esophageal cancer. The fluence of 75 J/cm^2 with a fluence rate of 160 mW/cm^2 in this phase II study was determined from the results of our preliminary experience.[8,14] The variable of total fluence depends on the lesion size. In this study, the range of esophageal surface areas that were treated was 3–9 cm^2, and multiple treatment fields were overlapped to cover large lesions. From the results of this study, the fluence of 75J/cm^2 is effective with tolerable toxicity for local failure after CRT. However, because of the risk of esophageal perforation, we should treat carefully if the lesion requires a large treatment field.

Salvage PDT provided an effective treatment for local failure at the primary site. To achieve CR by salvage PDT, early detection of local failure is critical. We reported previously that a submucosal tumor-like appearance is closely associated with local failure at the primary site.[21] Our previous report led us to believe that careful and close surveillance by endoscopy is needed to provide early detection of residual tumor at the primary site after completion of CRT. Although repeated endoscopic surveillance can be complicated, these efforts allow for early detection and provide a minimally invasive curative treatment with organ preservation.

In conclusion, salvage PDT is an effective and tolerable salvage treatment option for local failure after CRT for ESCC in patients whose failure lesion is limited to the submucosal layer without any metastasis.

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Int J Clin Oncol
DOI 10.1007/s10147-012-0385-9

ORIGINAL ARTICLE

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

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Received: 8 December 2011 / Accepted: 22 January 2012

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

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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].

Published online: 15 February 2012

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.

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

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.

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

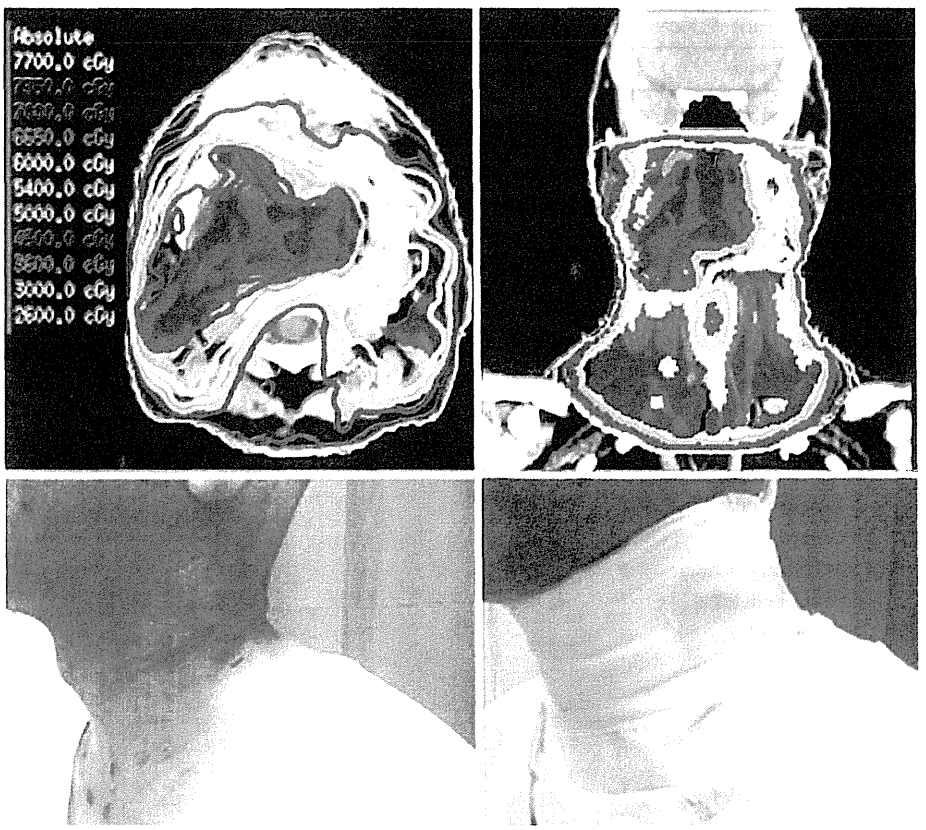

Fig. 1 Dermatitis Control Program Step 2. The case was a 44-year-old-male with T4N2cM0 oro-pharyngeal cancer. He was treated with induction chemotherapy followed by chemoradiotherapy. The irradiated area was covered with gauze and moistened with dimethyl isopropylazulene. It is very important that not 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

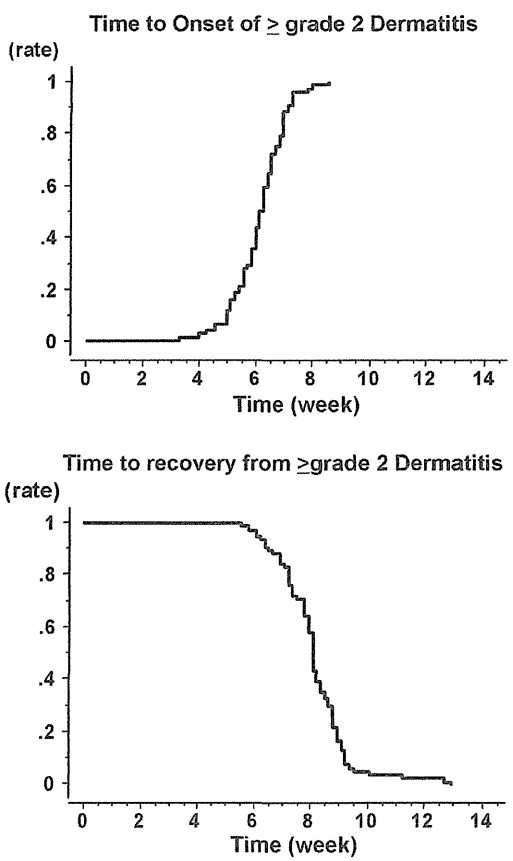

Fig. 2 Time to onset (upper) and recovery (lower) of > grade 2 dermatitis. Median time to onset of grade 2 dermatitis from the initiation of radiotherapy was 43.5 days (range 23–60 days), and median radiation dose at onset was 61.5 Gy (range 36–70 Gy). In several cases, dermatitis became worse after 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.

