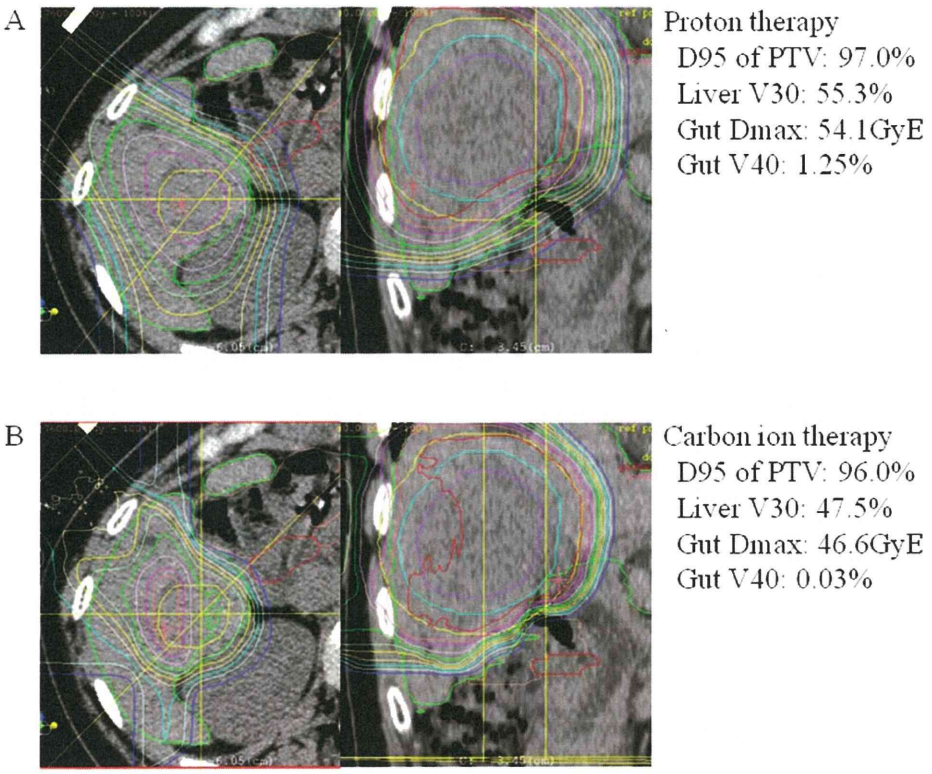

Figure 1. These images are from a representative case presentation of treatment plans for both (A) proton therapy and (B) carbon ion therapy. D95 indicates the dose received by at least 95% volume; PTV, planning target volume; Liver V30, percentage volumes of noncancerous hepatic portions (entire liver volume − gross tumor volume) that received ≥30 gray equivalents (GyE); Gut Dmax, the maximum exposure doses of the adjacent gut; Gut V40, percentage volumes of the adjacent gut that received ≥40 GyE.

hepatic movements. Doses were calculated on the basis of the pencil beam algorithm. Beam parameters, including energy level, the width of the spread-out Bragg peak, and degrader thickness, were selected adequately using FOCUS-M. Dose-volume histograms were calculated for all patients to evaluate the risk of radiation-induced liver disease.

Follow-Up and Evaluation Criteria

Patients underwent a complete blood count, biochemical profile, detection of tumor markers (including serum AFP and PIVKAII), and abdominal imaging studies (CT or MRI) every 3 months for 3 years after treatment and every 6 months thereafter. In general, for patients with HCC, the objective of all effective locoregional therapies is to obtain necrosis of the tumor regardless of the shrinkage of the lesion. Even if extensive tumor necrosis is achieved, this may not be accompanied by a reduction in the greatest dimension of the lesion. Consequently, several studies have indicated that World Health Organization and Response Evaluation Criteria in Solid Tumors criteria have no value in the assessment of tumor response after locoregional therapies in patients with HCC.[26,27] It has been reported that such tumors, even after complete response, tend to persist for a long period after the completion of particle therapy.[19] Therefore, local recurrence was defined either as the growth of an irradiated tumor or as the appearance of new tumors within the PTV based on criteria established in previous reports.[16,17,19,28] Acute and late toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0; National Cancer Institute, Bethesda, Md).

Statistical Analyses

The statistical significance of differences in each classification for both local control and overall survival rates was estimated by the Kaplan-Meier method and was compared using the log-rank test. Univariate and multivariate analyses using Cox proportional hazards regression

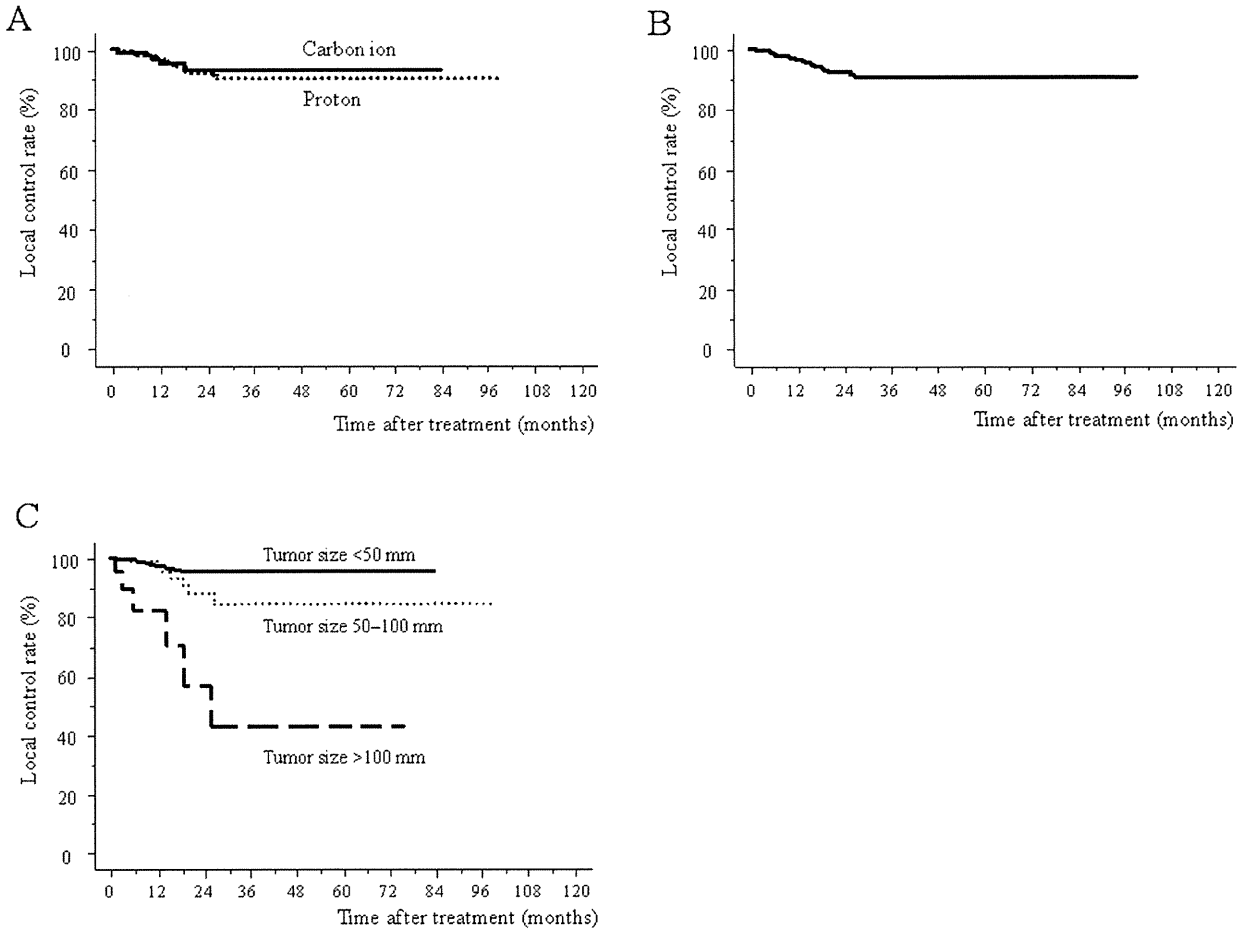

Figure 2. Local control rates after treatment are illustrated for (A) tumors that were treated with proton and carbon ion therapy, (B) all 386 tumors, and (C) all 386 tumors according to tumor size.

models were used to identify independent risk factors that predicted local control and overall survival rates. Differences of $P < .05$ were considered statistically significant, and variables with $P < .10$ were entered into a multivariate analysis using a Cox proportional hazards model. All statistical analyses were performed using SPSS statistical software (version 17.0 for Windows; SPSS, Inc., Chicago, Ill).

