapy planning and PBT is performes using RT-dedicated multi-detector-row helical computed tomography (CT) scanning in order to confirm the precise radiation dose to the targeted tumors. Respiratory-gating has been applied especially in radiotherapeutic management for patients with lung, esophagus and liver cancers.

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

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

Research activities

In the Radiation oncology division, the following research activities are in progress.

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

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

Number of patients treated with radiotherapy during 2007-2011

	2007	2008	2009	2010	2011
New patients	1097	1084	1080	1616	1440
New treatments	1363	1388	1385	1388	1388
Head and neck cancers	249	289	281	320	223
Lung and mediastinal cancers	391	390	370	411	329
Breast cancers	296	264	297	406	325
Gastrointestinal cancers	202	221	202	228	176
Hepatobiliary tract cancers	63	47	46	54	38
Urological cancers	114	112	120	151	100
Bone and soft tissue cancers	8	8	6	15	2
Hematological cancers	25	33	27	6	19
Others	15	24	35	20	19
Proton therapy	76	75	81	90	56
IMRT		6	4	31	83

Clinical trials

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

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

List of papers published in 2012
Journal

1. Hojo H, Zenda S, Akimoto T, Kohno R, Kawashima M, Arahira S, Nishio T, Tahara M, Hayashi R, Sasai K. Impact of early radiological response evaluation on radiotherapeutic outcomes in the patients with nasal cavity and paranasal sinus malignancies. J Radiat Res, 53:704-709, 2012
2. Nakamura K, Akimoto T, Mizowaki T, Hatano K, Kodaira T, Nakamura N, Kozuka T, Shikama N, Kagami Y. Patterns of practice in intensity-modulated radiation therapy and image-guided radiation therapy for prostate cancer in Japan. Jpn J Clin Oncol, 42:53-57, 2012
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Department of Pathology and Clinical Laboratories

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Introduction

The Department of Pathology and Clinical Laboratories (DPCL) is composed of two divisions; the Pathology Division (PD) and the Clinical Laboratory Division (CLD). Both divisions play a fundamental role in routine hospital service and support research activities at the National Cancer Center Hospital East (NCCH-E).

Seven pathologists, including 6 pathologists who are board-certified by the Japanese Society of Pathology, are assigned to the PD. Two are full-time staff, with the another being part-time. The others originally belong to the Pathology Division at the Research Center for Innovative Oncology (RCIO) and concurrently work at the DPCL. Also working in the division are 4 clinical laboratory technicians. Two doctors and 2 technicians, cytology experts and cytoscreeners, respectively, are all board-certified by The Japanese Society of Clinical Cytology.

The CLD consists of 6 subsections for i) general laboratory medicine, ii) hematology, iii) biochemistry/serology, iv) physiology, v) bacteriology and vi) blood transfusion. A total of 13 clinical laboratory technicians (11 full-time and 2 part-time) and 1 secretary work at the CLD.

Routine activities

The primary routine activity at the PD is surgical pathology. In 2012, 8,886 biopsy specimens, including 798 frozen sections and 919 review cases, and 2,281 surgical specimens were examined and pathologically diagnosed (see Table1 for details). Case conferences are held regularly with almost all of the clinical department/divisions, including 4 weekly case conferences with Head-and-Neck Surgery (Monday), Hematology and Chemotherapy (Wednesday) and Digestive Endoscopy Division (Tuesday) and Thoracic Surgery (Friday). Five thousand two hundred and thirty three (5,233) cytology specimens were evaluated (Table 2). Seven cases of autopsies were performed, and all cases were, or are to be presented and discussed in clinico-pathological conferences. Conference-style training sessions are open every Thursday morning for the residents.

The CLD provides accurate and reliable data to help understand each patient's conditions and support prompt decision making for all clinicians working at NCCH-E. Most of the essential laboratory test services are available on a round-the-clock basis. Most of the general laboratory tests for hematology, biochemistry, serology and urinalysis are automatically performed by an automated analyzer, which enables the Division

Table 1. Number of pathology samples examined at Pathology Division in 2012

Origin	Biopsy	Surgical	Autopsy
Gastrointestinal Oncology	2887		
Digestive Endoscopy	1617		
Head and Neck Surgery	695	396	1
Thoracic Surgery	535	449	2
Hematology and Medical Oncology	507		2
Breast Surgery	488	304	
Thoracic Oncology	378		1
Colorectal Surgery	364	425	
Gastrointestinal Oncology	341		1
Gastric, Hepatobiliary and Pancreatic Surgery	248	465	
Ambulant Treatment Center	224		
Urology	210	14	
Radiation Oncology	182		
Esophageal Surgery	83	172	
Orthopedic Surgery	25	19	
Obstetrics and Gynecology	23		
Dermatology	7		
Anesthesiology	4	2	
Plastic and Reconstructive Surgery	4	14	
Dental Division	3		
Others	61	21	
Total	8886	2281	7

Table 2. Number of cytology samples examined by the Pathology Division in 2012

Origin	
Thoracic Surgery	1275
Thoracic Oncology	1228
Urology	714
Obstetric and Gynecology	602
Head and Neck Surgery	405
Hepatobiliary and Pancreatic Oncology	329
Gastric, Hepatobiliary and Pancreatic Surgery	202
Hematology and Medical Oncology	136
Breast Surgery	114
Colorectal Surgery	108
Gastrointestinal Oncology	60
Diagnostic Radiology	12
Ambulant Treatment Center	12
Esophageal Surgery	12
Palliative Medicine	7
Radiation Oncology	3
Orthopedic Surgery	2
Anesthesiology	2
Others	10
Total	5233

to provide results within one hour after sample submission. A special computer-based ordering system is equipped to ensure sample-processing and data-transfer to and from outside commercial laboratories. The daily activities of each subsection are as follows (also see Table 3 for details):

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

Research activities

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

All the technicians working in the department are also highly motivated to develop advanced diagnostic technology and some results have been presented in several meetings including the one organized by the Japanese Society of Laboratory Medicine.

Clinical trials

The CLD actively participated in almost all of clinical trials carried out at NCCHE through the provision of laboratory data. The PD participated in 34 new trials in 2012.

