LYMPH NODE AND DISTANT METASTASIS AFTER EMR OR ESD

ESOPHAGEAL SQUAMOUS CELL carcinoma invading the muscularis mucosae or deeper is associated with increased risks of lymph node metastasis and distant metastasis. Follow-up examinations should therefore include confirmation of the presence or absence of lymph node metastasis and distant metastasis.[12] Lymph node metastasis and distant metastasis are usually detected within 2 years after EMR or ESD, but can occur after 4 years.[1,11] Regular long-term follow up is thus essential. To our knowledge, however, no study has clearly defined an effective protocol for follow up after EMR or ESD in patients with a high risk of lymph node metastasis or distant metastasis. At present, follow-up protocols are decided by individual hospitals. Many hospitals carry out computed tomographic (CT) examinations of the neck, chest, and abdomen at 6–12-month intervals,[1,8,10] and some include ultrasonography (US) of the neck and abdomen or endoscopic ultrasonography (EUS).[13]

Although no study has also defined an effective protocol for follow up after esophagectomy, many institutions carry out CT or US at 3–6-month intervals and modify this schedule as required by evidence of disease progression or the number of years after surgery.[14–16] A phase II study evaluating the efficacy of combined treatment with EMR and chemoradiotherapy is currently ongoing in patients with clinical stage I esophageal carcinoma (JCOG0508 trial). One of the major objectives of this trial is to evaluate the effectiveness of EMR and ESD for esophageal squamous cell carcinoma with submucosal invasion. This trial is registered with the UMIN Clinical Trials Registry, number UMIN553. In this clinical trial, CT of the neck, chest, and abdomen is carried out and tumor markers, such as squamous-cell carcinoma antigen, are measured at 4-month intervals during 3 years of follow up. The clinical practice guidelines for esophageal cancer proposed by the Japan Esophageal Society recommend that CT of the chest and abdomen, US of the neck and abdomen, and EUS are carried out at 6–12-month intervals during routine long-term follow up after EMR or ESD.[17]

INCIDENCE OF METACHRONOUS ESOPHAGEAL SQUAMOUS CELL CARCINOMA AFTER EMR OR ESD

PATIENTS WITH ESOPHAGEAL squamous cell carcinoma tend to have a high incidence of metachronous esophageal squamous cell carcinoma (10–15%), which can develop any time after treatment.[18–20] Long-term follow up is therefore essential. Patients with multiple LVL tend to have a high risk of metachronous esophageal squamous cell carcinoma.[18–20] Strict follow up by upper gastrointestinal endoscopy is thus mandatory.

INCIDENCE OF SECOND PRIMARY CANCER AFTER EMR OR ESD

PATIENTS WITH ESOPHAGEAL cancer are at high risk for a second primary cancer,[5] attributed to the presence of common risk factors for each cancer in the upper aerodigestive tract. The concept of field cancerization has also been implicated in the pathogenesis of second primary cancers.[21–24]

The incidences and types of second primary cancer differ depending on factors such as years of data collection, follow-up periods, and characteristics of hospitals. A national registry established by the Japan Esophageal Society found that double cancers develop in approximately 20% of patients with esophageal cancer, including 8% with synchronous cancers and 12.2% with metachronous cancers. The most common types of double cancer were, in descending order, gastric cancer, head and neck cancer, colorectal cancer, and lung cancer.[25]

One study reported that head and neck cancer was the most common double cancer.[5] Most studies estimate that double cancers of the head and neck develop in approximately 10% of patients with esophageal cancer. In the head and neck region, pharyngeal cancer is most common.[3,26] Esophageal cancers with a high risk of double cancer of the head and neck are characterized by the presence of multiple esophageal cancers or multiple LVL.[27–29]

Recent progress in endoscopic techniques such as magnifying endoscopy and image-enhanced endoscopy coupled with increased emphasis on screening the head and neck region in patients with esophageal cancer has facilitated the early detection of head and neck cancer on upper gastrointestinal endoscopy.[3,30,31] In response to this phenomenon, an image-enhanced laryngoscope was developed and recently introduced at departments of otolaryngology, facilitating the early detection of cancer on follow-up visits.[32,33]

Double cancers of the esophagus and the stomach have few common risk factors, in contrast to double cancers of the esophagus and the head and neck. Smoking is considered a risk factor for esophageal cancer and gastric cancer.[34] In Japan, however, the high prevalence of gastric cancer may be largely attributed to atrophy of the gastric mucosa due to *Helicobacter pylori* infection.[35,36]

Although standardized protocols for follow up after EMR or ESD have yet to be established to facilitate the early detection of a second primary cancer, regular follow up

of the head and neck, esophagus, and stomach by upper gastrointestinal endoscopy is essential. Moreover, cancer screening should include examination of the head and neck region by an otolaryngologist, examination of the lungs by chest radiography or CT, and colorectal examinations, including fecal occult blood tests or colonoscopy, carried out at suitable intervals.

JAPAN ESOPHAGEAL COHORT STUDY

PREVIOUS STUDIES HAVE reported that multiple LVL of background esophageal mucosa are associated with a very high risk of multiple cancers arising in the esophagus,[18–20] as well as in the head and neck region.[27–29] The ability to use the Lugol-voiding pattern as a biomarker for the risk of second primary cancers in the esophagus and the head and neck region after EMR or ESD in patients with esophageal cancer would facilitate early detection and treatment of metachronous multiple cancers, contribute to improved outcomes of EMR or ESD, and come closer to realizing an optimal surveillance period after EMR or ESD.

A multicenter cohort study (Japan Esophageal Cohort Study: JEC Study) is ongoing to investigate the risk of metachronous multiple cancers and to assess the time required for their development after EMR or ESD, using Lugol-voiding pattern as a biomarker in patients who have esophageal squamous cell carcinoma with invasion limited to the mucosa. This trial is registered in the UMIN Clinical Trials Registry, number UMIN1676.

The primary endpoint is the cumulative incidence of metachronous multiple cancers of the esophagus, as assessed by Lugol-voiding pattern. Secondary endpoints are to estimate: (i) the total annual number of cases of metachronous multiple cancer of the esophagus, as assessed by the Lugol-voiding pattern; and (ii) the cumulative incidence of metachronous multiple cancers of the head and neck region, as assessed by the Lugol-voiding pattern.

The procedure for follow-up observation was established by consensus. Upper gastrointestinal endoscopic examinations of the head and neck, esophagus, and stomach and Lugol chromoendoscopy were carried out at 3-month intervals for up to 6 months after EMR or ESD. Subsequently, these examinations were carried out at 6-month intervals. The head and neck region was examined by an otolaryngologist at the time of EMR or ESD and at 1-year intervals thereafter (Fig. 1).

A total of 331 patients were enrolled and have completed the predetermined follow-up observations. The data are now being analyzed. An optimal protocol for surveillance after EMR or ESD will be proposed on the basis of the study results.