RESULTS

Local Control Rates After Proton and Carbon Ion Therapies

Patients were followed either until death or to March 2010 (median follow-up, 31.0 months). Among 343 patients with 386 tumors, 223 patients developed recurrences after treatment. Nineteen patients developed extrahepatic metastasis, and 210 patients developed intrahepatic recurrences, including 23 local recurrences (proton therapy, 18 patients; carbon ion therapy, 5 patients). The longest interval to local recurrence was 27.1 months, and all local recurrences developed within 3 years. The 5-year local control rates for patients who received proton therapy and carbon ion therapy were 90.2% and 93%, respectively (Fig. 2A). The effective 3-year and 5-year local control rates for all 386 tumors were both 90.8% (Fig. 2B). An analysis of the local control rates according to the tumor factors identified above (see Treatment Protocols) is listed in Table 4. Univariate analysis revealed that tumor size was a significant risk factor for local recurrence in the proton therapy group, the carbon ion therapy group, and all patients. In multivariate analysis, tumor size was identified as an independent risk factor for local recurrence in the proton therapy group

Table 4. Univariate Analysis of Prognostic Factors for Local Control Rate

Factor	Proton Therapy, n=278		Carbon Ion Therapy, n=108		All Patients, n=386	
	LC Rate at 5 Years, %	*P*	LC Rate at 5 Years, %	*P*	LC Rate at 5 Years, %	*P*
Tumor size, mm		<.0001		.0062		<.0001
<50	95.5		94.5		95.3	
50-100	84.1		90.9		84.4	
>100	43.4		80		42.2	
Gross classification		.0901		.0943		.0219
Single nodular type	93.3		96		94	
Nonsingle nodular type	86.2		89.4		86.7	
Macroscopic vascular invasion		.2544		.0292		.0535
Yes	83.9		80.4		82.8	
No	92		94.8		92.8	
Perivascular location		.0704		.4267		.0403
Yes	85.5		86.8		85.7	
No	93.5		95.1		93.8	
Prior treatment history		.7332		.9000		.7629
Yes	91.5		95		92	
No	89.2		91.9		89.9	
Serum AFP, ng/mL		.5352		.6111		.4310
<100	90.9		95.1		91.8	
≥100	89		86.8		88.6	
Serum PIVKAII, mAU/mL		.0997		.3468		.2976
<100	94.5		90.1		93.4	
≥100	85.5		97.9		87.8	

Abbreviations: AFP, α-fetoprotein; LC, local control; PIVKAII, protein induced by vitamin K absence or antagonist II.

and in all patients (Table 5). In addition, the local control rates for all 386 tumors that measured <50 mm, 50 to 100 mm, and >100 mm were 95.3%, 84.4%, and 42.2%, respectively (Fig. 2C). In contrast, other tumor factors, including gross classification, macroscopic vascular invasion, perivascular location, treatment history, serum AFP level, and serum PIVKAII level, did not affect the local control rate in any tumor subset in multivariate analysis.

Overall Survival Rates of Proton and Carbon Ion Therapies

The 5-year overall survival rates for patients who received proton therapy and carbon ion therapy were 38% and 36.3%, respectively (Fig. 3A). The overall survival rates for all 343 patients at 3 years and 5 years were 59% and 38.2%, respectively (Fig. 3B). Univariate and multivariate analyses of the overall survival rates according to the 8 relevant tumor factors are provided in Tables 6 and 7, respectively. According to the univariate analysis, Child-Pugh classification, macroscopic vascular invasion, and serum AFP levels were the only factors that significantly affected the overall survival rates in all groups (proton therapy, carbon ion therapy, and all patients) (Table 6). The Child-Pugh classification was the only independent factor for overall survival in proton therapy, carbon ion therapy, and all patients according to the multivariate analysis (Table 7). The 5-year overall survival rates for Child-Pugh classifications A, B, and C were 46.6%, 8.7%, and 0%, respectively (Fig. 3C).

The 5-year overall survival rates for BCLC stages 0, A, B, C, and D were 80.8%, 52.7%, 23.7%, 30.6%, and 0%, respectively (Fig. 4A). According to the BCLC classification, hepatic resection was categorized as stage 0 and part of stage A. In total, 78 patients were categorized into the hepatic resection group. The 5-year overall survival rates for patients classified into groups according to whether they underwent hepatic resection (operable group) or received treatments (inoperable group) were 67.6% and 29.4%, respectively ($P < .0001$) (Fig. 4B).

Local Control and Overall Survival Rates According to the BED_{10}

We also analyzed the local control and overall survival rates after both proton and carbon ion therapies according

Table 5. Independent Risk Factors Related to the Local Control Rate: Multivariate Analysis

Factor	SE	Chi-Square Statistic	RR	95% CI	*P*
Proton therapy					
Tumor size, mm					.0030
50-100 (vs <50)	0.666	1.175	2.058	0.558-7.590	
>100 (vs <50)	0.703	10.463	9.725	2.450-38.596	
Single nodular type (vs nonsingle nodular type)	0.538	0.187	1.262	0.440-3.623	.6652
Perivascular location: Yes (vs no)	0.543	0.147	0.812	0.280-2.354	.7011
Serum PIVKAII ≥100 mAU/mL (vs <100 mAU/mL)	0.530	0.389	1.392	0.492-3.937	.5327
Carbon ion therapy					
Tumor size, mm					.4703
50-100 (vs <50)	1.569	0.069	0.662	0.031-14.322	
>100 (vs <50)	1.905	0.575	4.239	0.101-177.314	
Single nodular type (vs nonsingle nodular type)	1.231	1.110	3.658	0.328-40.853	.2921
Macroscopic vascular invasion: Yes (vs no)	1.585	0.347	2.544	0.114-56.848	.5557
All patients					
Tumor size, mm					.0002
50-100 (vs <50)	0.646	10.527	8.122	2.291-28.789	
>100 (vs <50)	0.562	2.146	0.439	0.146-1.321	
Single nodular type (vs nonsingle nodular type)	0.519	2.544	2.288	0.827-6.327	.1107
Macroscopic vascular invasion: Yes (vs no)	0.651	2.601	2.860	0.798-10.253	.1068
Perivascular location: Yes (vs no)	0.506	0.738	0.647	0.240-1.745	.3902

Abbreviations: CI, confidence interval; PIVKAII, protein induced by vitamin K absence or antagonist II; RR, relative risk; SE, standard error.

to the BED_{10} using a cutoff score of 100 (Fig. 5). The 5-year local control rates for tumors that were treated on the protocols characterized by BED_{10} values <100 and ≥ 100 were 93.3% and 87.4%, respectively, for proton therapy and 80.7% and 95.7%, respectively, for carbon ion therapy. The 5-year overall survival rates for patients who were treated on the protocols characterized by BED_{10} values <100 and ≥ 100 were 31.7% and 43.9%, respectively, for proton therapy and 32.3% and 48.4%, respectively, for carbon ion therapy. There was no significant difference in local control and overall survival rates, irrespective of the BED_{10} score, between proton therapy and carbon ion therapy.

Toxicities

All acute toxicities that occurred during treatment were transient, easily managed, and acceptable. However, grade ≥ 3 late toxicities were observed in 8 patients on proton therapy and in 4 patients on carbon ion therapy, and 4 of 12 patients were diagnosed with radiation-induced liver disease (Table 8). However, all of these patients with hematologic disorders were asymptomatic and required no further treatment. In addition, upper gastrointestinal ulcer, pneumonitis, and subcutaneous panniculitis healed with conservative management. Five patients who received proton therapy developed refractory skin ulcers, and 1 patient required skin transplantation. A salvage drainage operation also was required by 1 patient who developed infectious biloma 10 months after irradiation. No patients died of treatment-related toxicity.

DISCUSSION

We analyzed the safety and efficacy of particle therapy using proton and carbon ion beams for HCC in a single center. The key findings of this study are as follows: 1) particle therapy produced excellent local control and overall survival rates with acceptable adverse events, 2) the treatment results from carbon ion therapy appeared to be equivalent to those from proton therapy, and 3) tumor size was the only risk factor that affected the local control rate.

Local control rates for both proton therapy and carbon ion therapy exceeded 90% in the current study. These data are very similar to those related to particle therapy for HCC, whereas they are superior to data related to conformal radiotherapy.[16,18,29,30] Recent improvements in dose localization techniques, such as intensity-modulated radiotherapy, conformal 3-dimensional planning, and breathing motion management strategies, thus, have made it possible to irradiate smaller, well defined targets in the liver. However, these highly computer-assisted