List of papers published in 2012

Journal

Please refer to the section for the Division of Pathology at the Research Center for Innovative Oncology

Table 3. Number of laboratory tests performed in the Clinical Laboratory Division in 2008-2012

Section	2008	2009	2010	2011	2012
General laboratory medicine	196,233	230,610	265,517	264,452	282,716
Hematology	527,567	560,110	589,144	622,666	676,889
Biochemistry	1,424,263	1,493,858	1,569,963	1,648,755	1,811,244
Serology	125,409	136,127	139,759	146,104	141,224
Bacteriology	21,822	22,466	21,978	21,657	25,112
Blood transfusion	21,378	24,181	22,441	21,895	20,550
Physiology	34,258	39,232	43,215	43,275	45,408
Total	2,211,641	2,506,584	2,652,017	2,768,804	3,003,143

Clinical Trial Management Office

Toshihiko Doi

Introduction

The mission of the Clinical Trials Management Office (CTMO) is to facilitate the conducting of quality clinical trials at NCCHE, especially those which are all conducted as a sponsored initiated trial, to achieve registration. The CTMO will also assist investigators with infrastructure support, including Institutional Review Board (IRB) and initial regulatory guidance. A total of 30 staff members support the CTMO: 8 Clinical Research Coordinators (CRCs) (5 nurses and 3 pharmacologists), 10 data managers, 5 medical technologists, 1 free nurse and 7 secretaries. The CRCs coordinate and conduct patient care visits to ensure that all procedures are conducted with the optimum protocol compliance. The CRC teams interact with the investigators to ensure that patients receive appropriate medical evaluation and care when needed and will alert the investigator or investigators of any serious adverse events throughout the course of the protocol study. The clinical data manager teams contribute to the setting up, running and reporting of clinical trials and process data using a range of computer applications and database systems to support collection, cleaning up and management of patient data. They interact with the client as necessary to establish data review guidelines and data flow procedures. The team will also communicate/coordinate with the database manager to ensure the accuracy and completeness of the clinical data. Medical technologists conduct and supervise complex medical tests, clinical trials, and control complicated EKG/EUG pharmacokinetic/ pharmacodynamic (PK/PD) sampling management. The secretarial team supports the activities of the other teams.

Daily activities

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

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

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

New achievements and performance

The number of supported trials and patients under the administration of the CTMO increased in 2011, as in previous years. The CTMO has conducted and supported in excess of 130 registration trials as company sponsored trials. Among them, the numbers of phase 1 clinical trials have increased remarkably over the last few years. We have in particular joined/managed complicated and more early phase clinical trials (`first in man' clinical trial and multinational simultaneous phase 1 trial). In 2012, we managed Japanese phase 1 clinical trials and multinational simultaneous phase 1 trials as

early clinical trial development, such as a first in man trial of inhibitor MET/VEGFR. We have also participated in the clinical trials on rare cancer. We have the largest number of enrolled patients in the world part of the international collaborative trial thyroid, prostate, and pancreatic cancer. For clinical trials on colorectal cancer, we have played a central role in the world.

Our task is also to cooperate with more investigator initiated clinical trials (IITs) as phase 1 units than last year. The Japanese Government will provide support to the NCCH & NCCH-E with plans to establish an infrastructure enabling early-stage and exploratory clinical trials of new drugs and medical devices sponsored by industry and research institutions. The Phase 1 team has been started in collaboration with oncology experts to share updated trial information, to hold phase 1 meetings for patient recruitment, and brief meetings for information sharing. As a result of these meetings, we can achieve high-quality trial content with efficient recruitment of patients. Drug development is a costly and risky affair and involves a great deal of money and time. The CTMO will challenge newer and more advanced trials such as unapproved multi-drug combination trials and biomarker-driven trials. Furthermore, we will contribute to the worldwide network system for phase 1 trials to establish the acceleration of the pre-clinical and clinical development of investigational anti-cancer agents.

Table 1. The number of trials which CTMO supported

	2007	2008	2009	2010	2011
Phase1	17	14	25	31	35
Phase1/2	6	5	4	5	7
Phase2	21	22	18	21	31
Phase3	15	20	43	46	56
PMS[#1]	9	7	6	5	4
Total	68	68	96	108	133

#1 Post-marketing Study

Table 2. Proportion of clinial trials involved by CTMO

	2007	2008	2009	2010	2011
Proportion of clinial trials involved by CTMO (%)	88.0	87.3	91.7	92.4	91.9

Table 3. The number of domestic and global clinical trials

Trial type	2007	2008	2009	2010	2011
Domestic	56	49	53	58	76
Global or multi-nation	13	20	45	51	60
Total	69	69	98	109	136

Pharmacy Division

Keishiro Izumi, Yasuhiko Ichida, Akio Hiroi, Takashi Uemura, Reiko Matsui, Masahito Yonemura, Sonoko Kobayashi, Hiromi Shinano, Hideki Funazaki, Hiroko Ouchi, Shinya Suzuki, Ikuyo Ueda, Shinya Motonaga, Tomoko Ogawa, Mai Itagaki, Tomoka Hagihara, Kenji Kawasumi, Aya Ikeuchi, Takeshi Koike, Misaki Kobayashi

Introduction

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

Our residents' training program started in 2006. In 2012, six residents joined our Division. Presently, our Division has a total of eighteen residents. In addition, our Division has accepted 7 trainees from other institutions for our oncology-pharmacist training programs.Through this year, 3 terms of the training courses, we have educated 15 pharmacy students and 2 advanced-training pharmacy students.

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

New developments

Over the years, the services of our Division have been under continuous expansion and development. Last year, the Division started assigning a pharmacist as a dedicated member in ward (6B), but in addition, since June 2012, we have assigned three pharmacists as dedicated staff members in three wards (4B, 6B, PCU) since June 2012. These dedicated pharmacists have started evaluating high risk medications, drug interactions, and drug compatibilities in the wards and have monitored prescriptions and suggested medications through medical conferences or by attending medical team rounds. The Division has started assigned a pharmacist to the operation room for narcotic and muscle relaxant control for 4.5 hours each day.

Table 1.

	2010	2011	2012
Number of Prescriptions			
Prepared in hospital pharmacy			
Total	84,492	86,643	90,392
Inpatients	78,327	80,837	84,800
Outpatients	6,165	5,806	5,592
Taken to outside pharmacies	50,731	55,826	59,722
(% of prescription filled outside)	(89.2%)	(90.6%)	(91.4%)
Injections			
Total	157,958	159,730	160,105
Inpatients	132,407	132,969	126,428
Outpatients	25,551	26,761	33,677
Number of Prescriptions			
(Investigational new Drugs)	4,435	4,676	4,584
Aseptic Preparation of Injection Mixture			
Anticancer drugs	32,007	35,386	38,663
Others	4,689	3,320	3,994
Number of medication counseling sessions (for inpatients)			
Patients	5,063	5,067	6,418
Counseling sessions which earned a counseling fee	6,522	6,645	7,139
Number of medication counseling sessions (for outpatients)			
in the Outpatient Chemotherapy Center	5,705	6,701	8,965
in the pharmacy outpatient service	479	738	1,782
in the 'Nexavar' outpatient service	416	583	381
Number of calls on the Chemotherapy Hotline	980	1,468	1,665
Number of home medication checks	5,422	5,364	6,017

Nursing Division

Tomiko Ichihashi

Introduction

Recently, giving better treatment to cancer patients, residential care and treatment have become an integral part of patients' recovery and maintaining their quality of life. The nursing department has dealt with this issue by assigning nurses who exclusively specialized in helping patients go home safely. Our main task is to let those discharged return home without facing problems medically and physically.

To provide the continuity of care for the patient and their family, we started the integration of an outpatient clinic and ward nursing. We have prepared an educational course for the palliative care certified nurse in 2013, because of the improvement of patients' QOL and nursing skills in cancer nursing.

