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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/(α/β)), 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.

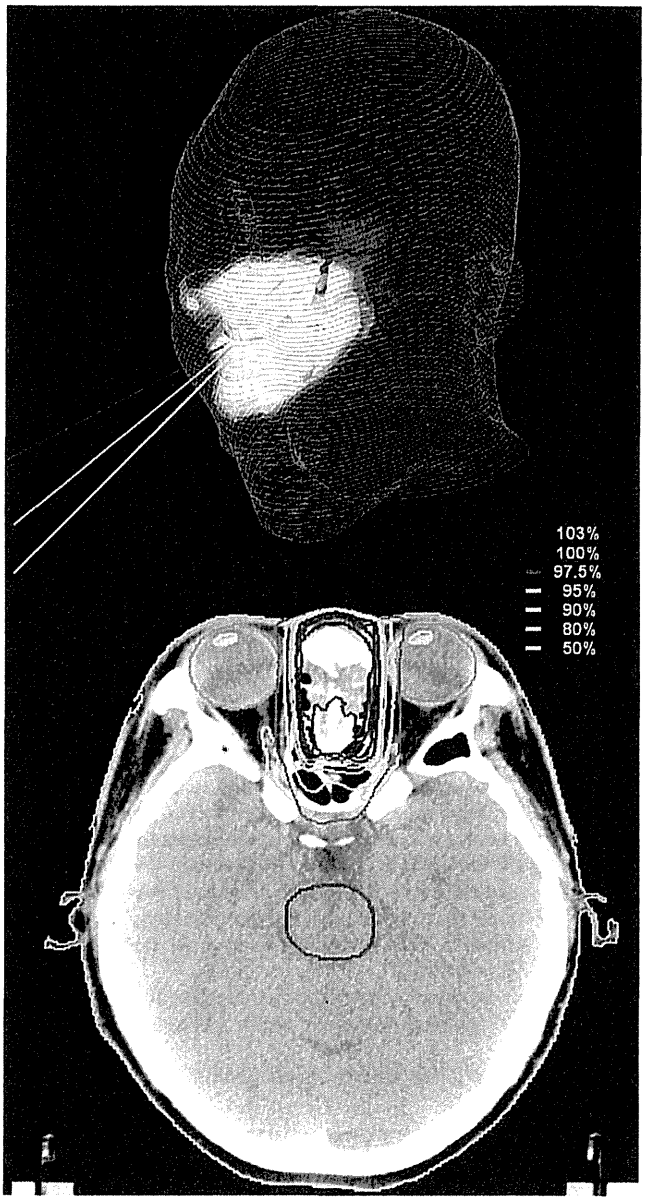

Fig. 1. Beam arrangement. Irradiation dose and volume for organs at risk was usually minimized using a noncoplanar three-field technique. In this case, curative high-dose irradiation to the tumor volume was provided, whereas overdose irradiation to the optic nerve was avoided.

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.

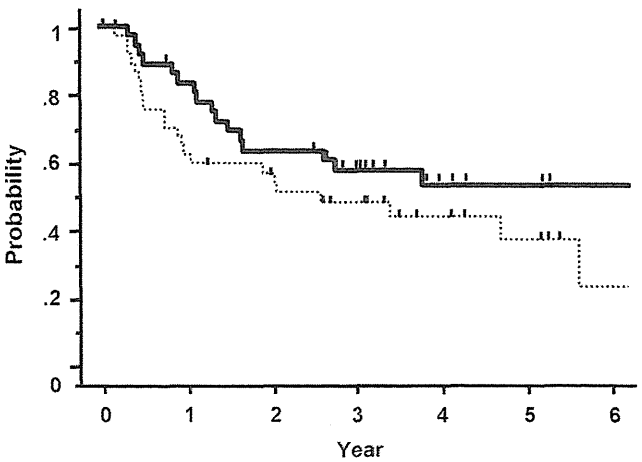

Fig. 2. Overall and progression-free survival. Solid line indicates overall survival curve; broken line indicates progression-free survival curve. With a median follow-up period of 45.4 months, 3-year overall survival and progression-free survival rates were 59.3% and 49.1%, respectively.

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.