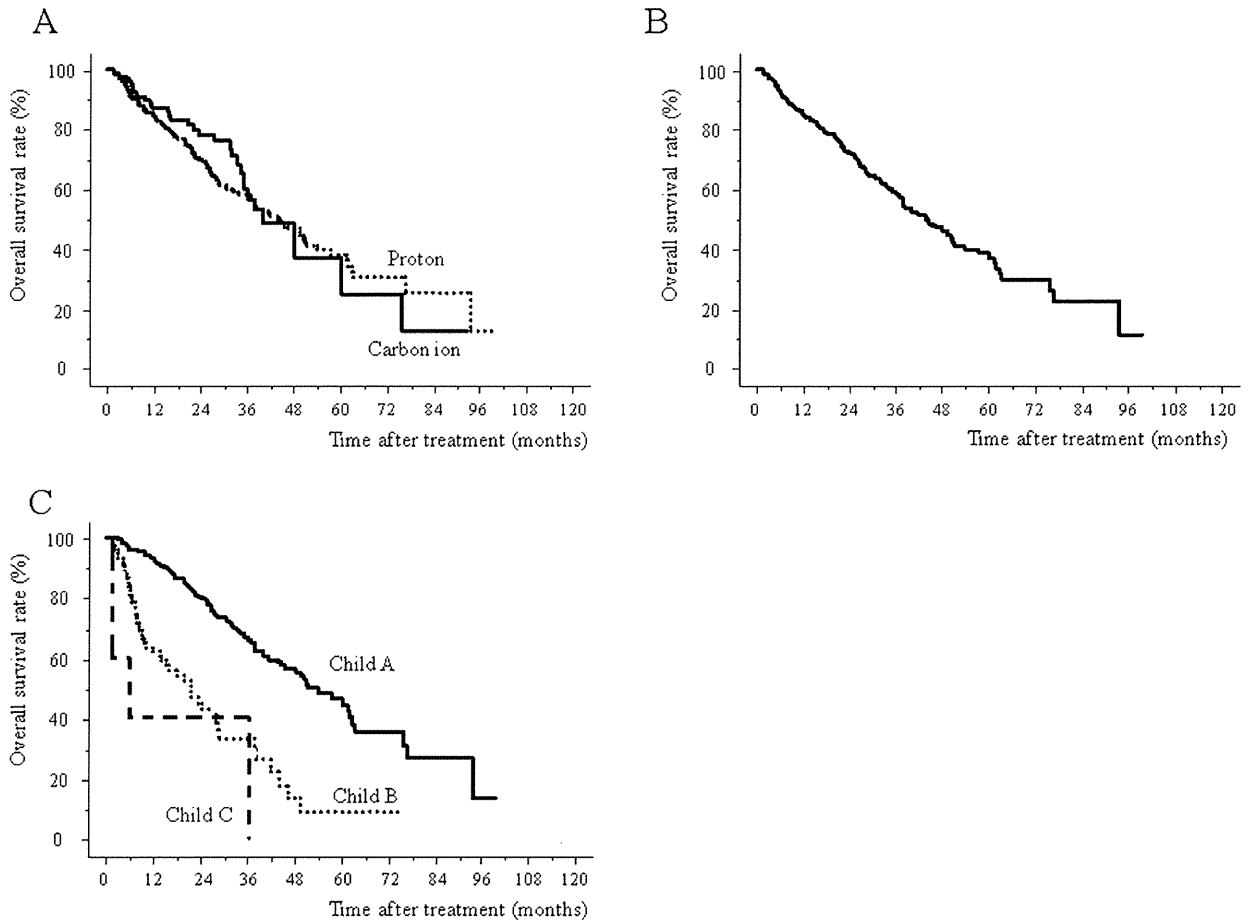

Figure 3. Overall survival rates after treatment are illustrated for (A) patients who received with proton and carbon ion therapy, (B) all 343 patients, and (C) all 343 patients according to Child-Pugh classification.

irradiation techniques using photon beams have achieved limited efficacy in treating patients with HCC. The local control rates produced by these conformal approaches remain in the 40% to 66% range for several reasons.[29,30] Radiation-induced liver disease still is observed frequently with conformal approaches when a sufficient dose is delivered to completely kill the cells of the entire tumor nodule. This is especially the true for large and centrally situated liver tumors.[31] In this regard, particle beams can achieve an excellent dose distribution to these targets. The area of radiation dose deposition can be controlled well by the beam energy, because there is a rapid drop-off in energy deposition beyond the target area. Indeed, such theoretical advantages of particle therapy were proven in part by the impressively high local control rate of approximately 90% in the current study. Therefore, we believe that it is reasonable to say that the tumor-eliminating capability of particle therapy is closely equivalent to that of hepatectomy, an outcome that has not been achieved with other radiation therapies.

Experience in the treatment of HCC by particle therapy has been accumulated mainly in Japanese centers, but there is increasing interest in other countries as well. There were 26 active proton therapy facilities as of February 2009, whereas there were only 3 carbon ion therapy facilities.[32] Until now, several proton treatment centers and 1 carbon ion treatment center have reported HCC treatments results.[16-19] However, except for the HIBMC, no single facility can deliver both proton and carbon ion beams. Therefore, our facility has a distinct advantage over other institutes with regard to comparing the efficacy of the 2 beams. To select proton therapy or carbon ion therapy, we made treatment plans for both proton and carbon ion therapy. When dose distributions were

Table 6. Univariate Analysis of Prognostic Factors for Overall Survival Rate

	Proton Therapy, n=242		Carbon Ion Therapy, n=101		All Patients, n=343	
Factor	OS Rate at 5 Years, %	*P*	OS Rate at 5 Years, %	*P*	OS Rate at 5 Years, %	*P*
Age, y		.7986		.6769		.6448
<70	37.3		43.9		39.4	
≥70	38.2		26.9		36.2	
Positive viral marker		.9754		.1805		.8586
Hepatitis B virus	34.9		44.6		32.4	
Hepatitis C virus	35.8		40.8		36.3	
None	46.7		33.9		46.6	
Performance status		<.0001		.2295		<.0001
0	43.5		43.7		43.6	
1 or 2 or 3	24.8		26.8		24.1	
Child-Pugh classification		<.0001		<.0001		<.0001
A	46.8		41.2		46.6	
B or C	8.2		33.3		8	
Tumor size, mm		.1438		.0003		.0038
<50	37.8		53.5		39.2	
50-100	37.4		17.9		33.8	
>100	41.1		0		39.8	
Macroscopic vascular invasion		.0003		.0055		<.0001
Yes	33.2		22		31.5	
No	40.3		47.8		40.2	
Serum AFP, ng/mL		.0026		.0024		<.0001
<100	42		30.9		42.6	
≥100	29.5		23.1		28.9	
Serum PIVKAII, mAU/mL		.0109		.4041		.0082
<100	40.4		58.4		41.8	
≥100	35.5		16.5		33.8	

Abbreviations: AFP, α-fetoprotein; OS, overall survival; PIVKAII, protein induced by vitamin K absence or antagonist II.

compared, there were many instances in which low-dose areas had spread into the surrounding normal liver during proton therapy planning. This was apparently because of the relatively large penumbra of proton beams. Consequently, dose distribution in a single beam appears to be better in carbon ion therapy than in proton therapy. However, in terms of beam arrangement, carbon ions are emitted from 3 fixed ports, such as vertical, horizontal, or 45-degree oblique; whereas a 360-degree rotating gantry can be used for protons. The high positioning accuracy achieved by irradiating patients in a supine position also was an advantage of proton therapy. Currently, 360-degree rotating gantries for carbon ion beams are under construction in Japan and Germany, and it is expected that these will enable the delivery of highly precise carbon ion beam arrangements and, thus, will improve the effectiveness of carbon ion therapy for HCC.

In addition to dose distribution, there are evident differences in biologic properties between the 2 beams, ie, the RBE. The RBE for proton therapy is comparatively simple. The International Commission on Radiation Units and Measurements has recommended 1.1 as a generic RBE for proton therapy based on an analysis of the published RBE values determined from in vivo systems.[33,34] All proton therapy centers, including the HIBMC, have accepted this recommendation. Conversely, the RBE for carbon ion therapy is complex, because there is no common model for selecting the RBE of carbon ion beams. In addition, it may vary depending on tissue type and the depth of the spread-out Bragg peaks.[32] Because of these differences, planning the physical dose distribution is substantially more complex for carbon ion beams than for proton beams; therefore, a direct comparison of proton therapy and carbon ion therapy is

Table 7. Independent Risk Factors Related to the Overall Survival Rate: Multivariate Analysis

Factor	SE	Chi-Square Statistic	RR	95% CI	*P*
Proton therapy					
Performance status 1-3 (vs 0)	0.200	9.283	0.544	0.368-0.805	.0023
Child-Pugh classification B or C (vs A)	0.204	29.731	0.329	0.220-0.490	<.0001
Macroscopic vascular invasion: Yes (vs no)	0.203	9.410	0.536	0.360-0.799	.0022
Serum AFP ≥100 ng/mL (vs <100 ng/mL)	0.198	2.281	1.349	0.915-1.990	.1310
Serum PIVKAII ≥100 mAU/mL (vs <100 mAU/mL)	0.199	1.231	1.248	0.844-1.844	.2672
Carbon ion therapy					
Child-Pugh classification B or C (vs A)	0.519	17.642	0.113	0.041-0.313	<.0001
Tumor size, mm					.0297
50-100 (vs <50)	0.569	6.795	4.412	1.445-13.468	
>100 (vs <50)	1.040	3.217	6.454	0.841-49.524	
Macroscopic vascular invasion: Yes (vs no)	0.625	0.647	1.654	0.486-5.631	.4211
Serum AFP ≥100 ng/mL (vs <100 ng/mL)	0.396	5.406	2.513	1.156-5.465	.0201
All patients					
Performance status 1-3 (vs 0)	0.180	10.852	0.554	0.389-0.787	.0010
Child-Pugh classification B or C (vs A)	0.182	45.663	0.292	0.204-0.417	<.0001
Tumor size, mm					.5976
50-100 (vs <50)	0.220	0.044	1.047	0.680-1.613	
>100 (vs <50)	0.375	0.656	0.738	0.354-1.539	
Macroscopic vascular invasion: Yes (vs no)	0.216	10.960	0.489	0.320-0.747	.0009
Serum AFP ≥100 ng/mL (vs <100 ng/mL)	0.176	4.848	1.474	1.044-2.083	.0277
Serum PIVKAII ≥100 mAU/mL (vs <100 mAU/mL)	0.186	0.922	1.196	0.830-1.724	.3371

Abbreviations: AFP, α-fetoprotein; CI, confidence interval; PIVKAII, protein induced by vitamin K absence or antagonist II; RR, relative risk; SE, standard error.

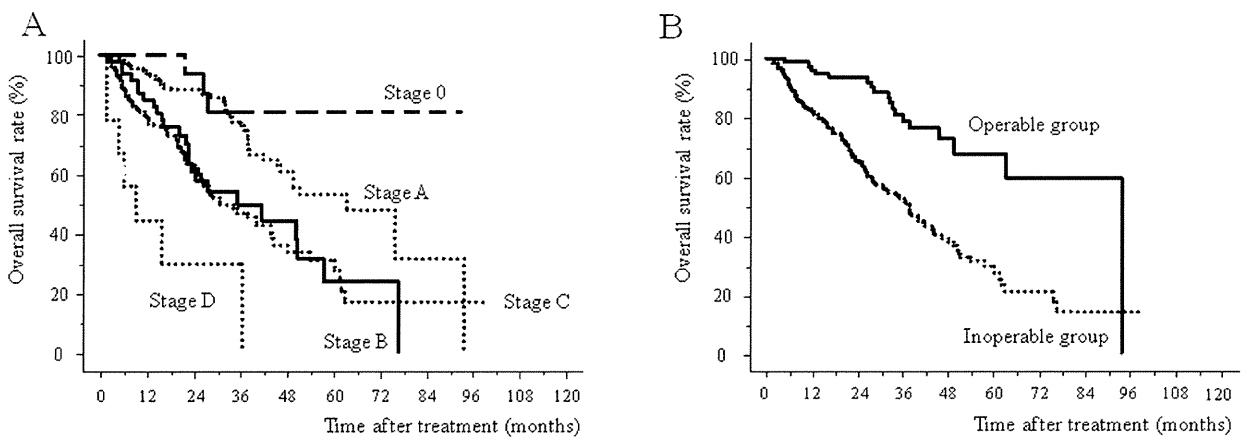

Figure 4. (A) Overall survival rates are illustrated for all 343 patients according to disease stage classified by the Barcelona Clinic Liver Cancer classification. (B) Overall survival rates are illustrated for all 343 patients according to the operative indication based on the Barcelona Clinic Liver Cancer classification.

not feasible. Under these circumstances, we established that the treatment results of carbon ion therapy were equivalent to those of proton therapy at our institute. These results may prove the validity of our treatment planning system for carbon ion therapy by using a variable RBE.

