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.

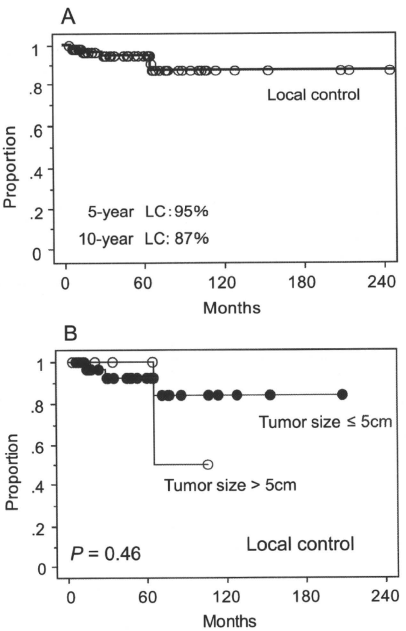

Fig. 1. (A) Local control rate for extramedullary plasmacytoma of the head and neck (EMPHN) (n = 67). (B) Comparison of local control rate according to the tumor size in patients treated with radiotherapy and without surgery (n = 42). Log–rank test was used for evaluation.

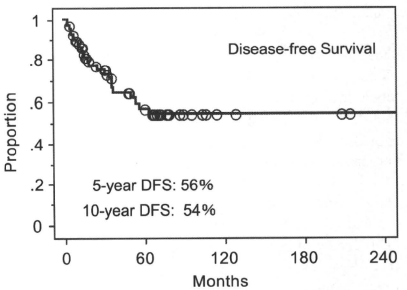

Fig. 2. Disease-free survival rate for extramedullary plasmacytoma of the head and neck (EMPHN) (n = 67).

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

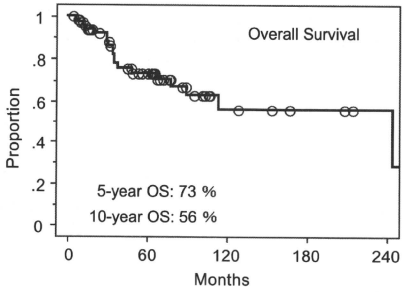

Fig. 3. Overall survival rate for extramedullary plasmacytoma of the head and neck (EMPHN) ($n = 67$).

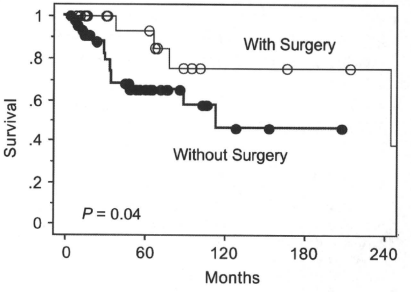

Fig. 4. Overall survival rates according to patients who received radiotherapy either with surgery ($n = 23$) or without surgery ($n = 44$).

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

						OS (%)		LCR (%)		DFS (%)	
Series (ref.)	Year	Institution	Numbers of patients	Follow-up (m)	Dose (median)	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.

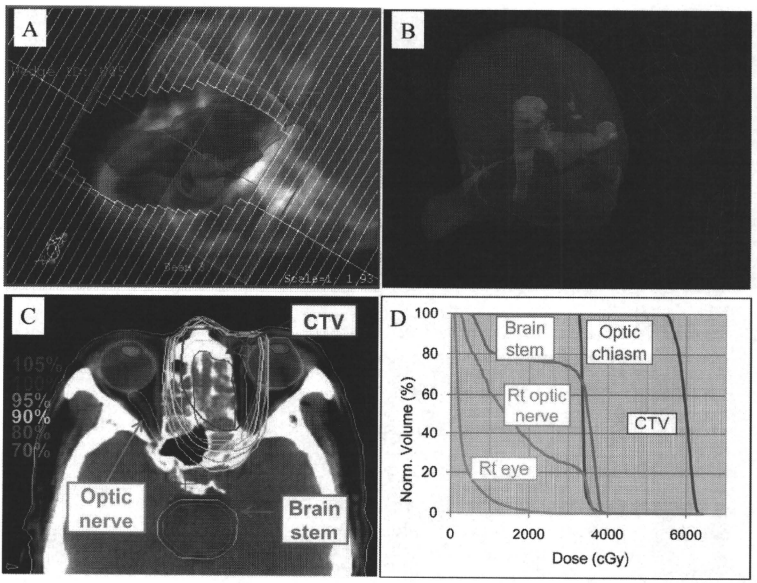

Fig. 5. A 70-year-old male patient suffered from a vast extramedullary plasmacytoma (EMP) located in the nasal and the paranasal cavities treated by three-dimensional conformal radiotherapy (3D-CRT). (A) A port of the 3D-CRT avoiding right optic nerve, right eye, and optic chiasm. (B) Directions and 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

