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DISEASES OF THE ESOPHAGUS

Original article

Submucosal tumor appearance is a useful endoscopic predictor of early primary-site recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma

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SUMMARY. **Chemoradiotherapy (CRT) for esophageal cancer is disadvantageous because of a high locoregional failure rate. Detecting early small recurrent cancers at the primary site is necessary for potential salvage treatment. However, most endoscopists are inexperienced and therefore, a role for surveillance endoscopy after complete remission (CR) has not been established. We retrospectively evaluated serial surveillance endoscopic images from patients eventually proved to have primary-site recurrence in order to identify useful endoscopic features for early diagnosis. From January 2000 to December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT, and 133 of them achieved CR. The surveillance endoscopic images stored at intervals of 1–3 months for the 16 patients with recurrence only at the primary tumor site and the 61 patients with no recurrence were collected for reexamination. Among 133 patients who achieved CR, 16 (12%) developed only local recurrence at the primary site. Thirteen of the 16 primary-site recurrent tumors (81%) appeared as submucosal tumors (SMT), with the remaining appearing as erosions or mild strictures. Of biopsy-proven recurrences, 81% were preceded by newly developed lesions such as SMT, erosions, or mild strictures detected by earlier surveillance endoscopies. For all 77 patients achieving CR with no metastasis, 86% of the evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies. Thirteen of the 21 evolving lesions were subsequently confirmed as recurrent cancer. Early primary-site recurrence of esophageal cancer after a complete response to CRT is detectable with frequent endoscopic surveillance. SMT appearance is a useful endoscopic sign of early recurrence, as well as a predictor of subsequent diagnosis of recurrence.**

KEY WORDS: **chemoradiotherapy, esophageal cancer, recurrence, surveillance.**

INTRODUCTION

Definitive chemoradiotherapy (CRT) is widely accepted as a standard treatment option in the management of locally advanced esophageal cancer because of its high response rate and significant survival benefit.[1,2] A major drawback to this nonsurgical approach is locoregional treatment failure. At least 40% of patients undergoing CRT experienced local failure, some of whom did not develop distant metastases.[1,3–5]

These primary-site recurrence patients are traditionally managed with salvage esophagectomy for a chance of long-term survival, particularly in those with an earlier pathological stage (T1N0 and T2N0).[6,7] However, high perisurgical mortality and morbidity rates are major concerns.[7,8] Recently developed nonsurgical techniques, such as salvage endoscopic mucosal resection and photodynamic therapy,

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have the advantages of greater safety and fewer treatment-related sequelae, while conferring promising survival benefits for local failures after definitive CRT.[9,10] Technically, endoscopic mucosal resection and photodynamic therapy are feasible only when the volume of the locally recurrent tumor is small enough to be amenable to these endoscopy-based procedures. Therefore, the application of these newer treatments depends crucially on the ability to identify early recurrent tumors by endoscopy.

A strategy of frequent surveillance endoscopy initiated early after remission of the cancer should theoretically improve the chances of detecting primary-site recurrent tumors in their early stages. This requires the prompt recognition of minute tumors arising from the former neoplastic bed, instead of from the uninvolved normal esophageal mucosa. However, the complete regression of cancer cells results in residual fibrosis, radiation-induced tissue injury, and the distortion of normal microstructures,[11,12] which may render relapsing neoplastic growth morphologically different from typical primary tumors. Apparently, most endoscopists are inexperienced in hunting for these difficult lesions. To our knowledge, no study of the skills in endoscopic detection of such lesions has been published. Not surprisingly, a follow-up endoscopy after the completion of CRT is considered 'optional' in the National Comprehensive Cancer Network clinical practice guidelines for esophageal cancer.[13] We believe that a reliable endoscopic diagnostic technique is necessary to support a strategy of intense endoscopic follow-ups.

As a cancer referral and research hospital, our institute is unique in its implementation of a vigorous endoscopic follow-up program after primary treatment for all patients with esophageal cancer. Therefore, it is possible to analyze the filed imaging data of endoscopic monitoring on the post-CRT mucosa. In the present study, we aimed to identify useful endoscopic findings through reviewing the image data pool to predict recurrent esophageal cancers limited to the primary site after complete remission (CR) is achieved by CRT.

MATERIALS AND METHODS

Patient population

Between January 2000 and December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT at the National Cancer Center Hospital East, Kashiwa, Japan. The CRT consisted of 50.4–60 Gy irradiation, together with two cycles of continuous infusion with 5-fluorouracil (5FU) and cisplatin. Up to four courses of CRT were added for those patients who showed a good initial response to treatment.[9]

Table 1 Clinical data of 133 patients achieving complete remission with definitive chemoradiotherapy

Characteristic		Number of patients	%
Sex			
Male		110	82.7
Female		23	17.3
Age (years)			
Mean	62		
Range	39–76		
T stage			
T1		30	22.6
T2		21	15.8
T3		70	52.6
T4		12	9.0
N stage			
N0		46	34.6
N1		87	65.4
M stage			
M0		123	92.5
M1		10	7.5
Clinical stage			
I		16	12.0
II		45	33.8
III		62	46.6
IV		10	7.5
Macroscopic classification			
Type 0		30	22.6
Type 1		19	14.3
Type 2		60	45.1
Type 3		24	18.0

Response to treatment was assessed at the completion of CRT. CR was defined when all the following criteria were met: (i) the disappearance of the tumor lesion or ulcer at the primary site, with negative biopsies; (ii) no esophageal stricture or any condition that prevented a thorough endoscopic examination of the whole esophagus; (iii) no remaining measurable disease or distant metastasis on computer tomography and chest roentgenography; and (5) these criteria were met for at least 4 weeks.

Of the 303 patients, 133 (43.9%) were defined as being in CR at the completion of CRT. Of these 133 patients, 110 were men, with a median age of 62 years. Pretreatment staging of their esophageal cancers was determined with the tumor-node-metastasis classification of the International Union Against Cancer.[14] Seventy (52.6%) patients had T3 tumors; most patients had N1 (65.4%) or M0 (92.5%) disease. Forty-five (33.8%) and 62 (46.6%) patients were classified as clinical stages II and III, respectively (Table 1).

Study design

After achieving CR, initial follow-up endoscopy to confirm CR was scheduled within at most 1–2 months for each patient, accompanied with other necessary studies for the assessment of metastases. After the confirmation of CR, follow-up endoscopy was scheduled every 2–3 months for the first year and every 4–6

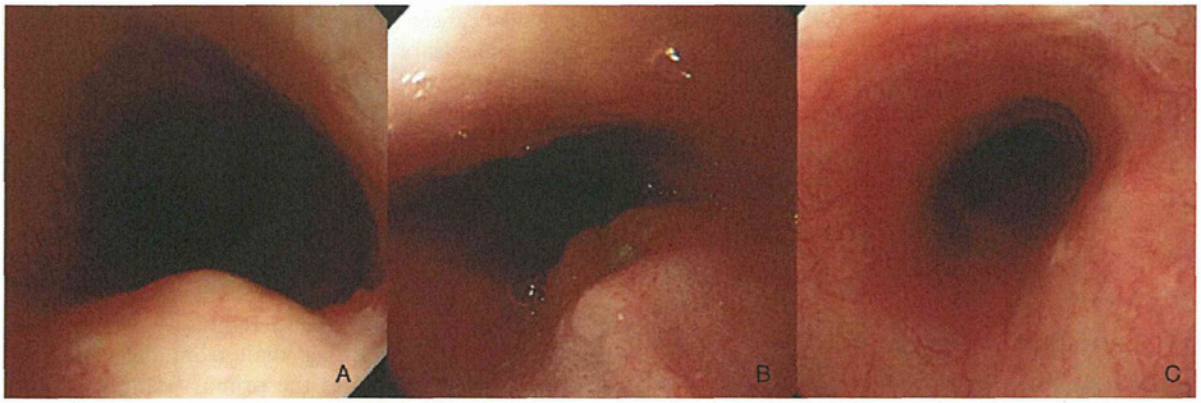

Fig. 1 Initially growing recurrent esophageal cancer at the primary tumor site after complete remission was achieved with chemoradiotherapy may be detected by endoscopy, with features of a submucosal tumor (A), a submucosal tumor with superficial ulcer (B), or a flat erosion (C).

months for 2 years thereafter. Lugol staining and multiple biopsies at the primary site were routinely required.[15] The diagnosis of local recurrence was determined by a positive biopsy.

Of the 133 CR patients, 61 had no recurrence, 56 developed lymph node or distant metastases, and the remaining 16 developed local recurrence at the primary tumor site with no evidence of metastasis. We excluded the 56 patients with lymph node or distant metastases from this study because for them, evaluation of the primary site was not important and only those patients eligible for salvage treatment on local tumors were of interest. Therefore, the endoscopic images of the remaining 77 patients were retrospectively enrolled. This population comprised patients with esophageal squamous cell carcinoma who achieved CR after the initial CRT and developed no metastasis during follow-up, regardless of local recurrence. All of the filed endoscopic images stored after achieving CR, both conventional endoscopy and Lugol-stained chromoendoscopy, were retrospectively collected for reexamination. The stored endoscopic images were evaluated by consensus among three endoscopists experienced in upper gastrointestinal cancer diagnosis (K. T., M. M., K. M.).

RESULTS

Upon the diagnosis of primary-site recurrence for the 16 patients, 13 (81%) had endoscopic findings resembling submucosal tumors (SMT), typically a focal bulge mostly covered by normal-appearing mucosa (Fig. 1A).[16] Eleven of the 13 tumors contained central eroded areas recognized as ulcers or erosions (Fig. 1B and 1C). The remaining three tumors were detected as flat erosions without features of SMT (Table 2).