FUTURE DIRECTIONS

THE GUIDELINES OF the National Comprehensive Cancer Network (NCCN) in the USA include a procedure for follow up after EMR in patients with Tis or T1a cancer.[37] These guidelines recommend that upper gastrointestinal endoscopy is carried out at 3-month intervals during the first year after EMR and at 1-year intervals thereafter. However, these recommendations are not supported by references, and their basis and validity remain unclear. The clinical practice guidelines for esophageal cancer proposed by the European Society for Medical Oncology (ESMO) recommend that appropriate action should be taken on the development of symptoms or other abnormalities because evidence showing that regular follow up can improve outcomes is lacking.[38]

Future studies are necessary to produce robust evidence supporting protocols for follow-up observation in patients with esophageal cancer. Patients should be enrolled and followed up in accordance with consensus-based protocols, such as the aforementioned JEC Study. Whether such protocols improve the outcomes and quality of life of patients with

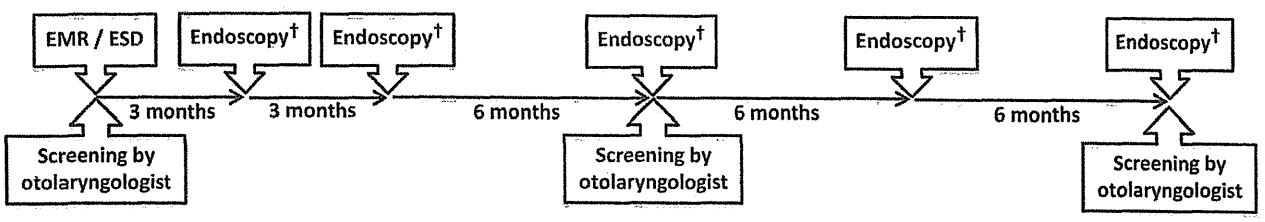

Figure 1 Surveillance after endoscopic mucosal resection or endoscopic mucosal dissection in the Japan Esophageal Cohort Study. †Head and neck region, esophagus, and stomach were examined and Lugol chromoendoscopy was carried out.

esophageal cancer and whether the proposed methods are sound from the viewpoint of medical economics should also be evaluated.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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ORIGINAL ARTICLE

A Dermatitis Control Program (DeCoP) for head and neck cancer patients receiving radiotherapy: a prospective phase II study

Sadamoto Zenda · Shinobu Ishi · Mitsuhiko Kawashima · Satoko Arahira · Makoto Tahara · Ryuichi Hayashi · Seiji Kishimoto · Tomiko Ichihashi

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Abstract
Purpose We speculated that a systematic program to manage radiation dermatitis might decrease the incidence of severe or fatal cases in head and neck cancer patients receiving radiotherapy. Here, we conducted a prospective phase II study to clarify the clinical benefit of a Dermatitis Control Program (DeCoP) that did not use corticosteroids.
Patients and methods Head and neck cancer patients scheduled to receive definitive or postoperative radiotherapy were enrolled. Radiation dermatitis was managed with a DeCoP consisting of a three-step ladder: Step 1, gentle washing; Step 2, gentle washing and moistening of the wound-healing environment; Step 3, prevention against infection, gentle washing and moistening of the wound-healing environment. The primary endpoint was the incidence of grade 4 dermatitis.
Results A total of 113 patients were registered between January 2009 and February 2010. Eighty patients received radiotherapy as an initial approach, while the remaining 33 received radiotherapy postoperatively. Grade 3 and 4 dermatitis events occurred in 11 (9.7%) and 0 (0%, 95% confidence interval 0–3.2%) patients, respectively. Median radiation dose at the onset of grade 2 dermatitis was 61.5 Gy (range 36–70 Gy) and median period between onset and recovery was 14 days (range 1–46 days).
Conclusion The Dermatitis Control Program has promising clinical potential. Radiation dermatitis might be manageable if gentle washing and moistening of the wound-healing environment is done.

Keywords Head and neck cancer · Cancer nursing · Dermatitis · Radiotherapy

S. Zenda (✉) · S. Ishi · M. Kawashima · S. Arahira · T. Ichihashi
Division of Radiation Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
e-mail: szenda@east.ncc.go.jp

S. Zenda · S. Kishimoto
Department of Head and Neck Surgery, Tokyo Medical and Dental University, Tokyo, Japan

M. Tahara
Gastrointestinal Oncology and Endoscopy, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

R. Hayashi
Head and Neck Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

Introduction

Chemoradiotherapy is now commonly used in the treatment of head and neck cancer. For example, single-agent cisplatin concurrent with radiotherapy is now the nonsurgical standard care for locally advanced squamous cell carcinoma of the head and neck (SCCHN) patients [1–3], and is also considered the standard adjuvant therapy for high-risk postoperative patients [4–6]. Recently, induction chemotherapy using cisplatin, 5-fluorouracil, and docetaxel followed by chemoradiotherapy has shown promise for locally advanced head and neck cancer patients at high risk of distant metastases [7, 8].

However, as treatment strength increases, so too does the risk of toxicity. Acute skin reactions like radiation dermatitis are common, and not only risk interrupting treatment but can even be fatal. Although various topical medications have been used to manage and treat radiation dermatitis, there remains no agreement on the best treatment plan [9, 10].

Among those being considered, there is strong evidence supporting the efficacy of a simple treatment plan that involves only gentle washing and moistening of the wound-healing environment [11, 12]. Here, we describe a prospective phase II study that uses a Dermatitis Control Program (DeCoP) incorporating a three-step plan, which includes gentle washing and moistening of the would-healing environment but no corticosteroid use, for head and neck patients receiving radiotherapy.

Patients and methods

This single institution prospective phase II study was approved by the institutional review board of the National Cancer Center Hospital before the start of patient enrollment. This trial was registered with UMIN-clinical trials registry (UMIN-CTR: UMIN000001579).

Eligibility

Patients fulfilling the following criteria were enrolled: histologically confirmed SCCHN; 20–75 years of age; Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2; normal organ function; and scheduled to receive definitive or postoperative radiotherapy (>50 Gy). Written informed consent for treatment was obtained from all patients before its initiation.

Treatment

The main protocol was the 'Dermatitis Control Program'. This systematic program consists of a three-step ladder (Table 1).

Supportive treatment for grade 0–1 radiation dermatitis (Step 1)

The basic concept of this step is 'watchful waiting'.

All treatments for radiation dermatitis prevention except gentle washing were avoided. All patients were instructed on how to wash with lukewarm water and mild soap for routine care. Physicians or expert nurses observed each patient for dermatitis at least twice a week.

Supportive treatment for grade 2 radiation dermatitis (Step 2)

The basic concept of this step is 'minimally required intervention'. The irradiated area was covered with gauze and moistened with either vaseline or dimethyl isopropyl-azulene. All outpatients and their families were instructed on how to cover and moisten the irradiated area. For inpatients, gauze coating was done by the patient or nurse. An example of Step 2 is shown in Fig. 1.

Supportive treatment for grade 3–4 radiation dermatitis (Step 3)

The basic concept for this step is similar to that of Step 2 except for the use of preventative action against infection. Physicians or experts including wound, ostomy, and continence nurses observed for dermatitis every business day. If no infection was noted, antibiotic drugs were not administered.

Table 1 Dermatitis Control Program steps

	Dermatitis grade (CTCAE ver. 3.0)			
	0	1	2	3
Step 1: Gentle wash	○	○	○	○
Step 2: Moistened wound environment		Δ	○	○
Step 3: Infection prevention		Δ	Δ	○

○, Treatment done unconditionally; Δ, treatment done if feasible

Toxicity

Adverse events related to acute toxicity by radiotherapy or chemoradiotherapy were coded according to the common terminology criteria of adverse events, version 3 (CTCAE ver. 3.0). According to these criteria, grade 2 radiation dermatitis includes moderate to brisk erythema, patchy moist desquamation mostly confined to skin folds and creases, and moderate edema. Grade 3 radiation dermatitis consists of moist desquamation other than skin folds or creases and bleeding induced by minor trauma or abrasion.