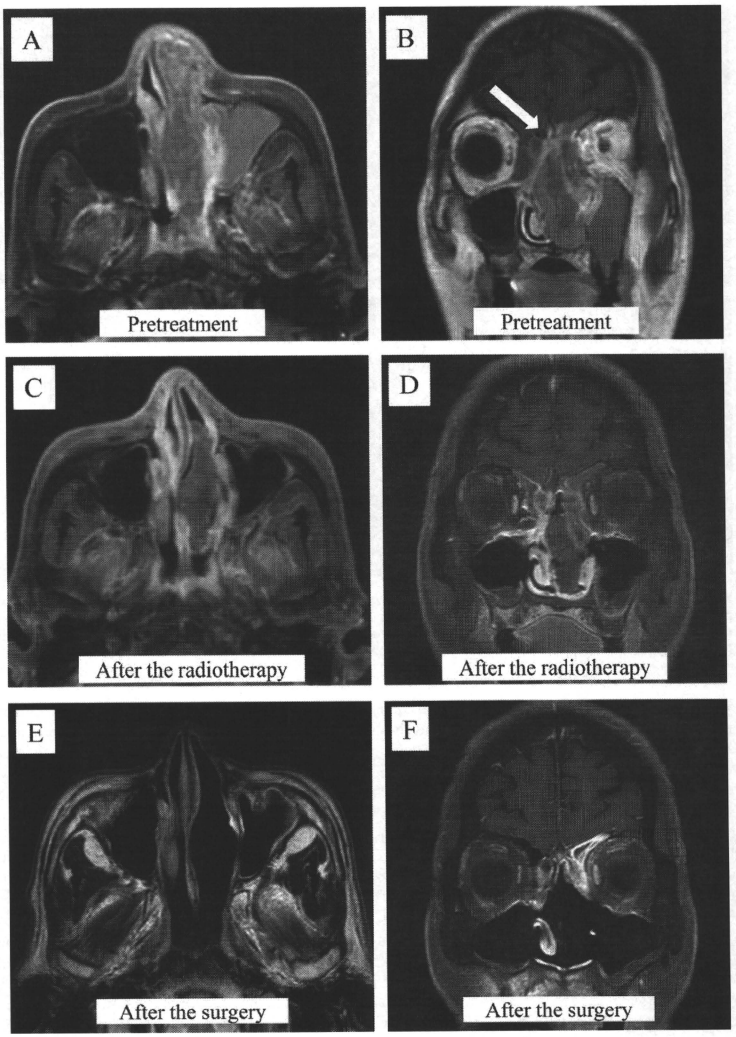

Fig. 6. Magnetic resonance imaging (MRI) of the 70-year-old male patient treated with the radiotherapy followed with the surgery. (A) Pretreatment images of the extramedullary plasmacytoma of the head and neck (EMP) located in the nasal cavity extended to the paranasal cavity. (B) A coronal image of 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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GYNECOLOGIC ONCOLOGY

Radiotherapy for Japanese elderly patients with cervical cancer: preliminary survival outcomes and evaluation of treatment-related toxicity

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Abstract
Purpose To examine the preliminary survival outcomes and treatment-related toxicity for elderly patients with cervical cancer treated with radiotherapy (RT).
Methods Forty patients ≥75 years old with cervical cancer who were treated with RT were evaluated. Of these 40 patients, 25 were classified as FIGO stage I or II and 15 as stage III or IVA. Thirty-five patients were treated with radical RT (RRT), and five were treated with surgery plus adjuvant RT (S + ART). External beam radiotherapy combined with high-dose-rate intracavitary brachytherapy was performed on 31 patients who were treated with RRT and on 2 patients who were treated with S + ART because of positive vaginal surgical margins. The patients' median age was 78 years (range 75–89 years). Concurrent chemotherapy (CCT) was performed on five patients (RRT: 3, S + ART: 2).
Results The median follow-up period was 20 months (range 1–85 months). Only one patient could not complete RT. The 3-year overall and disease-specific survival (OS and DSS) rates for all patients were 58 and 80%, respectively. Five patients experienced Grade 3 acute toxicity; two were treated with RRT (2/35), and three were treated with S + ART (3/5, 2 of them with CCT). Two patients experienced Grade 3 late toxicity; one was treated with RRT (1/35, with CCT) and the other was treated with S + ART (1/5). No Grade 4 or higher toxicity was experienced.
Conclusions RRT for elderly patients with cervical cancer is generally effective and safe, but severe toxicity may occur with more aggressive treatment modalities.