Acknowledgment This study was supported by the Foundation for Promotion of Cancer Research.

Conflict of interest There is no conflict of interest.

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Journal of Radiation Research, 2012, 53, 704–709
doi: 10.1093/jrr/rrs021 Advance Access Publication 10 July 2012

Impact of early radiological response evaluation on radiotherapeutic outcomes in the patients with nasal cavity and paranasal sinus malignancies

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(Received 13 January 2012; revised 28 March 2012; accepted 6 April 2012)

We analyzed the correlation between primary tumor response within 6 months after radiation therapy (RT) including proton beam therapy (PBT) and progression free survival rate (PFS) in patients with nasal cavity and paranasal sinus malignancies to clarify the impact of early radiological evaluation of treatment response on prognosis. Sixty-five patients treated between January 1998 and December 2008, and whose follow-up duration was more than 2 years were included. The *Response Evaluation Criteria in Solid Tumors* (version 1.1) was used for the evaluation of treatment. Median age was 59 years (range 21–83 years). Olfactory neuroblastoma ($n = 20$, 30%) and squamous cell carcinoma ($n = 15$, 23%) were the major pathological tumor types. The median follow-up duration was 51.6 months. Radiological response evaluation within 6 months after treatment demonstrated that 15% of the patients achieved complete response (CR), and 3-year progression free survival rates of all patients was 49.2%. The 3-year PFS rates according to response for the treatment were 55.6% in the patients with CR and 46.4% in those with non-CR, respectively ($P = 0.643$). However, the 3-year PFS rates were 80.% in the patients with CR and 10.% in those with non-CR ($P = 0.051$) in the patients with squamous cell carcinoma (SCC) histology. Radiological response evaluation within 6 months did not have a significant impact on prognosis when analysis included all histology, although early radiological response within 6 months after RT had a borderline significant impact on treatment outcomes for the patients with nasal and paranasal SCC.

Keywords: response evaluation; nasal cavity; paranasal sinuses; radiation therapy; proton beam therapy

INTRODUCTION

Malignancies of the nasal cavity and paranasal sinuses are extremely rare, representing only 3–5% of all head and neck cancer and less than 1% of all malignancies [1–5]. Most cases are curatively treated by craniofacial surgery and post-operative radiation therapy, either alone or in combination [1–4, 6]. However, several problems with these treatment strategies remain. In cases where the disease has spread deeply into the intracranial region, surgical approaches are often complicated by the risk of serious functional deformity and a lack of satisfactory surgical clearance [7, 8]. Therefore, definitive radiation therapies (RTs) including 3D-conformal radiation therapy (3DCRT) or intensity modulated radiation

therapy (IMRT) and proton beam therapy (PBT) are often performed as an alternative treatment [2, 4, 9].

Generally, total tumor eradication is a fundamental efficacy measure for treatments and is often considered a surrogate for overall survival in the case of non-surgical approaches [10, 11]. However, Zenda *et al.* reported that patients with nasal or paranasal malignancies occasionally survive for long periods without complete response at the primary tumor site [9]. To our knowledge, however, there have been few reports that have examined response evaluation for nasal or paranasal sinus malignancies after non-surgical approaches. Here, we conducted a retrospective analysis examining the correlation between radiological tumor response and prognosis in patients with malignancies of the nasal cavity and paranasal sinuses to clarify the impact of early radiological evaluation of treatment response on prognosis.

MATERIALS AND METHODS

Patients

Patients fulfilling the following criteria were included: (i) malignancies of the nasal cavity or paranasal sinuses, (ii) received RT including PBT as a curative setting at the National Cancer Center Hospital East (NCCHE) between January 1998 and December 2008 and (iii) had sufficient radiographic information, such as that obtained by magnetic resonance imaging (MRI) and computed tomography (CT) for response evaluation.

Pretreatment evaluation

Pretreatment evaluation included a physical examination, a direct flexible fiberoptic endoscopic examination, MRI and CT.

Tumor staging in the present study was based on sections of the nasal cavity and paranasal sinuses in the TNM classification of the Union for International Cancer Control (UICC; 7th edition), regardless of histology type. For olfactory neuroblastoma (ONB), a system devised by Kadish *et al.* [12], which is based on anatomic extension, was used. During the preparation of this article, Kadish A, B, and C ONB were reclassified as T1, T2 and T4. Radiologists, head and neck surgeons, and medical oncologists at our institution reviewed radiological evaluation for tumor staging.

Radiation therapy

Proton beam therapy (PBT)

We used a 3D CT planning system to prepare the treatment planning. In this system, the proton beam was generated with a Cyclotron C235 (Sumitomo Heavy Industries, Ltd, Tokyo, Japan) with an energy of 235 MeV. Based on our preclinical experiments, relative biological effectiveness was defined as 1.1. Dose distribution was optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Conventional radiation therapy

All photon beam RT was delivered using 6-MV X-rays and either 3D conformal techniques or IMRT, depending on the year of treatment and adjacent organs at risk.

Irradiation field

In general, primary tumors and metastatic lymph nodes were included in the irradiated field. Elective nodal irradiation was not performed. Gross tumor volume (GTV) was determined by pretreatment assessment with any or all of CT, MRI and Positron Emission Tomography-CT (PET-CT). Clinical target volume (CTV) was defined as the GTV plus a 5-mm margin and the sinuses adjacent to the GTV. In cases involving brain invasion, the area of T2 prolongation on MRI was also included in the CTV. Planning target volume (PTV) was basically defined as the CTV plus a 3-mm margin for PBT and a 5–7-mm margin for RT, but was finely adjusted where necessary in consideration of organs at risk.

Imaging analysis

Response to treatment at the primary site was evaluated using the *Response Evaluation Criteria in Solid Tumors* (RECIST 1.1) [13]. Radiological response evaluation was carried out using CT/MRI performed within 6 months after treatment. At least two radiologists determined radiological evaluations for treatment response. In response evaluations within 6 months, patients who had achieved complete disappearance of all target lesions were defined as CR, while the remaining patients were classified as non-CR patients. Overall survival (OS) 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. Progression-free survival (PFS) was defined as from the day of initiation of treatment to the first day of confirmation of progressive disease or death by any cause.

