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DOSE–VOLUME HISTOGRAM ANALYSIS OF THE SAFETY OF PROTON BEAM THERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Purpose: To evaluate the safety and efficacy of radiotherapy using proton beam (PRT) for unresectable hepatocellular carcinoma.

Methods and Materials: Sixty consecutive patients who underwent PRT between May 1999 and July 2007 were analyzed. There were 42 males and 18 females, with a median age of 70 years (48–92 years). All but 1 patient had a single lesion with a median diameter of 45 mm (20–100 mm). Total PRT dose/fractionation was 76–cobalt Gray equivalent (CGE)/20 fractions in 46 patients, 65 CGE/26 fractions in 11 patients, and 60 CGE/10 fractions in 3 patients. The risk of developing proton-induced hepatic insufficiency (PHI) was estimated using dose-volume histograms and an indocyanine-green retention rate at 15 minutes (ICG R15).

Results: None of the 20 patients with ICG R15 of less than 20% developed PHI, whereas 6 of 8 patients with ICG R15 values of 50% or higher developed PHI. Among 32 patients whose ICG R15 ranged from 20% to 49.9%, PHI was observed only in patients who had received 30 CGE (V30) to more than 25% of the noncancerous parts of the liver (n = 5) Local progression-free and overall survival rates at 3 years were 90% (95% confidence interval [CI], 80–99%) and 56% (95% CI, 43–69%), respectively. A gastrointestinal toxicity of Grade ≥2 was observed in 3 patients.

Conclusions: ICG R15 and V30 are recommended as useful predictors for the risk of developing PHI, which should be incorporated into multidisciplinary treatment plans for patients with this disease.

Hepatocellular carcinoma, Proton beam radiotherapy, Dose–volume histogram, Radiation tolerance of the liver.

INTRODUCTION

Recent improvements in diagnostic imaging and radiotherapy (RT) techniques have made high-dose radiotherapy a safe and effective treatment for selected patients with unresectable hepatocellular carcinoma (HCC) (1). Charged-particle radiotherapy can potentially deliver considerably larger doses of RT to liver tumors, with greater sparing of normal tissues, and proton beam radiotherapy (PRT) for HCC using aggressively high total and fractional RT doses has been investigated during the last 2 decades. The results have shown local control rates ranging from 75% to 96% and overall survival (OAS) rates exceeding 50% at 2 years in groups of patients that include those who had HCC tumors of ≥5 cm in diameter (2–4). HCC has a high propensity for venous invasion, which is frequently associated with multiple tumors within resected specimens (5–9). In this context, the extent of resection was determined while considering potential tumor spread via portal blood flow and the necessity of preserving a functional liver reserve (5, 7, 10). Even in preselected patients who underwent hepatectomy, more than 50% of tumors with diameters greater than 4 cm demonstrated microscopic vascular invasion (8, 11). Consequently, it will become more crucial to consider the influence of vascular invasion on undetectable tumor dissemination at the periphery of the gross tumor in RT for unresectable HCC.

Given the high probability of obtaining local control by using PRT, an appropriate definition of the clinical target volume (CTV) according to patterns of tumor spread and patients' functional liver reserves is extremely important in order to maximize the therapeutic ratio. Ideally, the entire portal segment that contains HCC nodules should be covered within the CTV when the tumor shows macro- or microscopic vascular invasion. This requires a considerably larger

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irradiated volume even with PRT, partly because of unavoidable uncertainty in treatment planning without using intraoperative ultrasonography (7). Another possible way to eradicate satellite HCC nodules, which are disseminated via portal blood flow, is transarterial chemoembolization (TACE). Currently, the standard treatment for patients with unresectable HCC that is not amenable to local ablation therapy is TACE instead of best supportive care (12). The OAS rate at 3 years after TACE ranges from 32% to 47% in patients with stage III cancer and with liver damage A to B, according to the staging system used in a nationwide cohort study conducted by the Liver Cancer Study Group of Japan (13). Considering that the tumoricidal effect of TACE in HCC with vascular invasion is frequently incomplete (13), a significant benefit of adding PRT to TACE would be expected. However, presently, there has been no robust evidence supporting this concept. Before we examine the validity of targeting the entire anatomical portal segment containing HCC in a multidisciplinary approach that includes PRT, practical methods to estimate the safety of PRT according to the dose–volume histogram (DVH) should be established in patients who have various levels of severity of liver dysfunction. Findings from our previous study consisting of 30 patients suggested that the risk of proton-induced hepatic insufficiency (PHI) could be predicted by the indocyanine green clearance test and the retention rate at 15 minutes (ICG R15) in combination with DVH parameters (14) such as percentages of hepatic noncancerous portions receiving doses of >30 cobalt-Gray-equivalent (CGE) (3). We have subsequently accumulated data from additional patients in clinical practice. The clinical results were evaluated, and we have again used the DVH analysis to examine the relationship between probability of PHI and dose–volume parameters.

METHODS AND MATERIALS

Patients

Patient eligibility was reported previously (3); in brief, they were required to have uni- or bidimensional measurable HCC nodules of ≤10 cm in maximum diameter on computed tomography (CT) and/or magnetic resonance imaging (MRI) without evidence of extrahepatic tumor spread. All patients had a white blood cell count of ≥2,000/mm^3; a hemoglobin level of ≥7.5 g/dl; a platelet count of ≥25,000/ mm^3; and adequate hepatic function (total bilirubin, ≤3.0 mg/dl; alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase of <5.0× normal; no ascites). Patients who had multicentric HCC nodules were not considered as candidates for PRT, except for those who fulfilled the following two conditions: (*1*) multiple nodules could be encompassed within a single clinical target volume; and (*2*) lesions other than those of the targeted tumor were judged to be controlled with prior surgery and/or local ablation therapy. This retrospective study was approved by the institutional ethics committee, and written informed consent was obtained from all patients.

Treatment Planning

ICG R15 was measured in all patients to quantitatively assess the hepatic functional reserve. Serological testing for hepatitis B surface antigen and anti-hepatitis C antibody was done. All patients were judged to be unresectable by expert hepatobiliary surgeons at our institution, based on the patient's serum bilirubin level, ICG R15, and expected volume of resected liver (10). Percutaneous fine-needle biopsies were performed for all patients unless they had radiologically compatible, postsurgical recurrent HCC (3).