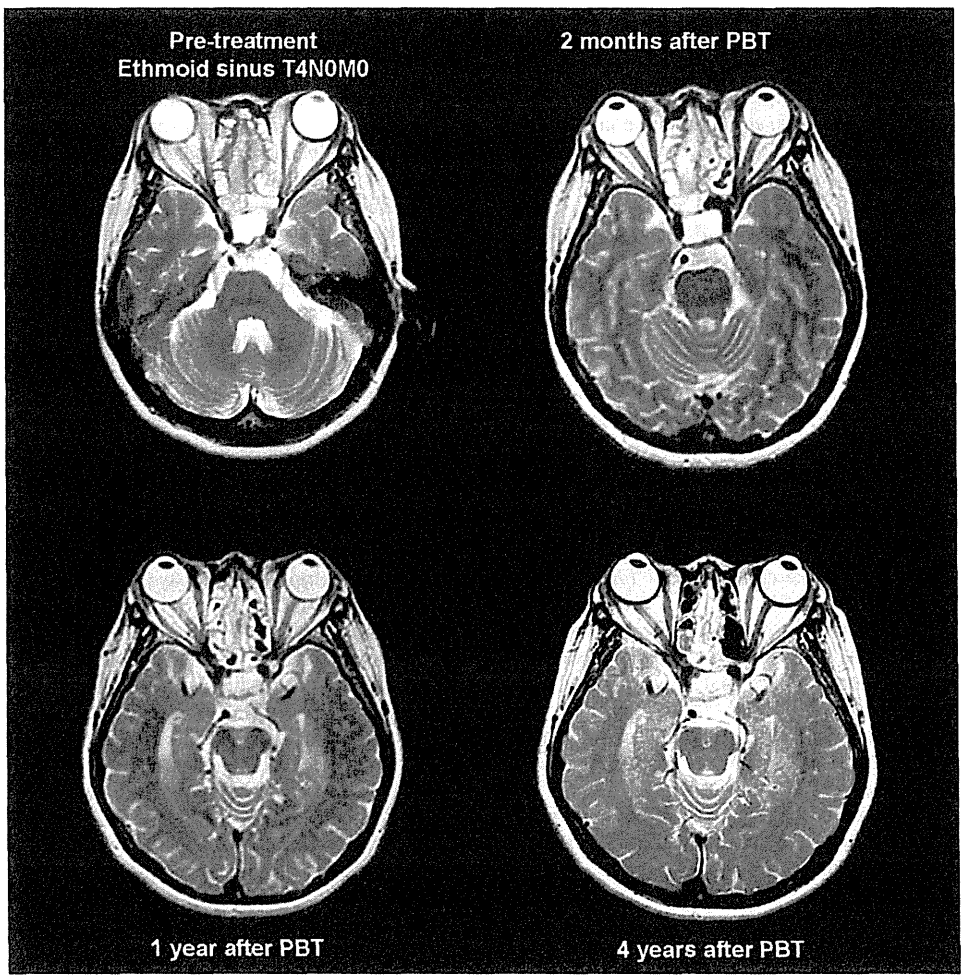

Fig. 3. Difficulty of response evaluation of proton beam therapy (PBT). The disease was undifferentiated carcinoma of the ethmoid sinus. Response evaluation at 2 months and 1 year after PBT was SD by the RECIST criteria; however, the patient has remained alive for more than 4 years without disease progression.

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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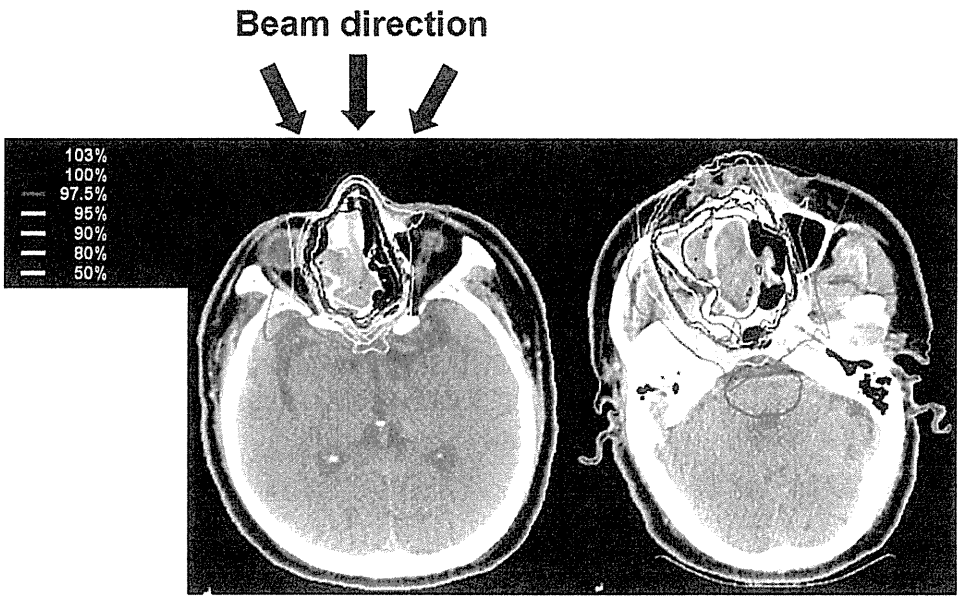