Images of surveillance endoscopies performed at intervals between CR and the diagnosis of recurrence in the 16 patients were sequentially examined. Newly developed gross lesions at the primary site with negative biopsies were interpreted as recurrent lesions. Evolving lesions were discovered in 13 (81%) patients, including six (38% of the 16 patients) SMT, five (31%) erosions, and two (12%) mild luminal strictures (Table 3).

For all 77 patients achieving CR and free of metastasis, lesions newly developed between CR and the most recent endoscopic surveillance were considered evolving lesions. Therefore, an evolving lesion may be eventually proven to be a recurrence or remain biopsy-negative at the most recent endoscopy. Six of the seven (86%) evolving SMT were subsequently confirmed as recurrent cancer by follow-up

Table 2 Endoscopic findings at primary-site with biopsy-proven recurrence

Endoscopic finding	Number of patients	%
SMT	13	81
SMT with erosion or ulceration	11	
SMT without erosion or ulceration	2	
Erosion	3	19
Total	16	100

SMT, submucosal tumor.

Table 3 Endoscopic findings of newly developed lesion for primary-site recurrent tumors

Preceding newly developed lesions with negative biopsies	Findings at diagnosis of recurrence	Number of patients
SMT	SMT	6
Erosion	SMT	4
Erosion	Erosion	1
Mild stricture	SMT	2
No newly developed lesion	SMT	1
No newly developed lesion	Erosion	2
Total		16

SMT, submucosal tumor.

Table 4 Primary-site biopsy results of the latest surveillance endoscopy for patients who achieved complete remission and remained free of metastasis

Evolving lesion found at preceding endoscopies	Numer of patients (%)	Biopsy result of the latest endoscopy	Number of patients (%)
SMT	7 (9)	Recurrence	6 (86)
		Negative	1 (14)
Erosion	8 (10)	Recurrence	5 (63)
		Negative	3 (37)
Mild stricture	6 (8)	Recurrence	2 (33)
		Negative	4 (67)
No evolving lesion	56 (73)	Recurrence	3 (5)
		Negative	53 (95)
Total	77 (100)		

SMT, submucosal tumor.

endoscopic biopsies. Similarly, five of eight (63%) evolving erosions and two of six (33%) evolving mild strictures were finally confirmed as recurrence. Fifty-six patients were never found to have evolving lesions throughout the follow-up, including three (5%) who were confirmed as recurrence upon the first appearance of an endoscopic lesion. In total, eight of the 21 (38%) patients who developed evolving lesions remained biopsy-negative at their most recent endoscopic follow-up (Table 4).

DISCUSSION

We discovered that the most frequent (81%) endoscopic indicator of primary-site recurrence at its earliest possible stage for a histological diagnosis is SMT. Eighty-one percent of biopsy-proved recurrences were preceded by newly developed lesions such as SMT, erosions, or mild strictures detectable with surveillance endoscopies. Most (86%) evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies, but the proportions were lower for other evolving lesions such as erosions (63%) and strictures (33%). This is the first study to describe the morphological changes of early recurring tumors by serial endoscopic observations at short intervals. Our findings will be helpful for improving the skills to detect potentially treatable primary-site recurrence after definitive CRT for esophageal squamous cell carcinoma.

For the endoscopic diagnosis of primary esophageal cancer, several features have been previously described to detect early stage squamous cell carcinoma: localized mucosal erosions in contrast to normal surrounding mucosa; circumscribed mucosal protuberances with irregular configurations; focal areas of mucosal coarsening and congestion; and, rarely, white mucosal plaques.[16] However, these features are not reliable when applied to early recurrent tumors arising from the mucosal bed of a former primary cancer that regressed after CRT. The original esophageal layering and vascular structures have been disrupted by the primary tumor. Furthermore, the expansion and arrangement of recurring neoplastic cells are disrupted by tissue reactions to previous chemotherapy and radiotherapy, as well as by subsequent repair processes. Tumor necrosis, foam cell formation, vascular granulation, inflammatory exudation, and fibrosis are frequent histological sequelae of CRT.[17,18] The minute foci of the initial neoplastic growth may arise from scattered residual cancer cells in deeper tissues, rather than from the superficial mucosal layer, as does the primary cancer.[11] These factors have largely precluded endoscopic ultrasound as a feasible tool in the assessment of residual or recurrent esophageal cancers.[19,20] For the same reason, the endoscopic diagnostic features for recurrent tumors are likely to be different from those for primary tumors.

We speculate that most of the SMT lesions discovered in our study were formed by expanding tumor cells in the submucosal layers, but barely reached the luminal surface because of their depth and constraining fibrosis. Although the overlying mucosa appeared normal, they manifest their first sign by bulging outward. Malignant cells can be captured by biopsy forceps only when they reach the surface in sufficient numbers, or more efficiently, destroy the surface to make an erosion. This might explain why all of the six newly developed SMT yielded negative results at their first biopsies but eventually proved to be recurrences (Table 3).

Several previous studies have aimed to improve the detection of local recurrence by measures other than endoscopy. In addition to pretreatment staging, F-18-fluorodeoxyglucose–positron emission tomography (FDG–PET) is highly sensitive (up to 96%) in detecting recurrent esophageal cancer, but with somewhat lower specificity (68–82%).[21–23] However, its utility in detecting locoregional recurrence is limited by its low specificity (57–75%) for postesophagectomy patients. Postsurgical inflammation and anatomical changes are largely responsible for the false positivity. Detecting small residual or early recurrent cancers is even more challenging because low tumor volume could greatly reduce the sensitivity of FDG–PET. Moreover, such lesions are not distinguishable from post-CRT inflammation or regional lymph-node metastasis.[24,25]

The results of our study disagree with the conventional belief that endoscopy is of limited utility in the management of esophageal cancer after CRT.[13,26] We believe that routine endoscopy, particularly focused on the primary tumor site, is advisable for all patients with esophageal squamous cell carcinoma after the completion of CRT. We also suggest regular endoscopic surveillance at least every three months for those who have achieved CR. The occurrence of

SMT-like lesions after CR is an alarming sign that deserves intensive investigation and follow-up if a modality of salvage treatment is available. Any evolving lesion at the primary site with negative biopsy should be followed closely.

Our retrospective study design has introduced a knowledge bias because the evaluating endoscopists were not totally blinded to the outcomes. Therefore, a randomized controlled trial comparing the clinical outcomes is necessary to establish the role of surveillance endoscopy after definitive CRT for esophageal squamous cell carcinoma.

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Pain control in head and neck radiotherapy

Multicenter phase II study of an opioid-based pain control program for head and neck cancer patients receiving chemoradiotherapy

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ABSTRACT

Background: The aim of this multi-center phase II study was to clarify the clinical benefit of an opioid-based pain control program for head and neck cancer patients during chemoradiotherapy.

Patients and methods: Head and neck cancer patients who were to receive definitive or postoperative chemoradiotherapy were enrolled. The opioid-based pain control program consisted of a three-step ladder, with basic regimens of:

Step 1: acetaminophen at 500–1000 mg three times a day.
Step 2: fast-acting morphine at 5 mg three times a day before meals for a single day.
Step 3: long-acting morphine administered around-the-clock, with a starting dosage of 20 mg/day and no upper limit set in principle.

Patients and methods: The primary endpoint of this study was compliance with radiotherapy.

Results: A total of 101 patients from 10 institutions were registered between February 2008 and May 2009 and included in the analysis. The major combination chemotherapy regimen was cisplatin alone (76%). The rate of completion of radiotherapy was 99% and the rate of unplanned breaks in radiotherapy was 13% (13/101, 90% confidence interval: 9.9–16.5%). Median maximum quantity of morphine used per day was 35 mg (range 0–150 mg).

Conclusions: Use of a systematic pain control program may improve compliance with CRT.

Several recent randomized phase III studies have confirmed the value of radiotherapy and concurrent high-dose single-agent cisplatin in almost all stages of locally advanced head and neck cancer [1–5], and platinum-based chemotherapy and concurrent radiotherapy regimens with or without induction chemotherapy are widely used in clinical practice [6–8].

One of the most common and debilitating toxicities among head and neck cancer patients is radiation-induced mucositis [9,10], and severe acute mucositis often results in unplanned treatment breaks, clinic visits and hospitalizations [11,12]. Unplanned breaks in radiotherapy for head and neck cancer are associated with significantly worse locoregional control [13–15]. Even short breaks may have a negative influence: in one retrospective analysis of 2225 patients from four centers [13], for example, an unplanned break of only 1 day resulted in a 0.68% lower 2-year local control rate, while other authors estimated that the tumor control rate is at least 1% lower for every day that radiation treatment is interrupted [16,17].

To investigate whether a systematic pain control program might help decrease unplanned treatment breaks by suppressing radiation-induced pain, we developed an opioid-based pain control program for the systematic management of radiation-induced pain. The aim of this multicenter phase II study was to clarify the clinical benefit of this opioid-based pain control program for head and neck cancer patients during chemoradiotherapy.

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Patients and methods

This multi-center phase II trial was approved by the institutional review boards of all participating institutions before patient enrollment occurred.

Eligibility

Enrollment criteria included histologically confirmed squamous cell carcinoma of the head and neck, age 20–75 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, normal organ function, scheduled receipt of definitive or postoperative radiotherapy (>50 Gy) with platinum-based chemotherapy, and no cancer pain at the time of recruitment. Written informed consent to treatment was obtained from all patients before the initiation of any treatment.