Radiation dermatitis was evaluated by physicians or nurses based on dermatitis grading according to the CTCAE ver. 3.0, followed by DeCoP performed according to the grading. The investigators' gradings were subsequently evaluated by a central review committee using photographs.

Irradiation methods

Irradiation dose and modality (conventional radiotherapy, intensity-modulated radiotherapy or proton beam therapy) varied according to primary site and tumor stage. Full-face immobilization (thickness 2 mm) was used for all patients to minimize set-up error. Target volumes were defined in accordance with International Commission on Radiation Units and Measurements Reports 50 and 62.

Treatment evaluation and statistical analysis

The primary endpoint of this study was the incidence of grade 4 dermatitis. Skin breakdown has the potential for

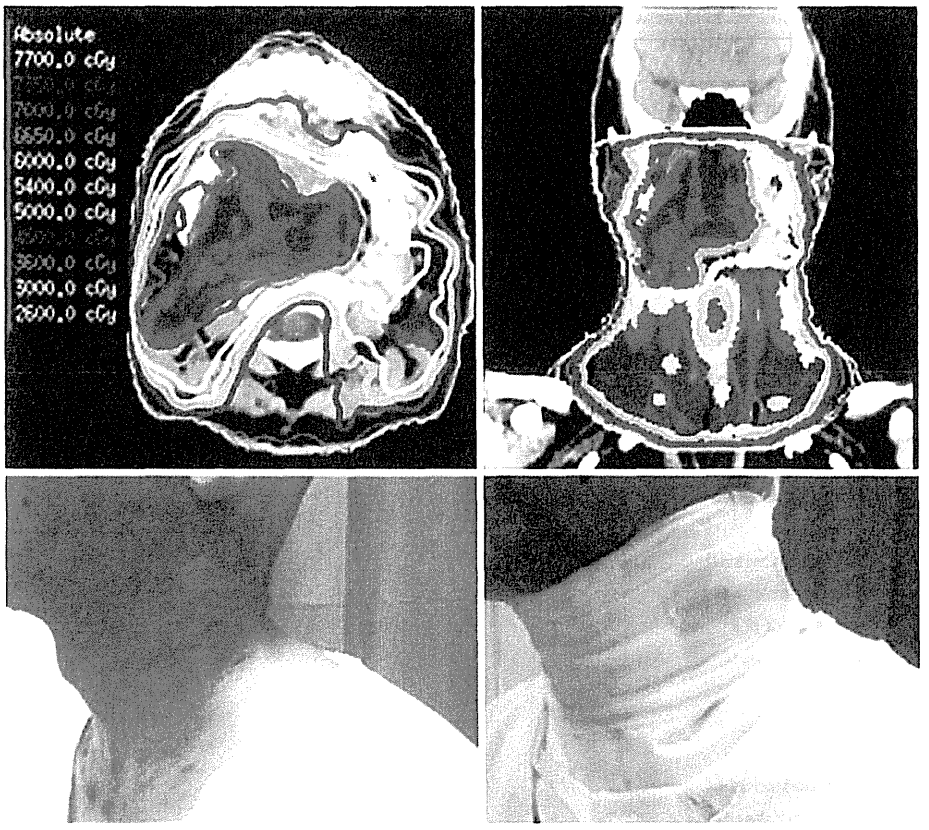

Fig. 1 Dermatitis Control Program Step 2. The case was a 44-year-old-male with T4N2cM0 oro-pharyngeal cancer. He was treated with induction chemotherapy followed by chemoradiotherapy. The irradiated area was covered with gauze and moistened with dimethyl isopropylazulene. It is very important that not only the physicians but also the co-medical staff understand where the radiation field is

infection, which risks disrupting radiotherapy treatment. Unplanned disruption was defined as one or more days of interruption, excluding weekends or days for planned machine maintenance.

If the true rate of grade 4 dermatitis was 7% or less and the true rate of disruption was less than 16%, the DeCoP was applied. To conduct statistical analysis with 90% power and a one-sided type-I error of 5%, a minimum of 104 patients were needed. However, we assumed that 15% of our patients would ultimately be excluded from analysis due to violation of the protocol or other reasons, and thus estimated that 120 patients were needed.

Descriptive statistics, including mean, standard deviation, median, range, and percentage, were used to describe patient demographics, and pathological and clinical characteristics.

Results

Patient characteristics

One hundred and twenty patients were registered between January 2009 and February 2010. Seven patients were excluded from analysis due to a change in treatment strategy (surgery for three patients, palliation for three patients) and refusal to participate after registration (one patient). The remaining 113 patients are characterized in Table 2.

With regard to treatment strategy, 80 patients (71%) received radiotherapy as an initial approach, and the remaining 33 (29%) in a postoperative setting. The major combination chemotherapy regimen was cisplatin alone (53/113, 47%).

Treatment compliance

All patients received the planned radiotherapy without any dose reduction. The rate of unplanned breaks in radiotherapy was 10.6% (12/113) owing to acute toxicity (two patients), PEG trouble (one patient), emergency tracheostomy (one patient), infection (three patients), unplanned machine trouble (one patient), patient discretion (two patients), and other reasons (two patients). Of these, the median interval of radiation interruption was 4 days (range 1–5 days), and no unplanned break of more than 1 week occurred.

Toxicity

The toxicity profile during radiotherapy/chemoradiotherapy is shown in Table 3. No fatal hematological events occurred.

Table 2 Patient characteristics

Characteristics	*n*
No. of patients	113
Age, years	
Median (range)	63 (22–87)
Gender	
Male/female	93/20
Performance status	
0–1/2	99/14
Primary site	
Naospharynx	13
Oropharynx	23
Hypopharynx	18
Larynx	33
Tongue, oral cavity	12
Unknown	14
Radiotherapy setting	
Postoperative RT	33
Definitive RT	80
Treatment strategy	
IC → CRT	25
CRT	43
RT alone	45
Radiation dose, Gy	
Median (range)	70 (54–70)
Combination	
Cisplatin alone	53
Chemotherapy	
Cisplatin and 5-FU	11
Cisplatin and S-1	2
Other platinum	1

CRT Chemoradiotherapy, *IC* induction chemotherapy, *RT* radiotherapy, *5-FU* 5-fluorouracil

Mucositis and dermatitis were the most common non-hematological toxicities.

Grade 2 and 3 dermatitis events were seen in 63 (56%) and 11 (9.7%) patients, respectively. No grade 4 dermatitis events were seen (0%, 95% confidence interval 0–3.2%). Median time until the onset of grade 2 dermatitis was 43.5 days (range 23–60 days) and the median radiation dose at onset was 61.5 Gy (range 36–70 Gy). Median period between onset and recovery was 14 days (range 1–46 days) and the median time until recovery from the initiation of radiotherapy was 57 days (range 39–91 days) (Fig. 2).

Grade 3 mucositis events in the categories 'clinical exam' and 'functional/symptomatic' occurred in about half of the patients for each. Weight loss was recorded in 22 grade 2 patients, but not in any grade 3 patients. No treatment-related deaths occurred.