The current study has established the equal effectiveness of proton and carbon ion therapies for HCC. With regard to this result, we speculate that the superior dose distribution compensates for the limitation of carbon ion beam arrangements at HIBMC. With the development of irradiation equipment, compared with proton therapy, carbon ion therapy will play a major role in the treatment of patients with HCC who have tumors adjacent to the gut and/or those whose liver function has deteriorated. However, carbon ion therapy requires huge economic resources, and this issue should be resolved in the future.

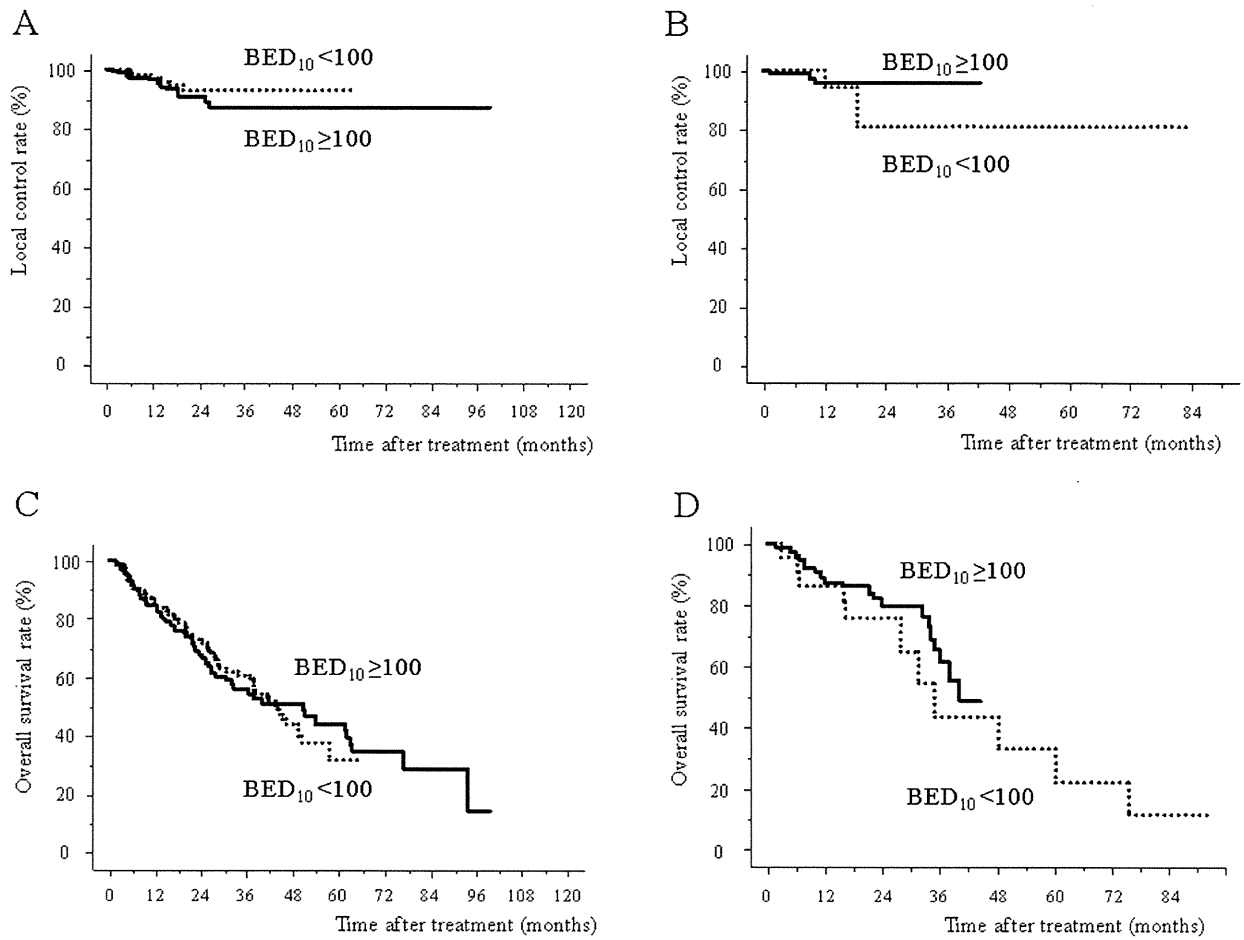

Figure 5. Local control rates are illustrated according to the radiobiologic equivalent dose for acute-reacting tissues (BED_{10}) for (A) proton therapy and (B) carbon ion therapy. Overall survival rates are illustrated according to the BED_{10} for (C) proton therapy and (D) carbon ion therapy.

Tumor size was the only significant risk factor for local recurrence after particle therapy (for proton therapy, carbon ion therapy, and all patients). Conversely, it is noteworthy that the 6 other tumor factors, including gross classification, macroscopic vascular invasion, perivascular location, prior treatment history, serum AFP levels, and serum PIVKAII levels, had no significant influence on the local control rate after either therapy. The application of local ablative therapies is contraindicated in tumors with vascular invasion,[9,35] and it has been reported by several studies that perivascular location significantly increased the local recurrence rate after RFA mainly because of the heat-sink effect.[8,9] In addition, hepatectomy frequently is abandoned to as a treatment for centrally situated tumors adjacent to the inferior vena cava and/or the main portal trunk in patients with cirrhosis, because these tumor locations tend to require major hepatectomy. In the current study, however, neither factor reduced the efficacy of proton therapy or carbon ion therapy in terms of the local control rate.

The local control rates achieved with proton therapy and carbon ion therapy for tumors <50 mm were 95.5%, and 94.5%, respectively. These data are similar or superior to those reported with local ablative therapies.[36] At the same time, the local control rates achieved with proton therapy and carbon ion therapy for tumors that measured from 50 mm to 100 mm in greatest dimension were 84.1% and 90.9%, respectively (Table 4). Because the upper limit of tumor size is 50 mm for local ablative therapies, these results clearly demonstrate the distinct advantage of particle therapy over other local therapies for tumors ≥50 mm. Taken together, in our opinion, particle

Table 8. Late Toxicities After Proton and Carbon Ion Therapy

	No. of Patients (%)								
	Grade 2			Grade 3			Grade 4		
Toxicity	Proton Therapy	Carbon Ion Therapy	All Patients	Proton Therapy	Carbon Ion Therapy	All Patients	Proton Therapy	Carbon Ion Therapy	All Patients
Dermatitis	12 (5)	5 (5)	17 (5)	4 (2)	0	4 (1)	1 (1)	0 (0)	1 (1)
Elevation of transaminase level	5 (2)	3 (3)	8 (2)	1 (1)	3 (3)	4 (1)	0 (0)	0 (0)	0 (0)
Upper gastrointestinal ulcer	3 (1)	1 (1)	4 (1)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Rib fracture	8 (3)	3 (3)	11 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pneumonitis	4 (2)	2 (2)	6 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subcutaneous panniculitis	6 (2)	2 (2)	8 (2)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Biloma	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Low albuminemia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea/anorexia/pain/ascites	4 (2)	2 (2)	6 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

therapy would be the best therapeutic option for patients who have tumors that preclude currently available local therapies because of tumor size, macroscopic vascular invasion, or deep tumor location.

According to the BCLC classification, the 5-year overall survival rate of patients in the operable group was 67.6%. This survival rate is comparable to reported data associated with hepatic resection.[21] It is noteworthy that the overall survival rate of patients classified with stage C disease at 5 years was 30.6% in the current study; this is far superior to other reported data.[21] Patients in this stage have macroscopic vascular invasion and/or extrahepatic metastasis. According to the BCLC classification, these patients usually are excluded from curative treatments and receive either TACE or sorafenib. In the current study, most of patients with stage C disease had macroscopic vascular invasion without extrahepatic metastasis. They were received proton and carbon ion therapies with curative intent, and the local control rates for these patients exceeded 80% (Table 4). These results suggest that some of patients with BCLC stage C disease may benefit from more aggressive local therapies, such as particle therapy.

Most of the treatment-related toxicities in the current study were transient, easily managed, and acceptable. Rib fracture and dermatitis were observed frequently in patients who were treated during the early period at our center. Most of these patients, including 1 patient with grade 4 dermatitis, were treated with only 1 portal to obtain an adequate spread-out Bragg peak. Thereafter, we used 2 or more portals and rarely observed such complications. Regarding intrahepatic structure-related complications, no studies, including ours, have reported blood vessel-related complications. This is a distinct advantage of particle therapy over other local therapies and supports our proposal that tumors in perivascular locations are appropriate candidates for particle therapy. In contrast, although less common, bile duct complications, including biloma and stenosis, have been reported in several studies.[16] In the current study, biloma formation was observed in 1 patient whose tumor was adjacent to the porta hepatis. The bile duct may stand as the single greatest obstacle of intrahepatic structures after particle therapy. It is almost impossible to predict bile duct complications before treatment; thus, tumors adjacent to the porta hepatis should be treated with caution.