Statistical analysis

The close-out date for survival analysis was 31 December 2010. Data were analyzed using StatView statistical software (Version 5.0, SAS Institute, Cary, NC, USA). Cumulative survival and tumor control rates were calculated using the Kaplan–Meier product-limit method. Survival curves were estimated using the Kaplan–Meier product-limits method with the log-rank test. P values of <0.05 were considered statistically significant.

RESULTS

Patient and treatment characteristics

A total of 75 patients with malignancies of nasal or paranasal sinuses were treated with RT including PBT at the

NCCHE between January 1998 and December 2008. Sixty-five patients met the inclusion criteria and were retrospectively analyzed in our study. Patient characteristics are listed in Table 1. The median age was 59 years (range, 21–83 years), with 39 male and 26 female patients. Most of the patients had T4 tumors ($n = 53$), and the majority of patients presented with a tumor of the nasal cavity ($n = 43$). Six patients presented with cervical lymph node metastasis at the time of diagnosis.

Medical records and pathological reports were reviewed to assess the histological examination results. ONB was the major histological type ($n = 20$), followed by squamous cell carcinoma (SCC, $n = 15$), melanoma ($n = 9$), adenoid cystic carcinoma (ACC, $n = 9$), undifferentiated carcinoma ($n = 6$), and others ($n = 6$) (Table 1).

RT was given to 13 patients. Three of the 13 patients received IMRT and the remaining 10 patients were administered 3DCRT. Median doses were 66 Gy (range, 66–70 Gy). Fifty-two patients received PBT, with median doses of 65 GyE (range, 60–70 GyE). A total of six patients had clinically positive cervical lymph nodes at the beginning of treatment. Three of six patients underwent a neck dissection and the remaining three patients received complete neck irradiation in the definitive setting.

Systemic chemotherapy

As the present data was compiled over a 10-year period, several treatment methods were used in our study. A total of 31 patients received chemotherapy in addition to radiation therapy. The chemotherapy regimens are listed in Table 2.

Treatment outcomes

Median interval between the end of treatment and radiological response evaluation was 9.5 weeks (range, 2–27 weeks). In the radiological response evaluation within 6 months, CR was achieved in 10 (15%) of the 65 patients. With a median follow-up period of 51.6 months (range, 25–125 months), the 3-year PFS and OS rates of all patients were 44.2% and 72.1%, respectively (Fig. 1). Loco-regional

Table 1. Patient characteristics (N = 65)

Characteristic		N
Age (range)		59 yrs (21-83 yrs)
Gender (male/female)		39/26
Primary site	Nasal cavity	43
	Ethmoidal sinus	11
	Maxillary sinus	5
	Sphenoid sinus	4
	Other site	2
Tumor type	ONB	20
	SCC	15
	ACC	9
	Melanoma	9
	Undifferentiated	6
	Others	6
T stage	T1 (Kadish A)	1
	T2 (Kadish B)	7
	T3	4
	T4 (Kadish C)	53
N stage	N0	59
	N1	3
	N2	3

Abbreviations: ACC, adenoid cystic carcinoma; ONB, olfactory neuroblastoma; SCC, squamous cell carcinoma; Undif, undifferentiated carcinoma

Table 2. Treatment methods and radiation schedules

Treatment			N
Chemotherapy	IC regimen	DOC + CDDP + TS-1	12
		CDDP + 5-FU	1
		CDDP + VP-16(+ADM)	2
		DOC + CPT-11	6
		none	44
	CRT regimen	CDDP	15
		CDDP + 5-FU	4
		5-FU	1
		DOC + CPT-11	1
		none	44
Radiotherapy	Modality	Proton	52
		Photon	12
		Electron	1
	RT dose schedule	60 GyE/15 fr	7
		65GyE/26fr	41
		66 GyE/33 fr	8
		70 GyE/28 fr	1
		70 Gy/33 fr	1
		70 GyE/35 fr	7

Abbreviations: ADM, doxorubicin; CPT-11, irinotecan; CRT, chemoradiotherapy; CDDP, cisplatin; DOC, docetaxel; 5-FU, 5-fluorouracil; IC, induction chemotherapy; TS-1, tegafur-gimeracil-oteracil; VP-16, etoposide

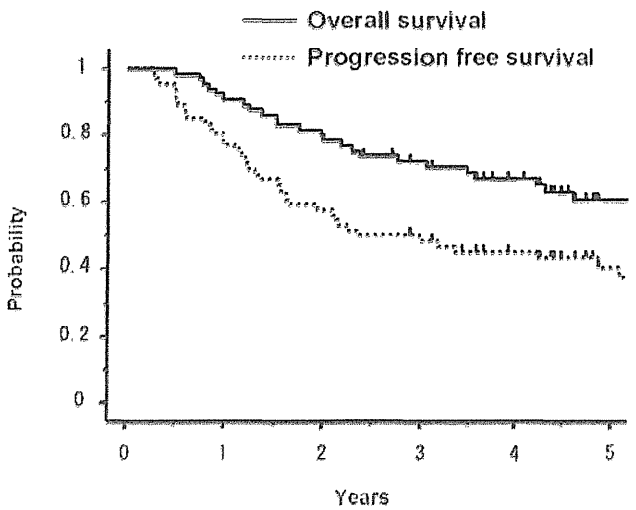

Fig. 1. PFS and OS curves of all patients. With a median follow-up period of 51.6 months, the 3-year PFS and OS rates of all patients were 44.2% and 72.1%, respectively.