Table 3 Toxicity

	Dermatitis grade (CTCAE ver. 3.0)				
	1	2	3	4	% 3 and 4
Leucopenia	23	34	4	1	4.4
Neutropenia	71	20	1	1	1.8
Anemia	13	30	1	2	2.7
Thromobocytopenia	16	6	3	0	2.7
Nausea	23	26	5	0	4.4
Mucositis					
CE	11	56	42	1	38.1
FS	15	44	47	0	41.6
Xerostomia	14	60	2	0	1.8
Dermatitis	39	63	11	0	9.7
Febrile neutropenia	–	–	1	0	0.9
Weight loss	19	22	0	0	0

CE Clinical exam, *FS* functional/symptomatic

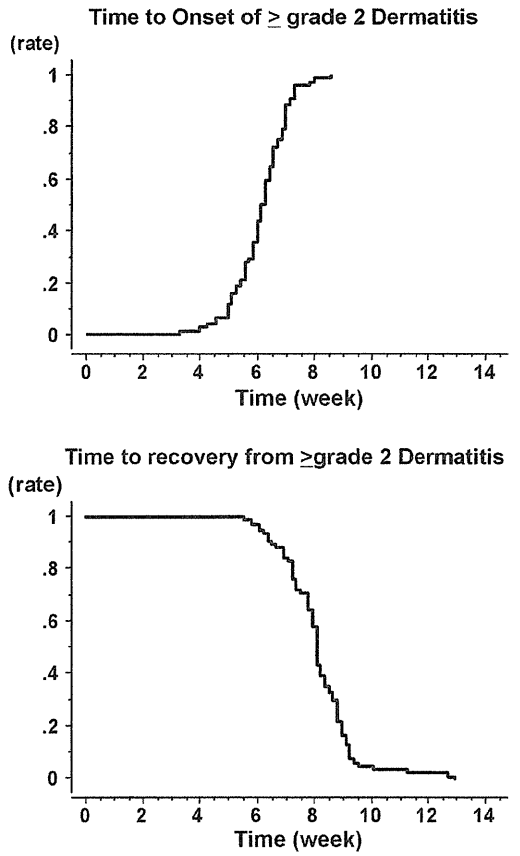

Fig. 2 Time to onset (upper) and recovery (lower) of > grade 2 dermatitis. Median time to onset of grade 2 dermatitis from the initiation of radiotherapy was 43.5 days (range 23–60 days), and median radiation dose at onset was 61.5 Gy (range 36–70 Gy). In several cases, dermatitis became worse after the end of treatment. Median time to recovery from grade 2 dermatitis from the initiation of radiotherapy was 57 days (range 39–91 days). Recovery did not take more than 6 weeks in any case

DeCoP data

All 113 patients received the planned dose of radiotherapy. The median radiation dose was 70 Gy (range 60–70 Gy) and the median duration of radiotherapy treatment was 49 days (range 33–63 days).

The frequency of using either Steps 2 or 3 to control dermatitis during radiotherapy was 63% (71/113), while at 2 weeks and 1 month after the end of radiotherapy it was 19% (21/113) and 2% (2/113), respectively.

Discussion

The primary endpoint of this study was the incidence of grade 4 dermatitis, which did not occur in any patient (0%, 95% confidence interval 0–3.2%). Grade 2 and 3 dermatitis events were seen in 63 (56%) and 11 (9.7%) patients, respectively. Given that radiotherapy is contraindicated in the presence of grade 4 dermatitis, these findings suggest that our DeCoP has good clinical potential.

To date, two randomized trials [11, 13] have assessed the effectiveness of washing. Roy et al. [13] conducted trials with 99 patients randomized to washing with soap and water or no washing, and found a significantly higher incidence of moist desquamation in the non-washing group; while Campell et al. [11] randomized 99 women receiving adjuvant radiotherapy for breast cancer into one of three groups with different washing practices, and found a significant reduction in itching score at the end of treatment and a reduction in erythema and desquamation scores at 6 or 8 weeks after treatment in patients who washed with soap and water independent of bolus dose.

Based on these results, we established Step 1 in our DeCoP as washing only.

Patients received elaborate instructions on how to wash properly. The median time to the onset of grade 2 dermatitis was 43.5 days (range 23–60 days). The frequency of Steps 2 or 3 at 2 weeks and 1 month after the end of radiotherapy was 19 and 2%, respectively. These results show that radiation dermatitis in head and neck lesions can be managed with minimal intervention.

This report has two major limitations. One is that, in our trial, we could not mention the prevention of dermatitis. Another is that it is not enough to mention whether corticosteroids are useful or not for the management of dermatitis because this trial is not a randomized study.

Given this minimal invasiveness, the DeCoP used here appears to be not only useful for clinical practice, but also effective as a control measure for large-scale randomized control trials investigating topical corticosteroids and other medications for dermatitis. Such studies are necessary because although corticosteroids remain frequently prescribed for the management of radiation dermatitis in clinical practice, the evidence for their effectiveness has been inconclusive [9, 12, 14–16].

To change our clinical practice, a further large-scale and qualified phase III study may play a great role.

In conclusion, the results above suggest that radiation dermatitis in head and neck lesions may be manageable if only gentle washing and moistening of the wound-healing environment is done during radiotherapy.

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Conflict of interest There is no conflict of interest.

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ORIGINAL ARTICLE

Strontium-89 (Sr-89) chloride in the treatment of various cancer patients with multiple bone metastases

Sadamoto Zenda · Yoshihiro Nakagami · Masamichi Toshima · Satoko Arahira · Mitsuhiko Kawashima · Yoshihisa Matsumoto · Hiroya Kinoshita · Mitsuo Satake · Tetsuo Akimoto

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Abstract
Background Although the use of Sr-89 chloride in the treatment of patients with prostate and breast cancer has been widely reported, little information is available about its use for other malignancies. Here, we retrospectively analyzed the clinical profile of Sr-89 chloride in various patients with painful bone metastases.
Methods Entry criteria were a pathologically proven malignancy, clinically diagnosed multiple bone metastases, and adequate organ function. Sr-89 chloride (Metastron) was given by single intravenous infusion at 2 MBq/kg over 2 min. Self-reported outcome measures were used as a response index, including pain diary data on a 0–10 numeric rating scale (NRS).
Results Fifty-four consecutive patients with painful bone metastases were treated with Sr-89 chloride at the National Cancer Center Hospital East between March 2009 and July 2011, consisting of 26 with breast/prostate cancer and 28 with other malignancies (lung 8, head and neck 6, colorectal 6, others 8). Thirteen (24 %) patients experienced a transient increase in pain, which was categorized as a flare-up response. Grade 3–4 anemia was observed in 6 patients, 3 of whom required blood transfusion. Regarding efficacy, response rates and complete response rates were 71.2 % and 34.6 %, respectively, and time to response from the initiation of treatment was 36 days (range, 13–217). No significant difference in response rates was seen between patients with breast/prostate cancer and other cancers (breast/prostate 69.2 %, other 73.1 %; $p = 0.76$).
Conclusions As in patients with breast and prostate cancer, Sr-89 chloride is a promising agent for the treatment of painful bone metastases in patients with various other malignancies.

Keywords Palliative care · Radiation oncology · Radiation therapy · Radionuclide · Pain control

Background

The prevalence of painful osseous metastases varies among different types of cancer. Approximately 65 % of patients with prostate or breast cancer and 35 % of those with advanced cancers of the lung, thyroid, and kidney develop symptomatic skeletal metastases. The management of bone pain in these patients remains challenging, and no standardized procedures have yet been adopted. In patients with multifocal osteoblastic metastases, systemic administration of radiopharmaceuticals is the preferred adjunctive therapy for pain palliation.

Similar to calcium, strontium is a divalent cation that is incorporated into hydroxyapatite in bone after intravenous injection [1]. Sr-89 chloride (Metastron) is the first U.S.

This study was presented in MASCC 2012 at New York. http://www.mascc.org/.