Keywords Cervical cancer · Radiotherapy · Elderly patients · Treatment-related toxicity

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Introduction

The population of elderly people has been rapidly increasing in Japan. According to statements by the Ministry of Health, Labor and Welfare, the average life expectancy for men and women in 2008 was 79 and 86 years old, respectively [1]. In particular, the life expectancy of a Japanese woman is the longest in the world. With an increasingly aged society, the number of elderly patients with various malignancies continues to

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increase. In addition, the number of younger cancer patients has also been increasing due to changes in lifestyle and viral infections. In Japan, malignant neoplasms have the highest mortality rate, surpassing cerebrovascular and heart diseases in 1981.

For cervical cancer, the most commonly afflicted age group is women in their late 30s to early 40s; the affliction of young women is usually emphasized [2–4]. However, the incidence of cervical cancer increases again after age 70, and the mortality rate increases with age. Therefore, the increase in the ratio of elderly patients with cervical cancer must be evaluated, and an appropriate treatment modality should be identified. Surgery and/or radiotherapy (RT) are the radical treatment modalities for cervical cancer. For advanced-stage disease, RT with or without concurrent chemotherapy (CCT) is usually the radical treatment of choice. For early-stage disease, the survival outcomes of surgery and RT are known to be similar [5–8]. Although RT seems to be a less invasive treatment, its long-term complications and negative impact on sexual function when compared with surgery are important considerations for younger patients [9–11]. Therefore, there is a trend emerging in which surgery is usually used for younger patients and RT is used for elderly patients. However, although it is obvious that RT plays an important role in the treatment of most stages (I–IVA) of cervical cancer, the recent increase in the elderly population may further increase RT's importance [12, 13].

In this study, we retrospectively analyzed the preliminary survival outcomes and evaluated treatment-related toxicity for Japanese elderly patients (≥75 years old) with cervical cancer treated with RT.

Materials and methods

Patients

At Kobe University Hospital between 2000 and 2009, 40 patients aged 75 or older who had cervical cancer and were treated with RT as the radical or postoperative adjuvant modality were retrospectively evaluated. Patients who received only palliative RT were excluded. Those patients who were followed for <6 months, except when this was due to recurrence or death, were also excluded. Between 2000 and 2005, 9 patients were treated, whereas 31 were treated between 2006 and 2009. Clinical staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) stages [14]. Among the 40 patients, 35 were treated with radical RT (RRT), and 5 were treated with surgery and adjuvant RT (S + ART). Six patients had pelvic nodal metastases (4 were clinical, 2 were pathological). Thirty-eight tumors were histologically confirmed as squamous cell carcinoma (SCC), and two were confirmed as adenocarcinoma. On the Karnofsky Performance Scale (KPS), 20 patients had scores >70, 17 had scores between 50 and 70, and 3 had scores <50. Twenty-five patients had stage I or II disease (IA: 1, IB: 4, IIA: 7, IIB: 13), and 15 had stage III or IVA disease (IIIA: 2, IIIB: 11, IVA: 2). The median age was 78 years (range 75–89 years). In addition, 29 of the 40 patients had concurrent medical complications. Three patients had a previous history of malignancy (breast cancer, colon cancer, and malignant lymphoma), and one had early-stage lung cancer concurrent with the advanced cervical cancer. Patient information according to clinical factors is shown in Table 1.