This has further led to increased patient awareness of their diet-related problems diet. We have also set up an outpatient section since September, 2010, which offers guidance to patients on a list of all kinds of cancer surgery like esophageal, epigastrial, abdominal, respiratory, head and neck and urinary cancer. Patients will be given a lecture about prevention of complications after surgery. We work together with other sections to reduce patient uneasiness and anxiety arising from the pre- and post-surgical situations, and to support the patients' decision about their treatment. As for nurses, all wards introduced a two-working-shift system in September, 2009. Furthermore, we now have an additional short-time two-working-shift system in order to support nursing care. Financially, we have contributed to increased profitability by establishing a 7 to 1 system to place nurses. We have a nursery home, which is on the go 24 hours a day. It can take care of children whose parents have to start working early in the morning.

We set these goals below for the purpose of clarifying our mission and raising the quality of care.

To shine with learning and act full of life.

1. To practice nursing with respect for the patient's preference and hope, to practical nursing skills.
2. To try to make our hospital a bright and rewarding work environment to increase the satisfaction of our staff.
3. To bring out each individual nurse's ability to work with each other to provide safe and comfortable care services.
4. To prepare for the educational course on palliative care certified nurse starting in 2013, for human resource development in the field of cancer nursing.
5. To take part in the hospital's administration in order to implement strategic hospital management.

Routine activities

In 2012, of the current 319 nurses, 42 are newly employed. The average number of outpatients per day was 777.3, while that of inpatients was 349.7. The average hospitalization term was 14.8 days. The number of chemotherapy treatments in The Medical Treatment Center per day was 89.7 and the number of operations conducted was 2571. We provided educational services for patients undergoing chemotherapy on how to deal with the side effects, and also provide telephone-follow-up services and hot-line-telephone services to solve patient problems and relieve anxiety once they have returned home.

The Division aims to improve nurse education to provide proper quality nursing services. Four courses have been initiated: (1) an introductory course for new employees; (2) a practical course; (3) a specialized cancer nursing course; and (4) a power up course.

In April, 2011, we established the post of head nurse in charge of nursing education to help nurses to study and to support their mental health.

There are 5expert nurses, 1 psychiatric mental health nurse and 21 certified expert nurses specializing in wound ostomy care (4), cancer pain (6), cancer chemotherapy (6), palliative care (1), infection control (2), breast care (2), swallowing and eating (2) and radiation (2). They are in charge of the specialized cancer nursing course education programs.

We have subsequently accepted trainees participating in the expert nurse course and certified expert nurse course.

As for nursing-related research projects, not only expert nurses and certified nurses, but also registered nurses in our hospital have both participated and attended external training programs. We gave 19 presentations at academic conferences in 2012.

Table1. The number of trainee (< 1 week)

	2009	2010	2011	2012
Postgraduate Nurse	6	14	6	5
Certified Expert Nurse	13	12	17	25
Expert Nurse	5	4	3	3
Others	1	0	0	0
Total	25	30	26	33
Nursing Student	172	156	141	139

Preface

The Research Center for Innovative Oncology (RCIO) was originally funded as a branch of the National Cancer Center Research Institute in 1994 at the Kashiwa campus. In order to focus more on translational research projects (TR) and mutual collaborative efforts between basic and clinical researchers, the National Cancer Center Kashiwa campus was reorganized in 2005, as a result of which the RCIO became part of the Hospital East. Originally, the RCIO consisted of five divisions: the Pathology, Investigational Treatment, Functional Imaging, Psycho-oncology, and Particle Therapy divisions and conducted numerous studies in collaboration with other academic institutions and industries. The RCIO have developed new endoscopic instruments such as narrow band imaging (NBI) in collaboration with Hospital East, which has already become one of the standard procedure in the world. Several new drug-delivery system (DDS) agents based on cutting-edge nanotechnology have originally been developed in RCIO and one of them is now under evaluation in an international phase III trial. We are also pioneers of proton-beam therapy, new imaging instruments such as super-MRI, and psycho-oncology, in which our researchers are leading these fields. In 2008, we organized the Clinical Trial section in order to manage and support investigator-initiated trials for facilitating more translational researches and early clinical trials. In 2011, the National Cancer Center Hospital East was selected as "a designated center for early and exploratory clinical trials" by the government and our RCIO has been playing a central role. For this purpose, we not only reorganized the RCIO through expanding to eight divisions and three support sections but also organized the Exploratory Oncology Research & Clinical Trial Center (NCC-EPOC) together with the Tsukiji campus. Detailed information of NCC-EPOC is available in another section. In 2012, our hospital was also selected as "a designated center for new endoscopic instrument development" and several exploratory studies with new diagnostic instruments/devices have been initiated. The number of the patients who received proton-beam irradiation has been rapidly increasing in recent years and this approach has achieved significant benefit in head and neck and prostate cancer. A supportive care center with a collaboration of psycho-oncology, palliative care, nursing, pharmacy, and social worker divisions is also being organized to provide a variety of support options for patients. With these activities we are actively establishing a top innovative cancer center with the best amenities for cancer patients in the world.

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Division of Pathology

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

Introduction

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

Routine activities

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

Research activities

The research activities of the Division of Pathology currently focus on the application of the morphological study of cancer tissue to the clinical course of the patient. These activities aim I) to elucidate new biological roles for cancer epigenetics and cancer-stromal interaction; II) to develop a new cancer treatment strategy (Preclinical study); and III) to design and perform experimental and clinicopathological studies on cancer. Prognostic factors and clinicopathological characteristics of various cancers have also been investigated in collaboration with the NCCH-E Diagnostic Pathology Section and other institutions.

I) Elucidate new biological roles for cancer epigenetics and cancer-stromal interaction: The neoplastic transformation by mutant *RAS* is thought to require remodeling of the expression of an entire set of genes. We investigated and elucidated the oncogenic role of EZH2, a histone modifier protein that is induced by oncogenic mutant *RAS*, through the Elk-1 signaling pathway using pancreatic cancers in a transgenic rat model. MEK-inhibition or *EZH2*-knockdown restored expression of a tumor suppressor, *RUNX3* and inhibition of the cancer cell growth. This is the first report on the epigenetic regulation of tumor suppressors including RUNX3 by oncogenic RAS signaling in pancreatic carcinogenesis (1). We previously reported that podoplanin (PDPN) expressed on stromal fibroblasts is the functional protein responsible for the promotion of tumor formation in mouse subcutaneous tissue. To elucidate the underlying molecular mechanism, we co-injected both the human lung adenocarcinoma cell line and human fibroblasts (hFbs) overexpressing wild-type podoplanin (WT-PDPN) and found that the activation state of RhoA in hFbs expressing WT-PDPN was high and the constitutive active RhoA enhanced tumor formation. These data indicated that the enhanced RhoA activity in hFbs expressing PDPN may be one of the mechanisms resulting in the promotion of tumor formation, suggesting that biomechanical remodeling of the microenvironment by stromal fibroblasts may play important roles in tumor progression (2).