S. Zenda (✉) · M. Toshima · S. Arahira · M. Kawashima · T. Akimoto
Departments of Radiation Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
e-mail: szenda@east.ncc.go.jp

Y. Nakagami · M. Satake
Departments of Radiology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

Y. Matsumoto · H. Kinoshita
Departments of Palliative Medicine, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

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Food and Drug Administration-approved radiopharmaceutical for bone pain palliation. The therapeutic effect derives from the beta particles, which have an energy penetration range of up to 6–7 mm in soft tissues and 3–4 mm in bone [2]. Sr-89 has a half-life of 50.5 days, and decays to stable yttrium-89, emitting high-energy beta particles (E_{max}, 1.46 MeV) and 0.01 % of gamma-rays (910 keV). Administration poses no radiation risk to others, and patients can accordingly be treated on an outpatient basis. Studies of Sr-89 pharmacokinetics have demonstrated that plasma clearance is variable (1.6–11.6 l/day), with overall total-body retention of 20 % in a healthy population at 90 days after injection, particularly in the normal skeleton. Osteoblastic lesions show as much as five times greater radiopharmaceutical uptake and more prolonged retention than areas of normal bone in the same patient (lesion/normal bone ratio, 5:1) [3, 4].

Although the clinical profile of Sr-89 for prostate or breast cancer patients has been widely described [3, 5–9], little information is available concerning patients with other malignant diseases. Here, we conducted a retrospective analysis to clarify the clinical profile of Sr-89 in patients with multiple bone metastases arising from various other cancers.

Patients and methods

Patients

Entry criteria were a pathologically proven malignancy, clinical presence of multiple bone metastases detected by bone scintigraphy, and adequate organ function.

Patients eligible for external-beam radiotherapy (RT) or surgery were basically excluded from Sr-89 candidates.

Written informed consent for treatment was obtained from all patients before the initiation of treatment. This study was approved by the Institutional Review Board of National Cancer Center Hospital, Japan.

Pretreatment evaluation

All patients underwent a complete blood count and serum chemistry testing at entry. Patients who fulfilled any of the following criteria were ineligible: (1) white blood cell count less than 2,000/mm^3; (2) platelet count less than 75,000/mm^3; (3) hemoglobin less than 9 g/dl; and (4) serum creatinine greater than 2.0 mg/dl or creatinine clearance less than 30 ml/min. All patients underwent bone scintigraphy before treatment. Information about pain and analgesic effect was obtained by physician interview in accordance with standard NRS practice.

Protocol treatment

Sr-89 chloride (Metastron) was given by single intravenous infusion at 2 MBq/kg over 2 min followed by a 20-ml saline flush. Premedication was not routinely performed.

Follow-up, response evaluation, and toxicity

Patients visited the outpatient clinic for a complete blood test and interview every 2 weeks from the initiation of treatment until 2 months after treatment. Self-reported outcome measures were used as response index, including pain diary data on a 0–10 numeric rating scale (NRS) [10, 11]. Complete response (CR) was defined as a minimum NRS of 10 % or less than that at the initiation of treatment, partial response (PR) as a minimum of 50 % or less than that at the initiation of treatment, and no response (NR) as a minimum NRS of equal to or greater than that at the initiation of treatment.

Toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Biweekly follow-up was continued until toxicities were easily manageable.

Statistical analysis

Survival curves were estimated using the Kaplan–Meier product-limits method with the log-rank test. Overall survival was calculated from the start of treatment to the date of death or last confirmed date of survival. Survival time was censored at the last confirmation date if the patient was alive. Univariate analysis was conducted using the log-rank test.

Results

Patient characteristics

Fifty-four consecutive patients with painful bone metastases were treated with Sr-89 chloride at the National Cancer Center Hospital East between March 2009 and July 2011. All patients were reviewed. Patient characteristics are listed in Table 1. Twenty-six patients (48 %) had breast or prostate cancer. Twenty-six (48 %) had received chemotherapy in the 6 months before the initiation of treatment, among whom the median interval between the last chemotherapy and protocol treatment was 87 days (range, 0–164). Thirty-one patients had received prior palliative radiotherapy for bone metastases.

Of the patients, 23 (43 %) had received bisphosphonate therapy before Sr-89 administration, and all these patients

Table 1 Patient characteristics

	Total	Breast/prostate	Other
Number of patients	54	26	28
Age, median (range) (years)	64 (34–89)		
Gender, male/female	25/29	12/14	13/15
PS, 0–1/2/3	22/23/9	14/9/3	8/14/6
Primary site			
Breast		15	
Prostate		11	
Lung			8
Head and neck			6
Colorectal			6
Other			8

PS performance status

Table 2 Toxicity

	Grade (CTCAE ver. 4.0)		
	3	4	% 3/4
Leucopenia	0	1	1.8
Neutropenia	0	1	1.8
Anemia	5	1	11.1
Thrombocytopenia	2	2	7.4

CTCAE common terminology criteria for adverse events

continued to receive bisphosphonates during and after Sr-89 administration. Sixteen (70 %) of the breast/prostate cancer patients received bisphosphonate therapy, although only 7 patients (25 %) of patients with other cancers received therapy.

Toxicity

Thirteen (24 %) patients experienced a transient increase in pain, which was classified as a flare-up response. Profiling of other nonhematological toxicities was hampered by the frequent use of additional supportive interventions during and after protocol treatment, including morphine or other medications. Hematological toxicity is summarized in Table 2. Grade 3–4 anemia was observed in 6 patients, 3 of whom required blood transfusion within 2 months after protocol treatment. One patient developed disseminated intravascular coagulation (DIC), which might have been related to either Sr-89 administration or primary disease progression or to both.

Efficacy

Two patients were excluded from response evaluation because of sudden death unrelated to the use of Sr-89

Fig. 1 Time to response (breast/prostate cancer vs. other). Time to response was calculated from the initiation of treatment to the day of pain relief (≥PR). Median time to response in breast/prostate cancer patients was 46 days (range, 13–217); that in other cancer patients was 31 days (range, 14–73). There was no significant difference between breast/prostate cancer patients and others

chloride. One patient with lung cancer died 7 days after Sr-89 administration. Hepatic failure caused by liver metastases was considered to be the main cause of death. Another patient with gastric cancer died 31 days after Sr-89 administration. At first visit after Sr-89, his performance status was 2. However, after the first visit, his condition was rapidly worsened by cachexia.

Overall response rate was 71.2 % and CR rate was 34.6 %. Median time to response was 36 days (range, 13–217 days). Median time to response in breast/prostate cancer patients was 46 days (range, 13–217), whereas that in other cancer patients was 31 days (range, 14–73) (Fig. 1).

Analgesic use at 2 months after treatment was decreased for only 11.5 % of patients. With a median follow-up period of 6.8 months, median survival time was 6.1 months and the 1-year overall survival rate was 28.0 %. Median survival time was significantly longer in patients with breast or prostate cancer than in those with other malignancies (Fig. 2).

Next treatment after Sr-89

After Sr-89 treatment, 9 patients received chemotherapy as a next treatment. The remaining 43 patients received best supportive care. Of those, 12 patients received palliative radiotherapy for bone metastases; median time from Sr-89 to next radiotherapy was 48 days (range, 13–252 days).