Table 1 Patient information according to clinical factors

Factors	Number of patients (total = 40)	%
Treatment period		
2000–2005	9	22.5
2006–2009	31	77.5
Age (years old)		
≤80	27	67.5
>81	13	32.5
Median age (range)	78 (75–89)	
Karnofsky performance scale score		
>70	20	50
50–70	17	42.5
<50	3	7.5
Stage (FIGO)		
IA	1	2.5
IB	4	10
IIA	7	17.5
IIB	13	32.5
IIIA	2	5
IIIB	11	27.5
IVA	2	5
Histology		
SCC	38	95
Adenocarcinoma	2	5
Nodal metastasis		
Yes	6	15
No	34	85
Medical complications		
Yes	29	72.5
No	11	27.5
History of other cancers		
Yes	4	10
No	36	90

SCC squamous cell carcinoma

Treatment

In our institution, RRT is recommended as the definitive treatment for patients with cervical cancer ≥75 years old. Surgery is considered if the following criteria are met: young age, high KPS score (>70), and FIGO I or II. Medical complications and histology (adenocarcinoma) are also important considerations. In addition, the patient's desired treatment choice (RT or surgery) is also considered. Indications for the use of ART are based on pathological findings (nodal metastasis, parametrium invasion, surgical margin, vascular invasion, and/or lymphatic invasion). Based on this institutional guideline, 35 patients were treated with RRT, and the remaining 5 were treated with S + ART. Among the 35 patients treated with RRT, 31 were treated with external beam radiotherapy (EBRT) combined with high-dose-rate intracavitary brachytherapy (HDR-ICBT), 3 were treated with EBRT alone, and 1 was treated with HDR-ICBT alone. The four patients treated with EBRT or HDR-BT alone had KPS scores = 50 or less. Of the 31 patients treated with EBRT combined with HDR-ICBT, 2 received boost irradiation for pelvic lymph node metastases. Two of the three patients treated with EBRT alone received boost irradiation for the primary tumor instead of HDR-BT. Among the five patients treated with S + ART, three received EBRT alone, and two received EBRT combined with HDR-ICBT because of positive vaginal surgical margins. CCT using a platinum-based regimen was performed on five patients. Three were treated with RRT with CCT, and two were treated with S + ART with CCT. At our institution, RRT with CCT is performed on younger patients (<80) with high KPS scores (>70) and FIGO IIB or higher. The presence of medical complications is also an important consideration. Based on these criteria, three patients were treated with RRT with CCT. Adjuvant CCT has been performed on patients with multiple pathological risk factors (at least 3) since 2008. Postoperative KPS score (>70) is also considered to be important because S + ART with CCT is a very aggressive treatment for elderly patients; two were ultimately treated with this modality. The patient distribution per treatment modality is shown in Table 2.

The patients who received EBRT combined with HDR-ICBT were initially treated with whole pelvic irradiation using a box field and high-energy 10 MV X-ray photons from a linear accelerator with a daily fraction size of 1.8–2.0 Gy delivered five times per week. A centrally shielded field using anterior/posterior opposed portals was applied just before starting HDR-ICBT. The patients who received EBRT alone were also initially treated with whole pelvic irradiation. A boost to the primary tumor was delivered using a three-dimensional conformal technique, and a pelvic lymph node boost was delivered using the anterior/posterior opposed portals. The median total dose of EBRT was 50.4 Gy (range 16.2–61.2 Gy). The HDR-ICBT was done with a Microselectron HDR (Nucletron, The Netherlands) using a 192-Iridium remote afterloading system at 1-week intervals during the period of EBRT. The median total dose to point A was 20.0 Gy (range 4.5–31.0 Gy) with a single fraction size of 4.0–6.5 Gy. Treatment planning for HDR-ICBT was performed at each irradiation using PLATO Brachytherapy Planning System version 3.2 (Nucletron, The Netherlands). Evaluation of the rectal and bladder dose was performed according to ICRU Report 38 [15].

Table 2 Patient distribution per treatment modality

	Number of patients	Use of CCT
RRT		
EBRT + HDR-ICBT (with nodal boost)	31 (2)	3
EBRT (with local boost)	3 (2)	0
HDR-ICBT	1	0
S + ART		
EBRT	3	1
EBRT + ICBT	2	1

RRT radical radiotherapy, *EBRT* external beam radiotherapy, *HDR-ICBT* high-dose-rate intracavitary brachytherapy, *S* surgery, *ART* adjuvant radiotherapy, *CCT* concurrent chemotherapy

Follow-up, evaluation of treatment-related toxicity, and statistical analysis

After completion of their treatment, most patients were followed up by gynecological and radiation oncologists every month during the first year, primarily because elderly patients tolerate RT less well and unexpected toxicity might be experienced. However, patients who lived far from our institution were followed up every 2–3 months. Afterward, follow-up was conducted every 3–6 months to detect recurrence and late toxicity. A gynecological examination was performed, and the tumor marker was checked at every visit. SCC Antigen was used for patients who had SCC, and Carcinoembryonic Antigen (CEA) was usually used for patients who had adenocarcinoma. Radiographic examinations (CT scan or MRI) were performed as necessary.