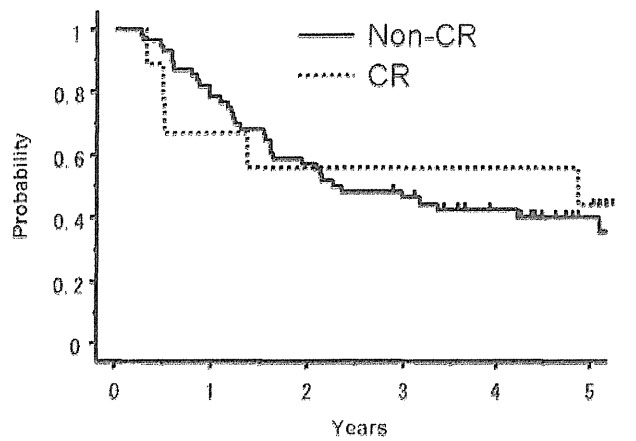

Fig. 2. PFS curves of all patients based on the results of radiological response evaluation within 6 months. The 3-year PFS rate was 55.6% in the patients whose response was CR and that of those whose response was non-CR was 46.4%, respectively ($P = 0.643$).

progression was observed in 52.3% of patients and distant metastasis was developed in 12.3% of patients. In the patients who achieved CR, the 3-year PFS rate was 55.6% and that of those whose responses were non-CR was 46.4%, respectively, which did not represent a statistically significant difference ($P = 0.643$) (Fig. 2).

In the patients whose histology was SCC, the 3-year PFS rate was 80.0% in the patients who achieved CR ($n = 6$) and 10.0% in those whose responses were non-CR ($n = 9$). The difference between patients with CR and those with non-CR was borderline significant ($n = 0.051$) (Fig. 3).

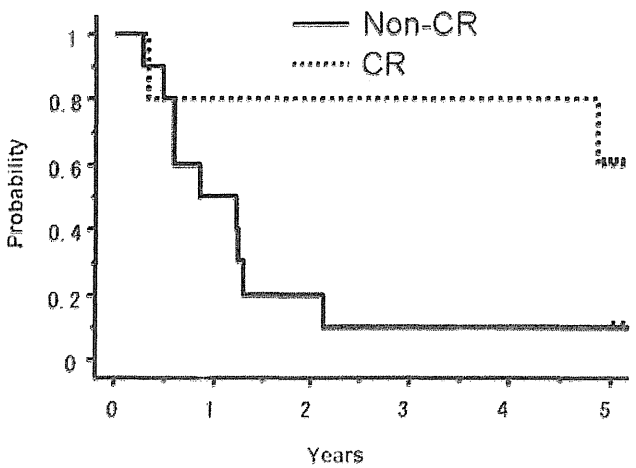

Fig. 3. PFS curves of the patients whose histology was SCC based on the results of radiological response evaluation within 6 months. The 3-year PFS rate was 80.0% in the patients who achieved CR and 10.0% in those whose responses were non-CR. The difference between patients with CR and those with non-CR was borderline significant ($P = 0.051$).

DISCUSSION

In the present retrospective study, we demonstrated that radiological response evaluation within 6 months after radiation therapy with or without chemotherapy in patients with malignancies of the nasal cavity or paranasal sinuses did not have a significant impact on prognosis such as PFS when we analyzed all patients included whose histologies were SCC and non-SCC. However, the results of this study demonstrated that the difference in the 3-year PFS of the SCC patients between those with CR and those with non-CR was borderline significant (80% vs 10%). This raised the possibility that early radiological response might serve as a surrogate for treatment outcomes (PFS) especially in patients with SCC histology.

The optimal treatment of malignancies in the nasal cavity and paranasal sinuses is controversial. Existence of risk organs such as brain nerves and extension to skull base often makes it difficult to remove tumors totally, indicating that RT would be an effective approach for nasal cavity and paranasal sinus malignancies. The 5-year OS rate after RT with or without surgery ranged from 15% to 55% [1–6]. Regarding the clinical outcomes after PBT, several studies including a study from our institution demonstrated that 5-year OS ranged from 70–80%, although the histological types of patients analyzed were not homogenous. These results indicated that clinical outcomes were slightly better than those after conventional radiation therapy [9, 14, 15, 16]. The main advantages of radiation therapy for nasal cavity and paranasal malignancies are to preserve organs and their functions by delivering enough total dose to the tumors while sparing excessive doses to the adjacent

critical normal structures such as the brain, brainstem and the optic structures. Among radiotherapeutic approaches, PBT can provide higher doses to tumors compared with 3DCRT or IMRT because of the unique physical properties of PBT. The physical properties of protons are rapid fall-off at the distal end of the Bragg peak and sharp lateral penumbra, depending on energy, depth and delivery [6, 15, 16].

The objective evaluation of tumor shrinkage is often considered a surrogate for survival [10, 17]. In esophageal cancer, endoscopic findings 4 or 6 weeks after concurrent chemoradiotherapy or RT alone have been used as a surrogate for survival [18, 19], while disease control rate and CR/partial response (PR) 8 weeks after registration are associated with longer survival in advanced non-small-cell lung cancer [17]. Initial loco-regional response is also important in radiotherapeutic outcomes of patients with head and neck SCC. However, the treatment response of nasal cavity or paranasal sinus malignancies, with the exception of SCC, appears to differ from those of other malignancies. The results of this study indicate that salvage treatment should be carefully considered in patients whose histologies are non-SCC, even if the patient does not achieve CR at the time of radiological response evaluation within 6 months. This raises the possibility that radiological response evaluation within 6 months after radiation therapy might not be optimal, especially in patients whose histologies are non-SCC, e.g. ONB, ACC or melanoma. However, early radiological response in patients whose histology was SCC would be important, similar to other SCCs of the head and neck cancer, such as hypopharyngeal cancer. There are a few reports regarding the optimal timing of radiological evaluation using CT or MRI after radiotherapy. Hermans *et al.* suggested using follow-up CT at 8–12 weeks after completion of radiotherapy with larynx and hypo pharynx [20]. In addition, response evaluation at eight weeks after the completion of treatment was often adopted in clinical trials for head and neck cancer [21, 22]. This might suggest that the optimal timing of radiological response evaluation in patients with nasal and paranasal sinus malignancies appears to be different according to the histological type, although the number of patients analyzed in this study is still not enough to draw a definite conclusion. There is a limit to the ability of morphological images, such as CT or MRI, to evaluate tumor shrinkage after radiotherapy of the nasal cavity or paranasal sinus malignancies without SCC; it is necessary to evaluate with dynamic images such as PET-CT.