Predictive factors

Age, primary site (breast/prostate vs. others), history of chemotherapy, and onset of flare-up response were

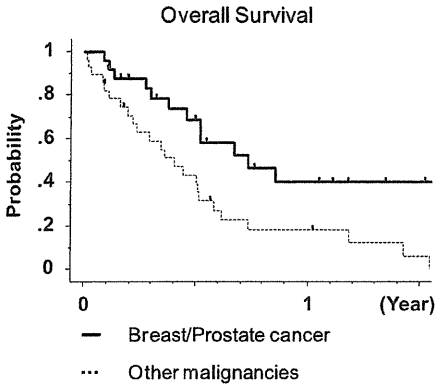

Fig. 2 Overall survival. Median survival time and 1-year survival rate were 8.0 months and 39.9 %, respectively, in patients with breast/prostate cancer, and 4.9 months and 17.9 % in those with other cancers. Overall survival was significantly longer in patients with breast/prostate cancer than in patients with other cancers ($p = 0.008$)

Table 3 Univariate analysis of predictive factors associated with response

	n	RR (%)	*P* value	HR (95 % CI)
Age (years)				1.01 (0.96–10.6)
Gender				
Male	23	73.9	0.70	0.78 (0.23–2.65)
Female	29	69		
Primary site				
Breast/prostate	26	72	0.76	1.21 (0.36–4.02)
Other	26	68.2		
Prior chemotherapy				
Yes	25	53.8	0.90	0.92 (0.28–3.07)
No	27	76.9		
Flare-up response				
Yes	13	53.8	0.12	2.86 (0.76–10.7)
No	39	76.9		

RR reponse rate, *HR* hazard ratio, *CI* confidence interval

investigated in univariate analysis (Table 3), but no significant predictive factor was identified.

Discussion

The clinical profile obtained in this study suggests that Sr-89 chloride may be of benefit in the treatment of painful bone metastases, not only in patients with breast and prostate cancer but also in those with various other malignancies.

Previous studies have identified hematological toxicity as one of the main side effects of Sr-89 chloride [6, 12, 13]. Hematological toxicities were present in the present study also but were of acceptable severity, albeit that the frequency of anemia was slightly higher than in previous reports. Further, the incidence of flare-up response was higher than with radiotherapy. Previous reports have shown similar results [6, 12], which appears to support the hypothesis that the incidence of flare-up response increases with increasing volume of bone metastases.

Among other findings, overall response rate was 71.2 % and CR rate was 34.6 %. Overall response rate was 69.2 % in breast and prostate cancer and 73.1 % in other cancers. These results showed that Sr-89 chloride had definite benefit in patients with painful bone metastases.

Our present results are of particular clinical valuable given the relative paucity of information about the clinical profile of Sr-89 chloride in cancers other than breast and prostate.

In this study, we used self-reported outcome measures as response index, including pain diary data on a 0–10 numeric rating scale (NRS). However, analgesic use was decreased for only 11.5 % of all patients at 2 months after treatment, and considerable discrepancy was seen between the results calculated by the diary and interview response indexes.

In clinical practice, analgesic use is seldom decreased even when the patient reports a decrease in bone pain. There are two major reasons for this: first, analgesics may also be required for other pain; and second, a decrease in analgesic use carries the risk that pain will recur. The recurrence of pain is a fatal outcome, particularly in patients receiving best supportive care. For these reasons, because a change in the amount of analgesics used does not reflect the response to Sr-89 chloride, we consider that this variable should not used as an index in clinical practice.

The predictive factors of response to Sr-89 are still controversial. Some investigators have found a better response in patients with good condition, and a poorer response with far-advanced metastatic disease [9, 14–16]. On the other hand, in some reports no significant difference was seen in patient background between responders and non-responders [17, 18].

In the present study, age, primary site (breast/prostate vs. other), history of chemotherapy, and onset of flare-up response were investigated in univariate analysis, but no significant predictive factor was identified.

The primary site of cancer and treatment history had no impact on the efficacy of Sr-89 chloride in univariate analysis, suggesting that Sr-89 chloride can be considered regardless of the primary site and treatment history.

Two major limitations of this study warrant mention. First, pain-free survival could not be evaluated because of the difficulty in conducting detailed and frequent interviews in patients receiving best supportive care. Second, the small scale and retrospective design of the study meant

that significant predictive factors of efficacy could not be adequately investigated.

Nevertheless, we consider that these results will be valuable for clinicians concerned with the difficult issue of bone pain control, particularly in view of the paucity of other data on this agent.

Conclusion

Sr-89 chloride may useful in the treatment of bone metastasis pain in patients with various malignancies, as it is in those with breast and prostate cancer.

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Conflict of interest We have no conflict of interest.

Ethical standard In the present study, written informed consent for treatment was obtained from all patients before the initiation of treatment. This study was approved in Institutional Review Board of National Cancer Center Hospital, Japan.

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鼻副鼻腔悪性腫瘍に対する陽子線治療

全田貞幹 秋元哲夫

要 旨

陽子線治療は，水素の原子核を加速したもので放射線治療の一種である。陽子線は体内に入っても表面近くではエネルギーを放出せず，停止する直前にエネルギーを放出して大きな線量を組織に与える性質（ブラッグ・ピーク）があり，病巣の深さや大きさに合わせてこのピークの深さや幅を拡げることにより精密な治療を実現できる。特に視神経や脳などの重要臓器が近接する鼻副鼻腔領域ではこの特性を最大限に生かすことが可能である。

当院ではこれまで鼻・副鼻腔腫瘍に対する陽子線治療の成績を組織型別，および進行度別（T4もしくはKadish C）で発表してきた。

嗅神経芽細胞腫では5年生存率93%，悪性黒色腫においても3年生存率58.0%，頭蓋内浸潤を伴う悪性腫瘍に対する治療成績も3年生存率59.3%と，他のモダリティーに対して遜色ないと考えられる。

一方晩期毒性に関する検討では1999年から2008年に当院で陽子線治療を行った鼻副鼻腔腫瘍の患者で1年以上の経過をfollowしている患者91名を対象に追跡を行ったところ追跡期間中央値57.5ヶ月（12.4～162.7）で，grade 3，4の毒性出現率はそれぞれ14.4%，6.6%であった。grade 2以上の毒性が発生するまでの期間は39.2ヶ月であった。視力低下grade 4を5例確認したが3例は4年以上経過してから発症していた。

毒性に関しては3年以上経過してから発症する例が多く，観察期間が短いと過小評価してしまう危険がある。既報や他のモダリティーとの比較をおこなう場合には観察期間を揃える必要があると考えられた。

今後新規治療の有用性を示すには自治療の特性に加え競合治療との比較検討が必須と考える。施設が限られランダム化試験が難しい背景を考慮し，質の高い多施設共同のコホート研究をはじめ各々の施設の協力関係を築くことが求められるだろう。

キーワード：鼻腔腫瘍，陽子線治療，晩期毒性

Proton beam therapy for nasal cavity and/or paranasal malignancies:

Sadamoto Zenda and Tetsuo Akimoto
Department of Radiation Oncology, National Cancer Center Hospital East

Summary

Proton beams are characterized by their rapid fall-off at the distal end of the Bragg peak and sharp lateral penumbra, depending on energy, depth, and delivery. These physical characteristics give proton beam therapy (PBT) a better dose distribution than X-ray irradiation, and PBT is now deemed a feasible and effective treatment modality that provides curative high-dose irradiation to the tumor volume without increasing normal tissue toxicity.

There are several published data about the outcomes of proton beam therapy for head and neck cancer from our institution. On the other hand, 91 patients who satisfied both criteria, definitive or postoperative PBT (> 50GyE) from January 1999 through December 2008, and more than 1 year follow-up, were traced to check the late toxicity. The median observation period was 57.5 months (range 12.4 ～ 162.7), and the median time to onset of Grade 2 or greater late toxicity except cataract was 39.2 months (range 2.7 ～ 99.8 months). Grade 4 visual loss occurred in 5 patients.