Treatment methods were published previously (3). In brief, gross tumor volume (GTV) was defined using a treatment-planning CT scan, and CTV and planning target volume (PTV) were defined as follows in all but 2 patients: CTV = GTV + 5 mm, and PTV = CTV + 3 mm of lateral, craniocaudal, and anteroposterior margins. CTV encompassed the entire volume of the right lobe in 1 patient who had a tumor of 4 cm in diameter that broadly attached to the bifurcation of the right anterior and posterior portal veins. In this patient, right portal vein embolization was done to facilitate compensatory hypertrophy of the left lobe for expected surgery. However, the patient was finally judged to be unresectable, and PRT was selected. Another patient was treated with a CTV encompassing the entire right anterior portal segment because a tumor of 2 cm in diameter had invaded the bifurcation of the right anterosuperior and anteroinferior portal vein associating with daughter HCC at the right anterosuperior portal segment. The beam energy and spread-out Bragg peak (15) were fine-tuned so that a 90% isodose volume of the prescribed dose encompassed the PTV.

Forty-six patients received PRT to a total dose of 76 CGE in 3.8 CGE once-daily fractions, four to five fractions in a week. Another 3 patients underwent 60 CGE /10 fractions/2 weeks, depending on availability of the proton beam. Eleven patients whose PTV encompassed the gastrointestinal wall received 65 CGE in 2.5 CGE /fraction, five fractions per week. All patients were treated using a 150- to 190-MV proton beam. The relative biological effectiveness of our proton beam was defined as 1.1 (16). No concomitant treatment such as TACE, local ablation, or systemic therapy was allowed during or after the PRT, unless a treatment failure was detected. Both scanning of CT images for treatment planning and irradiation by the proton beam were done during the exhalation phase using the respiration-gated irradiation system and intrahepatic fiducial markers as previously reported (3).

Outcomes

Death from any cause was defined as an event in calculation of OAS, whereas tumor recurrences at any site or patient deaths were defined as events in disease-free survival (DFS). An increase of the tumor diameter within the PTV was defined as local progression, and patients who died without evidence of local progression were censored at the time of last radiographic examination. Adverse events were reviewed weekly during the PRT regimen by means of physical examination, complete blood count, liver function tests, and other biochemical profiles as indicated. The severity of adverse events was assessed using the National Cancer Institute common terminology criteria for adverse events, version 3.0. After completion of PRT, reviews that monitored disease status, including CT and/or MRI examinations and long-term toxicity, were done at a minimum frequency of every 3 months in all 60 patients. The percentages of hepatic noncancerous portions (entire liver volume minus gross tumor volume) receiving CGE doses of >0 (V0), ≥10 (V10), ≥20 (V20), ≥30 (V30), ≥40 (V40), and ≥50 (V50) were calculated using PRT planning software (PT-PLAN/NDOSE System, Sumitomo Heavy Industries Ltd., Tokyo, Japan), and their influence on the outcomes were analyzed (3). Time-to-event analyses were done using Kaplan-Meier estimates from the start of PRT. The differences between time-to-event curves were evaluated with the log-rank test. Multivariate analyses were performed with Cox's proportional hazards model.

RESULTS

Patients

A total of 60 patients with HCC underwent PRT in our institution between May 1999 and July 2007. Approximately 1400 patients with HCC were newly presented to our institution during this study period and about 35%, 30%, 25%, and the remainder primarily treated with hepatectomy, TACE, percutaneous local ablation, and other treatments, respectively. Therefore 60 patients in this study corresponded to approximately 4% of overall, or 7% of patients with unresectable HCC. Patient characteristics at the start of PRT are listed in Table 1. All patients had underlying chronic liver disease. One patient had a history of schistosomiasis, and another patient had autoimmune hepatitis as the cause of liver cirrhosis. Five additional patients were diagnosed with liver cirrhosis caused by non-B, non-C hepatitis. A total of 24 patients received PRT as the first treatment for their HCC. Ten patients had postsurgical recurrences, 22 patients received unsuccessful local ablation and/or TACE to the targeted tumor, and 4 patients underwent successful local ablation to a tumor other than the target prior to PRT. Histological confirmation was not obtained in 1 patient who had a tumor with typical radiographic features compatible with HCC (3). Six patients had HCC nodules of ≤3 cm in diameter; however, they were not considered candidates for local ablation therapy because of the tumor locations, which were in close proximity to the great vessels or the lung.

Adverse events during PRT

All patients completed the treatment plan. Prolongation of the overall treatment time for more than 1 week occurred in 4 patients: treatment of 3 patients was extended due to availability of the proton beam machine, and 1 patient's treatment was extended because of fever associated with grade 3 elevation of total bilirubin that spontaneously resolved within a week. A total of 14 patients experienced transient grade 3 leukopenia and/or thrombocytopenia without infection or bleeding that necessitated treatment. In addition, 8 patients experiencing grade 3 elevation of transaminases without clinical manifestation of hepatic insufficiency maintained good performance status. PRT was not discontinued for these patients; nevertheless, these events spontaneously resolved within 1 to 2 weeks.

Estimation of the risk of PHI by DVH analysis

Development of hepatic insufficiency presented with anicteric ascites and/or asterixis within 6 months after completion of PRT in the absence of disease progression was defined as PHI. Eleven patients, all of whom received a total PRT dose of 76 CGE, developed PHI at 1 to 6 months (median, 2 months) after completion of PRT without elevation of serum bilirubin and transaminases of more than threefold above normal levels. DVHs for hepatic noncancerous portions were drawn according to pretreatment ICG R15 values (Fig. 1A–C). Results showed that all 20 patients with ICG R15 of <20% were free of PHI, regardless of the DVH, for 2 to 94 months (median, 44 months). On the other hand, 6 of 8 patients with pretreatment ICG R15 values of ≥50% died of PHI with (n = 3) or without (n = 3) evidence of HCC recurrence at 2 to 15 months (median, 8 months). There was no obvious relationship between DVH and development of PHI in these 8 patients, as shown in Fig. 1C.