Treatment

All study patients were recommended to undergo percutaneous endoscopic gastrostomy (PEG) before the start of radiotherapy. The main protocol was called the 'opioid-based pain control program', which consisted of a three-step ladder (Fig. 1).

Prescription Step 1

The basic regimen for mild pain was acetaminophen at 500–1000 mg three times a day. Loxoprofen sodium or diclofenac sodium was avoided on the basis that their adverse effects on renal function might have influenced compliance with platinum-based chemotherapy.

Prescription Step 2

The basic regimen for mild-intermediate pain was fast-acting morphine e.g. anhydrous morphine sulfate at 5 mg three times a day before meals. The main aim of this prescription was to avoid full dependence on PEG at an early phase of CRT. This regimen could be used concurrently with Prescription Step 1. If oral intake became impossible soon after the initiation of CRT, this regimen could be skipped and the patient moved directly from Step 1 to Step 3.

Prescription Step 3

The basic concept in this step was the use of long-acting morphine around the clock. The starting dosage was 20 mg/day, and no upper limit was set. The rescue dose was set as 1–6 of the main morphine dosage. In principle, intravenous administration of morphine was not performed; in case oral intake became difficult, sustained-released morphine sulfate in fractional doses administered via PEG was recommended instead.

Appropriate use of medications to control side effects of morphine was strongly recommended in Steps 2 and 3. Pain strength was evaluated at least weekly by physicians or nurses using the grading system for mucositis/stomatitis (functional/symptomatic) in Common Terminology Criteria of Adverse Events version 3.

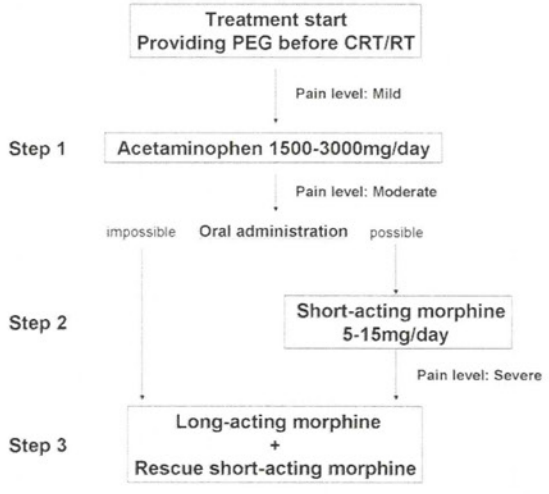

Fig. 1. Opioid-based pain control program. The main decision tree of the opioid-based pain control program is shown.

Toxicity

With regard to the acute toxicity of chemoradiotherapy, adverse events were coded according to the Common Terminology Criteria of Adverse Events version 3. Morphine-induced side effects were evaluated with regard to nausea, constipation, sleepiness, urinary retention, and respiratory depression.

Patient education about use of PEG

To allow CRT to be performed on schedule with minimum hospitalization, it was necessary that patients were able to use PEG alone at home. Expert nurses, including Wound, Ostomy and Continence (WOC) nurses, conducted educational sessions with all patients about how to use PEG during CRT.

PEG management ability was evaluated in each patient at the end of radiotherapy in a three-level score of perfect, possible with family support, and impossible.

Treatment evaluation and statistical analysis

The primary end point of this study was compliance with radiotherapy.

An unplanned treatment break in radiotherapy was defined as an interruption to radiotherapy of 1 day or more, excluding weekends or planned machine maintenance. In our group experience of definitive chemoradiotherapy from 2002 to 2006, 25% of all patients had treatment interruptions (unpublished data). With regard to postoperative radiotherapy, 24% of all patients had treatment interruptions which resulted in a total duration of treatment of more than 7 weeks in EORTC 22931 study [3]. On these basis, our present pain control program was considered worthy of additional study only provided that the true rate of interruption of radiotherapy was 20% or less, and not worthy of additional study if the true rate was 35% or more. With 80% power and a one-sided type-I error of 5%, the minimum number of patients required to evaluate the primary endpoint was 79.

We then calculated that 15% of patients might have a treatment break or cancellation due to reasons other than the failure of supportive management and that 10% might be excluded by violation of the protocol or other reasons. We therefore calculated a total sample size of 110 patients.

Patient demographic, pathologic, and clinical characteristics were described in terms of the mean, standard deviation, median, range, and percentage.

Results

Patient characteristics

One hundred and ten patients from 10 institutions were registered between February 2008 and May 2009. Nine patients were excluded from analysis because of patient discretion ($n = 5$) and change in strategy after registration ($n = 4$). The remaining 101 patients are characterized in Table 1. Median age was 60 years (range

Table 1
Patient characteristics.

No. of patients	101
Age	
Median (years, range)	60 (23–75)
Gender	
Male/female	89/12
Performance status	
0–1/2	101/0
Primary site	
Nasopharynx	24
Oropharynx	26
Hypopharynx	27
Larynx	6
Tongue, oral cavity	13
Unknown	5
Clinical stage	
II	12
III	10
IV	49
Recurrence	5
Postoperation	25
Radiotherapy setting	
Postoperative RT	25
Definitive RT	76
Treatment strategy	
IC → CRT	21
CRT	78
RT alone	2
Radiation dose	
Median (range)	70 (54–70)
Combination chemotherapy	
Cisplatin alone	77
Cisplatin and 5-FU	12
Cisplatin and docetaxel	1
Other platinum	9

Abbreviations: IC, induction chemotherapy; CRT, chemoradiotherapy; RT, radiotherapy.

23–75). The major primary site was the pharynx (76%), followed by the nasopharynx (24%), oropharynx (26%) and hypopharynx (27%).

With regard to treatment strategy, 76 patients (75%) received radiotherapy as an initial approach, and the remaining 25 (25%) in a postoperative setting. Median radiation dose was 70 Gy (range 54–70) and the major combination chemotherapy regimen was cisplatin alone (77/101, 76%).

Treatment compliance

One hundred of 101 patients completed radiotherapy. The remaining patient was scheduled for irradiation with 66 Gy, but this was cancelled at 62 Gy because of patient discretion. The rate of unplanned breaks in radiotherapy was 13% (13/101, 90% confidence interval: 9.9–16.5%), owing to acute toxicity in 2, PEG trouble in 2, emergency tracheostomy in 1, gastric ulcer in 1, unplanned machine trouble in 2, patient discretion in 3, and other reasons in 2. Of these, the median interval of radiation interruption was 1 day (range 1–4 days), and no unplanned break of more than 1 week was seen.

Morphine regimen

Morphine use is shown in Table 2. From the initiation of treatment to 1 month after the end of radiotherapy, median total morphine use per patient was 815 mg (0–6284 mg), and median maximum use per day was 35 mg (0–150 mg). Median radiation dose at the start of morphine was 28.8 Gy. The frequency of morphine-induced side effects of nausea, constipation, sleepiness, urinary retention, and respiratory depression was 26%, 32%, 12%, 0%, and 0%, respectively.

Table 2
Toxicity.

	Grade (CTCAE ver.3.0)				
	1	2	3	4	% 3 and 4
Leucopenia	18	45	20	0	20
Neutropenia	21	41	11	1	12
Anemia	35	33	13	1	14
Thrombocytopenia	29	14	5	0	5
Nausea	32	33	10	0	10
Mucositis					
CE	13	33	54	0	53
FS	8	32	61	0	60
Neuropathy					
S	1	2	0	0	0
M	0	0	0	0	0
Xerostomia	46	39	3	0	3
Dermatitis	25	52	24	0	24
Febrile neutropenia	–	–	1	0	1
Weight loss	19	22	0	0	0

Abbreviations: CTCAE, Common Terminology Criteria of Adverse Events; CE, clinical exam; FS, functional/symptomatic; S, sensory; M, motor.

The rate of patient use of Step 2 or Step 3 programs to control pain during CRT was 83% (84/101), while the rate of use of morphine at one month after the end of radiotherapy was 26% (26/101). A schema of the frequency of use of each prescription is shown in Fig. 2.

Toxicity

Toxicity profile during CRT is shown in Table 3. No fatal hematological events were seen. With regard to non-hematological toxicity, mucositis/stomatitis and dermatitis were the most common acute toxicities. Grades 2 and 3 dermatitis events were seen in 52 (52%) and 24 patients (24%), respectively, while no fatal events were seen.

With regard to mucositis/stomatitis, grade 3 events in the categories 'clinical exam' and 'functional/symptomatic' occurred in more than half of the patients. Grade 2 weight loss was seen in 22 patients (22%), while no grade 3 weight loss was seen.

No treatment-related deaths were seen.

The data about PEG

Ninety-eight of 101 patients (97%) were provided PEG, mostly via the direct method. There were four events (4%) of PEG-associated infection or peritonitis during the observation period. At the end of radiotherapy, 92 patients had used PEG in daily life, of whom 84 (91%) were able to manage PEG by themselves, 5 could do so with family support, and 3 could not manage on an outpatient basis.

On the other hand, of 83 patients who survived over 1 year without primary tumor, the rate of PEG dependence at 1 year after RT was 8.4% (7/83).

Discussion

The aim of this phase II study was to clarify the safety and efficacy profile of a systematic pain control program for head and neck cancer patients during chemoradiotherapy. Results suggested that this program might contribute to improving compliance with CRT in these patients.