We consider that a relatively short observation period will result in the underestimation of late toxicity.

In the present study, we found many events which would not usually be encountered without long-term follow-up, and an adequate understanding of the toxicity profile of PBT in these patients thus requires long-term follow-up.

Key words：Proton beam therapy, Nasal cavity, Late toxicity

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国立がん研究センター東病院粒子線医学開発分野
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国立がん研究センター東病院粒子線医学開発分野
全田 貞幹

陽子線治療の特徴

陽子は水素の原子核で，それを加速したものを治療応用したものが陽子線治療である。

陽子線治療は，エネルギーを粒子が停止する直前に放出するブラッグピークという性質を有しており[1]，それをさらに腫瘍の位置や大きさに調整することのできる拡大ブラッグピークを利用して，照射したい場所のみに線量を投与し腫瘍に近接する重要臓器を遮蔽することが理論上ほかのモダリティーより容易に達成することができる。陽子線の相対的生物学効果比（RBE; Relative Biological Effect）は1.1とほぼX線やガンマ線と同じであり，同じ物理線量の陽子線を照射した時の生物への効果は臨床的に同程度で，多くの共通の性質を持っている。つまり，陽子線照射の治療効果や，副作用を考慮する場合に，広く行われているX線やガンマ線による照射の経験やデータを，そのまま生かすことができる利点がある。現在の技術では実臨床において，いびつな形状や広い範囲に均一に照射することが難しくなっており予防照射を必要とする領域に対して陽子線治療は不向きと言える。

上記の特徴を考慮すると陽子線治療が最適な場合は

1. 腫瘍と正常重要臓器が近接しており通常の放射線治療では対処が困難。
2. 転移の少ない腫瘍で局所治療の比重が高い。
3. 手術治療を行うことで患者さんに大きな不利益が生じる可能性がある。

これら3つの条件は揃うときと考えることができる。

そのひとつが鼻副鼻腔，頭蓋底腫瘍である。

鼻副鼻腔悪性腫瘍に対する陽子線治療の治療成績

当院ではこれまで鼻・副鼻腔腫瘍に対する陽子線治療の成績を組織型別，および進行度別（T4もしくはKadish C）で発表してきた。

嗅神経芽細胞腫では5年生存率93%，悪性黒色腫においても3年生存率58.0%，頭蓋内浸潤を伴う悪性腫瘍に対する治療成績も3年生存率59.3%と，他のモダリティーに対して遜色ないと考えられる（表1）。鼻腔腫瘍は腫瘍の反応が他の疾患に比べて非常に遅く，治療後6ヶ月以上経って形態が残存しているが，PET-CTなどの機能診断では陰性となるケースがよくある。当院でも長期追跡の結果4年後にやっと消失を確認した嗅神経芽細胞腫の例を経験しており，陽子線治療の効果では一般的なresponse rateよりも1年腫瘍制御率のほうがよりよいサロゲートマーカーになりうると考える[2]。

鼻副鼻腔悪性腫瘍に対する陽子線治療の長期追跡による晩期毒性について

冒頭で陽子線の相対的生物学効果比（RBE; Relative Biological Effect）は1.1とほぼX線やガンマ線と同じであり，X線やガンマ線による照射の経験やデータを，そのまま生かすことができる利点がある，と触れたがブラッグピークの性質を利用することで晩期合併症の頻度は著しく改善することが理論的に可能と考えられている。しかしながら長期の成績に言及した論文は数少ない。

今回我々は1999年から2008年までに当院で陽子線治療を行った頭頸部がん患者の中で以下の条件を満たす91例について追跡調査を行った。

1. 1年以上生存している。
2. 陽子線治療後1年以降に国立がん研究センター東病院で診療を受けている。

患者背景を（表2）に示す。

半数以上がT4であり，もっとも多い原発部位は鼻腔であった。

結果は全観察期間の中央値が59.7ヶ月で致命的な晩期毒性（CTCAEver.3.0でGr.4）は6例（6.6%）に見られ，そのうち5例が失明であった。Gr.2以上の晩期毒性が発生するまでの期間の中央値は39.7ヶ月（範囲：3.7-115）であり，5年以上経過して失明に至った症例を2例経験した，詳細を表3に示す。これらの結果から，追跡が長期であればあるほどイベント数は増加し最低3年の追駅がなければ毒性の半分も拾い出すことは難しいということがわかった。

結果の解釈についてだが，諸家の報告との比較が困難であることには2つの理由がある。

①晩期毒性評価する指標が各施設で統一されていない。

②追跡期間に差があり，短いものは晩期毒性を過小評価している可能性がある。

表1　当院における鼻副鼻腔腫瘍の治療成績

著者	発表年	対象	治療成績	
西村ら[6]	2007	嗅神経芽細胞腫	5年生存率	93%
全田ら[7]	2011	悪性黒色腫	3年生存率	59.30%
全田ら[2]	2011	頭蓋底腫瘍	3年生存率	58.00%

表2　晩期毒性追跡91例の患者背景

年齢（歳）		57（17～84）
性別	男/女	53/38
原発巣	鼻腔	63
	副鼻腔	26
	その他	2
T stage	1（Kadish A）	4
	2（Kadish B）	17
	3	8
	4（Kadish C）	55
	再発	7
治療スケジュール	65GyE/26fr	62
	60GyE/15fr	17
	＞65GyE	10
	50-60GyE	2

表 3　陽子線治療後に失明をきたした症例のサマリー

Stage	治療レジメン	発症までの期間	現在の状態
T4	65GyE/26fr	6年6ヶ月	10年5ヶ月無病生存
Kadish A	65GyE/26fr	6年2ヶ月	7年3ヶ月無病生存
T4	65GyE/26fr	4年2ヶ月	5年2ヶ月無病生存
T4	60GyE/15fr	4年2ヶ月	4年6ヶ月無病生存
T4	60GyE/15fr	1年5ヶ月	4年7ヶ月他病死亡

①に関しては近年国内にも粒子線施設が複数新設され，多施設共同研究の余地が出てきたと考えるため各施設間で評価方法を統一し，前向き観察研究を行うことで非常に有用な結果が得られるのではと期待している。

②に関しては粒子線治療が安全であるという実験データのバイアスもあり初期に出た未熟な短期成績が実験データを裏付けるものであるとして公表されるケースが散見される。

Schulzら[3]は，頭蓋底腫瘍に対する放射線治療の晩期毒性（Gr.3以上）の発生頻度を1.3%と報告しているがその観察期間は2年未満であった。またDebusら[4]は髄膜腫に対する放射線治療で発生する晩期毒性の発生頻度は2.1%と報告しており，その観察期間中央値は35ヶ月であった。一方Leeら[5]は頭蓋底腫瘍に対する外照射の晩期毒性が34.6%発生すると報告しておりその観察期間中央値は56ヶ月であった。このように追跡期間が長くなると晩期毒性のデータはより真実に近づき数値は悪い方に傾くため，Up-dated resultとして晩期毒性のデータを下方修正する施設は少ない。

今回我々は長期観察することで既存のpublished dataから一部修正を行っている。

今後粒子線治療が外科や腫瘍内科，他分野の研究者に広く認知されるためには良いデータも悪いデータもすべて公表し世間での評価を受けることができる体制づくりが必要であると考える。

結　語

鼻副鼻腔腫瘍に対する陽子線治療の効果と安全性および今後の粒子線治療の課題について述べた。今後新規治療の有用性を示すには自治療の特性に加え競合治療との比較検討が必須と考える。