Among 32 patients whose ICG R15 values ranged from 20% to 49.9%, 5 patients developed PHI. The V0 to V50 in these 32 patients are shown in Fig. 2. Differences in distributions of these DVH parameters between patients who did

Table 1. Characteristics of patients

Characteristics	No. of patients (%)
Age (years)	
Median	70
Range	48–92
Gender	
Male	42 (70)
Female	18 (30)
ECOG performance status	
0–1	57 (95)
2	3 (5)
Viral markers	
Hepatitis B surface antigen-positive	3 (5)
Hepatitis C antibody-positive	49 (82)
Both positive	1 (2)
Both negative	7 (12)
Child-Pugh classification	
A	47 (78)
B	13 (22)
C	0
% patients with pretreatment ICG R15 values	
<20	20 (20)
20–40	25 (55)
40–50	7 (12)
≥50	8 (13)
Tumor size (mm)	
Median	45
Range	20–90
20–50	42 (70)
>50	18 (30)
Macroscopic vascular invasion	
Yes	42 (70)
No	18 (30)
Morphology of primary tumor	
Single nodular	45 (75)
Multinodular, aggregating	9 (15)
Diffuse	5 (8)
Portal vein tumor thrombosis	1 (2)
Serum alpha-fetoprotein level (IU/mL)	
<300	41 (68)
≥300	19 (32)
Histology	
Well-differentiated	15 (25)
Moderately-differentiated	28 (47)
Poorly-differentiated	7 (12)
Differentiation not specified	9 (15)
Negative (radiological diagnosis only)	1 (2)
Prior treatment	
None	24 (40)
Surgery	10 (17)
Local ablation/TACE	26 (43)

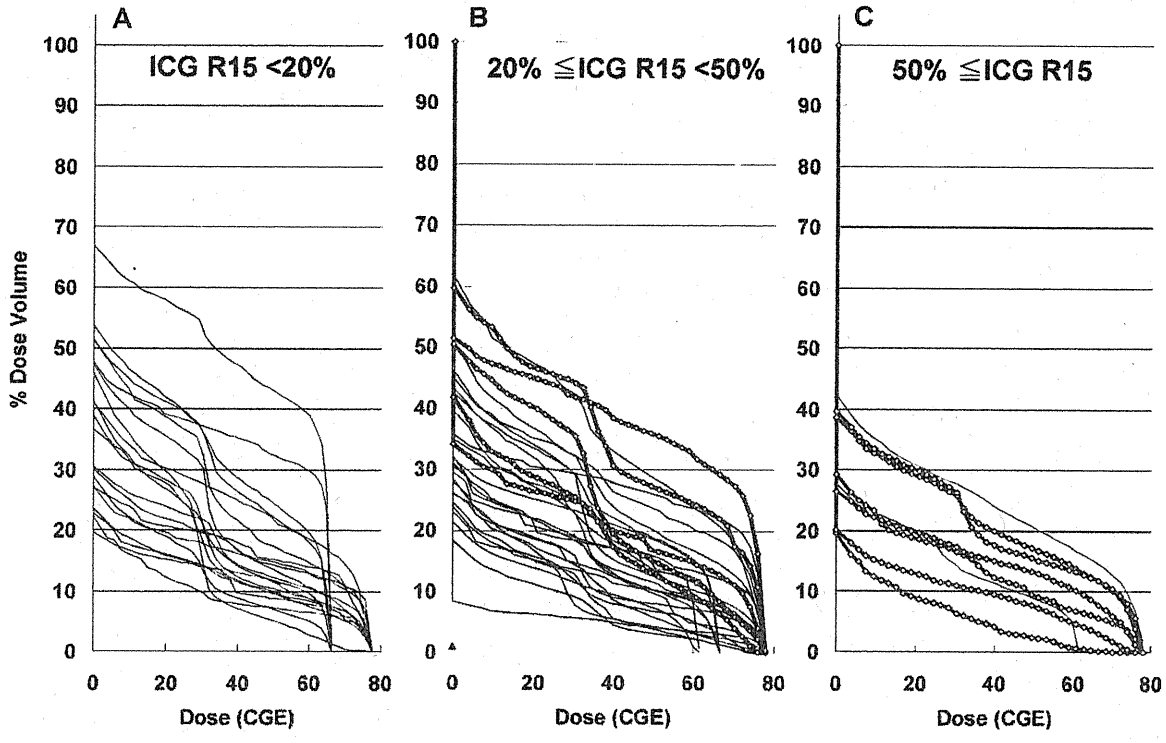

Fig. 1. DVH are shown for all patients according to their pretreatment ICG R15 values, as noted in each panel. Thick lines with rhomboid symbols represent DVHs for patients suffering from hepatic insufficiency within 6 months after completion of PRT.

and did not develop PHI were statistically significant, with p values of 0.012 in V0, 0.009 in V10, 0.012 in V20, 0.006 in V30, 0.016 in V40, and 0.024 in V50 (Mann-Whitney U test). The lowest p value was observed in the difference at V30. Among 32 patients whose ICG R15 values ranged from 20% to 49.9%, none of the 21 patients whose V30 were <25% experienced PHI, whereas 5 of 11 patients (45%) whose V30 was ≥25% developed PHI (p = 0.037, Mann-Whitney U test). The incidence of PHI was 2/25 (8%) in Child-Pugh class A patients, whereas PHI incidence was 3/7 (43%) in class B patients in this group of 32 patients (p = 0.218, Mann-Whitney U test). Of 5 patients who experienced PHI, 1 died at 8 months without evidence of HCC recurrence. PHI spontaneously resolved in 4 patients; 2 patients died of intrahepatic recurrence at 22 and 71 months, respectively; 1 patient died of brain metastasis at 8 months; and 1 patient was alive and disease free at 50 months. In both of the patients who survived for more than 4 years despite development of PHI, the pretreatment functional liver reserve was Child-Pugh class A and ICG R15 was less than 40%. On the other hand, all 3 patients who experienced PHI and died within 2 years had Child-Pugh class B liver functions. Relationships between ICG R15 and V30 according to occurrence of PHI in Child-Pugh class A and B patients are shown in Fig. 3a and b, respectively.

Other serious adverse events

Three patients experienced a gastrointestinal toxicity grade of ≥2. One patient developed hemorrhagic duodenitis associated with anemia at 2 months after completion of 76 CGE/20 fractions/30 days of PRT. The dose administered to the duodenum was estimated to be 50 to 80% of the prescribed dose. Bypass surgery was attempted to alleviate the symptoms; however, this patient died of postoperative hepatic failure at 6 months. Two patients received 65 CGE/26 fractions of PRT, with the entire circumference of the gastrointestinal walls covered within the PTV. One of these 2 patients experienced grade 3 hemorrhagic ulcer at the ascending colon, within the PTV. The patient was managed successfully with right hemicolectomy at 10 months; however, the patient