Fig. 1. Target volume and beam arrangement. GTV was defined as the gross tumor lesion determined with pretreatment CT/MRI and PET. CTV was defined as the region of the gross tumor lesion and adjacent sinuses. PTV was basically set as CTV plus 3-mm margin, with acceptance of fine-tuning to the PTV in 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

	No. of patients with toxicity grade shown*				
Toxicity	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.

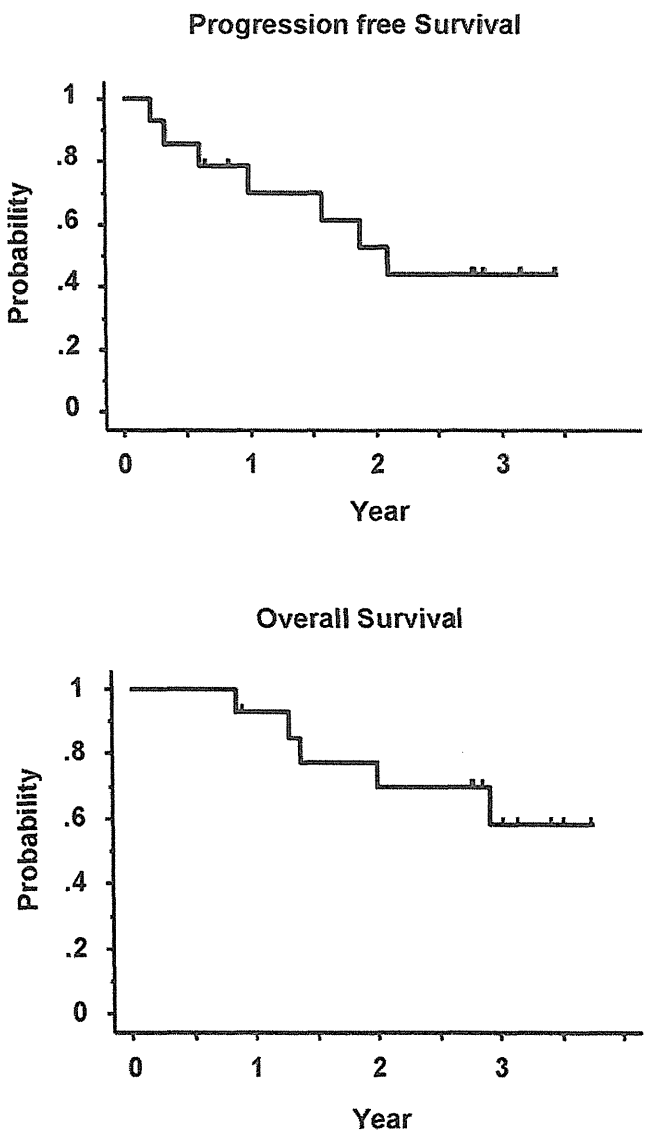

Fig. 2. Progression-free survival (PFS) and overall survival (OS). PFS and OS rates were estimated using the Kaplan-Meier product-limits method. Median PFS was 25.1 months, and 2-year PFS rates were 43.7%. Median survival time was not reached, and 3-year overall survival rate was 58.0% with a follow-up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

dose distribution characteristics of PBT over X-ray should minimize the risk of treatment-related bilateral visual impairment or treatment-related blindness.

Hasegawa *et al.* (16) showed that a certain degree of visual impairment had occurred in 28% of patients whose optic nerves were included in the irradiated volume in carbon ion radiotherapy. There is no report about a direct comparison between PBT and carbon ion radiotherapy.

Previous reports about various approaches to mucosal melanoma are summarized in Table 4.

Cervical lymph nodes were the most frequent site of first failure, and most patients who died finally had distant metastases. Several authors have suggested that aggressive local treatment should be initiated at the presentation of localized melanomas, on the basis that the achievement of local tumor control may increase in survival rate (6, 17). However, it remains controversial whether cervical lymph nodes should be included in the treatment field. We think that what we can do at present is to institute close follow-up after PBT and to detect signs of recurrence or regrowth as early as possible.