Grade 2 or greater gastrointestinal ulceration was observed in 5 patients whose tumors were adjacent to the gut. To minimize toxicity in these patients, we reduced the fraction size and initiated proton pump inhibitors immediately after treatment; and, ultimately, we were able to prevent the development of severity. The proximity of the gut is an important consideration in selecting particle therapy for patients with HCC. We introduced operative placement of a spacer between the tumor and the gut before particle therapy as a countermeasure for this limitation to ensure safe irradiation.[37,38]

To our knowledge, this is the first study to assess the clinical treatment results from both proton therapy and carbon ion therapy. However, our study has some important limitations: 1) the results of this study were achieved retrospectively and not through randomized or controlled trials; 2) during the study period, we used different treatment protocols for proton therapy and carbon ion therapy; and 3) the RBE of carbon ion beams for HCC

has not been completely clarified. Although further investigation is required, our data can serve as a basis for future refinement of beam selection.

In conclusion, both proton therapy and carbon ion therapy produce favorable results as treatment for HCC. Both therapies have great advantages in treating HCC, a condition that is a contraindication for other local therapies. Randomized clinical trials are required to compare particle therapy with other local therapies and to clarify the roles played by particle therapy in the HCC treatment algorithm.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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CLINICAL INVESTIGATION

MULTI-INSTITUTIONAL ANALYSIS OF SOLITARY EXTRAMEDULLARY PLASMACYTOMA OF THE HEAD AND NECK TREATED WITH CURATIVE RADIOTHERAPY

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Purpose: The purpose of this study was to elucidate the efficacy and optimal method of radiotherapy in the management of solitary extramedullary plasmacytoma occurring in the head and neck regions (EMPHN).
Methods and Materials: Sixty-seven patients (43 male and 24 female) diagnosed with EMPHN between 1983 and 2008 at 23 Japanese institutions were reviewed. The median patient age was 64 years (range, 12–83). The median dose administered was 50 Gy (range, 30–64 Gy). Survival data were calculated by the Kaplan-Meier method.
Results: The median follow-up duration was 63 months. Major tumor sites were nasal or paranasal cavities in 36 (54%) patients, oropharynx or nasopharynx in 16 (23%) patients, orbita in 6 (9%) patients, and larynx in 3 (5%) patients. The 5- and 10-year local control rates were 95% and 87%, whereas the 5- and 10-year disease-free survival rates were 56% and 54%, respectively. There were 5 (7.5%), 12 (18%), and 8 (12%) patients who experienced local failure, distant metastasis, and progression to multiple myeloma, respectively. In total, 18 patients died, including 10 (15%) patients who died due to complications from EMPHN. The 5- and 10-year overall survival (OS) rates were 73% and 56%, respectively. Radiotherapy combined with surgery was identified as the lone significant prognostic factor for OS ($p = 0.04$), whereas age, gender, radiation dose, tumor size, and chemotherapy were not predictive. No patient experienced any severe acute morbidity.
Conclusions: Radiotherapy was quite effective and safe for patients with EMPHN. Radiotherapy combined with surgery produced a better outcome according to survival rates. These findings require confirmation by further studies with larger numbers of patients with EMPHN. © 2011 Elsevier Inc.

Extramedullary plasmacytoma, Radiotherapy, Head and neck, Multi-institutional analysis.

INTRODUCTION

Plasma cell malignancies include multiple myeloma (MM), solitary plasmacytoma of the bone (SPB), and extramedullary plasmacytoma (EMP). EMP is a rare tumor representing approximately 3% of all plasma cell tumors, yielding an MM:SPB:EMP incidence ratio of approximately 40:2:1 (1–4). The incidence of EMP has been measured at 0.04 cases per 100,000 individuals (5). Although EMP can arise throughout the body, almost 90% of tumors arise in the head and neck, especially in the upper respiratory tract, including the nasal cavity, sinuses, oropharynx, salivary

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glands, and larynx (4, 6–10). The next most frequent site of occurrence is the gastrointestinal tract. A variety of other sites, including testis, bladder, urethra, breast, ovary, lung, pleura, thyroid, orbit, brain, and skin, can be involved, albeit infrequently (11–21). Patients typically present in the fifth to seventh decade of life with localized submucosal masses or swellings and symptoms related to compression and obstruction of local structures.

Solitary extramedullary (soft-tissue) plasmacytoma is less common than SPB but carries a better prognosis, because the majority of patients can be cured by local radiotherapy (22). The optimal management of EMP of the head and neck (EMPHN) is a matter of debate. Radiotherapy plays a central role in the treatment of EMP, even though the optimal radiationdose and the role of elective irradiation of regional lymphatics are still undetermined (23). Surgery can also be considered as an alternative first-line therapy (6). Surgery can achieve high rates of local control in certain situations. However, radical excision is often impossible because of the size of the tumor, the proximity of critical normal structures and the risk of poor cosmetic results. Potential morbidity associated with surgery and the radiosensitivity of EMP have made radiotherapy the mainstay of treatment at most centers (7, 24). On the contrary, the role of chemotherapy in the treatment of primary tumors or recurrent disease or in preventing or delaying progression to MM remains controversial (3, 25, 26). Adjuvant chemotherapy has not been shown to reduce relapse rates or to improve survival rates and, at present, has no place in the primary management of EMP (24, 27, 28). Therefore, close communication among radiation oncologists, surgeons, and hematological oncologists is crucial for the optimum care for this disease.

The purpose of this study was to elucidate the efficacy and the optimal method of radiotherapy in the management of EMPHN.

Table 1. Patients and tumor characteristics

	Number	Percentage (%)
Age	12–83 (64)*	
Gender (M/F)	43/24	
ECOG performance status (0/1/2/unknown)	46/18/1/2	
Tumor size	1–10 cm (3.5)*	
Sites		
Nasal/paranasal	36	54
Oropharynx	9	13
Nasopharynx	7	10
Orbita	6	9
Larynx	3	5
Salivary glands	2	3
Lymph nodes	2	3
Middle ear	1	1.5
Thyroid	1	1.5
Positive for M protein	15/59	22
Positive for Bence-Jones proteins	2/56	4
Concomitant disease		
Amyloidosis	2/67	3

* median age, median tumor size.

PATIENTS AND METHODS

Medical records of all patients treated for EMPHN at 23 institutions in Japan between 1983 and 2008 were retrospectively reviewed. Patients were identified from databases at each institution. This study was approved by the Kobe University Hospital and each relevant institutional Review Board. Patients were considered eligible for inclusion if they had a single lesion in the head or neck and a diagnosis of EMP based on a biopsy showing features characteristic of plasmacytoma, a negative skeletal survey, and a normal bone marrow biopsy. Patients with evidence of myeloma at the time of presentation were excluded. Then, a total of consecutive 67 patients from the 23 institutions were investigated. In general, patients were seen at follow-up evaluations every 3 months for the first 2 years, every 6 months for an additional 3 years, and then yearly or every other year thereafter. Follow-up imaging included fiberoptic endoscopy

Table 2. Details of treatments

	Total numbers of patients (%)	Age <50	Age ≥50	*p* value
Treatment policy				
Without surgery*	44 (66)	10	34	0.93*
Radiotherapy alone	39 (58)	8	31	
Radiotherapy combined with chemotherapy	5 (8)	2	3	
With surgery*	23 (34)	5	18	
Surgery followed by radiotherapy	19 (28)	4	15	
Radiotherapy followed by surgery with or without chemotherapy	4 (6)	1	3	
Radiation dose (BED: median, minimum, and maximum)				
Median: 50 Gy, 1.8–2 Gy per fraction				
≤40 Gy (BED: 46.7, 36, and 48)	13 (20)	4	9	0.41
40.1–45 Gy (BED: 51, 50.4, and 53)	4 (6)	1	3	
45.1–50 Gy (BED: 60, 55.2, and 60)	39 (58)	6	33	
50.1–64 Gy (BED: 72, 59.5, and 76.8)	11 (16)	4	7	
Radiation fields				
Primary sites	51 (76)	11	40	0.2
Primary sites and regional nodes	16 (24)	6	10	

Abbreviation: BED = biologically effective dose.
$\alpha/\beta = 10$.
*Subgroups treated radiotherapy without surgery ($n = 44$) or with surgery ($n = 23$) were evaluated by a chi-square test.

Table 3. Relationship of tumor size and radiation dose in patients treated with radiotherapy and without surgery

Radiation dose	Total numbers of patients (%)	Tumor size ≤5 cm	Tumor size >5 cm	*p* value
Without surgery (n = 42*)				
≤45 Gy	10	8	2	0.75
>45.1 Gy	32	27	5	
With surgery (n = 16†)				
≤45 Gy	5	4	1	0.33
>45.1 Gy	11	6	5	

*Two cases were excluded because their tumor sizes were not identified exactly.

†Seven cases were excluded with the same reason.

at each visit and computed tomography and/or magnetic resonance imaging every 6–12 months.

Statistical analysis

Statistical analysis was performed using Statview software (SAS Institute, Cary, NC) . Time to event was calculated from the starting date of radiotherapy to the event of interest, which was death (from any cause) for overall survival, first failure (death or disease) for disease-free survival (DFS), and local recurrence as confirmed by biopsy for recurrence rates. The Kaplan-Meier method was used to calculate the survival and recurrence curves. Follow-up duration was estimated for surviving patients. Differences in local recurrence rates between factors were calculated using the log–rank test.