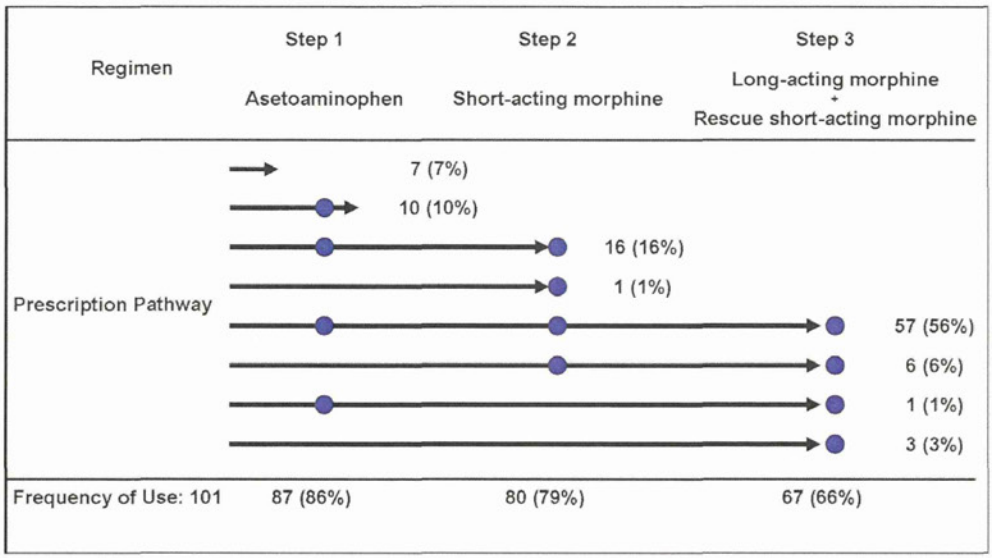

Fig. 2. The summary of prescriptions. Eight prescription pathway patterns were identified. Steps 1–3 was the most common route. Sixty-seven (66%) patients required Prescription Step 3 (long-acting morphine based regimen).

Table 3
Morphine use.

Rate of morphine use	84/101 (83%)
Median total quantity of morphine use per patient	815 mg (0–6286)
Median maximum quantity of morphine use per day	35 mg (0–150)
Morphine-free rate at 1 month after RT	75/10 (74%)
Morphine-induced SE	
Nausea	22 (26%)
Sleepiness	10 (12%)
Urinary retention	0 (0%)
Constipation	27 (32%)
Respiratory depression	0 (0%)

Abbreviations: RT, radiotherapy; SE, side effect.

The primary endpoint of this study was compliance with radiotherapy. Although many retrospective analyses have shown that unplanned treatment breaks have a significant negative impact on treatment outcome [13–15,18], only limited information about this is available from recent prospective trials. In the EORTC 22931 study [3], for example, 24% of all patients had treatment interruptions resulting in a total duration of treatment of more than 7 weeks. Lefebvre et al. [19] reported a randomized control trial which compared sequential chemotherapy and radiotherapy with alternating chemotherapy and radiotherapy, and showed that 23% of the alternating arm patients experienced an interruption to or delay in radiotherapy.

In our study, the rate of unplanned breaks in radiotherapy was 13% and the completion rate was 99%. Although therapeutic intensity in our study was not inferior to that of these two trials, our treatment compliance was better. These results suggest that systematic pain control programs may have a good impact on treatment compliance.

We consider that the provision of percutaneous endoscopic gastrostomy (PEG) before the start of radiotherapy was necessary to allow completion of the treatment schedule. However, complete dependence on PEG soon after starting CRT might result in a decrease in laryngo-pharynx function [20–23]. Taking fast-acting morphine three times a day preprandially at Step 2 might help avoid complete dependence on PEG at an early phase of CRT. In our study, the rate of PEG dependence at 1 year after RT was only 8.4% (7/83). We think the appropriate PEG use does not cause dysphagia in head and neck cancer patients treated with radiotherapy.

With regard to morphine use, the rate of patients using morphine to control pain during CRT was 83% (84/101), and the median maximum quantity of morphine use per day was 35 mg (0–150 mg). In contrast, the rate of patients using morphine at one month after the end of radiotherapy was 26% (26/101). These results suggest that radiation-induced pain worsened rapidly during radiotherapy but improved equally rapidly after the end of radiotherapy.

As an additional benefit of our systematic pain control program, the decrease in differences among physician orders facilitated the duties of nurses. Moreover, unusual changes in pain under this systematic program provided sensitive insight into the possibility of accidents, such as infection. We consider these changes as additional factors that also influenced our good results.

Finally, this program is relatively simple and can be easily implemented without special tools. Although few sustained-release morphine products suitable for administration via PEG are presently available, increased availability will facilitate broad application of the program. This opioid-based pain control program can therefore be widely used in other institutions.

Conclusion

Our opioid-based systematic pain control program during CRT may be helpful for improving compliance with CRT.

We are now planning a randomized control study to determine whether this program has a significant impact on treatment outcomes, including quality of life and overall survival.

Conflict of interest

We have no conflict of interest.

Acknowledgment

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CLINICAL INVESTIGATION **Head and Neck**

PROTON BEAM THERAPY FOR UNRESECTABLE MALIGNANCIES OF THE NASAL CAVITY AND PARANASAL SINUSES

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Purpose: The cure rate for unresectable malignancies of the nasal cavity and paranasal sinuses is low. Because irradiation with proton beams, which 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, provide better dose distribution than X-ray irradiation, proton beam therapy (PBT) might improve treatment outcomes for conditions located in proximity to risk organs. We retrospectively analyzed the clinical profile of PBT for unresectable malignancies of the nasal cavity and paranasal sinuses.

Methods and Materials: We reviewed 39 patients in our database fulfilling the following criteria: unresectable malignant tumors of the nasal cavity, paranasal sinuses or skull base; N0M0 disease; and treatment with PBT (>60 GyE) from January 1999 to December 2006.

Results: Median patient age was 57 years (range, 22–84 years); 22 of the patients were men and 17 were women. The most frequent primary site was the nasal cavity (n = 26, 67%). The local control rates at 6 months and 1 year were 84.6% and 77.0%, respectively. With a median active follow-up of 45.4 months, 3-year progression-free and overall survival were 49.1% and 59.3%, respectively. The most common acute toxicities were mild dermatitis (Grade 2, 33.3%), but no severe toxicity was observed (Grade 3 or greater, 0%). Five patients (12.8%) experienced Grade 3 to 5 late toxicities, and one treatment-related death was reported, caused by cerebrospinal fluid leakage Grade 5 (2.6%).

Conclusion: These findings suggest that the clinical profile of PBT for unresectable malignancies of the nasal cavity and paranasal sinuses make it is a promising treatment option. © **2011 Elsevier Inc.**

Proton beam therapy, nasal cavity, paranasal sinus, radiotherapy, craniofacial surgery, organ preservation.

INTRODUCTION

Malignant tumors that arise in the nasal or paranasal sinuses and that otherwise involve the base of the skull usually present a difficult clinical problem. Most cases are curatively treated by craniofacial surgery and postoperative radiotherapy, either alone or in combination (1–5). However, several problems with this strategy remain. In cases in which the disease has spread deeply to the intracranial region, surgical approaches are often complicated by serious functional deformity, and satisfactory surgical clearance is often markedly difficult to obtain (6 ,7). For theses cases, definitive radiotherapy is often performed as an alternative treatment, but aggressive irradiation of the intracranial region increases the risk of severe late toxicity (8–10).

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 (11). These physical characteristics give proton beam therapy (PBT) 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. However, few papers have described the use of PBT in unresectable malignancies of the nasal cavity and paranasal sinuses.

Here, we conducted a retrospective analysis to clarify the clinical profile of PBT for unresectable malignancies of the nasal cavity and paranasal sinuses.

METHODS AND MATERIALS

Patients

A total of 39 patients in our database fulfilling the following criteria were reviewed: unresectable malignant tumors of the nasal

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cavity, paranasal sinuses, or skull base; no lymph node metastases or distant metastases; and treatment with definitive PBT (>60 GyE) from January 1999 to December 2006. Unresectable disease was defined as the inability of a surgeon to perform complete resection because of functional or technical limitations. Patients recruited for other clinical trials were excluded from this analysis.

Pretreatment evaluation

Pretreatment clinical evaluation was performed using magnetic resonance imaging (MRI), cervical, chest, and abdominal computed tomography (CT), or positron emission tomography (PET)–CT. Tumor staging in the present study was based on the sections on the nasal cavity and paranasal sinuses in the TNM classification of the International Union Against Cancer (UICC 6th), regardless of histology type. Radiological evaluations for staging were jointly reviewed by radiologists, head-and-neck surgeons, and medical oncologists at our institution.

Efficacy and toxicity evaluation

Overall survival was calculated from the start of treatment to the date of death or last confirmed date of survival. 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. Local control was defined as the lack of progressive disease at the primary site.

The pattern of treatment failure was defined as the first site of failure, with local failure indicating recurrence or persistent disease after PBT at the primary site, regional failure indicating neck lymph node metastases after PBT, and distant failure indicating recurrence at any site beyond the primary site and neck lymph nodes.

Acute and late toxicities were graded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0). Time to onset of toxicity Grade 2 or greater was defined as from the day of initiation of treatment to the first day of confirmation of late toxicity of Grade 2 or greater.