Both acute and late treatment-related toxicity were evaluated using medical records and CTC-AE version 4.0 [16]. Acute toxicity was defined as those events that occurred within 90 days from the start of the treatment, and late toxicity was defined as those events that either occurred >90 days from the start of the treatment or persisted beyond 90 days.

Statistical analyses were performed using Sigma Plot 9.0 software (Systat Corporation, CA, USA). Survival rates were calculated with the Kaplan–Meier method and compared with the use of log-rank test. The follow-up period was calculated from the start of the treatment. P values <0.05 were considered statistically significant.

Results

Patient status and patterns of failure

The median follow-up period for all patients was 20 months (range 1–85 months). The median follow-up period for survivors was also 20 months (range 6–85 months). Of the initial 40 patients, 38 completed the treatment as planned, 1 completed with a delay due to concomitant heart disease, and 1 could not complete the treatment because of acute toxicity. These two patients who experienced delay or cancellation had lower KPS scores (<50). Seven patients experienced recurrence: four locally, one in the para-aortic lymph nodes, one distantly, and one with only tumor marker (SCC Antigen) elevation. Even though a thoracic-abdominal contrast enhanced CT scan, a pelvic MRI, a gynecologic examination and cytology were performed, a recurrent tumor could not be detected at any site. However, this patient was presumed to have microscopic recurrence because SCC Antigen increased continuously. Regarding the clinical stages, one patient was classified as IIA, one as IIIA, and five as IIIB. Six of the seven patients with recurrence were treated with RRT, and one was treated with S + ART. During the period of this study, nine patients died. Among them, five died because of the primary disease, and four died from other causes. The patient who could not complete the treatment had persistent disease and died of the primary disease. Of the remaining two patients who experienced recurrence, one with the para-aortic lymph nodes metastases is alive with the disease and one with tumor marker elevation apparently died from a different cause. The patient who had early-stage lung cancer concurrently with the cervical cancer received the left lower lobe resection after completion of RT. The pathological diagnosis was adenocarcinoma, pT2N0M0. This patient experienced multiple bone metastases (bilateral sacroiliac joints and lumber spine) about 22 months after surgery. Bisphosphonate has been continuously administered, and the patient is doing well without pain.

Preliminary survival outcomes

The 3-year overall and disease-specific survival (OS and DSS) rates for all the patients were 58 and 80%, respectively (Fig. 1a, b). The 3-year OS rate for patients in FIGO stage I or II was 69%, and the rate for stage III or IVA patients was 40% ($P = 0.04$). The 3-year DSS rate for patients in FIGO stage I or II was 89% and that for stage III or IVA patients was 66% ($P = 0.04$). The patients were also divided into two groups according to age; there were 27 patients aged ≤80 years with a median follow-up of 26 months (range 1–85 months) and 13 patients aged >80 years with a median follow up of 14 months (range 7–61 months). The 3-year OS rates for patients aged ≤80 and >80 years were 62 and 42%, respectively ($P = 0.89$). The 3-year DSS rates for patients aged ≤80 and >80 years were 75 and 100%, respectively ($P = 0.21$). Survival was also analyzed according to KPS score. The 3-year OS rates for patients with KPS scores >70 and ≤70 were 61 and 55%, respectively ($P = 0.15$). The 3-year DSS rates for patients with KPS scores >70 and ≤70 were 92 and 65%, respectively ($P = 0.11$).