Recently, there have been many studies that have demonstrated the clinical usefulness of new imaging modalities, particularly PET-CT in response evaluation for RT with or without chemotherapy [17, 23]. In our clinical practice, the changes in positivity of PET-CT before and after RT provided helpful information regarding the decisions for salvage treatment. In the present study, however, we could not evaluate local response using PET-CT in addition to CT and MRI, because PET-CT before and after treatment was only available in a limited number of patients. Hence, investigation regarding the clinical usefulness of PET-CT including other new imaging modalities in response evaluation for nasal and paranasal malignancies other than SCC is warranted in future prospective trials.

Limitations of our study are as follows. First, the number of patients according to histological type was small, resulting in insufficient statistical differences between each group, and second, the optimal response evaluation of lymph nodes metastases could not be sufficiently discussed.

In conclusion, the results of this study demonstrated that radiological response evaluation within 6 months did not provide significant impact on prognosis when analysis included all histology such as ONB, although early radiological response within 6 months after radiation therapy had a borderline significant impact on treatment outcomes (PFS) for nasal and paranasal malignancies in patients with SCC histology. Hence, further study is warranted to ensure the impact of histological type on the outcomes of early radiological response evaluation.

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Jpn J Clin Oncol 2012;42(8)691–696
doi:10.1093/jjco/hys096
Advance Access Publication 3 July 2012

Induction Chemotherapy with Docetaxel, Cisplatin and S-1 Followed by Proton Beam Therapy Concurrent with Cisplatin in Patients with T4b Nasal and Sinonasal Malignancies

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Received February 11, 2012; accepted May 29, 2012

Objective: For the treatment of patients with T4b nasal and sinonasal malignancies, definitive chemoradiotherapy was contraindicated due to the risk of brain damage and blindness. However, combination chemotherapy with docetaxel, cisplatin and S-1 is well tolerated and effective. We conducted a retrospective analysis to evaluate the efficacy and feasibility of induction chemotherapy using docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin.

Methods: Thirteen patients treated with docetaxel, cisplatin and S-1 were analyzed. Docetaxel, cisplatin and S-1 consisted of 60–70 mg/m^2/day docetaxel on day 1, 70 mg/m^2/day cisplatin on day 1 and 60–80 mg/m^2/day S-1 on days 1–14. Treatment was repeated every 3–4 weeks with a maximum number of three treatment cycles. According to the response to docetaxel, cisplatin and S-1, patients received either proton beam therapy concurrent with 20 mg/m^2/day cisplatin on days 1–4 every 3 weeks or proton beam therapy alone.

Results: Neutropenia represented the most common Grade 3/4 hematological toxicity (76.9%), while the most frequently observed non-hematological toxicity was nausea (23.0%). After the completion of docetaxel, cisplatin and S-1, the overall response rate was 38.4% (5 of 13), with 1 patient achieving complete response and 4 patients achieving partial response. Subsequently, 10 patients received proton beam therapy concurrent with cisplatin, 2 received proton beam therapy alone and 1 received palliative radiation. No severe toxicity was observed during proton beam therapy. After the completion of proton beam therapy, 11 patients (84.6%) achieved complete response and no brain damage or blindness occurred.

Conclusions: Induction chemotherapy with docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin is well tolerated and displays promising antitumor activity that warrants further investigation.

Key words: nasal – sinonasal – induction chemotherapy – proton – head and neck

INTRODUCTION

Nasal and sinonasal malignancies are rare, representing only 3–5% of all head and neck cancers (HNC) (1,2). Although a variety of malignancies arise in this region, squamous cell carcinoma is most frequent, followed by adenocarcinoma and adenoid cystic carcinoma (3). As the nasal and sinonasal regions have limited anatomical access and permit the asymptomatic growth of malignancies, most patients first realize symptoms when tumors reach a large size or invade the surrounding normal critical organs, and are often initially diagnosed with unresectable disease (4). These patients are not candidates for gross total resection and are typically treated with either definitive radiotherapy or concurrent chemoradiotherapy. However, due to the proximity of critical organs to malignancies in the nasal and sinonasal sinuses, 15–30% of the patients develop radiation-induced serious complications, including brain necrosis, hearing loss, meningitis, unilateral or bilateral blindness, optic neuritis, cataracts, osteoradionecrosis and central nervous system damage (5–7). Despite the use of radiotherapy with or without chemotherapy, outcomes are often poor in these patients due to the high occurrence of local relapse, as reflected in the reported 5-year overall survival (OS) rate of only 15% (8).

To reduce radiation-induced toxicity and improve treatment outcomes for locally advanced nasal and sinonasal malignancies, we previously evaluated two treatment strategies involving induction chemotherapy (IC) and proton beam therapy (PBT) (9). In the first approach, we demonstrated that IC led to reduced tumor sizes and avoided brain damage and ocular/visual toxicity that often results from radiotherapy (9). We also examined IC with irinotecan plus docetaxel (ID) for olfactory neuroblastoma, but the relatively poor treatment outcomes suggested that ID was not a suitable approach (9). We subsequently performed a Phase I clinical study of IC with docetaxel, cisplatin and S-1 (TPS) and found that this treatment was well tolerated, feasible and showed a good antitumor activity with locally advanced HNC, which included several nasal and sinonasal malignancies (10). As the response rate to TPS was 70%, IC combined with TPS appears to be a superior approach than IC with ID.

In addition to IC, we have also evaluated the use of PBT for the treatment of nasal and sinonasal malignancies (11,12). PBT was anticipated to improve tumor local control probability and decrease acute and late toxicities of the surrounding normal tissue (13–15). A previous retrospective analysis of 14 patients with olfactory neuroblastoma from our institute who were treated with PBT displayed excellent local control and survival outcomes without serious adverse effects, suggesting that PBT allows the delivery of tumoricidal doses with minimal complications (11).

Here, we conducted a retrospective analysis to evaluate the efficacy and feasibility of IC with TPS followed by PBT concurrent with cisplatin for the treatment of T4b nasal and sinonasal malignancies.

PATIENTS AND METHODS

Patients

We reviewed the case records of 13 patients who were treated for T4b nasal and sinonasal malignancies at the 'Search' between January 2006 and March 2012. Tumor staging in the present study was evaluated based on sections of the nasal cavity and sinonasal sinuses using the TNM classification of the UICC 6th edition, regardless of the histology type.