Proton beam therapy

Treatment planning was performed on a three-dimensional CT planning system. In this system, the proton beam was generated with 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 (12). Proton beam therapy at our institution is conducted using passive irradiation with dual-ring double-scatter methods. Dose distribution is optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Gross tumor volume (GTV) was determined by pretreatment with CT, MRI, and PET-CT, either alone or in combination. Clinical target volume (CTV) was defined as the GTV plus a 5-mm margin and the sinuses adjacent to the GTV. In cases with 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 but could be finely adjusted where necessary in consideration of organs at risk. Beam energy and spread-out Bragg peak were fine-tuned such that the PTV was at least covered in a 90% isodose volume of the prescribed dosage. The irradiated dose was minimized by delivery of the proton beam with two or three beam arrangements (Fig. 1). The biologically equivalent dose (BED) using a linear-quadratic model was defined as follows: $BED = nd\ (1+ d/\ 1/(\alpha/\beta))$, where n is the fractionation number, d is the daily dose, and α/β ratio was 3.0 Gy for normal tissue (12).

Dose constraints for organs at risk at 2.5 GyE per fraction were as follows: (*1*) surface of brainstem, 51 GyE; (*2*) center of brainstem, 46 GyE; (*3*) optic nerves of the healthy side/chiasm, 46 GyE; and (*4*) optic lens, 9 GyE.

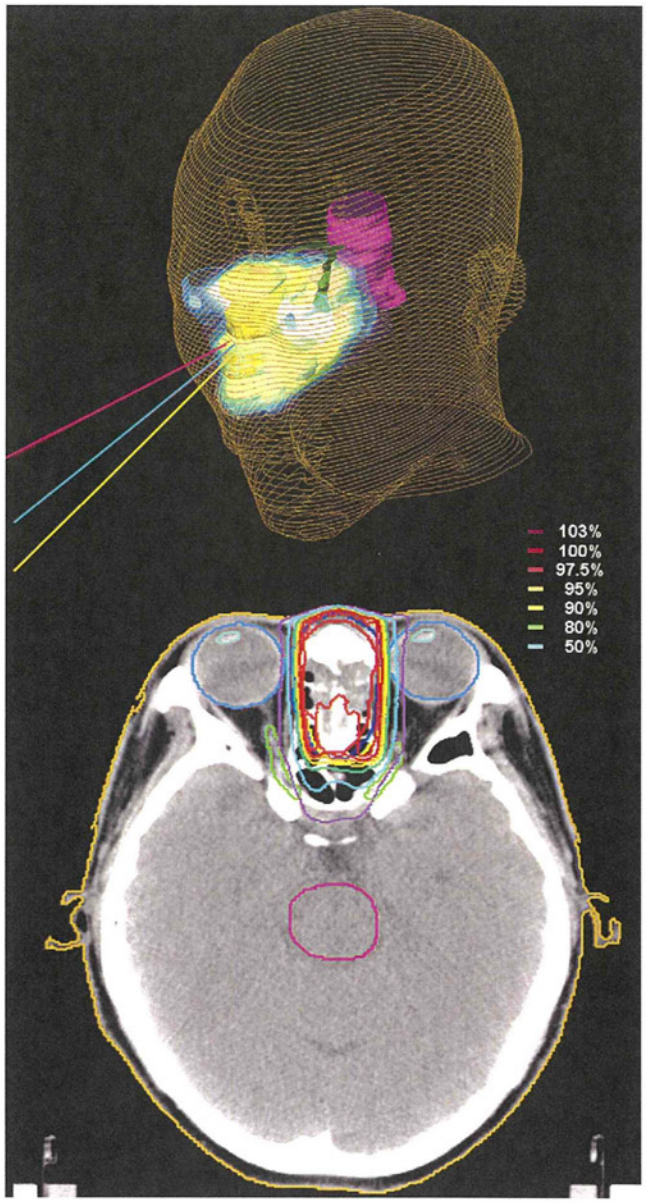

Fig. 1. Beam arrangement. Irradiation dose and volume for organs at risk was usually minimized using a noncoplanar three-field technique. In this case, curative high-dose irradiation to the tumor volume was provided, whereas overdose irradiation to the optic nerve was avoided.

Statistical analysis

Overall and progression-free survival time were estimated by the Kaplan–Meier product–limits method using commercially available statistical software (StatView version 5.0, SAS Institute, Cary, NC).

Univariate analysis was conducted using the log-rank test and multivariate analysis using the Cox proportional hazard model.

RESULTS

Patient characteristics

All patients had T4 disease and an Eastern Cooperative Oncology Group performance status of 0 or 1. Median age

was 57 years (range, 22–84 years). The major primary site was the nasal cavity (n = 26, 67%). One patient with squamous cell carcinoma from the ductus nasolacrimalis was included.

Regarding treatment, 10 patients received induction chemotherapy before PBT, whereas 29 patients had no prior treatment. One patient received PBT concurrent with cisplatin, whereas the remaining patients received PBT alone. The most common treatment was PBT alone at 65 GyE in 26 fractions. Patient characteristics are listed in Table 1.

Efficacy and failure pattern

With a median follow-up period of 45.4 months (range, 1.3–90.9 months), median survival time was not reached. The 3-year and 5-year overall survival rates were 59.3% and 55.0%, whereas the 3-year progress-free survival rate was 49.1% (Fig. 2).

Local control rates at 6 months and 1 year were 84.6% and 77.0%, respectively.

A total of 23 patients were confirmed to have tumor progression, consisting of 9 (23.0%), 5 (12.8%), and 9 (23.0%) patients with local, regional, and distant failure, respectively.

Table 1. Patient characteristics and treatment (N = 39)

Characteristic	N
Age, y (range)	57 (22–84)
Sex, male/female	22/17
Performance status	
0	25
1	14
2	0
Primary site	
Maxillary sinus	4
Sinonasal	4
Sphenoid sinus	4
Nasal cavity	26
Ductus nasolacrimalis	1
Tumor type	
SCC	11
ACC	5
ONB	9
Melanoma	6
Undifferentiated	3
Others	5
Treatment	
Induction chemotherapy	
Yes	10
No	29
Concurrent chemotherapy	
Yes (CDDP)	1
No	38
PBT dose schedule	
70 GyE/28 fr	3
70 GyE/35 fr	2
66 GyE/33 fr	1
65 GyE/26 fr	27
60 GyE/15 fr	6

Abbreviations: ACC = adenoid cystic carcinoma; CDDP = cisplatin; ONB = olfactory neuroblastoma; PBT = proton beam therapy; SCC = squamous cell carcinoma; Undif = undifferentiated carcinoma.

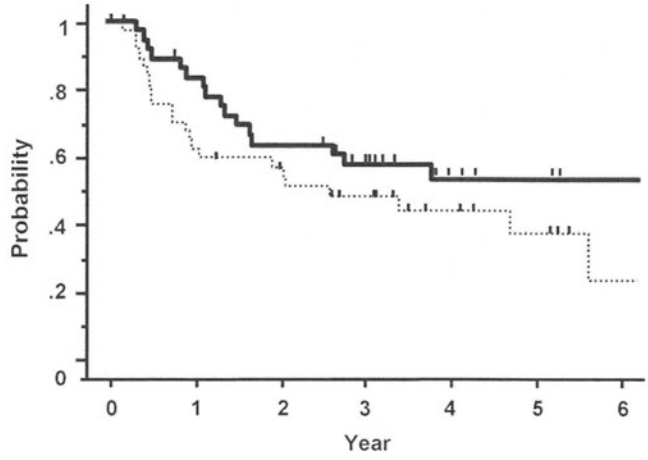

Fig. 2. Overall and progression-free survival. Solid line indicates overall survival curve; broken line indicates progression-free survival curve. With a median follow-up period of 45.4 months, 3-year overall survival and progression-free survival rates were 59.3% and 49.1%, respectively.

Time to the onset of local, regional and distant metastases was 9.4, 12.1, and 11.3 months, respectively. Nine of these patients (39.1%) received second-line treatment. Salvage surgery was performed for 1 patient with local failure and 3 patients with regional failure.

Prognostic factors

In univariate analysis, age, sex, tumor type (squamous cell carcinoma vs. others), primary site (nasal cavity vs. others), history of induction chemotherapy and RT dose were investigated (Table 2). Tumor type (squamous cell carcinoma) had

Table 2. Results of univariate analysis (N = 39)

Covariate	3-Year OS and PFS rates	Hazard ratio (95% CI)
Age		
OS		1.01 (0.99–1.04)
PFS		1.01 (0.98–1.04)
Sex (female vs. male)		
OS	62.5% vs. 56.9%	0.87 (0.34–2.21)
PFS	48.6% vs. 49.6%	1.17 (0.51–2.65)
Tumor type (SCC vs. other)		
OS	48.0% vs. 63.7%	2.17 (0.81–8.55)
PFS	40.0% vs. 52.1%	1.12 (0.45–2.85)
Primary site (nasal cavity vs. other)		
OS	69.2% vs. 37.0%	0.37 (0.15–0.95)
PFS	60.6% vs. 25.0%	0.55 (0.23–1.30)
Induction chemotherapy (yes vs. no)		
OS	70.0% vs. 56.7%	0.67 (0.22–2.05)
PFS	66.7% vs. 38.5%	0.50 (0.17–1.50)
Radiation dose		
OS		1.04 (0.88–1.22)
PFS		0.94 (0.81–1.08)

Abbreviations: BED = biologically equivalent dose; CI = confidence interval; OS = overall survival; PFS = progression-free survival; SCC = squamous cell carcinoma.