CONCLUSIONS

In conclusion, PBT for mucosal melanoma showed promising local control benefit and enough feasibility. To confirm the efficacy and safety, a phase II study of hypofractionated PBT for mucosal melanoma of the head and neck (UMIN-000001505) using the same treatment schedule as the present study is now ongoing in Japan.

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SUPPORTIVE CARE INTERNATIONAL

Family member perspectives of deceased relatives' end-of-life options on admission to a palliative care unit in Japan

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Abstract
Purpose Our goal was to better facilitate the desire of terminally ill patients to die in a favorite place, which may not always be the case for patients admitted to palliative care units. Our aims were to assess the perspectives of bereaved family members about (1) available and preferred places of care when their ill loved one was admitted to a palliative care unit and (2) why patients preferred to live at home but could not.

Methods A questionnaire was answered by 407 of 663 bereaved family members of cancer patients who were admitted to 95 inpatient palliative care units in Japan.
Results Seventy-three percent of respondents answered that a palliative care unit was the only available option. Patients lacking other places for care preferred their home (49%), a hospital (26%), or a long-term care facility (28%). Only 9% retrospectively considered that living at home was feasible for the following reasons: anxiety about the patient's deteriorating physical condition (85%), insufficient care at home compared to a hospital (84%), imminent hospitalization (63%), and the patient's concern about being burdensome (60%).
Conclusion Seventy-three percent of terminally ill cancer patients admitted to palliative care units had no other options for care. Improving outpatient treatment at palliative care units and establishing a palliative care system in patients' homes would greatly benefit patients and their families.

Keywords Attitude to death · Home care · Terminal care · Palliative care · Neoplasms · Retrospective studies

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Introduction

Dying in a favorite place is an important goal in achieving a good death [1–3]. In the Western countries and Japan, home is the most strongly preferred place to die [4–6], but this is not achievable by many patients [4, 5, 7–9]. In Japan, 55%, 15%, and 29% of 2,549 people chosen from the general population preferred the home, general hospital, or a palliative care unit mainly within a hospital as places to die of cancer, respectively [6]. In contrast, in 2009, the percentages of cancer patients dying at home, in a hospital, or at a

palliative care unit were 7%, 84%, and 7%, respectively [9, 10]. This large discrepancy between a person's wishes for a "good death" and actual circumstances must, therefore, be addressed by the health care community to provide patients with the best possible medical treatment and the most ethical and compassionate care.

A systematic review aimed at addressing this problem identified six factors strongly associated with patients' reasons for death at home: poor health, personal preference, intensity of home care, living with relatives, and extended family support [11]. In contrast, only a few individuals in the general population responded that living at home at end-of-life would be feasible if they became terminally ill [12]. Although several factors regarding patients and family members were significantly related to death at home, the evidence is insufficient with respect to the experiences of the patients and family members who preferred end-of-life home care even though it was not possible.

Patients may experience problems when admitted to palliative care units. Specialized palliative care in Japan has been developed primarily in palliative care units since 1990 and expanded since 2002 to include palliative care teams in general wards. One of the aims of the Cancer Control Act implemented in 2007 was to promote early palliative care for more patients. Therefore, the health care system in 2008 required palliative care units to enhance cooperation with regional general practitioners (GPs) and district nurses. Most patients whose symptoms were relieved by treatment in a palliative care unit were nevertheless not discharged. Thus, a nationwide survey reported that, in 2009, 86% of patients admitted to palliative care units died there, and the mean length of stay was 42 days [9, 13]. Moreover, 49% of the 318 bereaved family members queried by the survey regarded the referrals to palliative care units as "too late" [14]. This indicates that admission to palliative care units often means a comparatively short stay until death. A negative image of palliative care units is held by terminal cancer patients [15, 16], family members [15, 16], physicians [16], nurses [16], and the general population [17]. Further, 39% of those surveyed were emotionally distressed by the information that they received regarding discontinuing cancer treatment and admission to a palliative care unit [18]. The Japanese national health care system has recently restricted prolonged and unnecessary hospitalization, making it difficult for advanced cancer patients to transfer to appropriate care facilities when their treatment ends. It is assumed that not all patients were admitted to their preferred palliative care units.

Therefore, our aims here were to assess the perspectives of bereaved family members about (1) available and preferred places of care upon admission of their relative to a palliative care unit and how the quality of care provides patients with a comfortable end-of-life and "good death" and (2) why patients preferred to live at home but could not.