Treatment Plan

Induction Chemotherapy

Patients received three cycles of TPS chemotherapy followed by PBT concurrent with cisplatin. The chemotherapy regimen consisted of a 1 h infusion of docetaxel at 60–70 mg/m^2/day on day 1, a 2 h infusion of cisplatin at 70 mg/m^2/day on day 1 and S-1 twice daily on days 1–14 at 60–80 mg/m^2/day. The treatment was repeated every 3–4 weeks with a maximum number of three treatment cycles. Ciprofloxacin was administered as a prophylactic on days 5–15.

Chemotherapy Concurrent with PBT

After the completion of TPS, patients received PBT concurrent with cisplatin, which was administered at 20 mg/m^2 daily for 4 days. The treatment was repeated every 3 weeks with a maximum of three treatment cycles. The total dose of PBT was 65 cobalt Gray equivalents (GyE) for 4–5 fractions per week in 2.5 GyE once-daily fractions.

PBT planning was performed using a three-dimensional computed tomography (CT) planning system. In this system, the proton beam was generated using a Cyclotron C235 with an energy of 235 MeV at the exit. Relative biologic effectiveness was defined as 1.1, based on our preclinical experiments (16). Dose distribution was optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Gross tumor volume (GTV) was determined by examination using CT, magnetic resonance imaging (MRI) and/or positron emission tomography-CT. Clinical target volume (CTV) was defined as the GTV plus a 5 mm margin and the sinuses adjacent to the GTV. In cases of tumor invasion into the brain, the area of T2 prolongation on MRI was also included in the CTV. Planning target volume (PTV) was basically defined as the CTV plus a 3 mm margin, but was finely adjusted where necessary in consideration of organs at risk. Beam energies and spread-out Bragg peaks were fine-tuned such that the PTV was minimally covered by a 90% isodose volume of the prescribed dosage. The irradiated dose was minimized by the delivery of the proton beam with two or three beam arrangements.

Elected nodal irradiation was not planned because of the low incidence of lymph node metastases in these diseases.

Evaluations

Pretreatment evaluation consisted of complete history and physical examinations, complete blood counts, liver function tests, chest X-rays and ECGs. All patients were imaged with CT and MRI scans of the head and neck. Bone scans and CT scans of the abdomen or chest were performed when clinically indicated. Treatment responses were assessed radiographically according to RECIST 1.0 criteria after the third cycle of chemotherapy and on the completion of chemoradiotherapy. The National Cancer Institute Common Toxicity Criteria (version 3.0) was used to describe chemotherapy- and chemoradiation-related toxicities.

Statistical Methods

The follow-up time for each patient was calculated as the time from the start of treatment to 31 March 2012. A survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on an intention-to-treat population, defined as all patients enrolled in the study who received at least one dose of chemotherapy. Progression-free survival (PFS) was calculated from the date of the first administration of chemotherapy to the first documentation of disease progression, subsequent therapy or death. OS was determined from the date of the first administration of chemotherapy to the date of death or the last confirmation of survival. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc. Chicago, IL, USA).

RESULTS

Patient Characteristics

The clinical and disease characteristics of the 13 patients with histologically proven tumors examined in this retrospective analysis are summarized in Table 1. The median patient age was 47 years (range, 28–60 years). The primary tumor sites involved the nasal cavity (9 of 13) and ethmoid sinus (4 of 13). The leading histology was olfactory neuroblastoma. No patients had clinical or pathologic evidence of neck disease at the time of initial treatment.

Nine patients (69%) completed the three cycles of planned IC. Three patients who were refractory to IC did not receive the third cycle of IC, while one patient received only one cycle due to disease progression. Ten patients received PBT concurrent with cisplatin and two patients received PBT alone, while the patient who experienced disease progression during IC received palliative radiotherapy.

Adverse Events

The acute toxicities experienced during the TPS treatment are listed in Table 2. Although 10 patients (76.9%) experienced Grade 3 or 4 neutropenia and 3 patients (23.0%) experienced Grade 3 nausea, toxicity was as expected and manageable.

Acute toxicity scores of chemoradiotherapy are summarized in Table 3. Two patients (16.6%) experienced Grade 3 mucositis, which developed on the hard palate and to a lesser degree on the cheek and pharynx. Interference with

Table 1. Patient characteristics

Characteristic	No. of patients ($n = 13$)
Age (years)	
Median	47
Range	28–60
Sex	
Male	9
Female	4
ECOG performance score	
0	13
Site of primary tumor	
Nasal cavity	9
Ethmoid sinus	4
Histology	
Olfactory neuroblastoma	7
Squamous cell carcinoma	3
Adenocarcinoma	1
Undifferentiated carcinoma	1
Small cell carcinoma	1

Table 2. Toxicities experienced during induction chemotherapy

Toxicity	No. of patients ($n = 13$)				Percent Grade 3–4
	Grade				
	1	2	3	4	
Hematological toxicity					
Leukopenia	1	7	5	0	38.4
Neutropenia	0	2	4	6	76.9
Febrile neutropenia	0	0	0	0	0
Anemia	8	5	0	0	0
Thrombocytopenia	5	2	0	0	0
Non-hematological toxicity					
Nausea	6	2	3	0	23.0
Vomiting	2	4	0	0	0
Anorexia	7	6	0	0	0
Mucositis	2	0	0	0	0
Diarrhea	2	0	0	0	0

Table 3. Toxicities experienced during proton beam therapy

Toxicity	No. of patients ($n = 12$)				Percent Grade 3–4
	Grade				
	1	2	3	4	
Hematological toxicity					
Leukopenia	9	3	0	0	0
Neutropenia	0	1	0	0	0
Febrile neutropenia	0	0	0	0	0
Anemia	8	4	0	0	0
Thrombocytopenia	5	0	0	0	0
Non-hematological toxicity					
Mucositis	0	1	2	0	16.6
Anorexia	4	5	0	0	0
Nausea	4	3	0	0	0
Vomiting	2	0	0	0	0
Infection	0	0	0	0	0

nutrition was minor, and no patients required a feeding tube. No brain damage or blindness was recorded. In addition, late toxicities were not observed at the time of March 2012.