Table 3. Toxicity in study patients ($N = 39$)

	Grade (CTCAE v.3.0)					
	1	2	3	4	5	% 3–5
Dermatitis	17	13	0	0	0	0
Conjunctivitis	1	1	0	0	0	0
Mucositis	4	4	0	0	0	0
Hearing loss	0	1	0	0	0	0
Cataract	0	0	1	0	0	2.6
CSF leakage	0	0	0	0	1	2.6
Neuropathy						
CN-II	0	1	0	1	0	2.6
CN-VI	0	0	1	0	0	2.6
Brain necrosis	2	1	0	0	0	0
Soft tissue necrosis	0	0	0	0	0	0
Bone necrosis	0	2	1	0	0	2.6
Treatment-related death: 2.6%						

Abbreviations: CN = central nerve; CSF = cerebrospinal fluid; CTCAE v3.0 = common terminology criteria for adverse events v3.0.

a slight tendency to worsen overall survival, albeit without statistical significance ($p = 0.10$). The primary site (nasal cavity) had a significant influence on overall survival ($p = 0.04$). These two factors were subject to multivariate analysis, but no independent prognostic factors were identified.

Toxicity

Toxicity profile is summarized in Table 3. No severe acute toxicities were seen. The most common acute toxicities were dermatitis, with Grade 2 and 3 dermatitis occurring in 13 (33.3%) and 0 (0%) patients, respectively.

With regard to late toxicity, median time to onset of Grade 2 or greater late toxicity was 35.1 months (range, 4.1–61.2 months). Osteonecrosis caused by exodontia after PBT was observed in 2 patients. Occurrence of late toxicity was not significantly associated with age, gender, primary site, BED, or history of induction chemotherapy.

Grade 3 to 5 late toxicities occurred in 5 patients (12.8%), namely cerebrospinal fluid (CSF) leakage, cataract, decrease in visual acuity, central nerve–VI disorder, and bone necrosis in 1 patient each. One treatment-related death was recorded, caused by CSF leakage Grade 5 (2.6%). At the time of writing, 3 of the 5 patients with severe late toxicity remain alive. Severe toxicity after PBT is detailed in Table 4.

DISCUSSION

The present study suggests that the safety and efficacy profiles of PBT are sufficient for use in the treatment of unresectable malignancies of the nasal cavity and paranasal sinuses.

One strategy with curative intent is craniofacial surgery followed by radiotherapy. Complete surgical resection followed by postoperative radiotherapy has been shown to provide the best local control and overall survival in patients with nasal or paranasal sinuses carcinoma (2–5). In cases in which the status of the surgical margin is positive, however, the risk of recurrence is significantly high (6). These cases are often treated with radiotherapy as an alternative, but outcomes have remained poor (4, 10); in their series, for example, Hoppe *et al.* (10) reported a 5-year survival rate of definitive (chemo) radiotherapy for unresectable carcinoma of the paranasal sinuses of only 15%. Considerable improvement in treatment strategies for these conditions has therefore been sought.

In the present study, 3-year PFS and overall survival rates in patients treated with definitive PBT were 49.1% and 59.3%, respectively. Only 23.0% of all disease progression was local recurrence or persistence. These results are substantially better than those reported previously for radiotherapy and suggest that definitive PBT may be a promising treatment option for patients who are not candidates for surgery.

Response rate could not be shown in the present study. We consider that response evaluation for the primary site using the Response Evaluation Criteria in Solid Tumor (RECIST) criteria, complete response or partial response (CR/PR), is not useful with regard to nasal cavity and paranasal tumors because patients with long survival often show the persistence of the tumor form on CT or MRI after PBT (Fig. 3). On the other hand, local failure means disease progression at the primary site in CT or MRI after PBT, and local failure can be determined at any time if evidence of disease progression is seen.

On this basis, the present study shows the rate of local control and failure in place of response rate. A method that optimizes response evaluation for malignancy of the nasal cavity and paranasal sinuses is required.

In the present study, no factors associated with treatment outcome were detected. Although T stage and performance status are important factors influencing the treatment outcome of malignancies in various fields, all patients in our

Table 4. Late toxicity in study: Grade 3–4 (severe toxicity)

Case no.	Age (y)	Sex	Treatment	Tumor site	Toxicity	Time to onset	Recurrence	Status
11	58	Male	IC → PBT (70 GyE/28 fr)	Sphenoid sinus	Brain necrosis Grade 2 CN-VI disorder Grade 3	35.2 mo	None	Alive 65.6 mo
12	61	Female	IC → PBT (65 GyE/26 fr)	Nasal cavity	CSF leakage Grade 5	13.6 mo	None	Treatment-related death
25	63	Male	IC → PBT (65 GyE/26 fr)	Nasal cavity	Bone necrosis Grade 3	38.7 mo	None	Alive 45.4 mo
27	79	Male	PBT (60 GyE/15 fr)	Nasal cavity	Visual Loss Grade 4	16.6 mo	None	Alive 38.1 mo
30	73	Female	PBT (65 GyE/26 fr)	Nasal cavity	Cataract Grade 3	4.0 mo	Distant	Died 23.8 mo

Abbreviations: CSF = cerebrospinal fluid; CN = central nerve; fr = fractions; IC = induction chemotherapy; PBT = proton beam therapy.

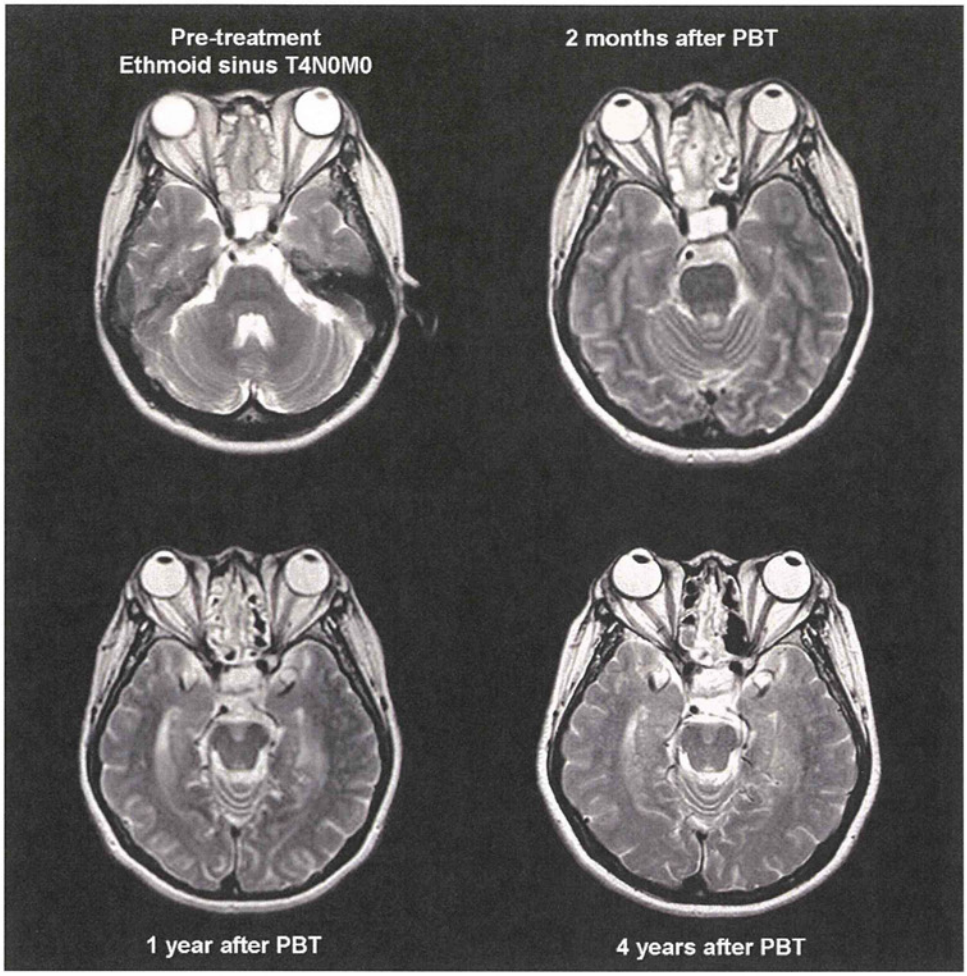

Fig. 3. Difficulty of response evaluation of proton beam therapy (PBT). The disease was undifferentiated carcinoma of the ethmoid sinus. Response evaluation at 2 months and 1 year after PBT was SD by the RECIST criteria; however, the patient has remained alive for more than 4 years without disease progression.

study had T4 disease and good performance status, which might in turn explain why no prognostic factor was found.

With regard to late toxicity, conventional radiotherapy is associated with a number of potentially severe complications, leading to radiation-induced injuries to the visual pathways, central nervous system, and adjacent bone structures. The incidence of radiation-induced unilateral or bilateral blindness has been reported to be as high as 10% to 30% (13–16). With the recent widespread adoption of intensity-modulated radiation therapy (IMRT), several studies have reported improvements in rates of severe toxicity (10, 17, 18), albeit without any improvement in efficacy. Previous studies on craniofacial surgery (6, 19), for example, have reported rates of severe complication of approximately 10% to 15%.

Consistent with this, Grade 3 to 5 late toxicities in the present series were seen in 5 patients (12.8%), and one treatment-related death cause by CSF leakage was identified. Considering that all patients had unresectable and very advanced disease, this safety profile appears acceptable. Although advances in treatment plans for PBT have led to lower doses to critical organs and decreased late toxicity (20, 21), further reductions in toxicity remain possible.

As part of ongoing physics evaluations, our group is presently conducting further recalculations of treatment plans for patients with fatal late toxicity using Monte Carlo methods.

CONCLUSION

Our findings suggest that the clinical profile of PBT for unresectable malignancies of the nasal cavity and paranasal sinuses is sufficient to establish it as promising treatment option. Further investigation to reduce late toxicity is warranted.