II) Development of a new cancer treatment strategy (Preclinical study): We established a novel murine model of cancer cachexia using N-inv of human pancreatic cancer cells. Mice with N-inv showed a loss of body weight, skeletal muscle and fat mass without appetite loss, which are compatible with an animal model of cancer cachexia. Activation of astrocytes in the spinal cord connected with N-inv was observed in our model. Experimental cachexia was suppressed by disrupting neural routes or inhibiting the activation of astrocytes. These data provided the first evidence that N-inv induces cachexia *via* astrocytic activation of the neural route in pancreatic cancer (3).

III) Experimental and clinicopathological studies on cancer: The histological predictive and prognostic factors for in various histological types of lung cancers (4-10), gastrointestinal tract cancers (11-13), pancreatic tumors (14) and other tumors (15) are

also being investigated and reported in collaboration with the clinical divisions of the NCCH-E and other institutions. We have also participated in multicenter trials on pathological studies (16-20).

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Division of Functional Imaging

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

Introduction

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

Research activities

In vivo visualization of intratumoral heterogeneity would be an innovation that could contribute to improved cancer therapy. To date, however, conventional nuclear medicine tests have failed to visualize heterogeneity *in vivo* because of limited spatial resolution. Recently, newly-developed SPECT scanners dedicated to small animal imaging have been able to obtain excellent spatial resolution of <1 mm, but few studies have focused on the evaluation of intratumoral heterogeneity. We investigated the optimal conditions of acquisition and reconstruction to achieve *in vivo* SPECT visualization of intratumoral heterogeneity under the limited conditions of actual small animal imaging.

The acquisition for 30 min with pinhole apertures of 1.4 mm-diameter, but not 1.0 mm, and optimizing the reconstruction parameters could yield the best spatial resolution of 1.3 mm. The minimal radioactivity concentration for visualization of heterogeneous tumor interiors was estimated to be as high as 0.2–0.5 MBq/mL. By administering liposomes containing ^{111}In to tumor-bearing mice, SPECT imaging successfully showed heterogeneous intratumoral ^{111}In distribution *in vivo* (1).

We also tried to clearly visualize the heterogeneous distribution of hypoxia inducible factor 1α (HIF) activity in tumor tissues *in vivo*. We synthesized ^{125}I-IPOS, an ^{125}I labeled chimeric protein probe that was designed to visualize HIF activity. ^{125}I-IPOS accumulated well in FM3A tumors and high resolution SPECT/CT fusion images successfully demonstrated the heterogeneity of ^{125}I-IPOS intratumoral distribution. SPECT-MRI fusion images could provide more detailed information about the intratumoral distribution of ^{125}I-IPOS (2). High resolution SPECT images successfully demonstrated heterogeneous intratumoral distribution of ^{125}I-IPOS. SPECT/CT fusion images, or SPECT-MRI fusion images, would be useful to understand the features of heterogeneous intratumoral expression of HIF activity *in vivo*.

Pancreatic cancers highly express $\alpha_v\beta_3$ integrin. We previously demonstrated that SPECT with ^{111}In-DOTA-c(RGDfK) successfully detected pancreatic cancers in a hamster carcinogenesis model (3). We synthesized RGD-liposomes loaded with ferrioxamine B (Fe-deferoxamine) as MR contrast agents. The RGD-liposomes also showed high affinity to $\alpha_v\beta_3$ integrin. In PANC-1 bearing nude mice, MR studies revealed that RGD-liposomes loaded with ferrioxamine B enhanced the T/M signal ratio on T1 images by 40% compared with RKG-liposomes as a control. Therefore, RGD-liposomes might be possible candidates for *in vivo* MR imaging of pancreatic cancer.

Magnetic resonance (MR) imaging can provide anatomical images of experimental animals with high spatial resolution and high tissue contrast. Taking advantage of these high resolutions, we visualized the interiors of small lymph nodes of mice using an MR lymphography (MRL) technique. In MRL, superparamagnetic iron oxide (SPIO) is used as contrast media to reduce signals from normal lymphatic tissues and, in contrast, highlight small metastatic foci. This MRL technique is anticipated to become a valuable diagnostic imaging tool for sentinel lymph node (SLN) metastasis in breast cancer as well as esophageal cancer. We found that this MRL technique can highlight not only metastatic foci, but also hyperplastic lymphatic tissues which are frequently seen in inflammatory lymph nodes. This finding suggests that the metastatic foci in lymph nodes cannot precisely be differentiated from hyperplastic lymphatic tissue by means of MR lymphography, and this should draw the attention of the radiologist to the pitfalls of the MRL technique in SLN diagnosis (4).

Since 2011, we have been developing multiple-animal MR imaging techniques to increase the throughput of preclinical MRI research. This year, we developed a new multi-animal hepatic MR imaging system which is less susceptible to motion artifacts.

In addition, a new post-processing technique was developed to promote precise interpretation of multiple-animal MR images.

Clinical trials

Clinical trials of hypoxia PET tests are ongoing using 2 kinds of radiopharmaceuticals: one was F-18 labeled fluoroarabinofuranosyl nitroimidazole (FAZA) and the other was Cu-62 labeled diacetyl methyl-thiosemicarbazone (ATSM). Patients with lung cancer and those with head and neck cancer were tested to investigate the clinical and pathological features of tumors with high avidity to these radiopharmaceuticals. The effects of systemic chemotherapy on the cerebral metabolism and cognitive function in breast cancer patients were evaluated with MR spectroscopy.

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Division of Science and Technology for Endoscopy and Surgery

Kazuhiro Kaneko, Masaaki Ito

Introduction

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

One of the characteristic natures of early-stage cancer is the growth of blood vessels (neovascularity). Using two narrow wavebands of light (blue, 390-445 nm; and green, 530-550 nm) that have excellent absorption characteristics in circulating hemoglobin, narrow band imaging (NBI) endoscopy may provide better images of the capillaries in the mucosal surface.

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

Routine activities

The present research activities mainly focus on the development of new instruments for endoscopic diagnosis and new endoscopic treatment modalities. Since posing a problem in the present condition is required in development research regarding endoscopy, our division collaborates with Endoscopy division. Therefore, endoscopic diagnosis are routinely performed for cancer patients, endoscopic treatment, such as EMR or ESD, are performed in patients with early GI tract cancers. We perform lectures to resident doctors regarding individual projects. Furthermore, meeting is constantly conducted with the faculties including students from the Faculties of Technology and Science of University.

Research activities

Research studies have been conducted in various fields for cancer patients using endoscopy in the GI tract and head and neck to establish strategies for prevention, or endoscopic diagnosis and treatment. In addition, ongoing studies have been designed to develop new devices or procedures in innovative and less invasive laparoscopic surgery for gastrointestinal malignancies. These projects are being conducted as prospective clinical studies and preclinical studies in collaboration with not only commercial manufacturers but also University, Faculties of Technology and Science.