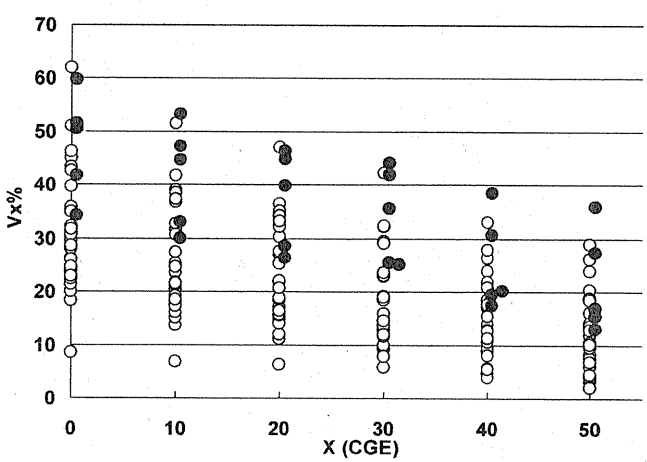

Fig. 2. Distribution of V0 to V50 in DVHs for 32 patients whose pretreatment ICG R15 values ranged from 20% to 49.9%. Open circles represent values for patients who did not experience PHI, whereas closed circles represent those who developed PHI.

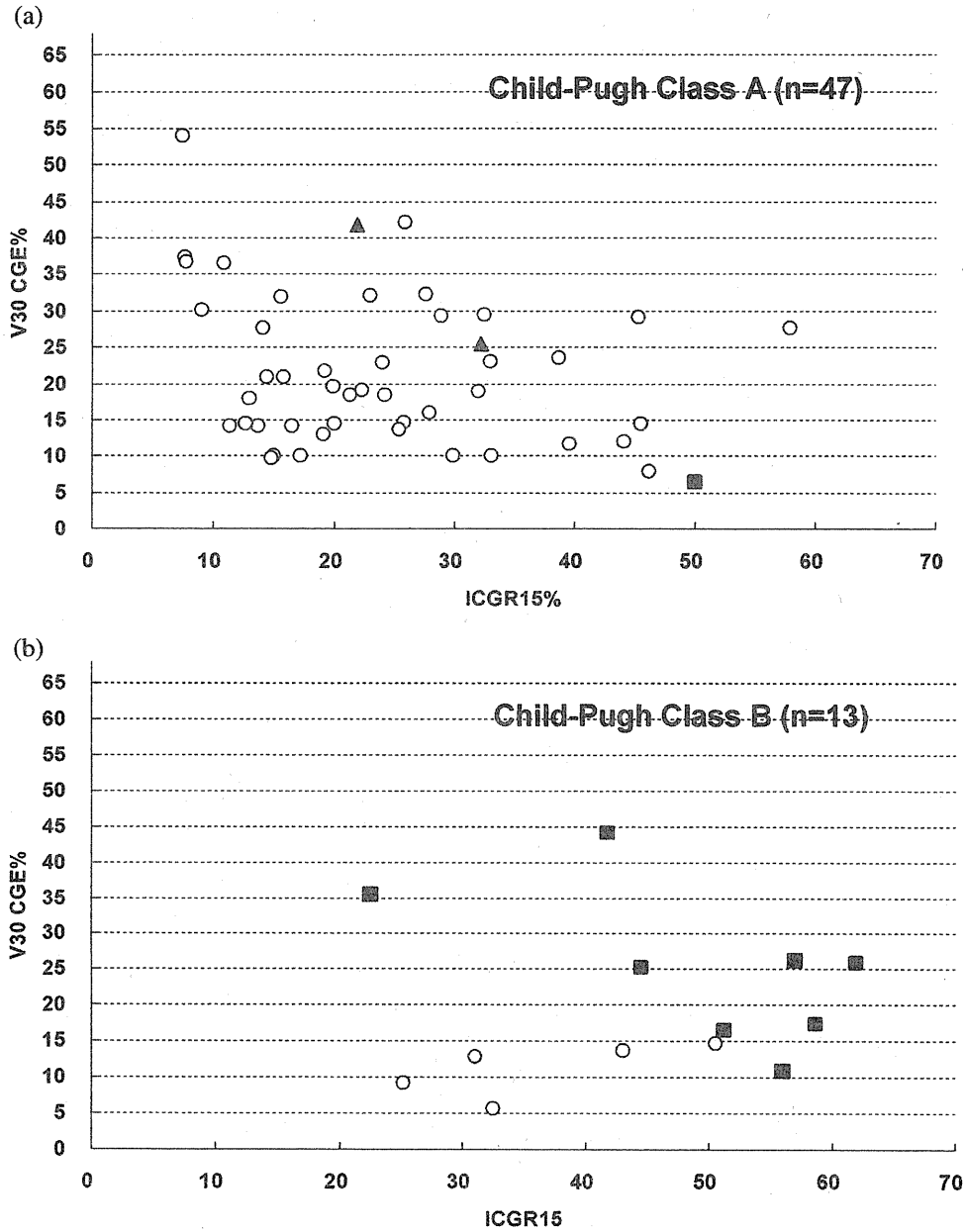

Fig. 3. Scattergram of V30 in each patient who had pretreatment liver functions classified as Child-Pugh class A (a) and class B (b), as shown in each panel, according to the ICG R15 value. Open circles represent values in patients who did not experience PHI. Closed squares represent those who developed PHI and died within 2 years with ($n = 5$) or without ($n = 4$) disease recurrence. Closed triangles represent those who experienced transient PHI and survived for more than 4 years after commencement of PRT.

died of local recurrence and subsequent hepatic failure at 23 months. The other patient developed grade 2 esophagitis within the PTV at 7 months. Repetitive balloon dilatations were required to alleviate the patient's dysphagia; however, the patient was alive without disease and taking a normal diet at 30 months. There were no other observations made of adverse events of Grade ≥3 in any of the patients.

Tumor control and survival

At the time of analysis in August 2009, 42 patients had already died because of intrahepatic recurrence in 27, nodal recurrence in 1, distant metastasis in 3, hepatic insufficiency without recurrence in 9, comorbidity in 1, and senility in 1. Forty of these 42 patients had been free from local progression until death; the durations ranged from 2 to 77 months (median, 20 months). Two patients who experienced local progression died subsequently. A total of 15 patients were alive at 25 to 92 months (median, 43 months) without local progression. Three patients were alive at 49, 53, and 94 months, respectively, after salvage treatment for local progression, using local ablation in 2 and TACE in 1 A total of 37 patients achieved complete disappearance of the primary tumor at 1 to 50 months (median, 10 months) post-PRT. Eighteen patients had residual tumor masses on CT

and/or MRI for 2 to 44 months (median, 21 months) until the time of death or last follow-up visit without local progression. The local progression-free (LPF) rates at 3 and 5 years were 90% (95% confidence interval [CI], 80%–99%) and 86% (95% CI, 74%–98%), respectively.