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CLINICAL INVESTIGATION **Head and Neck**

PROTON BEAM THERAPY AS A NONSURGICAL APPROACH TO MUCOSAL MELANOMA OF THE HEAD AND NECK: A PILOT STUDY

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Purpose: The aim of this pilot study was to assess the clinical benefit of proton beam therapy for mucosal melanoma of the head and neck.

Methods and Materials: Patients with mucosal melanoma of the head and neck with histologically confirmed malignant melanoma and N0 and M0 disease were enrolled. Proton therapy was delivered three times per week with a planned total dose of 60 Gy equivalents (GyE) in 15 fractions.

Results: Fourteen consecutive patients were enrolled from January 2004 through February 2008. Patient characteristics were as follows: median age 73 years old (range, 56 to 79 years); male/female ratio, 7/7; and T stage 1/2/3/4, 3/2/0/9. All patients were able to receive the full dose of proton therapy. The most common acute toxicities were mucositis (grade 3, 21%) and mild dermatitis (grade 3, 0%). As for late toxicity, 2 patients had a unilateral decrease in visual acuity, although blindness did not occur. No treatment-related deaths occurred throughout the study. Initial local control rate was 85.7%, and, with a median follow-up period of 36.7 months, median progression-free survival was 25.1 months, and 3-year overall survival rates were 58.0%. The most frequent site of first failure was cervical lymph nodes (6 patients), followed by local failure in 1 patient and lung metastases in 1 patient. On follow-up, 5 patients died of disease, 4 died due to cachexia caused by distant metastases, and 1 patient by carotid artery perforation cause by lymph nodes metastases.

Conclusions: Proton beam radiotherapy showed promising local control benefits and would benefit from ongoing clinical study. © **2011 Elsevier Inc.**

Proton beam therapy, Mucosal melanoma, Head and neck.

INTRODUCTION

Although rare worldwide, mucosal melanoma of the head and neck is relatively common in Japan (1). Most reports to date have described small series of patients over long time periods but have not led to any consensus in the approach to treatment. A surgical approach incorporating postoperative radiotherapy has been recognized as a community standard, and the 5-year survival rate of head and neck mucosal melanoma varies from 20% to 45% (2–5). This surgical approach is often complicated by serious cosmetic and functional deformity, and, particularly for nasal and sinonasal mucosal melanoma, satisfactory surgical clearance is often markedly difficult to obtain.

Several reports have described the use of radiotherapy alone for mucosal melanoma of the head and neck, with 5-year survival rates slightly less than those of the surgical approach (6–8). Regarding radiotherapy, The review by Trotti *et al.* (9) of four reports of radiotherapy for mucosal melanoma showed 3-year local control rates of 36% to 61%. In Japan Wada *et al.* (10) recently reported a series of 66 cases of mucosal melanoma of the head and neck, 21 of whom were treated with radiotherapy as the main modality. The rate of complete response in these 21 cases was 29%, and the 3-year disease-specific survival rate was 33%. Since X-ray irradiation has a limitation of dose distribution for tumor areas in proximity to organs at risk, like optic nerve and brain stem, it is often difficult to give enough dosage to planned target volume.

Proton beam therapy (PBT) is characterized by rapid fall-off at the distal end of the Bragg peak and a sharp lateral penumbra, depending on the energy, depth, and delivery (11).

Because of its physical characteristics, PBT provides better dose distribution than X-ray irradiation. PBT is deemed a feasible and effective treatment modality that provides curative high-dose irradiation to the tumor volume without increasing normal tissue toxicity. However, the use of PBT

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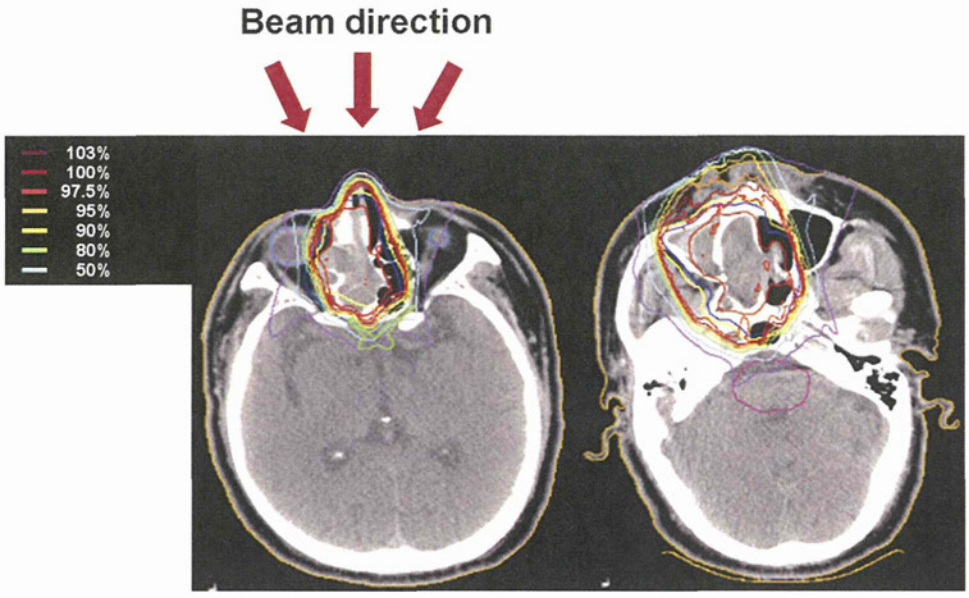

Fig. 1. Target volume and beam arrangement. GTV was defined as the gross tumor lesion determined with pretreatment CT/MRI and PET. CTV was defined as the region of the gross tumor lesion and adjacent sinuses. PTV was basically set as CTV plus 3-mm margin, with acceptance of fine-tuning to the PTV in consideration of organs at risk. Irradiation dose and volume for organs at risk were usually minimized by using a noncoplanar three-field technique.

for mucosal melanoma of the head and neck has not been reported. Here, we conducted a pilot study to examine the utility of hypofractionated PBT as a newly developed treatment modality for mucosal melanoma of the head and neck.

METHODS AND MATERIALS

Patients

Entry criteria for this retrospective study were (*1*) pathologically proven mucosal melanoma of the head and neck; (*2*) clinical TNM status of N0M0; (*3*) Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; (*4*) adequate organ function; and (*5*) no active concomitant malignancy. This treatment was approved by the institutional review board of the National Cancer Center Hospital, and written informed consent to treatment was obtained from all patients before the initiation of treatment.

Pretreatment clinical evaluation was performed using magnetic resonance imaging (MRI); cervical, chest, and abdominal computed tomography (CT); and/or positron emission tomography-CT (PET-CT). Radiological evaluations for staging were jointly reviewed by radiologists, surgeons, and oncologists at our institution. In the present study, all diseases were staged with the International Union Against Cancer criteria for carcinoma of the nasal cavity or paranasal sinus (12).

Table 1. Patient characteristics

Characteristic	Parameter	No. of patients (n = 14)
Age	Median (range)	73 (56-79)
Gender	Male/female	7/7
Performance Status	0 to 1/2	14/0
Primary site	Nasal cavity	11
	Paranasal sinus	3
TNM stage	T1N0M0	3
	T2N0M0	2
	T3N0M0	0
	T4N0M0	9

Treatment

PBT was delivered three times per week for a planned total dose of 60 Gy equivalents (GyE) in 15 fractions using a 150- to 190-MeV proton beam. The biologically equivalent dose (BED) using a linear-quadratic model is defined as BED = nd [1+ d/1/(α/β)], where n is the fractionation number, d is the daily dose, and the α/β ratio was 2.5 ($Gy_{2.5}$) for malignant melanomas (6). When n = 15 and d = 4 were substituted, BED was 156 $Gy_{2.5}$.

Treatment planning was performed with a three-dimensional CT planning system. In this system, the proton beam was generated with a Cyclotron C235 with an energy of 235 MeV at the exit. Relative biologic effectiveness was defined as 1.1, based on our preclinical

Table 2. Adverse events

Toxicity	No. of patients with toxicity grade shown* 1	2	3	4	% 3-4
Dermatitis	7	5	0	0	0
Mucositis	9	2	3	0	21
Infection	0	0	0	0	0
Hearing loss	1	0	0	0	0
Neuropathy					
CN-II	0	0	2	0	12
CN-V	0	0	0	0	0
Keratitis	0	2	0	0	0
Memory impairment	0	0	0	0	0

Treatment-related death: 0%.

* Using Common Terminology Criteria for Adverse Events vesion.3.0.

experiments (13). PBT at our institution is passive irradiation with dual-ring double-scatter methods. Dose distribution was optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Gross tumor volume (GTV) was determined with pretreatment CT, MRI, and/or PET-CT. The clinical target volume (CTV) was defined as the GTV plus a 5-mm margin and sinuses adjacent to GTV. In cases with brain invasion, the area of T_2-weighted prolongation on MRI was also included in the CTV. The planning target volume (PTV) was basically defined as the CTV plus a 3-mm margin but could be finely adjusted where necessary in consideration of organs at risk. The beam energy and spread-out Bragg peak were fine-tuned such that the PTV encompassed a 90% isodose volume of the prescribed dosage. Irradiation dose and volume for organs at risk was usually minimized using a noncoplanar three-field technique (Fig. 1).

Dose constraints for organs at risk at 4 GyE per fraction were (*1*) surface of brainstem, 45 GyE; (*2*) center of brainstem, 33 GyE; (*3*) optic nerves of the healthy side/chiasm, 42 GyE; and (*4*) optic lens, 13 GyE.