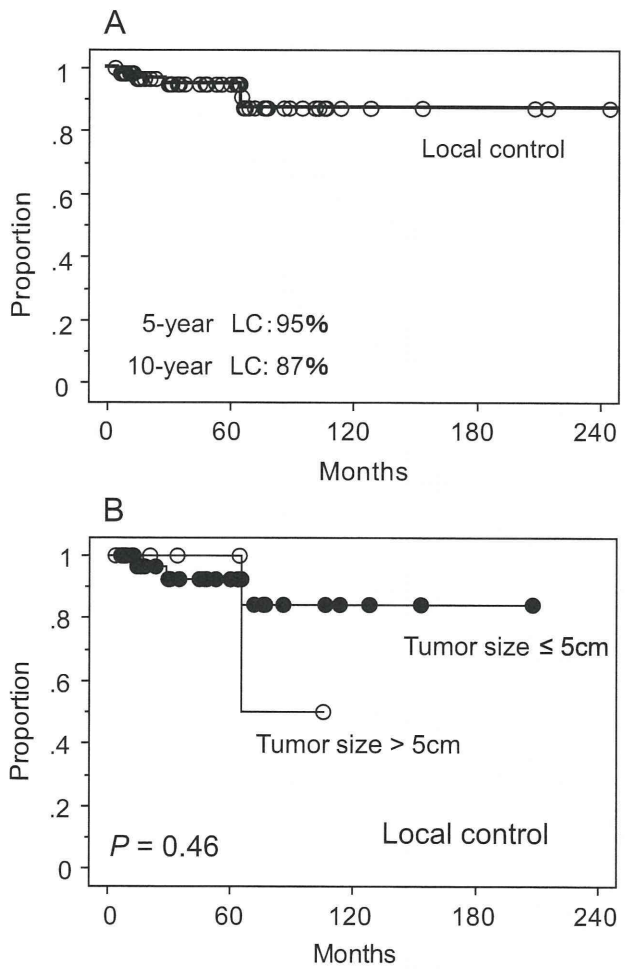

Fig. 1. (A) Local control rate for extramedullary plasmacytoma of the head and neck (EMPHN) (n = 67). (B) Comparison of local control rate according to the tumor size in patients treated with radiotherapy and without surgery (n = 42). Log–rank test was used for evaluation.

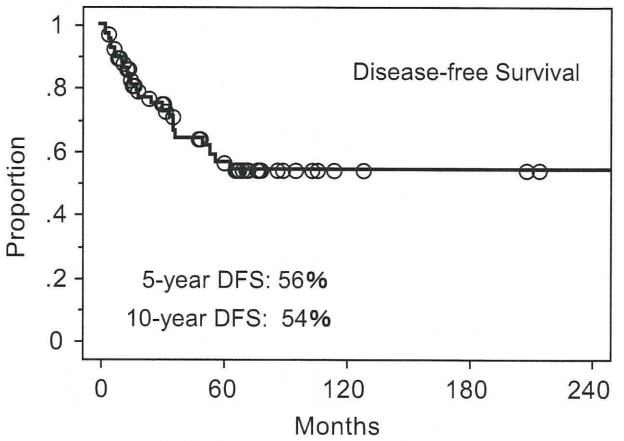

Fig. 2. Disease-free survival rate for extramedullary plasmacytoma of the head and neck (EMPHN) (n = 67).

RESULTS

Patients and treatments

Details of tumor characteristics are shown in Table 1. The median age at diagnosis was 64 years, with a range of 12–83 years. In this study, 43 patients were male, and 24 patients were female. The median tumor size was 3.5 cm (range, 1–10 cm). The most frequent tumor sites were nasal or paranasal cavities. Proportions of patients with positive M protein, Bence-Jones protein, and concomitant disease are listed in Table 1. External beam radiation therapy was used in all cases. A 4- to 10-megavolt photon beam was primarily applied for 57 patients, whereas a telecobalt gamma ray was used for 8 patients. Electron beam irradiation was used for 2 patients. The radiation dose ranged from 30 to 60 Gy, with a median dose of 50 Gy. Treatment policies, radiation dose, and radiation fields are listed in the Table 2. Although all patients were treated with 1.8–2 Gy per fraction, total doses were ranging from 30 to 64 Gy, and biological effective doses (BED) were ranging from 36 to 76.8 Gy calculated by using a ration of α/β = 10 (Table 2). The treatment methods, choice of total dose, and choice of irradiation for regional lymph nodes were depending on each physician's decision. Treatment choice was not differ significantly according to the age (<50 or ≥50) (Table 2). Radiation dose did not differ significantly as a function of tumor size in a subgroup without surgery (p = 0.75) and in a subgroup with surgery (p = 0.33) (Table 3).

Local control

The median follow-up duration was 63 months. Local recurrences developed in 7.5% of patients (5 of 67). The mean

Table 4. Patterns of recurrence according to the radiation fields

Radiation fields	Total numbers of patients	Controlled (%)	Sites of recurrence		
			Local (%)	Regional lymph nodes (%)	Progression to MM or distant metastases (%)
Primary tumor	51	29	4*	1	21*
Primary tumor and regional lymph nodes	16	13	1	0	2
Total	67	42 (62)	5 (7.5)	1 (1.5)	23 (34)

Abbreviation: MM = multiple myeloma.
*4 patients experienced both local recurrence and progression to MM.

time from diagnosis to local recurrence was 65 months (median, 52 months). The overall 5- and 10-year local control (LC) rates were 95% and 87%, respectively (Fig. 1A). Only a single patient recurred locally, whereas 4 other patients had both local and distant diseases. Of 5 patients who developed local recurrences, 3 died of the disease. Regarding 2 other patients who experienced local recurrence, 1 was successfully treated and is alive without disease and the other developed multiple myeloma. Next, among 44 patients who treated radiotherapy and without surgery, influence of tumor size on local controllability was evaluated. Although 2 patients were excluded because their tumor size was not exactly determined, the tumor size was not a significant factor for the local control in the 42 patients ($p = 0.46$, Fig. 1B).

Disease progression and progression to MM

Disease progression was observed in 36% of patients (25 of 67). The 5- and 10-year DFS rates were 56% and 54%, respectively (Fig. 2). Among patients with disease progression, 8 patients (12%) were diagnosed with progression to MM. The median duration of progression to MM was 18 months (range, 6–71 months). Among other 17 patients, 1 experienced local recurrence alone, 4 patients did both local and distant recurrence, and 12 did distant recurrence alone. Next, patterns of failure sites and the radiation fields were investigated (Table 4). Only 1 patient who was treated to the primary tumor site without regional lymph nodes irradiation experienced regional lymph nodes recurrence, while none who were irradiated both primary and regional lymph nodes did. Salvage treatment was performed as follows: radiotherapy in 7 patients, chemotherapy in 9 patients, and surgery in 2 patients (including a patient treated with chemotherapy and surgery). The remaining 7 patients were followed only by careful observation.

Survival

The overall 5- and 10-year survival rates were 73% and 56%, respectively (Fig. 3). The cause-specific 5- and 10-year survival rates were 82% and 76%, respectively. At last follow-up, 18 patients had died. Among those patients, 10 (15%) had died of the disease, whereas 8 patients (12%) died of other diseases.

Prognostic factors for overall survival

Several factors were evaluated to determine whether they influenced overall survival. Radiotherapy combined with surgery was identified as the lone significant prognostic factor for overall survival (OS) ($p = 0.04$), whereas tumor size, age, gender, radiation dose, and chemotherapy were not predictive (Fig. 4, Table 5). To exclude the possibility

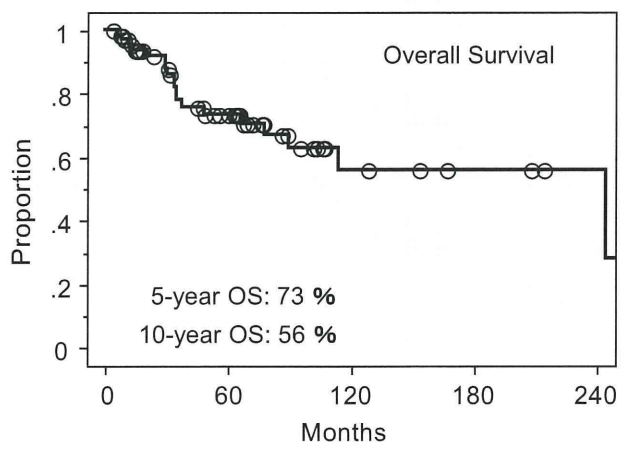

Fig. 3. Overall survival rate for extramedullary plasmacytoma of the head and neck (EMPHN) ($n = 67$).

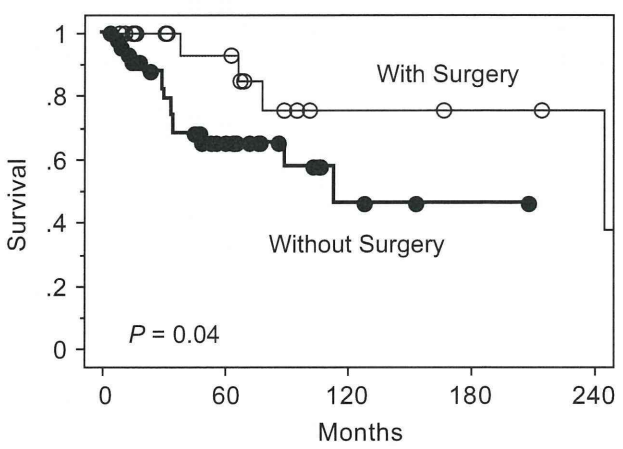

Fig. 4. Overall survival rates according to patients who received radiotherapy either with surgery ($n = 23$) or without surgery ($n = 44$).