Developing research into novel endoscopy systems is being performed. Hypoxia imaging is being used to detect neoplastic lesions of the head and neck and alimentary tracts, with two types of visualized images, such as pseudocolour StO_2 imaging with an StO_2 overlay image. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm and rare earth nanoparticles, doped yttrium oxide. This system is capable of penetrating through the gastrointestinal wall and obtaining images. With a low-temperature atmospheric pressure plasma system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnostic system using photosensitizing agents, such as hypericin, has been constructed. A novel tattooing system under endoscopy has been developed, for which a patent is currently being applied. Ongoing projects are to develop needle graspers for a needle ultrasonic coagulator in the surgical field.

Clinical trials

A first in human clinical trial of hypoxia imaging is ongoing on the endoscopic diagnosis of neoplasia of the esophagus, stomach, and colorectum. We conducted a proof-of-the-concept trial for 40 patients with neoplastic lesions in the esophagus including the pharynx, stomach and colorectum. In this first in human trial (UMIN 000004983), two types of StO_2 images were used. One was a pseudocolour StO_2 image that showed StO_2 levels as different hues, and the other was an StO_2 overlay image that overlapped the StO_2 levels in blue on a white light illumination image to detect the background mucosa. In a system using near-infrared light with nanoparticles, nanoparticles of rare earth act as fluorescent agents. Nanoparticles are attached to a probe, and when the probe is attracted to the surface of cancer cells, irradiation of the nanoparticles with near-infrared light causes them to fluoresce, outlining the tumorous lesion. Molecular imaging endoscopy using of this system with an InGaAs CCD imaging device has currently been developed in collaboration with the Faculty of Technology of University. Preclinical studies, such as the use of a low-temperature atmospheric pressure plasma system and photodynamic diagnosis (PDD) with hypericin, are being performed using appropriate animal models.

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Journal

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2. Yano T, Muto M, Minashi K, Iwasaki J, Kojima T, Fuse N, Doi T, Kaneko K, Ohtsu A. Photodynamic therapy as salvage treatment for local failure after chemoradiotherapy in patients with esophageal squamous cell carcinoma: a phase II study. Int J Cancer, 131:1228-1234, 2012
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Division of Developmental Therapeutics

Masahiro Yasunaga

Drug delivery system in cancer chemotherapy

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

A phase 3 study of NK-105, a paclitaxel incorporating micelle, is now underway in Japan, Taiwan, and Korea in patients with metastatic breast cancer. Phase 2 trials of NC-6004, a cisplatin incorporating micelle, and NK012, an SN-38 incorporating micelle, are underway in Japan and other countries. A Phase 1 study of K-912, an epirubicin incorporating micelle will begin soon. In addition to clinical trials, an anticancer incorporating micelle conjugated with a monoclonal antibody (mAb) is being developed.

Cancer stromal targeting (CAST) therapy

In spite of the recent success of monoclonal antibody (mAb) drug conjugate (ADC) therapy in patients with hypervascular and special tumors recognized by a particular mAb, there are several issues to be solved before ADC can be recognized as a universal therapy for any type of cancer. In particular, most human solid tumors possess abundant stroma that hinders the distribution of ADC. To overcome these drawbacks, we developed a unique strategy involving cancer-stromal targeting (CAST) therapy using a cytotoxic immunoconjugate bound to the collagen 4 or fibrin network in the tumor stroma from which the payload can be released gradually and distributed throughout the tumor, resulting in the arrest of tumor growth due to induced damage to tumor cells and tumor vessels. Our findings have also suggested that the conjugate-design, in parallel with the choice of targeting antibodies, should be selected to maximize the therapeutic effect depending on the distinct stromal structure of each individual tumor (1).

Noninvasive diagnostic test for colorectal cancer

Several methods for the early detection of colorectal cancer (CRC) to reduce its mortality rate have been reported. The potential of a fecal miRNA test has therefore been investigated for the early detection of CRC. CRC patients (n=299) and healthy volunteers (n=116) with no abnormalities detected by screening colonoscopy were enrolled in this case control study. The value of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve using miR-17, -18a, -19a, -19b, -20a, -92a, -106a, -135b, and -146a was greater than than 0.7. The overall sensitivity and specificity in the validation study were 67.5% (170/252) and 75.3% (61/81), respectively. Further comparative study of this test for CRC screening is needed (2).

Pharmacogenomics study

Fcγ receptor IIa (FcγRIIa) plays an important role in antibody-dependent cellular cytotoxicity (ADCC) and inflammation. A pharmacogenomics study in Japanese population suggested that L273P could have functional significance in ADCC responses through FcγRIIa (3).

List of papers published in 2012
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Division of Cancer Immunotherapy

Tetsuya Nakatsura

Introduction

Our Division aims to investigate evidenced-based cancer immunotherapy, repeating basic research and translational research. This Division is focused on developing not only more effective immunotherapeutic strategies, but also immunological methods for the suppression of recurrence or for cancer prevention.

Research activities

RFA for HCC induces GPC3 peptide-specific CTLs

Glypican-3 (GPC3), a carcinoembryonic antigen, is an ideal target for anticancer immunotherapy against hepatocellular carcinoma (HCC). We attempted to compare the induction of the GPC3-specific T-cell-mediated immune response after locoregional therapies in HCC patients and tumor-bearing mice. Twenty-seven HCC patients treated with locoregional therapies, including radiofrequency ablation (RFA), surgical resection and transcatheter arterial chemoembolization (TACE), were prospectively enrolled in this study. Additionally, we performed RFA experiments using a mouse model. The GPC3-specific T-cell response was investigated pre-treatment and post-treatment by an interferon-γ enzyme-linked immunospot assay using peripheral blood mononuclear cells from HCC patients and lymph node cells from tumor-bearing mice. Circulating GPC3-specific cytotoxic T lymphocytes (CTLs) increased in 5 of 9 patients after RFA and in 4 of 9 patients after TACE, but in only 1 of 9 patients after surgical resection. All 7 patients with GPC3-expressing HCCs exhibited an increase in GPC3-specific CTLs after RFA or TACE, whereas none of the 7 patients did after surgical resection. The number of increased GPC3-specific CTLs after RFA was significantly larger than that after surgical resection (P=0.023). Similarly, the frequency of GPC3-specific CTLs after RFA was significantly greater than that after surgical resection in the mouse model (P=0.049). We validated for the first time the stronger effect on the immune system brought about by RFA compared with surgical resection for HCC patients and tumor-bearing mice. The combination treatment with RFA and immunotherapy is a reasonable strategy against HCC (1).