Methods

Procedure

Our study was a component of a large cross-sectional anonymous nationwide survey, the Japanese HOspice and Palliative Care Evaluation study (J-HOPE study), of bereaved families of cancer patients, the latter having been admitted to 95 inpatient palliative care units in Japan and died between November 2004 and October 2006. Detailed methods have been described elsewhere [19]. Briefly, we mailed information and questionnaires to randomly selected bereaved family members in June 2007 and to nonresponders again in August 2007. Completion and return of the questionnaire was regarded as consent to participate. The institutional review board of each hospital confirmed the ethical and scientific validity of our study.

Participants

Primary physicians identified potential J-HOPE study participants according to these criteria: (1) bereaved family members of an adult cancer patient (one family member was selected for each patient), (2) age ≥20 years, (3) capable of replying to a self-administered questionnaire, (4) aware of the diagnosis of malignancy, and (5) no serious psychological distress. We identified up to 80 potential participants at each institution and admitted 7,892, of whom 663 were randomly allocated to this study.

Questionnaire

We used a two-part questionnaire that asked randomly allocated participants unique and common questions for all J-HOPE study participants. The unique questions inquired about available and preferred places of care on admission to palliative care units and the reasons why patients preferred to live at home but could not. Specifically, we asked whether they had alternatives to palliative care units. If they answered no, we then asked whether patients preferred home, a hospital offering

acute care, or a long-term care facility. If they preferred home, we asked whether this would have been feasible in retrospect, and why this was not possible. We show the questions in the "Appendix."

Common questions were designed to measure the quality of palliative care and dying. Respondents rated their *overall care satisfaction* (as defined in Morita et al. [20]): "Overall, were you satisfied with the care in the palliative care unit?" provided by palliative care units according to the following scale: 1=very dissatisfied to 6=very satisfied. In addition, respondents completed a subset of the Good Death Inventory (GDI), comprising 18 items (out of 54) in 18 domains to measure the quality of dying. The GDI has good psychometric properties. The subscale score ranged from 1=absolutely disagree to 7=absolutely agree [21]. We used "dying in a favorite place" domain to evaluate place of dying. The concepts of *overall care satisfaction* and GDI appear similar but are in fact different, with the former assessing care provided and the latter evaluating the quality of dying. Further, the Pearson's correlation coefficients showed only a medium effect size (r=0.39) [21].

The questionnaire also asked for each patient's gender, age, primary cancer site, length of time since referral, length of stay in a palliative care unit, and bereaved family members' gender, age, relationship, health status, number of visits to patients in the final week of life, and surrogate family caregivers.

Analyses

We calculated descriptive statistics for each variable. To compare the characteristics of respondents and nonrespondents, Fisher's exact test or Wilcoxon test was conducted as appropriate. To explore the significance of factors related to the perception of available alternatives to palliative care units, univariate analysis was conducted using a logistic regression model. Further, to assess the influence of available choices and preferences of care location on quality of care and dying, univariate analysis was conducted using the Wilcoxon test. We examined overall satisfaction with care in palliative care units and "dying in a favorite place" according to the GDI subscale. All analyses were performed using the SAS statistical package version 9.2 (SAS Institute, Cary, NC, USA).

Results

The questionnaire was answered by 407 (61%) out of 663 bereaved family members of cancer patients. Table 1 summarizes the characteristics of the patients and those of their bereaved family members. The mean age of the patients was 70±12 years; 53% were male; and primary cancer sites were gastrointestinal tract (26%), lung (24%), liver, and pancreas (16%). The mean age of family members was 58±13 years; 34% were male; and spouses and children accounted for 45% and 43% of the total, respectively. No significant difference of patients' characteristics was seen between respondents and nonrespondents, except that the respondents stayed significantly longer at palliative care units.

Available and preferred places of care

Seventy-three percent of bereaved family members thought that their only option was a palliative care unit (Table 2). Of those for which no other options existed, respondents indicated that patients preferred home (49%), acute hospital (26%), or a long-term care facility (28%). Of those who preferred home, only 9% of respondents retrospectively thought that this was feasible.

Reasons why patients preferred to live and die at home but could not

Respondents frequently indicated the following reasons for patients not being able to live at home as they desired: anxiety about worsening physical condition (85%), insufficient care at home compared to a hospital (84%), anxiety about immediate hospitalization (63%), and concern about being a burden to the family (60%) (Table 3).

Factors related to the perception that only palliative care units were available

Univariate logistic regression analysis showed that older family members thought that palliative care units were the only option (odds ratio (OR)=1.25, p=0.03), but no other significant relationship was found between the characteristics of patients and those of their bereaved family members related to their perception of available places of care (Table 4).