Of 5 patients who experienced local progression, 3 patients underwent 65 CGE/26 fractions, and 2 patients received 76 CGE/20 fractions of PRT. All 3 patients who received 60 CGE/10 fractions were free from local progression at 6, 30, and 51 months, respectively. LPF rates at 3 and 5 years for 46 patients who received 76 CGE/20 fractions were 97% (95% CI, 92%–100%) and 93% (95% CI, 83%–100%), respectively. LPF rates at 3 years for 11 patients who underwent 65 CGE/26 fractions of PRT were 56% (95% CI, 16%–95%) and was worse than that in patients who received 76 CGE/20 fractions with statistical significance ($p = 0.005$).

A total of 32 patients developed intrahepatic tumor recurrences that were outside of the PTV at 1 to 62 months (median, 20 months). Nine of these tumors occurred within the same segment of the primary tumor. Nodal recurrence at the hepatoduodenal ligament and distant metastasis were observed as the first sites of failure in 2 and 3 patients, respectively. In addition to the above-mentioned five deaths from PHI or postsurgical mortality, 4 patients died of hepatic failure because of underlying liver disease at 17 to 23 months, and 2 patients died from other reasons (comorbidity or senility) without evidence of HCC recurrence. Seven patients remained alive and disease free at 27 to 51 months (median, 30 months). The median survival time for all 60 patients was 41 months, and actuarial OAS rates at 3 and 5 years were 56% (95% CI, 43%–69%) and 25% (12%–39%), respectively. DFS rates at 3 and 5 years were 18% (95% CI, 7%–29%) and 4% (95% CI, 0%–12%), respectively, as shown in Fig. 4. Two Child-Pugh class A patients who underwent PRT with the CTV covering the entire right lobe or right anterior portal segment were alive and disease free at 50 and 26 months, respectively. The former patient had a pre-PRT ICG R15 of 22% and received a V30 of 42% and experienced transient PHI that resolved spontaneously; the latter patient, whose corresponding parameters were 8% and 37%, respectively, did not experience PHI.

Factor analysis

Univariate analyses revealed that factors related to functional liver reserve and occurrence of PHI had significant influence on OAS ($p < 0.05$). Liver function (Child-Pugh class A or B) and prior treatment (none or recurrent) were independent and significant prognostic factors ($p < 0.002$), and occurrence of PHI had marginal significance ($p = 0.011$) by multivariate analysis, as shown in Table 2. The DFS rate at 3 years for 24 patients who had no prior treatment for HCC was 35% (95% CI, 14%–56%), whereas DFS for the remaining 36 patients was 7% (95% CI, 0%–17%) ($p = 0.011$). In Child-Pugh class A patients, OAS at 3 and 5 years for those who had no prior treatment ($n = 17$) was 76% (95% CI, 56%–97%) and 59% (95% CI, 33%–86%), respectively, and 63%

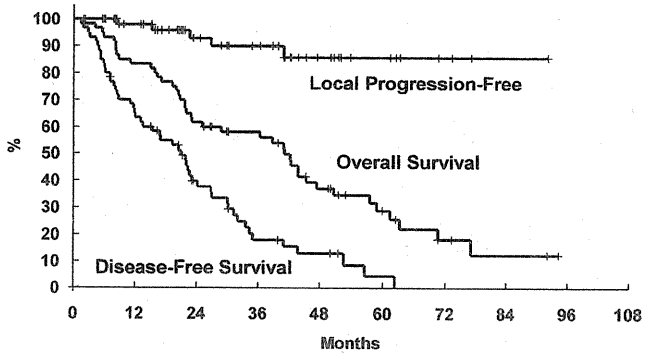

Fig. 4. Kaplan-Meier estimation of local progression-free survival, OAS, and disease-free survival rates for all 60 patients.

(95% CI, 45%–80%) and 25% (95% CI, 7%–42%), respectively, for 30 patients with recurrent tumor ($p = 0.060$). In Child-Pugh class B patients, the 2-year OAS for patients without PHI ($n = 5$) was 80% (95% CI, 45%–100%), while 8 patients who developed PHI died within 2 years with ($n = 5$) or without ($n = 3$) HCC recurrence ($p = 0.009$).

DISCUSSION

The promising tumoricidal effect of PRT using aggressive escalation of total and fractional doses, which has been repeatedly reported previously, was reproduced in this study (3, 4). The estimated actuarial local progression-free rate within the PTV in patients receiving 76 CGE/20 fractions exceeded 90% at 3 years. DFS at 3 years for patients who underwent PRT as an initial treatment ($n = 24$) was 35%, and, among them, OAS at 3 years was 76% in Child-Pugh class A patients ($n = 17$). These results are comparable to those observed after surgical treatment (17). Although the number of patients was small, these data indicate that appropriate local control with PRT may provide survival benefit in adequately selected patients with unresectable HCC. The fact that 9 of the 32 intrahepatic HCC recurrences occurred within the same anatomical portal segments showed that it should still be possible to improve the progression-free rate by defining the CTV so it covers undetectable tumor spread via the portal blood flow.

As shown in Fig. 3, no patient who had ICG R15 of less than 20% experienced PHI. In addition, only Child-Pugh class A patients with pre-PRT ICG R15 of less than 40% survived for longer than 4 years despite development of PHI. One of them underwent systematic portal segmental irradiation with the CTV covering the entire right lobe, and the details for this patient will be reported separately. On the other hand, all patients who had pre-PRT liver functions classified as Child-Pugh class B and/or ICG R15 of 40% or higher died within 2 years when they developed PHI. This suggests that the role of systematic portal irradiation requiring a large irradiated volume should be pursued further in Child-Pugh class A patients with favorable ICG R15 values; otherwise, the CTV should be confined to the GTV with adequate margins. Furthermore, in patients who have ICG R15 of 50% or