GPC3-derived peptide vaccine against HCC

We conducted a phase I clinical trial using this GPC3-derived peptide vaccine in patients with advanced HCC, which has recently been concluded. In this study, 33 patients with advanced HCC received GPC3 peptide vaccination with dose-escalation. Peptides were emulsified with IFA and administered in liquid form by intradermal injection on days 1, 15 and 29. The $GPC3_{298–306}$ peptide was used in HLA-A24-positive patients and the $GPC3_{144–152}$ peptide in HLA-A2-positive patients. In this trial, we collected evidence of immune responses, demonstrated antitumor effects, and demonstrated the safety of our GPC3-derived peptide vaccine. One patient manifested a partial response (PR) and 4 out of 19 patients with stable disease (SD) exhibit tumor necrosis or regression that did not meet the criteria for PRs. Two months after initiation of treatment, the disease control rate (PR+SD) was 60.6%. When we analyzed the frequency of GPC3-specific CTLs *ex vivo* with interferon γ (IFNγ) enzyme-linked immunospot (ELISPOT) assays, we could detect GPC3 peptide-specific CTLs in the peripheral blood of most patients. In parallel with this, we established several $GPC3_{144–152}$ peptide-specific CTL clones from peripheral blood mononuclear cells (PBMCs) of patients vaccinated in this trial. Tumor biopsies were performed in seven patients and the infiltration of $CD8^+$ T cells was assesses with immunohistochemistry. In five cases, we observed a marked intratumoral infiltration of $CD8^+$ T cells upon vaccination. A correlation between immunological and clinical responses is nowadays a required as proof for the clinical efficacy of immunotherapy. The frequency of GPC3 peptide-specific CTLs in the peripheral blood correlated with overall survival in HCC patients who received the peptide vaccination. In a multivariate analysis, the frequency of GPC3-peptide-specific CTLs constitute the only predictive factor for overall survival in this trial. Analysis of all 33 patients showed a median overall survival of 12.2 mo (95% CI, 6.5–18.0) in patients with a high frequency of GPC3-specific CTLs, compared with 8.5 mo (95% CI, 3.7–13.1) in individuals with a low GPC3-specific CTL frequency ($p = 0.033$). These observations suggest that GPC3-derived peptide vaccines represent a novel immunotherapeutic strategy for patients with HCC, with a potential to improve overall survival. We subsequently conducted a phase II

study of the GPC3-derived peptide vaccine as an adjuvant therapy for patients with HCC (UMIN-CTR: 000002614). Forty patients with HCC who had undergone surgery or radiofrequency ablation were enrolled in this phase II, open-label, single-arm trial. Ten vaccinations were performed over 1 y after curative treatment. Primary endpoints were the 1- and 2-y recurrence rates, while secondary endpoints were immunological responses, as measured with an IFNγ ELISPOT assay. The correlation between the time of recurrence and immunological responses is currently being analyzed. In the phase I trial, we did not confirm whether the tumor-infiltrating lymphocytes detected after vaccination were GPC3 peptide-specific. To address this issue, we are initiating a pilot study of liver biopsies performed before and after GPC3 peptide vaccination for advanced HCC (UMIN-CTR: 000005093). GPC3 is overexpressed in several malignant tumors, including ovarian clear cell carcinoma (CCC), which is normally characterized by a poor prognosis due to low sensitivity to conventional chemotherapy. We confirmed that a $GPC3_{144–152}$ peptide-specific CTL clone can recognize HLA-A2-positive and GPC3-positive ovarian CCC cell lines using an IFNγ ELISPOT assay, and that is can kill ovarian CCC cell lines. We are currently conducting a phase II study with a GPC3-derived peptide vaccine in ovarian CCC patients (UMIN-CTR: 000003696). We expect that the results of these trials will provide a rationale for larger randomized clinical trials that will determine the efficacy of GPC3-derived peptide vaccines. In addition, as the antitumor effect of the peptide vaccine alone is not dramatic in advanced cancer patients, we aim to develop combinational approaches or strong antigen-specific immunotherapeutic strategies, including adoptive cell transfer approaches following lymphodepletion. Finally, clinical trials of the adoptive cell transfer of GPC3-specific CTLs in patients with HCC in Japan are planned. Well-designed clinical trials using an innovative immunotherapeutic approaches will lead to the development of efficient new therapies for the treatment of GPC3-expressing tumors (2, 3).

Clinical trials

We are performing a Phase II study of GPC3 peptide vaccine as adjuvant treatment for HCC after surgical resection or RFA and a clinical study for evaluating immunological efficacy of GPC3 peptide vaccine in patients with advanced HCC. We are also currently conducting a phase II study with a GPC3 peptide vaccine in ovarian CCC patients and a phase I study with a GPC3 peptide vaccine in pediatric cancer patients.

List of papers published in 2012
Journal

1. Nobuoka D, Motomura Y, Shirakawa H, Yoshikawa T, Kuronuma T, Takahashi M, Nakachi K, Ishii H, Furuse J, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Kinoshita T, Komori H, Baba H, Fujiwara T, Nakatsura T. Radiofrequency ablation for hepatocellular carcinoma induces glypican-3 peptide-specific cytotoxic T lymphocytes. Int J Oncol, 40:63-70, 2012
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Psycho-Oncology Division

Asao Ogawa, Daisuke Fujisawa, Hiroya Kinoshita

Introduction

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

Research activities

Risk Factors for Depression in Cancer Patients

Various risk factors for depression in cancer patients have been suggested but have been examined separately in studies with relatively small sample sizes. We designed and executed a study which examined the risk factors of depression in lung cancer patients, using the largest consecutive sampling.

A total of 1334 consecutively recruited lung cancer patients were selected, and data on cancer-related variables, personal characteristics, health behaviors, physical symptoms, and psychological factors were obtained. The participants were divided into groups with or without depression using the Hospital Anxiety and Depression Scale. Among the recruited patients, 165 (12.4%) manifested depression. The results of a binary logistic regression analysis were significant (overall R2, 36.5%), and a greater risk for depression was strongly associated with psychological factors, such as personality characteristics (neuroticism) and the coping style (low fighting spirit, helplessness/hopelessness, and anxious preoccupation). Although the contributions of cancer-related variables, personal characteristics, health behaviors, and clinical state were relatively low, significant correlations were also seen for cancer stage, cancer type, sex, and age. Depression was most strongly linked with personality traits and the coping style, and preventive interventions using screening instruments to identify these risk factors may be useful.

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

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

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

A survey questionnaire was mailed to consultation-liaison psychiatrists at 375 government-designated cancer hospitals regarding their consultation-liaison services. A total of 375 survey questionnaires were sent to consultation-liaison psychiatrists, with a response rate of 64.8%. Designated cancer hospitals with approved palliative care teams were significantly more likely to have a consultation-liaison psychiatrist in the palliative care team than those in non-approved palliative care teams [80/80 (100%) versus 110/153 (73%); P ¼ < 0.008]. Approved palliative care teams had double the number of referrals, conducted rounds more frequently and held conferences more frequently. Psychiatrists of the approved palliative care teams spent more of their time on palliative care consultations, adhered more closely to consultation processes and contributed more actively to the integration of developmental perspectives in treatment plans. In Japan, most designated cancer

hospitals with approved palliative care teams were more likely to integrate psychiatric consultation-liaison services into their palliative care programs. Systematic strategies for integration between palliative care and consultation-liaison psychiatry would contribute to the provision of appropriate psychosocial care for cancer patients and families at all stages.