Table 5. Prognostic factors for overall survival

Prognostic factors	*p* value
Tumor size	
≤5 cm (*n* = 45) vs. >5 cm (*n* = 13)	0.59
Age	
≤50 (*n* = 15) vs. >51 (*n* = 52)	0.3
Gender	
Male (*n* = 43) vs. female (*n* = 24)	0.95
Radiation dose	
≤40 Gy (*n* = 13) vs. >40.1 Gy (*n* = 54)	0.82
≤45 Gy (*n* = 17) vs. >45.1 Gy (*n* = 50)	0.73
≤50 Gy (*n* = 56) vs. >50.1 Gy (*n* = 11)	0.72
Surgery	
With surgery (*n* = 23) vs. without surgery (*n* = 44)	0.04
Chemotherapy	
With chemotherapy (*n* = 9) vs. without chemotherapy (*n* = 58)	0.75

of selection bias, an influence of age was evaluated. As shown in the Table 2, the cohorts of patients who were treated radiotherapy combined without surgery, and of patients with surgery, proportions of younger subgroup (≤50 years) and that of older subgroup did not differ significantly ($p = 0.93$). Of course, although larger numbers of cases and prospective studies will be needed, our results (Fig. 4) might not be influenced by a selection bias especially in regard with age.

Morbidities associated with radiotherapy

Acute morbidity was examined according to CTCAE version 3.0. Data regarding radiation dermatitis and radiation mucositis were obtained from 44 (66%) patients. Of these, 8 patients had Grade 2 radiation dermatitis, and 27 patients had Grade 1 radiation dermatitis (Table 6). A single patient experienced Grade 3 radiation mucositis, 13 patients experienced Grade 2, and 20 patients experienced Grade 1. No patient experienced morbidity after radiotherapy.

Table 6. Adverse effects after the radiotherapy according to CTCAE ver. 3.0

	Grade					
	0	1	2	3	4	5
Dermatitis	9	27	8	0	0	0
Mucositis	10	20	13	1	0	0

A case successfully treated with radiotherapy combined with surgery

A 70-year-old male suffered from a vast tumor located in the nasal cavity and extending to the paranasal cavity. At first, a radical surgery was planned, but the planned procedure seemed to be extremely invasive because the tumor had invaded into the base of the skull. Therefore, radiotherapy was employed as an initial treatment for this disease, and a total of 60 Gy (in 30 fractions over 6 weeks) was delivered using three-dimensional conformal radiotherapy (Fig. 5). At 3 months after the completion of radiotherapy, a residual tumor was observed at the concha nasalis media, and a less invasive tumorectomy was performed. The case was not expected to be cured by a single modality (either surgery or radiotherapy), but radiotherapy combined with surgery was successfully applied to the extensive EMPHN tumor (>5 cm in diameter) (Fig. 6).

DISCUSSION

Our study represents one of the largest in terms of scale (that is, a large number of patients with solitary EMP of the head or neck regions treated at multiple institutions with sufficient follow-up duration) (Table 7).

Solitary EMP is believed to be radiosensitive. However, because of the rarity of the disease, there have been few reports concerning the effective radiation dose. Several investigators have reported that local control rates of 80–100% are consistently found after moderate doses of radiotherapy (2–4, 25, 29–37). Tsang *et al.* (29) achieved local control in 13 of 14 (93%) of patients with a dose of 35 Gy. The only failure was in a patient with a large primary tumor (>5 cm). Similarly, Jyothirmayi *et al.* (30) achieved local control in 6 of 7 patients with doses of 35–45 Gy (median dose, 40 Gy in 20 fractions). The only failure was in a patient

Table 7. Comparison and reviews of literatures for plasmacytoma of the head and neck

Series (ref.)	Year	Institution	Numbers of patients	Follow-up (m)	Dose (median)	OS (%)		LCR (%)		DFS (%)	
						5-y	10-y	5-y	10-y	5-y	10-y
Liebross (4)	1999	Single	22	44	40–60 (50)	73	50	95	95	56	NA
Chao (37)	2005	Single	16	66	40–50.4 (45)	85	54	100	100	75	75
Tournier-Rangeard (32)	2006	Single	17	80	40–65 (52.6)	82	63	88	73	64	54
Bachar (41)	2008	Single	68	96	10–50 (35)	76	56	91	88	NA	NA
Creach (34)	2009	Single	18	82	34–56 (50.4)	80	54	NA	NA	74	53
Present study	2010	Multiple	67	63	30–60 (50)	73	56	95	87	56	54

Abbreviations: DFS = disease-free survival; LCR = local control rate; OS = overall survival.

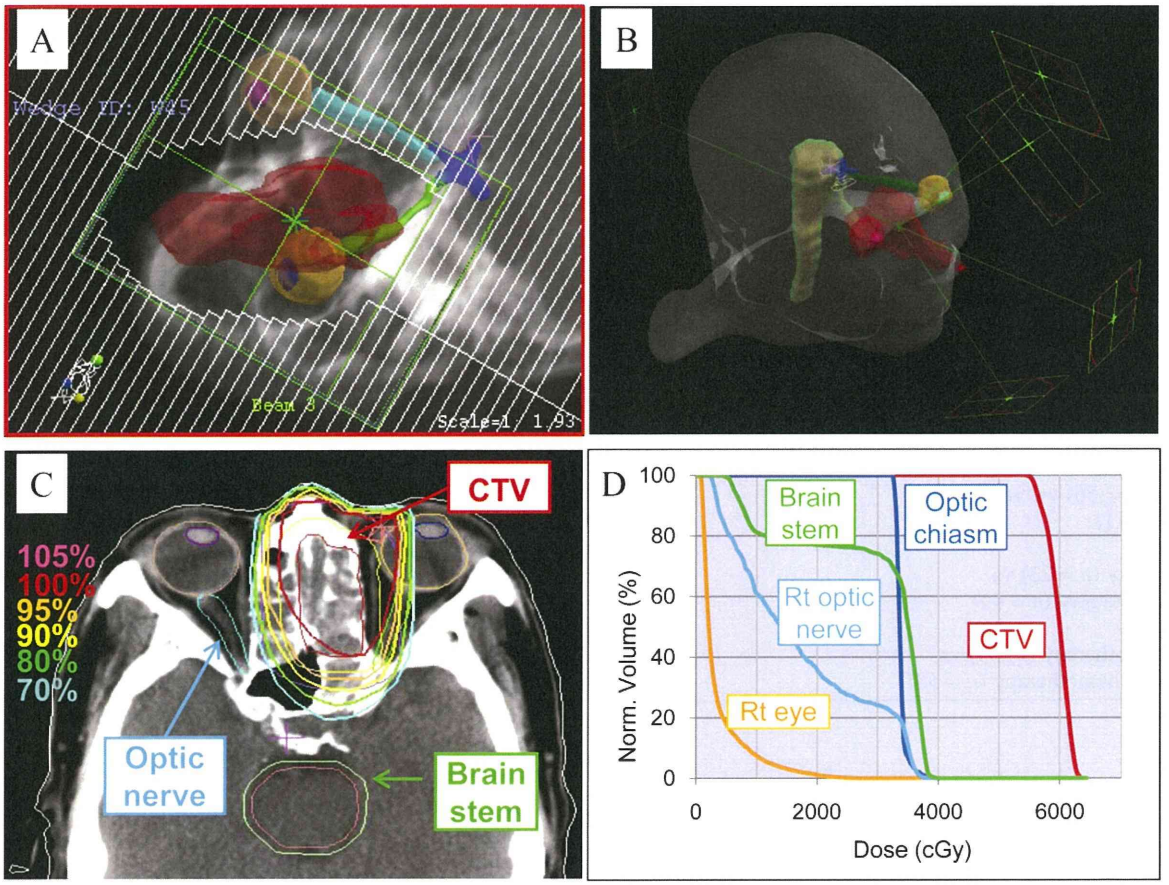

Fig. 5. A 70-year-old male patient suffered from a vast extramedullary plasmacytoma (EMP) located in the nasal and the paranasal cavities treated by three-dimensional conformal radiotherapy (3D-CRT). (A) A port of the 3D-CRT avoiding right optic nerve, right eye, and optic chiasm. (B) Directions and images of the five ports illustrated by using Xio software. (C) The isodose curves for the patient. (D) The dose–volume histogram (DVH) of the 3D-CRT plan.

with an extensive nasopharyngeal tumor. Holland *et al.* (25) also reported poorer local control in tumors >5 cm and similarly observed no evidence of a radiation dose–response effect over a dose range of 16–62 Gy (median dose, 46 Gy). Several series have reported 100% local control rates. Bolek *et al.* (31) reported 100% local control in 10 patients with doses ranging from 9 to 50 Gy (median dose, 45 Gy) and concluded by recommending a dose of 40 Gy in 20 fractions. Shih *et al.* (3) reported on 10 patients with SEP, seven of whom were treated with radiotherapy, using doses of 47–65 Gy. Tounier-Rangeard *et al.* (32) reported that a minimum dose of 45 Gy is recommended to the clinical target volume (CTV) of an EMPHN tumor. Mendenhall *et al.* (33) reported a study of 81 patients composed of a literature review and their own patients. These authors found a local control rate of 94% when the dose to the CTV was greater than 40 Gy and a rate of 69% when the dose to the CTV was less than 40 Gy. Creanch *et al.* (34) reported excellent local control in their series of 16 consecutive patients receiving a median dose of 50.4 Gy. The optimal radiation dose recommended by the UK Myeloma Forum in their 2004 guidelines is in the range of 40–50 Gy (35). In the guideline, tumors with SEP <5 cm have an excellent chance of local control with radiation doses of approximately 40 Gy in 20 fractions. There is a higher risk of local failure in tumors >5 cm, which require a higher dose (approximately 50 Gy in 25 fractions). From these previous investigations, it seems that the optimal radiation dose is in the range of 40–50 Gy, although tumor size might be a critical factor affecting local control. In our series from multiple institutions, with a similar median dose of 50 Gy administered (range, 30–60 Gy), the local control rate was similar and consistent with these previous reports (Table 7). From the results of our series, significance of regional lymph node irradiation seemed to be still undetermined. However, it was at least speculated that progression to multiple myeloma or distant metastases was observed more frequently and seemed to be much more important than regional lymph nodes (Table 4). The subject whether, in any subgroup of plasmacytoma of the head and neck, single modality of radiotherapy could achieve comparable or favorable treatment outcome should be discussed and further investigated. For example, overall survival rate of a subgroup consisted of 20 cases treated with radiotherapy, without surgery, and whose tumor sizes were less than 3 cm were almost similar to those of all 67 cases with or without surgery (5-year OS: 76% vs. 73%; and 10-year OS: 51% vs. 56%, respectively) (data not shown). Therefore, a single modality of radiotherapy might be applied if a tumor