Table 2. Factors related to overall survival

Factor	No. of patients	% of OAS at 3 years (MST, months)	Univariate *p* value	Multivariate *p* value, hazard ratio (95% CI)
Age				
<70	29	55 (41)	0.660	0.087
≥70	31	61 (42)		0.52 (0.24–1.10)
Gender				
Male	42	62 (41)	0.332	0.194
Female	18	44 (42)		0.62 (0.29–1.30)
Tumor size (mm)				
<50	36	66 (44)	0.178	0.070
≥50	24	46 (23)		0.54 (0.28–1.05)
Pretreatment ICG R15				
<40%	45	67 (44)	0.002	
≥40%	15	33 (15)		
Child-Pugh classification				
A	47	68 (45)	<0.001	<0.001
B	13	23 (15)		0.19 (0.07–0.50)
Serum alfa-fetoprotein level (IU/mL)				
<300	41	61 (42)	0.617	0.618
≥300	19	53 (39)		0.83 (0.39–1.74)
PHI				
No	49	65 (44)	0.001	0.011
Yes	11	18 (9)		0.29 (0.11–0.76)
% of patients receiving V30				
<25%	40	57	0.724	
≥25%	20	60		
Total dose = 65 Gy				
Yes	11	44 (29)	0.646	0.185
No	49	61 (42)		1.88 (0.73–4.76)
Prior treatment				
None	24	67 (47)	0.112	0.002
Recurrence	36	53 (36)		0.32 (0.15–0.66)

Abbreviations: OAS = overall survival; MST = median survival time; CI = confidence interval; PHI = proton-induced hepatic insufficiency.

higher, the indication for PRT should be considered with extreme caution to prevent life-threatening PHI, as shown in Fig. 3.

Results of this retrospective study showed 56% OAS at 3 years in all patients and 68% in 47 Child-Pugh class A patients. All of them were judged strictly as unresectable and not amenable to local ablation. Therefore, a survival benefit of adding PRT to TACE could be expected, which should be tested in randomized trials. Suitable candidates for such a study may be patients who have unresectable HCC of >4 cm in diameter (*i.e.*, a high probability of microscopic vascular invasion) or who show macroscopic vascular invasion, which is amenable to selective segmental TACE as a curative treatment. Nevertheless, before developing that kind of randomized study, data should still be compiled regarding the safety and patterns of failure after PRT combined with TACE while ICG R15 and V30 are taken into account. Preliminary results of hypofractionated stereotactic body radiotherapy for patients with relatively small primary or metastatic liver tumors showed 70% to >90% of objective response rates and 20 or more months of median survival time (1, 18–20). Mature data regarding the relationship between oncological outcomes and tumor characteristics, as well as functional reserve of the liver, are needed to optimize cost-effectiveness of localized, high-dose RT using X-ray or charged particles for treatment of this disease. Nonetheless, RT should have no role in preventing multifocal tumorigenesis, which will be continuously encountered by multidisciplinary approaches (21).

The risk of developing serious gastrointestinal sequela after PRT is another important issue to consider in patients who have HCC located adjacent to the digestive tract. We attempted once-daily fractionation of PRT with 65 CGE/26 fractions. However, 2 of 11 patients who received this treatment developed gastrointestinal toxicity grade of ≥2. Moreover, these 11 patients showed significantly worse LPF rates than those who received 76 CGE/20 fractions of PRT. Three patients who received 60 CGE/10 fractions of PRT were controlled locally. Although our current data are based on a limited number of patients, precluding definitive conclusions, they suggest a low α/β ratio (22) of HCC, and this assumption should be examined further in clinical trials. Based on currently available data, efforts to exclude the gastrointestinal loop from the PTV by using, for example, surgical manipulations, seem to be positively considered in order to expand the role of PRT for HCC.

CONCLUSIONS

In conclusion, PRT achieved excellent local progression-free rates when aggressive, high-dose/fractionation was administered. Child-Pugh class A patients with ICG R15 of less than 40% tolerated PRT of a large irradiated volume well, despite development of transient PHI. However, in Child-Pugh class B patients, it seems reasonable to minimize the irradiated volume to prevent detrimental liver damage induced by PRT and underlying liver diseases. A V30 of less than 25% in the noncancerous portion of the liver is considered an indicator of the safety of PRT in patients who have pre-PRT ICG R15 of 20% to 50%. We believe that there are extremely few indications for PRT in patients who have ICG R15 of 50% or higher. Gastrointestinal toxicity is a major drawback of PRT for tumors adjacent to the gastrointestinal tract, and surgical manipulation to exclude the intestinal loop from the PTV should be positively considered as indicated. If these issues are carefully considered, with special attention to the patterns of tumor spread, when determining the

CTV, aggressive high-dose PRT could become a legitimate treatment for a certain population of patients with unresectable HCC for whom there is no standard treatment available other than TACE or liver transplantation.

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CLINICAL INVESTIGATION

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.

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.

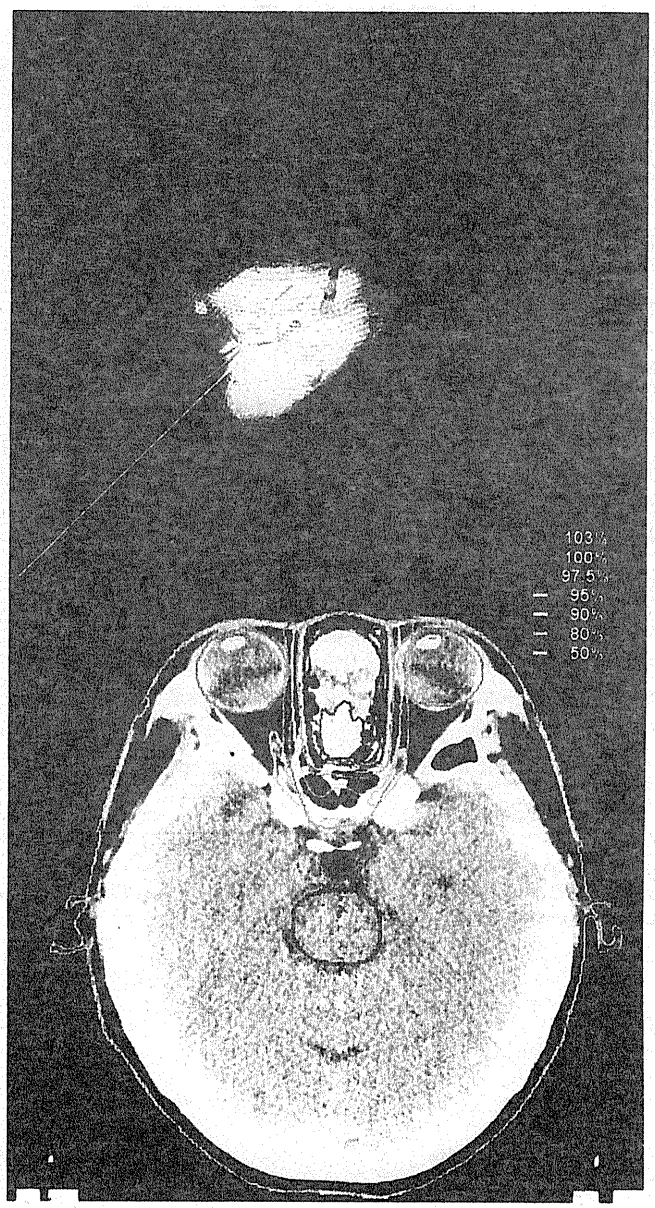

Fig. 1. Beam arrangement. Irradiation dose and volume for organs at risk was usually minimized using a noncoplanar three-field technique. In this case, curative high-dose irradiation to the tumor volume was provided, whereas overdose irradiation to the optic nerve was avoided.