Influence of available and preferred places of care on quality of care and dying

The Wilcoxon test showed no significant differences in overall satisfaction with care (p=0.46) and evaluation of dying in a favorite place (p=0.28) compared with care

Table 1 Characteristics of patients and their bereaved family members

	Respondents		Nonrespondents		*p* value
	Number	Percent	Number	Percent	
Patients					
Gender (male)	217	53	144	56	0.40
Age (years, mean±SD)	70±12		69±13		0.52
<60	86	21	59	23	
60–69	86	21	51	20	
70–79	131	32	86	34	
≥80	99	24	60	23	
Cancer site					0.93
Gastrointestinal tract	107	26	66	26	
Lung	96	24	64	25	
Liver and pancreas	64	16	36	14	
Head and neck	28	7	17	7	
Gynecology	26	6	14	5	
Others	81	20	59	23	
Time at palliative care unit (days, mean±SD)	44±72		41±73		0.02
<15	112	28	98	38	
15–29	91	22	54	21	
30–59	103	25	61	24	
≥60	96	24	43	17	
Bereaved family members					
Gender (male)	139	34	–		
Age (years, mean±SD)	58±13		–		
<50	102	25			
50–59	110	27			
60–69	103	25			
≥70	88	22			
Relationship to patients					
Spouse	185	45	–		
Child	174	43			
Others	46	11			
Health status when caring for dying patients					
Good	79	19	–		
Moderate	219	54			
Fair	85	21			
Bad	19	5			
Number of visits during patients' final week of life					
Daily	282	69	–		
4–6 days	56	14			
1–3 days	54	13			
None	11	3			
Surrogate family caregivers					
Yes	292	72	–		
No	111	27			

Not all percentages add up to 100% due to missing values

SD standard deviation

options other than a palliative care unit (Table 5). In contrast, bereaved family members' responses indicated that the quality of dying in a favorite place was decreased if patients preferred to be at home ($p<0.001$). However, the overall satisfaction with care was not significantly different ($p=0.73$).

Table 2 Available and preferred places of care other than palliative care units

	Number	Percent
Available places of care other than palliative care units		
Only palliative care unit was available	296	73
Other places were available	111	27
Preferences for other places for care (n=296)[a]		
Home	144	49
Acute hospital	78	26
Long-term care facility	82	28
Feasibility to live and die at home in retrospect		
Feasible	13	9
Not feasible	130	90

Not all percentages add up to 100% due to missing values

[a] Bereaved family members with only the option for admission to a palliative care unit

Discussion

Our findings reveal that 73% of terminally ill cancer patients admitted to palliative care units do not have the ability to select where they wish to live out their tragically shortened lives. There was no significant correlation between the status of patients and their families and the types of available care facilities, indicating that this represents a shared problem among the general population. We found that the quality of dying was poorer when patients preferred to live and die at home, even though they were equally highly satisfied with their care received at palliative units. This would suggest the need for ongoing assessment of their preferred place of dying. To our knowledge, this is the first study to explore these aspects of terminally ill cancer patients' experiences with Japan's health care systems for providing end-of-life care.

Our findings also indicated that only a few bereaved family members retrospectively perceived home as a

Table 3 Reasons why patients preferred to live and die at home but could not

	Number	Percent
Anxiety about deteriorating physical condition	123	85
Insufficient care at home compared to hospital	121	84
Anxiety about immediate hospitalization	91	63
Patient's concern about burdening the family	86	60
Inadequate living environment	71	49
24-h consultation not available	67	47
Absence of family care	64	44
Absence of visiting physician/nurse	55	38
Financial burden	39	27

Not all percentages add up to 100% due to missing values. Bereaved family members of patients who preferred to, but could not choose end-of-life home care (n=144)

Table 4 Factors related to the perception of no other choices other than palliative care

	OR	95% CI	p value
Patients' characteristics			
Gender (reference = "male")	1.24	0.79–1.93	0.35
Age	1.19	0.98–1.45	0.08
Cancer site (reference = "gastrointestinal tract")			
Lung	1.50	0.80–2.81	0.40
Liver and pancreas	1.14	0.58–2.25	0.78
Head and neck	1.12	0.45–2.79	0.80
Gynecology	1.49	0.55–4.04	0.63
Others	1.20	0.63–2.27	0.92
Time at palliative care unit	1.05	0.87–1.28	0.60
Bereaved family members' characteristics			
Gender (reference = "male")	0.91	0.57–1.44	0.68
Age	1.25	1.02–1.53	0.03
Relationship to patients (reference = "spouse")			
Child	0.82	0.51–1.34	0.68
Others	0.83	0.45–1.53	0.75
Health status when caring dying patients	1.00	0.75–1.33	1.00
Number of visits for patients last week	1.09	0.83–1.44	0.52
Surrogate family caregivers	0.90	0.55–1.46	0.67