施設が限られランダム化試験が難しい背景を考慮し，質の高い多施設共同のコホート研究をはじめ各々の施設の協力関係を築くことが求められるだろう。

著者のCOI：全田　貞幹
日本化薬株式会社：講演料
メルク・セローノ社：講演料
ブリストル・マイヤーズスクイブ社：講演料

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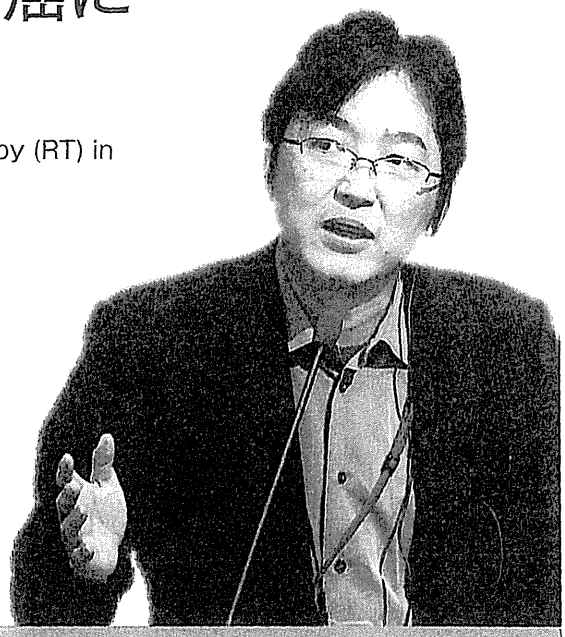
局所進行頭頸部扁平上皮癌に対する国内第Ⅱ相試験

Phase Ⅱ study of Cetuximab with Concomitant boost Therapy (RT) in Japanese Patients with LA-SCCHN.



国立がん研究センター東病院臨床開発センター粒子線医学開発部分野医員
全田 貞幹

Summary

頭頸部癌は全悪性腫瘍の5.2%を占め増加が予想される癌であり，そのほとんどが局所進行頭頸部扁平上皮癌（LA-SCCHN）である。LA-SCCHNに対する放射線療法にセツキシマブを併用することは，海外第Ⅲ相試験（Bonner試験）で放射線療法単独よりも優越していることが示されている。わが国でも日本人に対しての安全性・有効性を確認するための国内第Ⅱ相試験（EMR62241-053）を2009年3月から2010年1月に実施した。

試験概要

基本的にBonner試験とほぼ同じであり，LA-SCCHNの中・下咽頭癌，喉頭癌のStageⅢ/Ⅳの患者を対象としている。セツキシマブを1週目に400mg/m^{2}を投与し，その後，週に1回250mg/m^{2}を維持投与した。放射線療法は1週遅れてスタートし，定型照射法によるconcomitant boostのみで，72Gy/42fractionsの照射を行った（図）。

主要評価項目は，Bonner試験が出ているが治療コンプライアンスとして70%以上のrelative dose intensity（RDI）と放射線療法の完遂率をみた。副次評価項目は奏効率で放射線治療終了後8～12週の間にCTとMRIを撮影し，Response Evaluation Criteria in Solid Tumors（RECIST）評価を行った。また安全性に関しては，Common Terminology Criteria for Adverse Events（CTCAE）Ver.3.0によって評価した。

結　果

登録した27名のうち22名の患者が解析対象となり，うち21名が男性であった（表）。年齢中央値は海外に比べて年齢層が高い67歳である。原発部位は中咽頭の割合が海外よりやや少ないがHPV陽性・陰性にかかわらず喫煙者が多いという結果になった。セツキシマブの投与状況については，RDIが90%を超えたものがほとんどで，少しスキップしたものも80%以上をキープしており，ほぼ

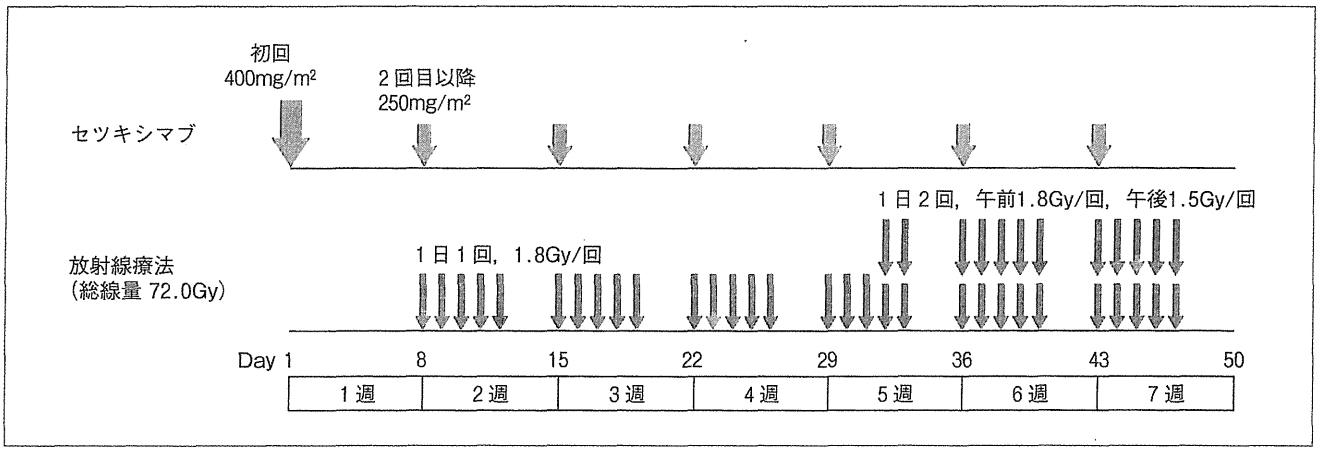


図 投与および照射スケジュール

（アービタックス®注射液100mg 適応追加，2012年12月）

表 患者背景

		全症例（ITT）（22例）
性別	男性	21（95.5%）
	女性	1（4.5%）
年齢（歳）	中央値（範囲）	67（53～81）
年齢区分	65歳未満	7（31.8%）
	65歳以上	15（68.2%）
KPS	90	8（36.4%）
	100	14（63.6%）
原発部位	中咽頭	6（27.3%）
	下咽頭	8（36.4%）
	喉頭	8（36.4%）

KPS：Karnofsy Performance Status

（アービタックス®注射液100mg 適応追加，2012年12月）

100%設定した基準を満たしていた。放射線療法については，毒性により長期の延期を要した患者はおらず，全例が72Gyを完遂した。

副次評価項目（放射線療法終了後8週目）の奏効率は81.8%であった。Bonner試験での放射線療法とセツキシマブの併用群の奏効率が73.5%であったことから，少なくとも日本のデータが劣っているわけではないことがわかる。

安全性についてはセツキシマブの特徴的な有害事象であるざ瘡様皮疹もしくは皮膚炎を呈したうち，3例に重篤な症状が出たが，治療の遅延に影響するほどではなかった。また，1例だけであったがinfusion related reactionがあり，おそらく国内では耳鼻咽喉科の先生が主に使用することを考えると，こういったinfusion reactionへの対応についても発信していく必要があると思われる。

まとめ

今回行った国内第II相試験は，22名のLA-SCCHNにおいて，放射線療法＋セツキシマブ併用療法のコンプライアンスは100%で，抗腫瘍効果の奏効率が80%を超えていた。副作用についても，日本人において特別な反応が起こるわけではないことがわかったため，今後は日本からも海外に情報を発信していくことが期待される。