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.

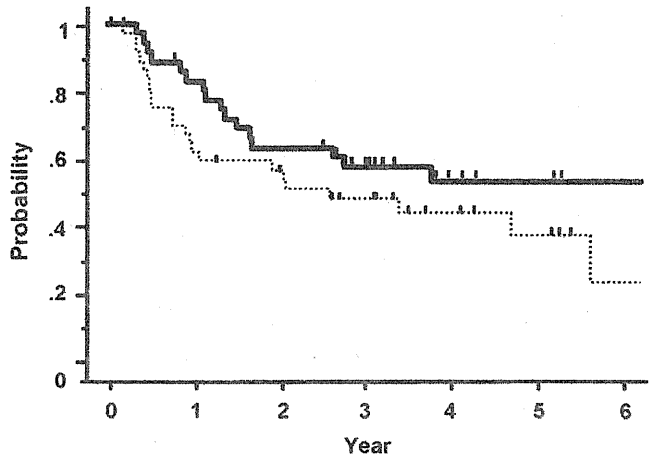

Fig. 2. Overall and progression-free survival. Solid line indicates overall survival curve; broken line indicates progression-free survival curve. With a median follow-up period of 45.4 months, 3-year overall survival and progression-free survival rates were 59.3% and 49.1%, respectively.

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.

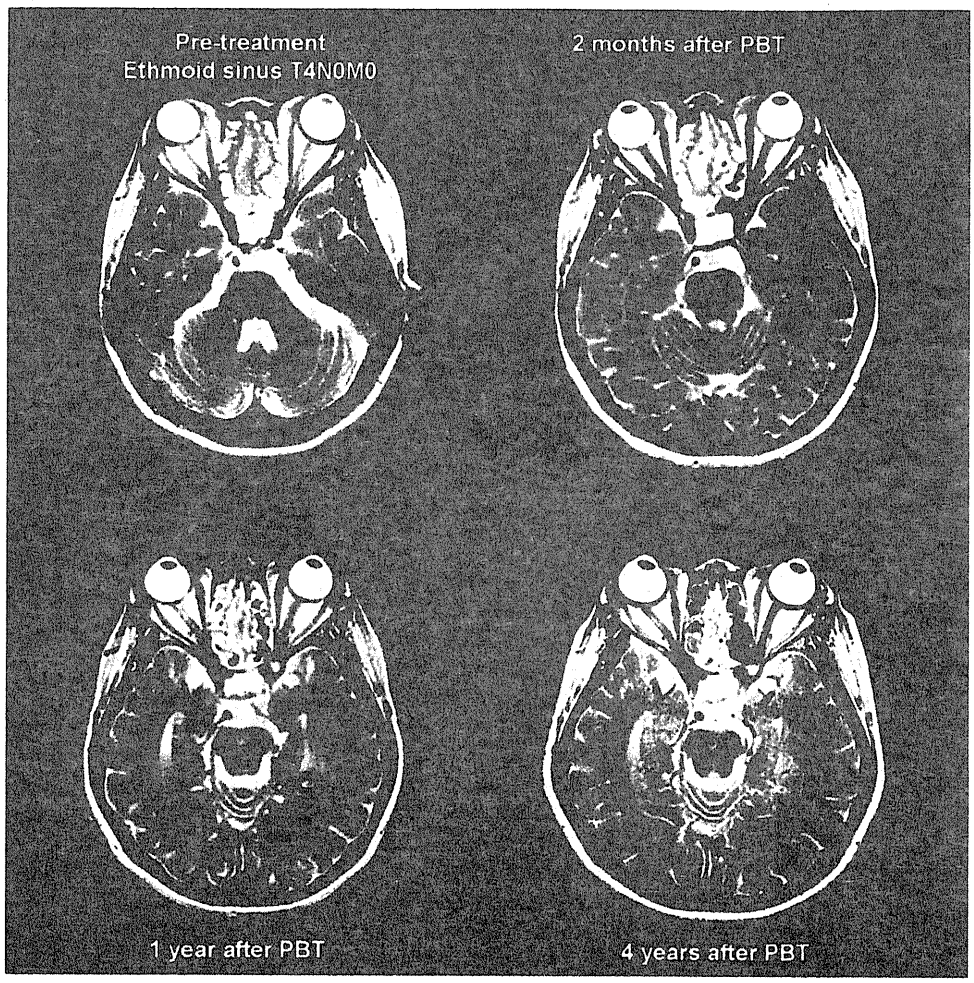

Fig. 3. Difficulty of response evaluation of proton beam therapy (PBT). The disease was undifferentiated carcinoma of the ethmoid sinus. Response evaluation at 2 months and 1 year after PBT was SD by the RECIST criteria; however, the patient has remained alive for more than 4 years without disease progression.

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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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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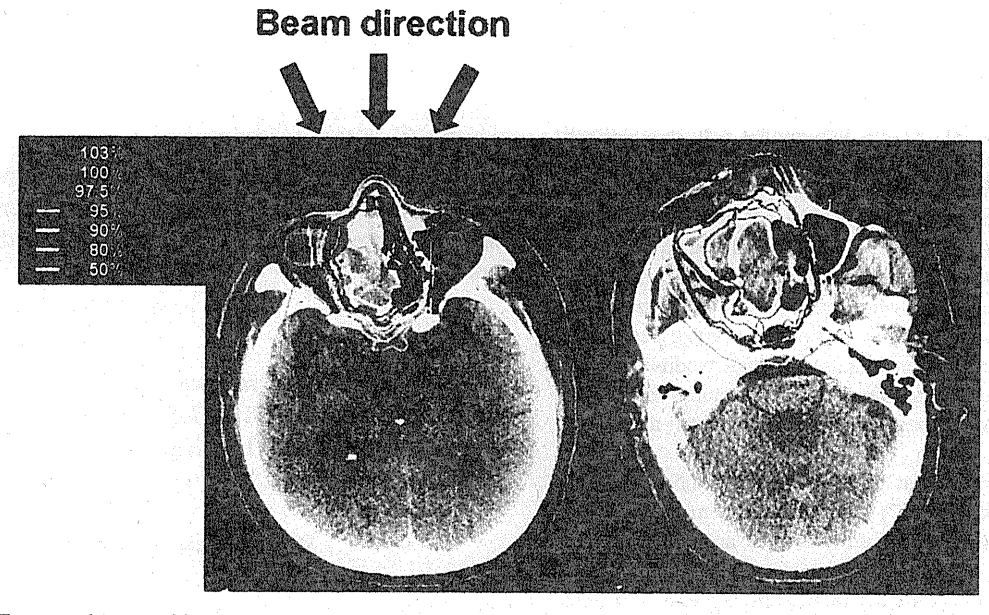