List of papers published in 2012
Journal

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Division of Radiation Oncology and Particle Therapy

Tetsuo Akimoto, Mitsuhiko Kawashima, Sadatomo Zenda, Teiji Nishio, Ryosuke Kohno

Introduction

The aim of research in the Radiation Oncology and Particle Therapy Division is to develop innovative treatment techniques and conduct clinical trials for proton beam therapy (PBT) with or without chemotherapy for various cancers to establish the definitive role of PBT in cancer treatment. Another important goal is to establish standard treatments for various cancers and optimal irradiation techniques including total dose, fractionation and radiation fields of PBT.

Routine activities

The staff of the Radiation Oncology and Particle Therapy Division consists of 7 consultant physicians (radiation oncologist) and 3 medical physicists. We have had more than 200 new patients for proton beam therapy. PBT quality assurance is regularly performed by medical physicists and radiation technologists, and a conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. PBT is routinely based on three-dimensional radiation therapy planning, and uses RT-dedicated multi-detector-row helical computed tomography (CT) scanning in order to confirm the precise radiation dose delivered to the targeted tumors. Respiratory-gating has been applied especially in the patients with lung, esophagus and liver cancers. The selection of treatment approaches is determined through clinical conferences between the radiation oncologist, surgical oncologists and medical oncologists.

The PBT team is composed of 6 operating staff members and 1 technician who sets up the compensator and aperture; the technicians are sent from the system manufacturers and work in collaboration with the other staff members of the Division. There are 2 treatment rooms for PBT and both rooms are routinely used for rotational gantry treatment.

Research activities

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

1) Evaluation of the feasibility of PBT combined with chemotherapy for inoperable locally advanced non-small cell lung cancer and locally advanced esophageal cancer.
2) Proton dose distribution measurements using a MOSFET detector with a simple dose-weighted correction method for LET effects.
3) Hypofractionated PBT for localized prostate cancer.
4) PBT for pediatric malignancies.
5) Development and clinical applicability of linear scanning treatment using a pencil beam.
6) Development of an algorithm for pencil beam activity using measured distribution data of positron emitter nuclei generated by proton irradiation of targets containing ^{12}C, ^{16}O, and ^{40}Ca nuclei in preparation for clinical application.
7) Dose-volume histogram analysis of the safety of proton beam therapy for unresectable hepatocellular carcinoma.
8) A feasibility study of a molecular-based patient setup verification method using a parallel-plane PET system.

Clinical trials

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

1) A phase II study of PBT for malignant melanoma of the nasal cavity.
2) A phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.

Table 1. Number of patients treated with radiotherapy during 2007-2011

	2007	2008	2009	2010	2011
New patients	78	52	57	107	200
Head and neck cancers	22	13	24	39	49
Lung and mediastinal cancers	17	22	13	12	24
Hepatocellular carcinoma	6	6	6	12	27
Prostate cancer	31	11	14	42	93
Others	2	0	0	2	7

The changes in the number of patients treated with PBT

List of papers published in 2012

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2. Nakamura K, Akimoto T, Mizowaki T, Hatano K, Kodaira T, Nakamura N, Kozuka T, Shikama N, Kagami Y. Patterns of practice in intensity-modulated radiation therapy and image-guided radiation therapy for prostate cancer in Japan. Jpn J Clin Oncol, 42:53-57, 2012
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Division of Translational Research

Katsuya Tsuchihara, Sachiyo Mimaki, Hideki Makinoshima, Shingo Matsumoto, Hiroyasu Esumi, Takayuki Yoshino, Atsushi Watanabe, Tomomitsu Nasuno

Introduction

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

Routine activities

A weekly conference and journal club is held with all the researchers, technical staff, visiting scientists, and graduate students. Lab members are strongly encouraged to participate and chair the basic and translational research conferences held in Research Center for Innovative Oncology.

Research activities

Development of Anti-austeric Drugs

Cancer cells in solid tumors frequently encounter a hypoxic and nutrient-deficient microenvironment. Austerity, which is resistance to nutrient starvation, is a characteristic feature of various cancer cells. Since most non-cancerous tissues seldom encounter such nutrient-deficient circumstance, targeting austerity is a promising new strategy for selective cancer treatment. Arctigenin, a major component of *Arctium lappa* (the greater burdock) is one of the anti-austerity compounds identified in this division. Preclinical studies revealed that a crude extract of *Arctium lappa* possessed equivalent anti-austeric abilities. With the aim of the clinical application of *Arctium lappa*, a phase I clinical trial recruiting advanced pancreatic cancer patients was done. According to the determined appropriate dose, an investigator-initiated phase II clinical trial has been started.

Implication of biomarkers for cancer therapy

To explore more effective genomic biomarkers in anti-EGFR antibody treatment for advanced colorectal cancer, a multi-centered retrospective study combined with whole exon sequencing and copy number variation analyses (BREAC study) is being conducted. More than 100 characteristically anti-EGFR antibody-sensitive and –resistant cases have been enrolled. To clarify the effectiveness and feasibility of multiplex trans-organ pan-cancer genomic biomarker testing, an intramural expert panel has been organized and an ABC study (Analyses of Biopsy samples for Cancer genomics) has been started. More than 100 cases were enrolled in the first 7 months.

Molecular epidemiology of lung adenocarcinoma

Whole exon sequencing was adopted to clarify the mutation profiles of Japanese lung cancer. Somatic mutations of 97 cases of archived lung adenocarcinoma and of 55 cases of small cell lung cancer specimens were identified. Largely diverse mutation patterns of individual tumors were exhibited.

List of papers published in 2012
Journal

1. Bando H, Yoshino T, Yuki S, Shinozaki E, Nishina T, Kadowaki S, Yamazaki K, Kajiura S, Tsuchihara K, Fujii S, Yamanaka T, Ohtsu A. Clinical outcome of Japanese metastatic colorectal cancer patients harbouring the KRAS p.G13D mutation treated with cetuximab + irinotecan. Jpn J Clin Oncol, 42:1146-1151, 2012
2. Yamagata Y, Aikou S, Fukushima T, Kataoka H, Seto Y, Esumi H, Kaminishi M, Goldenring JR, Nomura S. Loss of HGF activator inhibits foveolar hyperplasia induced by oxyntic atrophy without altering gastrin levels. Am J Physiol Gastrointest Liver Physiol, 303:G1254-1261, 2012
3. Kawamoto Y, Tsuchihara K, Yoshino T, Ogasawara N, Kojima M, Takahashi M, Ochiai A, Bando H, Fuse N, Tahara M, Doi T, Esumi H, Komatsu Y, Ohtsu A. KRAS mutations in primary tumours and post-FOLFOX metastatic lesions in cases of colorectal cancer. Br J Cancer, 107:340-344, 2012
4. Tomitsuka E, Kita K, Esumi H. An anticancer agent, pyrvinium pamoate inhibits the NADH-fumarate reductase system - a unique mitochondrial energy metabolism in tumour microenvironments. J Biochem, 152:171-183, 2012
5. Magolan J, Adams NBP, Onozuka H, Hungerford NL, Esumi H, Coster MJ. Synthesis and evaluation of anticancer natural product analogues based on angelmarin: targeting the tolerance towards nutrient deprivation. ChemMedChem, 7:766-770, 2012
6. Inazuka F, Sugiyama N, Tomita M, Abe T, Shioi G, Esumi H. Muscle-specific knock-out of NUAK family SNF1-like kinase 1 (NUAK1) prevents high fat diet-induced glucose intolerance. J Biol Chem, 287:16379-16389, 2012
7. Sakai C, Tomitsuka E, Esumi H, Harada S, Kita K. Mitochondrial fumarate reductase as a target of chemotherapy: from parasites to cancer cells. Biochim Biophys Acta, 1820:643-651, 2012