Treatment-related toxicity

The details regarding acute toxicity are shown in Table 3. The most common acute toxicity was diarrhea (18/40

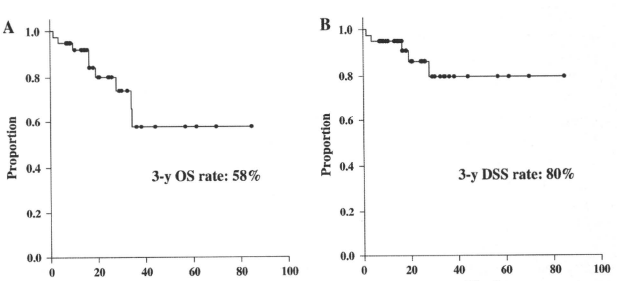

Fig. 1 Preliminary overall and disease-specific survival (OS and DSS) rates for all patients ($n = 40$) using the Kaplan–Meier method with a median follow-up of 20 months (range 1–85 months). The 3-year OS and DSS rates were 58% (**a**) and 80% (**b**), respectively

Table 3 Acute treatment-related toxicity according to treatment modality (CTC-AE version 4.0)

	RRT (use of CCT), total: 35	S + ART (use of CCT), total: 5
Gastrointestinal		
Grade 1–2	Diarrhea: 16 (2), gastrointestinal pain: 2	Diarrhea: 1(1)
Grade 3	Diarrhea: 1	Intestinal infection: 1(1)[a], intestinal obstruction: 1
Grade 4	0	0
Genitourinary		
Grade 1–2	Urinary frequency: 3, cystitis: 1	Urinary tract obstruction: 1
Grade 3	Cystitis: 1	Cystitis: 1, urinary tract obstruction: 1(1)[a]
Grade 4	0	0

RRT radical radiotherapy, *S* surgery, *ART* adjuvant radiotherapy, *CCT* concurrent chemotherapy

[a] Same patient

patients, 45%). Grade 3 acute toxicity occurred in five patients, but no Grade 4 or greater acute toxicity was experienced. Among the five patients with Grade 3 acute toxicity, two were treated with RRT (2/35 patients, 5%) and three were treated with S + ART (3/5 patients, 60%). As for the patients treated with RRT, one experienced Grade 3 diarrhea and selectively cancelled her treatment at 16.2 Gy after nine fractions, and the other experienced Grade 3 cystitis. As for the patients treated with S + ART, one receiving CCT experienced a Grade 3 small intestine infection during RT and a urinary tract obstruction soon after the completion of RT, the different one receiving CCT experienced Grade 3 cystitis during RT, and the remaining one experienced a small intestine obstruction soon after RT. The patient who could not complete RT was managed by the administration of anti-diarrheal agents and continuous intravenous transfusion. RT was postponed, but after recovery from the diarrhea, the patient refused to restart RT. The patients who experienced cystitis or small intestine infections were managed by the administration of antibiotics and intravenous transfusions without delaying the RT. The urinary tract obstruction was resolved by urological intervention. The small intestine obstruction was managed by conservative treatment, such as fasting, antibiotic administration, and continuous intravenous transfusion. In both the urinary tract and small intestine obstructions, abdominal CT scans were performed immediately after the symptoms occurred, and progressive disease was excluded.

Currently, Grade 3 late toxicity has occurred in two patients (2/40 patients, 5%). One of these two patients (treated with RRT with CCT) experienced Grade 3 hemorrhagic cystitis. The other patient (treated with S + ART) experienced a Grade 3 acute small intestine obstruction and a Grade 3 late small intestine obstruction. No Grade 4 or greater late toxicity was experienced. The hemorrhagic cystitis was managed by endoscopic hemostasis. The small intestine obstruction was also managed by conservative treatment. Abdominal CT scans were performed in both cases and progressive disease was excluded before starting the toxicity management. The details regarding late toxicity are shown in Table 4.

Table 4 Late treatment-related toxicity according to treatment modality (CTC-AE version 4.0)

	RRT (use of CCT), total: 35	S + ART (use of CCT), total: 5
Gastrointestinal		
Grade 1–2	Rectal bleeding: 2	0
Grade 3	0	Intestinal obstruction
Grade 4	0	0
Genitourinary		
Grade 1–2	Cystitis: 2	0
Grade 3	Cystitis: 1(1)	0
Grade 4	0	0
Other		
Grade 1–2	Lymphedema: 2	Lymphedema: 1
Grade 3	0	0
Grade 4	0	0

RRT radical radiotherapy, *S* surgery, *ART* adjuvant radiotherapy, *CCT* concurrent chemotherapy