Treatment Outcomes

Efficacy data for the TPS therapy are listed in Table 4. All patients enrolled in the present study were assessable for a response to TPS. Objective response rate (ORR) was documented in five patients (38.4%), including one patient with complete response (CR) and four with partial responses (PRs) after the IC of TPS (Figs 1 and 2). After the completion of chemoradiotherapy, ORR was documented in 12 patients (92.3%), including 11 with CR and 1 with PR. Each ORR to TPS according to the histology was 14.2% for patients with olfactory neuroblastoma, 33.3% for patients with squamous cell carcinoma and 100% for patients with others.

The median follow-up time was 56.5 months (range, 0.6–63.5months), and the 5-year PFS and OS were 33.8 and 75.5%, respectively. Eight of the 13 patients were alive at the time of this report with no evidence of disease, while 2 patients were alive with disease. Two patients died due to local disease progression and one died as a result of distant metastasis.

Local relapse developed in three patients. The median time to local relapse was 14.4 months (range, 0.3–25.1 months). Relapses occurred within the irradiated region in two patients and on the margin of the irradiated region in one patient. Of the three patients with local relapses, two subsequently died of their disease, while one patient is presently alive with disease and continue to receive chemotherapy. Regional relapse developed in four patients; two of

Table 4. Treatment outcomes

CR	PR	SD	PD	RR (%)	95% CI
Induction chemotherapy ($n = 13$)					
1	4	7	1	38.4	17.7–64.4
IC → PBT with cisplatin[a] or palliative RT					
11	1	0	1	92.3	66.6–98.6

CR, complete response; PR, partial response; PD, progression disease; RR, response rate; SD, stable disease.
[a]Two patients did not receive cisplatin due to refractory disease following TPS.

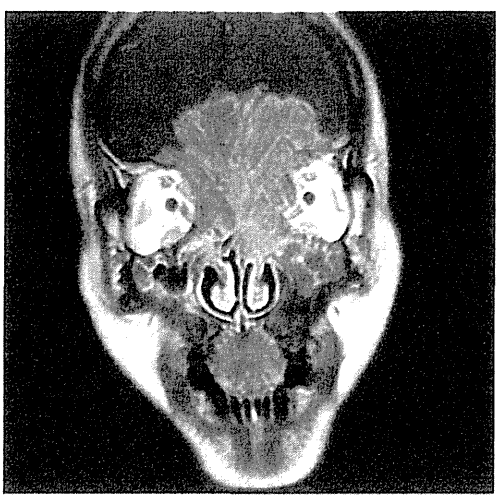

Figure 1. Coronal magnetic resonance imaging (MRI) of a patient with a T4b squamous cell carcinoma in the nasal cavity, with invasion of the orbit and intracranial extension.

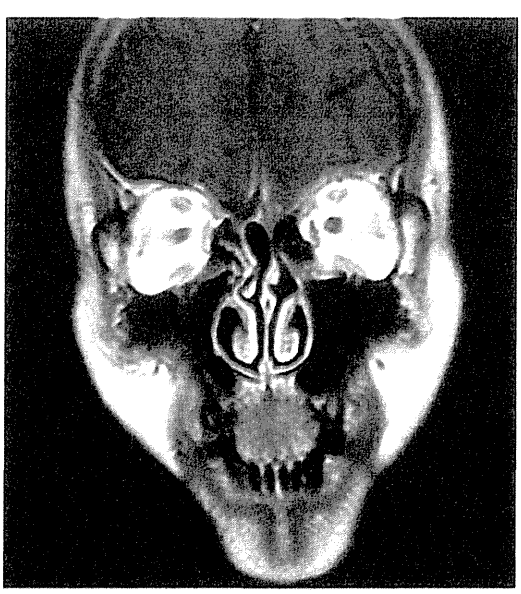

Figure 2. The MRI was repeated after three cycles of docetaxel, cisplatin and S-1, demonstrating a complete response.

these patients are presently alive with disease, while two patients who underwent elective neck dissection are alive with no relapse. Finally, one patient developed distant metastasis to meninges 9.1 months after the start of treatment and was dead with disease.

DISCUSSION

In the present retrospective study, we evaluated the efficacy of IC using TPS followed by PBT concurrent with cisplatin. Of the 10 patients who received PBT concurrent with cisplatin, 9 patients (90%) achieved CR, and the 5-year OS rate was 77.7%, with no brain damage or blindness recorded. Our study suggests that IC with TPS followed by PBT concurrent with cisplatin is well tolerated and displays reducing complication and promising antitumor activity.

The efficacy of chemotherapy for nasal and sinonasal malignancies is unclear (5), as it is generally used for palliative treatment of advanced or recurrent disease. However, favorable responses obtained with various chemotherapeutic regimens have prompted several institutions to modify standard therapeutic approaches in an attempt to improve treatment outcomes. Recently, chemotherapy has been evaluated as part of multimodality therapy delivered in either induction or concomitant settings (17,18). For example, Licitra et al. (17) reported the retrospective analysis of 49 patients with resectable sinonasal cancer who were treated with IC (cisplatin, fluorouracil and leucovorin) followed by surgery and post-operative radiotherapy. The objective response to IC and 3-year OS were 43 and 69%, respectively, suggesting that IC may play a role in surgery-sparing treatment approaches. In a similar study, Lee et al. (18) reported that a subgroup of 16 patients with Stage III or IV sinonasal carcinoma who received IC consisting of three cycles of cisplatin and fluorouracil achieved an 87% clinical response, indicating that IC could be an avenue for further improving the suboptimal results often encountered with reductions in tumors in close proximity with important structures. In the present retrospective study, after the completion of TPS, the overall response rate was 38.4% (5 of 13), with one patient achieving CR and four patients achieving PR. Neutropenia was the most common Grade 3 and 4 hematological toxicity (76.9%), while the most frequently observed non-hematological toxicity was nausea (23.0%). IC of TPS was well tolerated, feasible and showed good antitumor activity, which enabled the reduction in large tumor masses without severe toxicity.