OR >1 means no other available choices than palliative care units

OR odds ratio, *CI* confidential interval

Table 5 Influence of available choices and preferences of place on quality of care and dying

	Overall satisfaction		Dying in a favorite place	
	Mean±SD	p value	Mean±SD	p value
Available places of care other than palliative care units				
Only palliative care unit was available	5.0±0.9	0.46	5.1±1.5	0.28
Other places were available	5.0±0.9		5.4±1.3	
Preferences for other than palliative care units				
Home	5.0±0.9	0.73	4.7±1.5	<0.0001
Other than home	5.0±1.0		5.6±1.4	

SD standard deviation

feasible alternative. Our survey of 595 subjects in the general population found that only 9% answered "possible" to the feasibility of dying at home [12]. In Japan, almost all bereaved family members we studied and, by inference, those in the general population think that living at home while suffering a terminal illness was impossible. Bereaved family members pointed out that their inability to provide adequate practical care and support were the major reasons that prevented patients from remaining home until they died. Therefore, we propose two strategies for allowing terminally ill cancer patients to be dying at home. The first strategy involves improving outpatient care at palliative care units. This will enable patients to stay at home as long as possible and then be admitted to palliative care units as inpatients when death is imminent. The second strategy aims to improve the palliative care system in the home. The latter is a social infrastructure problem. Home palliative care services are well established in the USA and in some European countries such as the UK, Sweden, Italy, and Spain [22, 23]. At present, Japan is still in the developmental stage of providing this type of care. The first strategy, therefore, is more feasible than the second one for immediately and significantly improving end-of-life care.

Factors affecting the implementation of the first strategy include late referrals to palliative care [14, 24–27] and palliative care units not providing adequate treatment at home or at outpatient facilities [9]. Providing patients with specialized palliative care services at home or at outpatient facilities could provide substantial benefits before admission to a facility. Palliative care units must shift focus more on palliation from care for imminently dying patients [13] and caring for terminally ill cancer patients at home for as long as possible. The hypothesis that a prolonged stay at home would contribute to quality of dying is supported by evidence that the general population's preferences for places to live at the end-of-life and to die are different [6]. Improvements in outpatient care may also contribute to removing the negative image of palliative care units as the final residence for these patients [15–17].

We suggest that health care professionals should undertake the following measures: (1) facilitate coping as the patient's condition deteriorates and alleviate family anxiety, (2) alleviate burdens on the family by, for example, using regional resources including respite and day care as well as improvements in managing symptoms, and (3) provide sufficient palliative home care including managing symptoms, helping with living arrangements, and offering 24-h consultation and family care. Yamagishi et al. [28] concluded that the current quality of palliative home care at the regional level is insufficient. For example, Japanese GPs have little experience in providing home care for terminal cancer patients, and 35% and 50%, respectively, could not administer oral or subcutaneous opioids or haloperidol. The authors indicated the importance of the following activities: (1) educating GPs about managing symptoms, (2) providing available palliative care consultation services, (3) establishing systems to support home care technology, and (4) helping coordinate systems to alleviate burdens on family. The views of bereaved family members that we report here support these proposals.

Consistent with Japanese thinking that fighting vigorously against cancer is an important component of a good death [1] was our finding that 26% of terminally ill cancer patients preferred acute hospital care. However, many palliative care units in Japan have admissions policies requiring patients to discontinue cancer therapy. Some patients and family members complained about this policy [15–17] and, therefore, preferred acute hospital care.

This study has several limitations. First, our survey represents the retrospective views of bereaved family members regarding end-of-life choices and patients' preferences of places of care. Consequently, our findings may be subject to recall bias. However, bias from surrogate respondents can be justified because end-of-life decision-making is more often entrusted to families rather than to patients in Japan [29–31]. Second, there was insufficient information regarding physical and psychological symptoms. This may influence the feasibility of living at home during terminal disease. Third, the subjects were limited to the bereaved family members of patients who had been admitted to palliative care units. Our findings might not be applicable to families in other settings.

In conclusion, 73% of terminally ill cancer patients admitted to palliative care units did not have access to other facilities. For patients to die at home in relative comfort and with dignity, we propose two strategies aimed to improve outpatient care at palliative care units, thereby prolonging residence at home and enhancing the home palliative care system.