Fig. 1. Target volume and beam arrangement. GTV was defined as the gross tumor lesion determined with pretreatment CT/MRI and PET. CTV was defined as the region of the gross tumor lesion and adjacent sinuses. PTV was basically set as CTV plus 3-mm margin, with acceptance of fine-tuning to the PTV in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

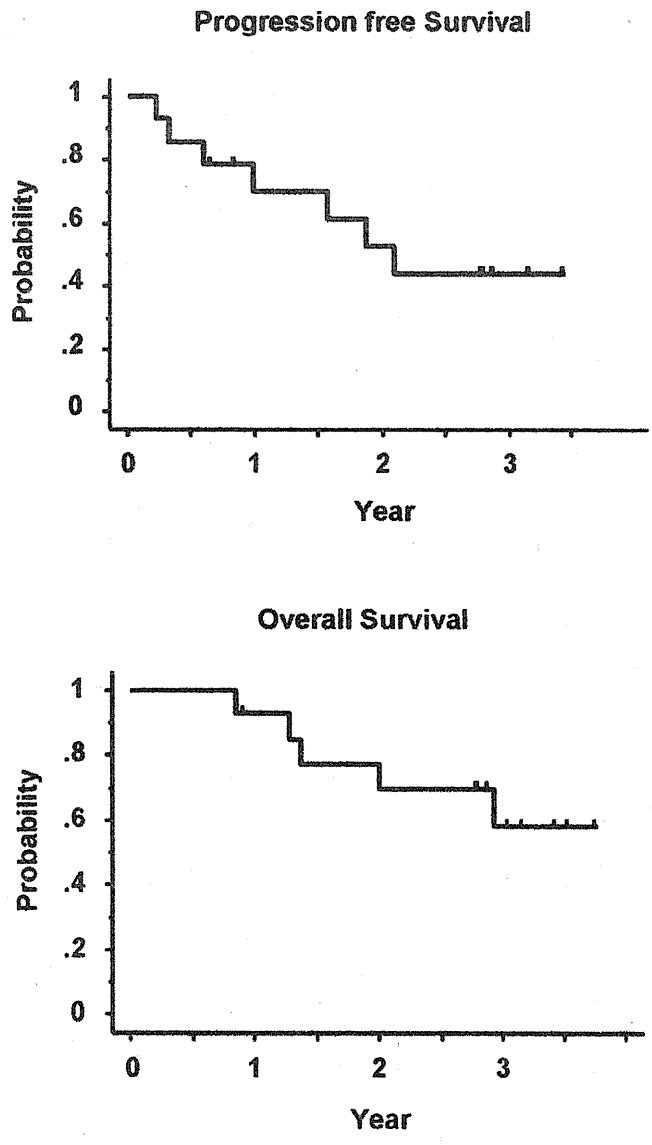

Fig. 2. Progression-free survival (PFS) and overall survival (OS). PFS and OS rates were estimated using the Kaplan-Meier product-limits method. Median PFS was 25.1 months, and 2-year PFS rates were 43.7%. Median survival time was not reached, and 3-year overall survival rate was 58.0% with a follow-up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

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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Clinical Investigation

Outcome of T4 (International Union Against Cancer Staging System, 7th edition) or Recurrent Nasal Cavity and Paranasal Sinus Carcinoma Treated with Proton Beam

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Summary

This study evaluated seventeen patients with unresectable carcinomas of the nasal cavity and paranasal sinus (NCPS) who were treated by proton beam therapy (PBT). Total doses of 72 - 89 GyE were given. Overall survival was 47% at two and 16% at five years, and local control 35% at two and 18% at five years. Grade 4 morbidity was seen in 2 patients. Unresectable NCPS carcinomas may be treated to high dose with PBT and some durable responses are seen.

Purpose: To investigate the clinical features, prognostic factors, and toxicity of treatment for unresectable carcinomas of the nasal cavity and paranasal sinus (NCPS) treated with proton beam therapy (PBT).

Methods and Materials: Seventeen patients (13 men, 4 women) with unresectable carcinomas of the NCPS who underwent PBT at the University of Tsukuba between 2001 and 2007 were analyzed. The patients' median age was 62 years (range, 30–83 years). The tumors were located in the nasal cavity in 3 patients, the frontal sinus in 1, the ethmoid sinus in 9, and the maxillary sinus in 4. The clinical stage was Stage IVA in 5 cases, IVB in 10, and recurrent in 2. The tumors were deemed unresectable for medical reasons in 16 patients and because of refusal at a previous hospital 4 months earlier in 1 patient. All the patients received PBT irradiation dose of 22–82.5 GyE and a total of 72.4–89.6 GyE over 30–64 fractions (median 78 GyE over 36 fractions) with X-ray, with attention not exceeding the delivery of 50 GyE to the optic chiasm and brainstem.

Results: The overall survival rate was 47.1% at 2 years and 15.7% at 5 years, and the local control rate was 35.0% at 2 years and 17.5% at 5 years. Invasion of the frontal or sphenoid sinus was a prognostic factor for overall survival or local control. Late toxicity of more than Grade 3 was found in 2 patients (brain necrosis in 1 and ipsilateral blindness in 1); however, no mortal adverse effects were observed.

Conclusion: Proton beam therapy enabled a reduced irradiation dose to the optic chiasm and brainstem, enabling the safe treatment of unresectable carcinomas in the NCPS. Superior or posterior extension of the tumor influenced patient outcome.

Keywords: Carcinoma, Nasal cavity, Paranasal sinus, Proton beam therapy

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