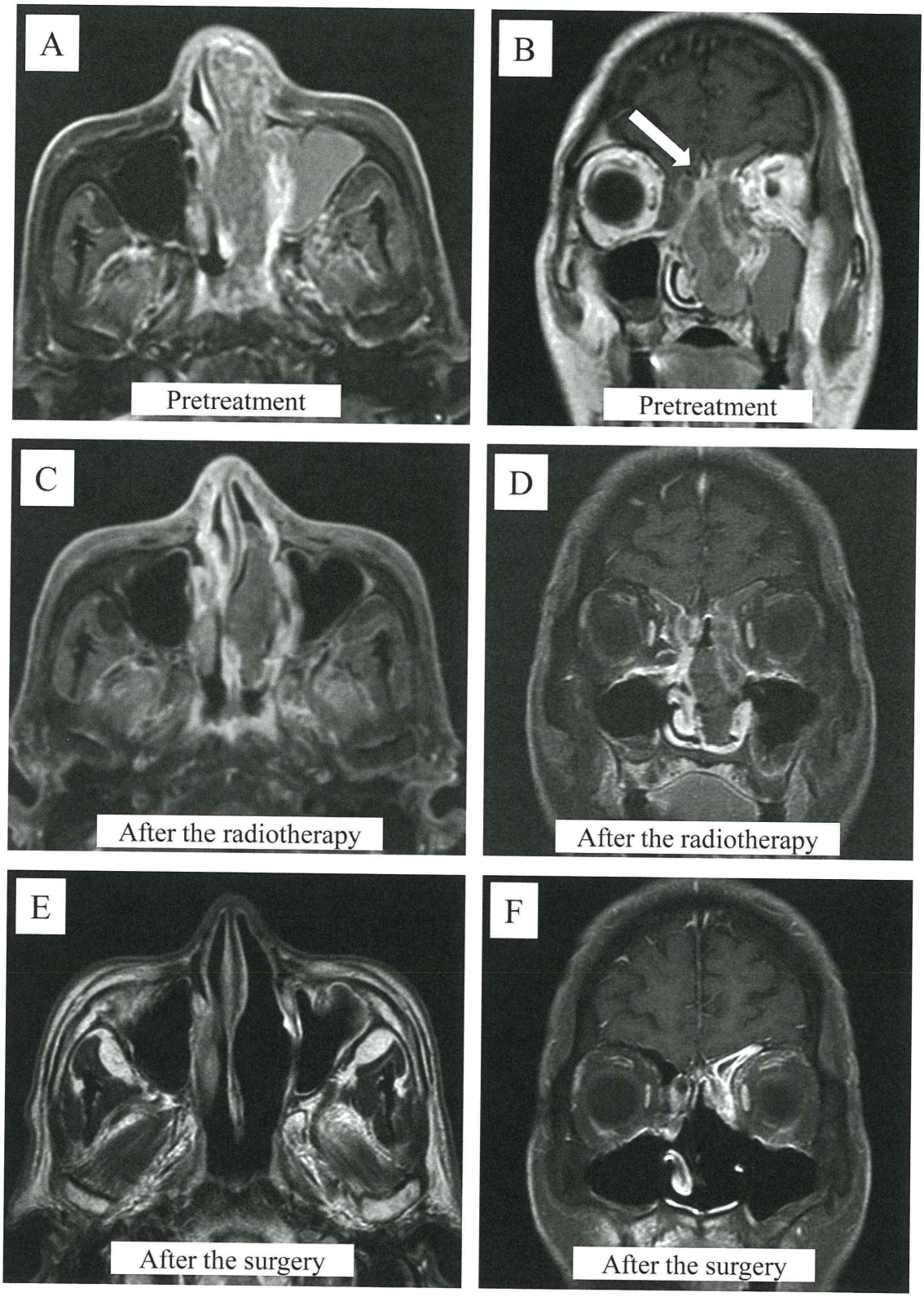

Fig. 6. Magnetic resonance imaging (MRI) of the 70-year-old male patient treated with the radiotherapy followed with the surgery. (A) Pretreatment images of the extramedullary plasmacytoma of the head and neck (EMP) located in the nasal cavity extended to the paranasal cavity. (B) A coronal image of MRI showing an invasion of the base of the skull. (C, D) Axial and coronal images of the residual tumor at the concha nasalis media shrunk after the radiotherapy. (E, F) Images of nasal and paranasal cavities after the surgical removal.

size was less than 3 cm. Although local controllability by either a single modality of radiotherapy or a combination of radiotherapy and surgery seemed to be satisfying, it might be discussed whether the local controllability could be truly led to prolong OS of the disease or not. In this study, population who received chemotherapy was small, and it was difficult to evaluate the efficacy of the chemotherapy. Further investigation, for example, into the significance of radiotherapy combined with chemotherapy might be evaluated. On the contrary, with using recent technological advances such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy, IGRT, or particle therapy, morbidities might be reduced compared with the morbidities of this study treated by conformal X-ray beams. Employment of such modalities might be recommended in the recent future.

Progression to multiple myeloma is also important for the outcome of solitary EMP. Unlike SPB, which progresses to disseminated disease in approximately 60% of cases, solitary EMP has a better prognosis, with 8–44% of patients developing multiple myeloma (1, 2, 4, 6, 9, 25, 27, 28, 32, 38–41). In our series, although 12% of patients developed MM (with an average time to myeloma development of 17 months), 18% of patients experienced distant metastases but were not diagnosed with progression to MM. In the literature, progression to multiple myeloma usually occurs within 2 years of the initial diagnosis, but has occurred up to 15 years later, indicating the need for long-term follow-up of patients (4, 6, 28, 39, 41, 42). As shown in the Table 4, there were only 1 patient who was treated to primary tumor site that experienced a regional lymph node recurrence. Therefore, it was still difficult to answer the question whether regional lymph nodes should be included in the radiation field form our series. However, significance of regional lymph node irradiation seemed to be undermined, because our series included various primary sites, various tumor size, and inhomogeneous total dose. Therefore, further larger scale investigation might be needed. Although the results of our series show a rather small percentage of patients developing MM, longer and careful follow-up observation might be needed.

The role for surgery in the treatment of EMPHN is undetermined. Alexiou *et al.* (7) compared the outcomes of EMP patients treated with surgery alone, radiotherapy alone, or combined surgery and radiotherapy in a detailed and large-scale review. Most of the patients were treated with surgery alone (56%) or a combined-modality treatment (20%), and only 11% were treated with radiotherapy alone. Overall and recurrence-free survival rates were best in those treated with combined therapy ($p = 0.0027$). The authors concluded that patients with plasmacytoma localized to the upper aerodigestive tract benefit from a combined approach. On the contrary, there are some criticisms of the analysis, because the review included patients from a long period (almost a century, 1905–1997), and appropriate radiotherapy might not have been available in any meaningful form for at least half of this period. In the guidelines regarding this disease published by Soutar *et al.* (35), it is recommended that radical surgery should be avoided in EMPHN. In the same report, complete surgical removal was suggested to be considered for solitary EMP at other sites if feasible. Bachar *et al.* (41) demonstrated that patients with involved surgical margins should receive adjuvant radiotherapy. However, no recommendation for adjuvant radiotherapy should be made for patients with negative margins who have undergone complete surgical excision. The authors reported that they found a similar local recurrence rate for patients treated with either radiation or surgery alone (12.5%). They also indicated that complete surgical excision is often not possible, especially in the upper aerodigestive tract, because adjacent vital organ structures may preclude radical intervention. For such patients, either radiotherapy followed by surgery, if needed, or surgical excision followed by radiotherapy is recommended. In our series, a group of 19 patients who received surgery followed by postoperative radiotherapy and 4 patients who received radiotherapy and surgery showed significantly better overall survival. This result indicates that combining radiotherapy with surgery might be less invasive and may represent an optimal strategy for treating EMPHN.

Some authors believe that EMP and multiple myeloma are different phases of the same disease process (43), whereas others believe that they are different diseases (44). If solitary EMP is an initial stage of MM, chemotherapy might play a more important role in management of the disease. However, in the literature and in our series, progression to MM occurred in a rather small proportion of patients. There is no published evidence on the role of adjuvant chemotherapy in the treatment of SEP, although it may have a role in selected high-risk patients. Susnerwala *et al.* (9) reported a higher failure rate in "high-grade" tumors using the MM grading criteria of Bartl *et al.* (36). Tsang *et al.* (29) and Holland *et al.* (25) suggested that patients with tumors >5 cm are at higher risk of failure. The UK Myeloma Forum (35) has suggested that chemotherapy is considered for EMP in the following cases: patients with tumors larger than 5 cm, patients with high-grade tumors, patients with refractory and/or relapsed disease, and patients with MM.

In conclusion, radiotherapy was effective and safe for patients with EMPHN. Radiotherapy combined with surgery produced a better outcome in terms of survival. These findings should be confirmed using further investigations with larger numbers of patients with EMPHN.

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