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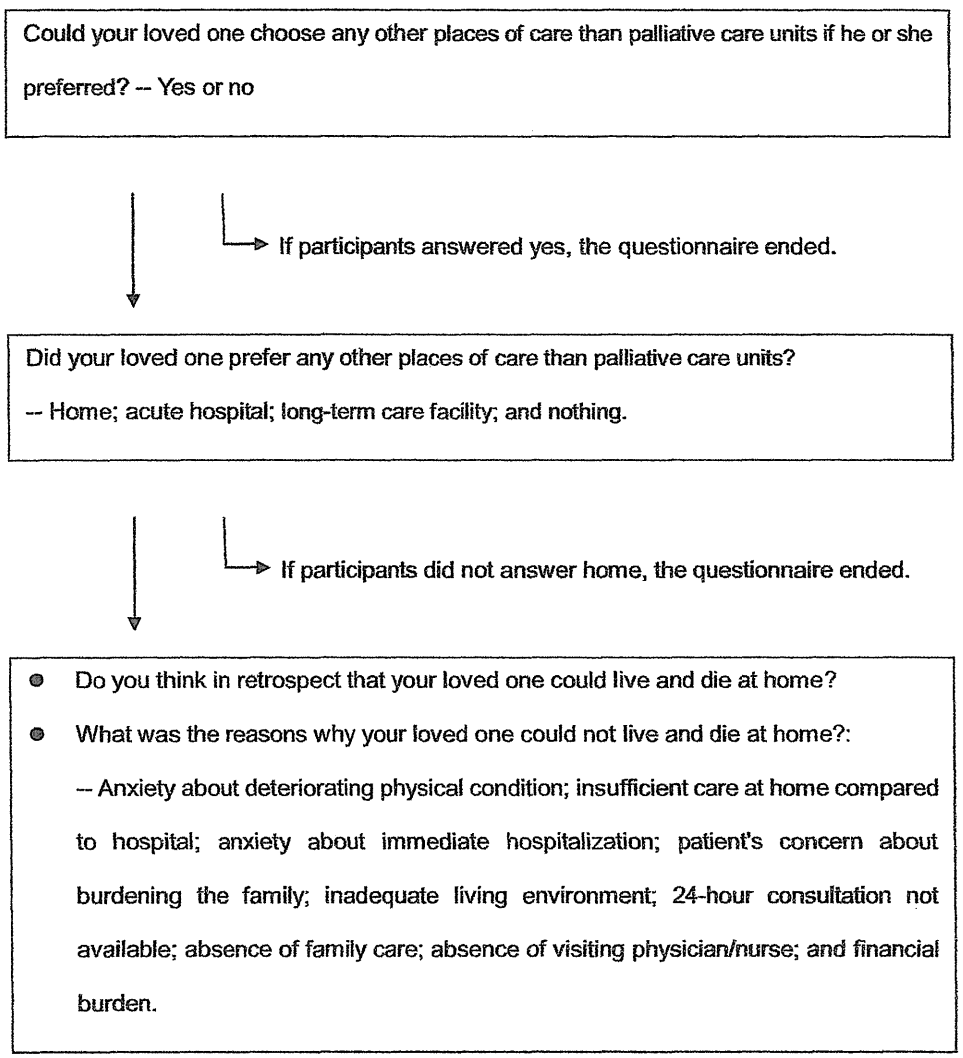
Conflict of interest None.

Appendix. Questionnaire of this study



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Original Article

A Scale for Measuring Feelings of Support and Security Regarding Cancer Care in a Region of Japan: A Potential New Endpoint of Cancer Care

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Abstract

Context. Having a sense of security about the availability of care is important for cancer patients and their families.

Objectives. To develop a scale for the general population to evaluate feelings of support and security regarding cancer care, and to identify factors associated with a sense of security.

Methods. A cross-sectional anonymous questionnaire was administered to 8000 subjects in four areas of Japan. Sense of security was measured using five statements and using a seven-point Likert scale: "If I get cancer 1) I would feel secure in receiving cancer treatment, 2) my pain would be well relieved, 3) medical staff will adequately respond to my concerns and pain, 4) I would feel secure as a variety of medical care services are available, and 5) I would feel secure in receiving care at home." We performed an exploratory factor analysis as well as uni- and multivariate analyses to examine factors associated with such a sense of security.

Results. The five items regarding sense of security were aggregated into one factor, and Cronbach's α was 0.91. In the Yamagata area where palliative care services were not available, the sense of security was significantly lower than in the other three regions. Female gender ($P = 0.035$), older age ($P < 0.001$), and having cancer ($P < 0.001$) were significantly associated with a strong sense of security.

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