To evaluate the risk of radiation-induced complications in normal tissue, dose–volume histograms were calculated for all patients. Patients were immobilized with custom-made immobilization devices that provided high reproducibility at every treatment fraction. Patient setup was verified before the delivery of each fraction, using a digital radiography subtraction system.

Evaluation of toxicity and efficacy

Toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Weekly follow-up was continued until acute toxicity was easily manageable, and posttreatment MRI was performed at 6 to 10 weeks after the end of PBT to rule out treatment-induced empyema and brain necrosis. To confirm local control, MRI was performed every 3 to 6 months after the end of treatment, and distant metastases were assessed by CT/PET-CT. The achievement of initial local control was confirmed when all of the following criteria were fulfilled: (*1*) patients were alive at 1 year after the initiation of treatment; (*2*) no progressive disease was detected at the primary site for 1 year; and (*3*) no recurrence was detected at the primary site for 1 year.

Statistical analysis

Overall survival time 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 confirmed date of survival if the patient was alive. Progression-free survival (PFS) time was defined from the day of initiation of treatment to the first day of confirmation of progressive disease at any site or any cause of death. Overall survival time, PFS time, and local control period were estimated using the Kaplan-Meier product-limits method.

RESULTS

Patient characteristics

Fourteen consecutive patients with mucosal melanoma of the head and neck were treated with PBT at the National Cancer Center East from March 2004 through February 2007. All patients agreed to participate in the present study. Patient characteristics are listed in Table 1. Median age was 72 years (range, 56 to 79 years). Most patients had a good performance status, and over half the patients had T4 disease.

Toxicity

Major adverse reactions to PBT are listed in Table 2. The most common acute toxicities were mucositis (grade 3, 21%) and mild dermatitis (grade 3, 0%). All patients were able to receive the full dose of PBT (60 GyE) given with a median duration of 36 days (range, 33–42 days). Blindness did not occur, although 2 patients had a unilateral decrease in visual acuity. No treatment-related deaths occurred throughout the study.

Efficacy

Initial local control rate was 85.7% (12/14 patients, 95% confidence interval [CI], 57.2%–98.2%). One patient had recurrent disease, and 1 patient died within 1 year after the initiation of treatment.

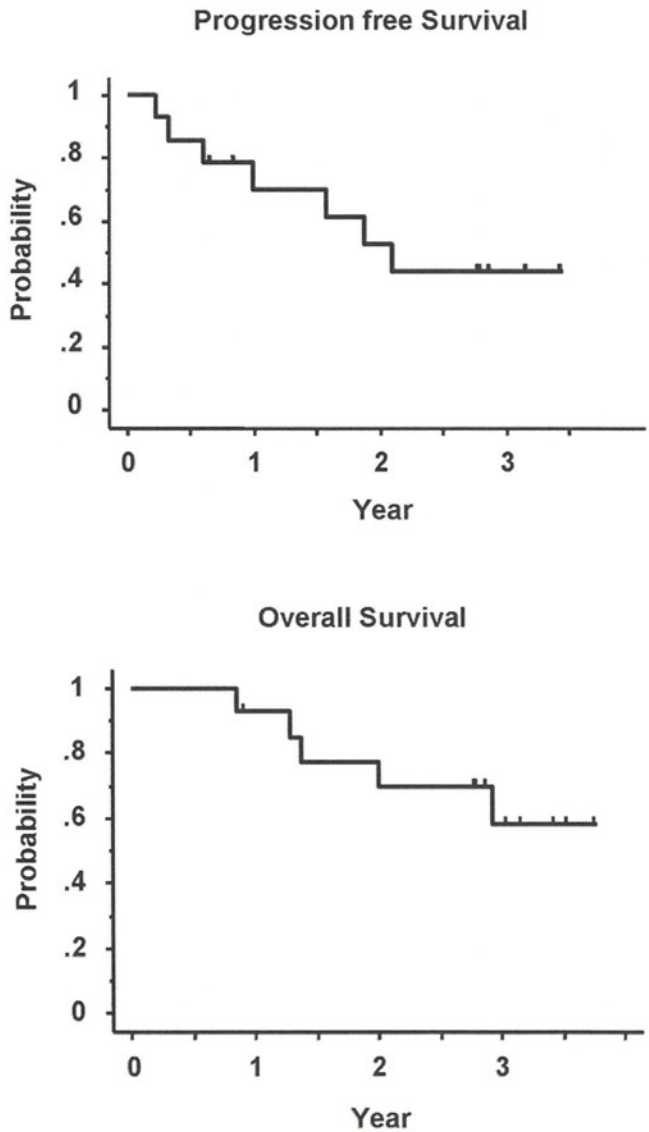

Fig. 2. Progression-free survival (PFS) and overall survival (OS). PFS and OS rates were estimated using the Kaplan-Meier product-limits method. Median PFS was 25.1 months, and 2-year PFS rates were 43.7%. Median survival time was not reached, and 3-year overall survival rate was 58.0% with a follow-up period of 36.7 months.

Table 3. Failure pattern in detail

Case	Time to failure	Failure site	Second-line treatment	Status (time)	Cause of death
1	2.7 M	LN II	Observation	Alive (35.2 M)	
2	22.5 M	LN Ib	Salvage Surgery	Death (35.1 M)	DOD/LM
3	3.8 M	LN Ib, II	Observation	Death (15.4 M)	DOD/DM
6	30.1 M	LN Ib, II	Salvage Surgery	Alive (37.0 M)	
8	11.9M	LN II	Radiation	Death (18.6 M)	DOD/DM
9	7.1 M	LN Ib, II	Salvage Surgery	Death (23.9 M)	DOD/DM
10	8.1 M	Lung	Observation	Death (10.1 M)	DOD/DM
11	18.6 M	Primary site	Observation	Alive (42.7 M)	

Abbreviations: M = months; LN = lymph node; DOD = died of disease; LM = lymph node metastases; DM = distant metastases.

Median PFS was 25.1 months, and 2-year PFS rate was 43.7%. Median survival time with a follow-up period of 36.7 months was not reached, and 3-year overall survival rate was 58.0% (Fig. 2).

Failure pattern and second-line treatment

Six of 14 patients were alive at the end of follow-up with no evidence of disease, while the remaining 8 patients had evidence of disease progression. The most frequent site of first failure was a cervical lymph node outside of the PTV (6/8 patients), followed by local failure in 1 patient (1/8), and lung metastases in one patient (1/8). Failure pattern details are shown in Table 3. With regard to lymph node metastases, 4 patients (4/6) experienced progress within 1 year, and all failure sites were lymph node level Ib or II.

Cause of death

On follow-up, 5 patients died of disease, 4 patients due to cachexia caused by distant metastases and 1 patient by carotid artery perforation cause by lymph nodes metastases.

DISCUSSION

In this study, hypofractionated PBT showed good local control for mucosal melanoma of the head and neck and acceptable toxicity. Prognosis of mucosal melanoma of the head and neck remains poor. In their review of more than 1,000 patients, Mandolis *et al.* (14) reported 5- and 10-year survival rates of 17% and 5%, respectively. Overgaard *et al.* (6) reported a significant relationship between dose per fraction and response, with complete response rates of 59% when fractions of more than 4 Gy were used, compared to 24% with fractions lower than or equal to 4 Gy, while a univariate analysis by Wada *et al.* (9) revealed that a high dose per fraction (3Gy) and high biologically equivalent total dose were associated with better local control and survival.

From these findings, our treatment schedule was planned with consideration for two premises: hypofractionation and high BED. Carbon ion radiotherapy is a promising nonsurgical modality for mucosal melanoma of the head and neck. Yanagi *et al.* (15) reported that with a median follow-up period of 49.2 months, 3-year survival rates were 46.1% in mucosal melanoma patients treated with carbon ion radiotherapy.

The 3-year overall survival rate was 58.0% in the present study. In comparison with the surgical approach or carbon ion therapy, the efficacy of PBT seemed not to be inferior, although recruiting number of patients was small. With regard to late toxicity, decreased visual acuity occurred in 2 patients. Generally, it is often inevitable that the PTV in stage T4 disease with paranasal and/or intracranial invasion includes the unilateral or bilateral optic nerves. In these patients, the better

Table 4. Published cases of late toxicity

Author (study)	Year	Location	Modality	No.of patients	% Treatment outcome	Late toxicity (severe morbidity)
Owens *et al.* (3)	2003	Sinonasal	S	20	5YSR 45%	Not mentioned
			S + RT	24	5YSR 29%	
Temam *et al.* (4)	2005	Sinonasal +α	S/S + RT	30/39	5YSR 20%	Not mentioned
Krengli Owens *et al.* (5)	2006	Head and neck	S/S + RT/others	17/42/15	3YSR 31%	>Grade 3 11% Stenosis of the nasocrimal duct Dry-eye syndrome Optic nerve toxicity Bone necrosis
Wada Owens *et al.* (10)	2004	Sinonasal +α	RT/S+RT	21/10	3YSR 33%	Grade 4 6% soft tissue necrosis; fatal bleeding
Gilligan and Slevin (7)	1991	(Para)-nasal	RT	28	5YSR 17.9%	None
Yanagi *et al.* (15)	2009	Head and neck	Carbon	72	3YSR 46.1%	Grade 2 skin, mucosa*
Present study	2010	Paranasal	Proton	14	3YSR 58.0%	Gade 3 12% unilateral visual acuity

Abbreviations: 5YSR = 5 year survival rate; S = surgery.
* Visual loss after carbon ion radiotheraphy was not mentioned.