Discussion

Choosing a treatment for elderly patients with various malignancies is usually difficult. Careful evaluation of their general condition and concomitant medical problems must be performed before the treatment begins. Compared with young patients, safer and more effective modalities should be chosen because severe toxicity may lead to cancellation or delay of the treatment and subsequent loss of quality of life [17–21]. Generally, RT is thought to be less invasive than surgery or chemotherapy. Moreover, with recent technical developments, a reduction of radiation-related toxicity has been achieved, and the safety of RT is

increasing markedly. Therefore, RT is usually chosen for elderly patients as a single modality, although sometimes RT is combined with surgery and/or chemotherapy. Certainly, RT has taken on a greater role in aging societies such as Japan. For example, in this study, just 9 patients were treated from 2000 to 2005, but 31 were treated from 2006 to 2009.

Although there are several large retrospective studies that have analyzed treatment results and prognostic factors, whether age is a negative prognostic factor remains controversial [12, 13, 22–27]. However, most reports have demonstrated that RT is effective for elderly patients. For example, Ikushima et al. analyzed 727 patients with cervical cancer and reported that the 5- and 10-year disease-specific survival rates of 132 patients aged ≥75 years were 66 and 57%, respectively. Thus, age was not a significant prognostic factor in that study [13]. Chen et al. analyzed a total of 295 patients. They reported that the 5-year cause-specific survival rates of 79 patients aged ≥70 years with respect to FIGO stage were 100% for IB, 85% for IIA, 78% for IIB, and 42% for III. Thus, again age was not a significant prognostic factor in this case [26]. On the other hand, Brun et al. analyzed a total of 308 patients and reported that the 5-year survival rate of 31 patients aged ≥75 years was 42% and that age was a significant prognostic factor. However, they also reported that the survival of those over 75 years was not different from that of the rest of the population [23]. Although the median follow-up of our study was shorter and the number of cases is currently smaller, our observed survival rates are reasonable compared with previous reports. Our results also indicate that the clinical stage might have prognostic value in determining survival outcomes, but age did not have prognostic value in such an elderly population. Interestingly, the DSS rate of patients aged >80 years was 100%. Whether "slow oncological progression" was associated with this result is unclear because of the small number of patients and the short follow-up period. Therefore, this result cannot be used as evidence for a more limited treatment choice at present. However, RRT alone should be the first choice for patients >80 years old. The survival rates of the patients with high KPS scores (>70) were better than those with low KPS scores (≤70), but the difference was not significant. KPS was not a significant prognostic factor in this preliminary result, but it may have a large impact on long-term survival. To evaluate survival outcomes accurately and verify prognostic factors such as clinical stage, age, and KPS, more cases need to be analyzed, a longer follow-up period is needed, and the results need to be compared with those of a younger population. Finally, the most appropriate treatment choice for elderly patients should be established.

Both acute and late toxicity should be evaluated carefully to establish a safe modality that achieves better survival outcomes and preserves the quality of life of elderly patients with cervical cancer. Lindegaard et al. reported that treatment was completed as planned in 68% of cases, delayed in 29% of cases, and stopped prematurely in 3% of cases. They concluded that elderly patients with cervical cancer in otherwise good health may tolerate radical radiotherapy with acceptable toxicity and reasonable survival rates [28]. In our study, 38 of 40 (95%) patients completed the treatment as planned; 1 (2.5%) completed after a delay and 1 (2.5%) could not complete the treatment. The two patients who experienced delay or cancellation of the treatment had KPS scores <50 and had RRT performed, but they could not receive HDR-BT. This result also indicates that elderly patients in good health can tolerate RRT (EBRT combined with HDR-ICBT). However, those with a poor performance status should be treated carefully; in some instances, a less invasive RRT (EBRT alone) must be chosen. For elderly patients in good health, tolerance for more aggressive treatment modalities such as RRT with CCT or S + ART with or without CCT should be discussed carefully. In our study, 8 patients with KPS scores >70 were treated with these more aggressive modalities (RRT with CCT: 3, S + ART: 3, S + ART with CCT: 2). As described above, the indications for the use of these aggressive modalities involved age, KPS, FIGO stage, and pathological risk factors. Regarding the patients treated with RRT with CCT, all of them were <80 years old and had KPS scores >70. Two of them were FIGO IIB and the remaining one was IIIB. Regarding the patients treated with S + ART with or without CCT, 4 were 75, and 1 was 76 years old. All of them had KPS scores >70 and had stage II disease (IIA: 2, IIB: 3). Adjuvant CCT has been performed on patients with postoperative KPS scores >70 and multiple pathological risk factors (at least 3) since 2008. As a result, two were treated with S + ART with CCT. One had wide parametrium invasion and both vascular and lymphatic invasion. The other had a large tumor (>4 cm), parametrium invasion, vascular invasion, and a positive vaginal surgical margin. Although nodal metastasis was the most important prognostic factor, two patients who had pathological nodal metastasis did not receive adjuvant CCT. This was because one had postoperative KPS score = 50, whereas the other was one of the oldest patient treated in 2000 and adjuvant CCT was not performed for elderly patients at that time. Therefore, they were treated with S + ART without CCT. All of the patients treated with these aggressive modalities completed the treatment without delay, but three of them (37.5%) experienced Grade 3 acute toxicity during and soon after the completion of RT. These results indicate that these aggressive modalities are not always safe in terms of