Section of Translational Medicine and Development

Takeharu Yamanaka, Izumi Miki, Yuko Kineri, Rika Kojima

Introduction

Established in April 2012, our Section provides a multifaceted support to accelerate the development of translational research. The emerging field of "personalized medicine" holds great promise in the fight against cancer but achieving this goal will require massive amounts of genomic and clinical data and a sophisticated infrastructure to manage and analyze the data. Our team has now completed a step in building this infrastructure. Currently, we have established a data repository for the National Cancer Center East (NCCE) genome research as well as a routine biostatistics/bioinformatics support which is available to help the planning and design stages of a variety of projects.

Another upfront requirement toward personalized medicine includes the arrangement of environment for developing companion diagnostic genetic tests. With such devices, physicians can modify regimens to reflect pharmacogenetic differences among patients. We are tackling problems which are associated with the "E" part in the well-known ACCE criteria for evaluating a genetic test (Analytic validity, Clinical validity, Clinical utility, and associated Ethical, legal and social implications; See www.cdc.gov/genomics/gtesting/ACCE/). Especially with regard to handling the "legal" aspect, our section now takes the role in the office of technology licensing which catalyzes commercial and non-commercial applications of the NCC's innovations through stewardship of the intellectual property.

Routine activities

Translational Research Center
- data management for genomic data from clinical studies
- comprehensive support for biostatistics/bioinformatics aspects

Design and Analysis of Clinical Trials
- biostatisticians support the design and analysis aspects of clinical trials, especially with biomarkers. Several international or nationwide phase III trials are currently under support.

Center for Collaborative Research
- office of technology licensing for strategic management of the intellectual property of NCCE
- platform for linking up NCCE with industrial partners regionally and internationally.

Regulatory Affairs
- members of several expert panels for regulatory affairs led by PMDA and MHLW

Office of Communications and Public Relations
- best source for up-to-date and accurate information about the NCCE Research Center for Innovative Oncology

List of papers published in 2012
Journal

1. Kuno H, Onaya H, Iwata R, Kobayashi T, Fujii S, Hayashi R, Otani K, Ojiri H, Yamanaka T, Satake M. Evaluation of cartilage invasion by laryngeal and hypopharyngeal squamous cell carcinoma with dual-energy CT. Radiology, 265:488-496, 2012
2. Takeda M, Okamoto I, Yamanaka T, Nakagawa K, Nakanishi Y. Impact of treatment with bevacizumab beyond disease progression: a randomized phase II study of docetaxel with or without bevacizumab after platinum-based chemotherapy plus bevacizumab in patients with advanced nonsquamous non-small cell lung cancer (WJOG 5910L). BMC Cancer, 12:327, 2012
3. Katsuya H, Yamanaka T, Ishitsuka K, Utsunomiya A, Sasaki H, Hanada S, Eto T, Moriuchi Y, Saburi Y, Miyahara M, Sueoka E, Uike N, Yoshida S, Yamashita K, Tsukasaki K, Suzushima H, Ohno Y, Matsuoka H, Jo T, Suzumiya J, Tamura K. Prognostic index for acute- and lymphoma-type adult T-cell leukemia/lymphoma. J Clin Oncol, 30:1635-1640, 2012
4. Ishitsuka K, Yamanaka T, Katsuya H, Junji Suzumiya, Tamura K. Reply to J.J. Castillo et al. J Clin Oncol, 30:3561, 2012
5. Matsuoka H, Arao T, Makimura C, Takeda M, Kiyota H, Tsurutani J, Fujita Y, Matsumoto K, Kimura H, Otsuka M, Koyama A, Imamura CK, Tanigawara Y, Yamanaka T, Tanaka K, Nishio K, Nakagawa K. Expression changes in arrestin beta 1 and genetic variation in catechol-O-methyltransferase are biomarkers for the response to morphine treatment in cancer patients. Oncol Rep, 27:1393-1399, 2012
6. Watanabe A, Kohnoe S, Sonoda H, Shirabe K, Fukuzawa K, Maekawa S, Matsuda H, Kitamura M, Matsuura H, Yamanaka T, Kakeji Y, Tsujitani S, Maehara Y. Effect of intra-abdominal absorbable sutures on surgical site infection. Surg Today, 42:52-59, 2012

Clinical Trial Section

Akihiro Sato, Hiromi Hasegawa, Yoshihiro Aoyagi, Tomohisa Sudo, Kaori Tobayama, Miki Fukutani, Kayo Toyosaki, Noriko Suzuki, Takako Tomisawa, Kayoko Ohsumi, Satoru Ueno, Shogo Nomura, Yasutaka Watanabe, Mie Yamada, Mai Kikuchi, Natsuko Takagi, Hiroko Tahara, Yukie Hayashi, Yasuko Nishikubo, Minako Honda, Harumi Nakazima, Rie Ehara, Kyoko Kaneko, Tomoko Watanabe, Akiko Nakayama, Yukiko Abe, Yumi Nakatani, Miho Takanashi, Kazushi Endo

Introduction

Established in 2008, the Clinical Trial Section supports Investigator Initiated Clinical Trials (IITs) Programs at the National Cancer Center Hospital East (NCCH-E) through the Clinical Data / Coordinating Center. Our section consults on development strategy, and supports project management and protocol development. The Section consists of 6 groups (IRB office, CRC for IITs, Research Concierge, Data Management, Clinical Trial Management, and Statistics).

Routine activities

Data management group
- Data base and CRF form design
- Data management
- Central monitoring
- System administration

Clinical Trial management group
- Project management
- Study management
- Site visit monitoring
- Medical writing

Statistical group
- Study design
- Statistical analysis
- Consultation

CRC Group
- Support IITs that are conducted in NCCH-E

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

IRB Office
- Oversees all IRB activities

Research activities and clinical trials

CRC Office for IITs
- CRCs, in 2011 supported 48 IITs including a Sponsor Investigator IND trial. A total of 497 patients participated in the IITs.

Data Management, Clinical Trial Management, Statistical Groups
- Seven clinical studies, a medical device and a new anticancer drug study, and first-in- man phase 0 study, are active as of 2011
- Started the consultation for statistics design and analysis for IITs by our biostatistician

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

We focused research activities on clinical trial methodology. We are developing a new EDC system, sampling source document verification (SDV) method and comprehensive information sharing infrastructure for early clinical trials.