Although squamous cell carcinoma is the most frequent pathology of HNC, olfactory neuroblastoma was most often observed in the present study. We speculate that the dominance of olfactory neuroblastoma among patients was due to referrals from institutions in the surrounding area with limited experience treating this type of carcinoma. Rosenthal et al. (19) reported that patients with olfactory neuroblastoma had excellent local and distant control rates with local therapy alone, but found higher rates of systemic failure for patients with neuroendocrine carcinoma, undifferentiated sinonasal carcinoma and small cell carcinoma. Although data concerning the response of nasal and sinonasal malignancies to IC are limited, several authors have reported the effectiveness of chemotherapy in the treatment of olfactory neuroblastoma, squamous cell carcinoma, undifferentiated carcinoma and adenocarcinoma. In the present study, about half of the patients had olfactory neuroblastoma, and the response rate after the completion of IC followed by PBT concurrent with cisplatin was high. This further emphasizes the need for accurate pathologic diagnosis of nasal and sinonasal malignancies, which may allow the use of separate IC as dictated by the histological analyses.

PBT approaches that would allow decreased irradiation doses to the surrounding critical organs while simultaneously delivering curative high-dose irradiation doses to tumors is critical for minimizing severe complications (5–7). Improvements of local control rates in treatment plans with lower doses to critical organs have been demonstrated when proton plans have been compared with photon plans in patients with nasal and sinonasal malignancies (13–15). Weber et al. (20) examined the long-term toxicity in patients with advanced sinonasal malignancies treated with proton/photon accelerated fractionated radiation and found that at a median dose of 69.6 GyE, 5.6% of the patients developed Grade 3 late visual/ocular toxicity, and no Grade 4–5 late visual/ocular toxicity, vascular glaucoma, retinal detachment or optic neuropathy were observed. Our group previously examined the clinical outcomes of 39 patients with unresectable malignancies treated with PBT at our institution between 1999 and 2006 and demonstrated that most patients experienced Grade 1–2 dermatitis in the acute phase, and 5 patients (12.8%) experienced Grade 3 or greater were observed (12). In the present study, 12 patients received PBT and no brain damage or blindness was recorded. When radiation is combined with concurrent chemotherapy, the acute and long-term side effects are occasionally more pronounced, and greater care and attention to the dose to normal surrounding organs is required for preventing complications. In the present study, 10 patients received PBT concurrent with cisplatin and no brain damage or blindness was recorded, suggesting that IC led to reduced tumor size and PBT could allow the delivery of tumoricidal doses with minimal complications.

Several limitations of the study warrant mention. First, this study includes the inherent limitations of a retrospective study. Second, only a small number of patients with biased histological types of cancer were examined. Here, sufficient doses of chemoradiotherapy without severe complications were achieved using IC and PBT; however, we cannot make definitive conclusions regarding the safety or side effect because of these limitations. Although it is difficult to conduct a prospective study as nasal and sinonasal malignancies are rare, additional patients are needed to confirm these results.

In conclusion, our retrospective analysis revealed that IC with TPS followed by PBT concurrent with cisplatin was well tolerated and effective in patients with locoregionally advanced malignancies of the nasal cavity and paranasal sinuses. This treatment approach demonstrated promising activity and minimal toxicity to warrant Phase II testing and may represent a suitable substitute for chemoradiotherapy alone for patients with T4b nasal and sinonasal malignancies.

Conflict of interest statement

None declared.

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Jpn J Clin Oncol 2012;42(9)861–864
doi:10.1093/jjco/hys093
Advance Access Publication 19 June 2012

Short Communication

Early Clinical Outcomes of Anal Squamous Cell Carcinoma Treated with Concurrent Chemoradiotherapy with 5-Fluorouracil Plus Mitomycin C in Japanese Patients: Experience at a Single Institution

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Received March 2, 2012; accepted May 21, 2012

Concurrent chemoradiotherapy with 5-fluorouracil plus mitomycin C has been established as a standard therapy for non-metastatic anal squamous cell carcinoma in the West. However, there have been few reports of chemoradiotherapy for anal squamous cell carcinoma in Japan. We retrospectively investigated seven consecutive anal squamous cell carcinoma patients who were treated with concurrent chemoradiotherapy consisting of 5-fluorouracil plus mitomycin C with a total irradiation of 59.4 Gy. The patients consisted of two males and five females. Clinical stages II/IIIA/IIIB accounted for four, one and two patients, respectively. Full-dose irradiation was completed in all patients. Median relative dose intensities of 5-fluorouracil and mitomycin C were both 99%. All patients achieved complete response. At a median follow-up of 37.5 months, one patient experienced local recurrence. The most common grade 3/4 acute toxicities were dermatitis in 100% and anal pain in 71%. There was no treatment-related death. Concurrent chemoradiotherapy appears to be tolerable and effective in Japanese patients with anal squamous cell carcinoma.

Key words: anal squamous cell carcinoma – chemoradiotherapy – 5-fluorouracil – mitomycin C

INTRODUCTION

Anal canal cancer is an uncommon disease, accounting for only 1.9% of gastrointestinal cancers in the USA, with an estimated 5290 new cases in 2009 (1). The incidence of anal canal cancer in the general population has increased over the last 30 years, from 10 to ~20 per million (2). In the past, anal canal cancer was routinely treated by abdominoperineal resection (APR), a radical procedure that involves the removal of the anorectum and the creation of a permanent colostomy. In an early series, the 5 year survival following APR for anal canal cancer was 40–70%, with a perioperative mortality of 3% (3–7). A subsequent small case series of patients with squamous histology treated with chemoradiotherapy (CRT) without APR showed a 5 year overall survival of 67% and a 5 year colostomy-free survival of 59% (8). This good clinical outcome with CRT for anal squamous cell carcinoma (ASCC) was confirmed in several randomized phase III trials, and CRT consisting of 5-fluorouracil (5-FU) plus mitomycin C (MMC) is now the standard of care for patients with ASCC in terms of better prognosis with anal preservation (9–16). All of these studies were conducted in Western populations, however, and the efficacy of CRT in Asian populations has not been reported.