acute toxicity. As for late toxicity, although the median follow-up was shorter, Grade 3 late toxicity was experienced by 2 of 40 (5%) patients, and no Grade 4 or higher late toxicity was experienced in our study. Several authors reported that the occurrence rates of Grade 3 or greater late morbidities were less than approximately 10%, and our results are compatible with those of previous reports [12, 13, 28, 29]. However, we should emphasize that Grade 3 late toxicity was only experienced in patients treated with the more aggressive modalities (RRT with CCT: 1, S + ART: 1). Aggressive modalities may be tolerable for patients with a good performance status, but they can easily cause severe acute or late toxicity compared with RRT alone. Considering these results, when aggressive treatment modalities are performed in elderly patients, management of both acute and late toxicity is very important to avoid delay or cancellation and to maintain quality of life. The finding that patients with KPS scores >70 can tolerate aggressive modalities with appropriate management, whereas those with KPS scores <50 may not tolerate even RRT alone, is also very important. KPS should be considered as one of the determinants in selecting a treatment modality for elderly patients.

In conclusion, the number of elderly patients with cervical cancer is increasing, and RRT provides good survival outcomes with acceptable toxicity. However, indications for the use of more aggressive modalities should be assessed carefully, even for patients who are in quite good health. Therefore, to establish appropriate treatment strategies, including combinations of RT with less invasive surgery and/or chemotherapy, larger studies and prospective studies should be performed. Finally, better survival outcomes and preservation of the quality of life may be achievable for the growing elderly population.

Conflict of interest We declare that we have no conflict of interest.

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CASE REPORT

Histiocytic sarcoma with two immunohistopathologically distinct populations

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Abstract This report is a case of histiocytic sarcoma (HS), in which tumor cells consist of two immunohistopathologically distinct populations (A) oval CD68+lysozyme+CD163− cells and (B) abundant cytoplasm or spindle-shaped CD68+lysozyme−CD163+ cells. Cervical lymph node was infiltrated mainly by population (A), where chemotherapy was quite effective. On the other hand, vast majority of infiltrated tumor cells in the hilar lymph node belonged to population (B), in which the cells were resistant to chemo-radiotherapy. Considering the poor prognosis of HS, the expression of CD163 could be a marker for resistance to chemo-radiotherapy. It is also notable that CD163-negative stage of HS may exist and still be reactive for the treatment.

Keywords Histiocytic sarcoma · CD163 · Chemotherapy · Histiocyte

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1 Introduction

Histiocytic sarcoma (HS) is an exceedingly rare lymphohematopoietic malignant neoplasm composed of tumor cells showing morphologic and immunophenotypic features of mature tissue histiocytes. Neoplasms, which were originally classified as "histiocytic lymphoma" by Rappaport [1], have encompassed a biologically heterogenous group of disorders. However, the majority are now known to be high-grade T or B cell non-Hodgkin lymphoma. Diagnosis of HS is based mainly on the immunohistochemical findings. In particular, CD163 has been recognized as a new macrophage-related differentiation marker, which is more specific than the conventional histiocyte-related molecules, such as CD68 and lysozyme [2, 3].

In this study, a case of HS with tumor cells consisting of two distinct phenotypes both pathologically and chemosensitivity is being described.

2 Case report

A 73-year-old man was admitted because of gradual enlargement of the left cervical lymph node in October 2006.