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FULL PAPER

Single institutional experience of the treatment of angiosarcoma of the face and scalp

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Objective: Angiosarcoma is a rare malignant neoplasm with a poor prognosis. A retrospective study was performed to accumulate radiotherapy (RT) data.

Methods: Data from 17 patients with angiosarcoma of the face and scalp (AFS) who were treated with definitive RT between January 1999 and July 2011 were retrospectively analysed. The total radiation dose was 70 Gy, and the fractional doses were 2.0–2.5 Gy. Combined with RT, chemotherapy using docetaxel alone, recombinant interleukin-2 immunotherapy alone and both of these was performed in 10, 4 and 2 patients, respectively. Three patients underwent limited surgery before RT.

Results: The response rate was 82%, and the median overall survival (OS) rate was 26 months. Locoregional

relapse alone, distant metastasis alone and both of these were confirmed in 4, 5 and 4 patients, respectively. Patients treated with docetaxel showed a better prognosis ($p=0.0477$), a distant metastasis-free rate ($p=0.0063$) and a better in-field control rate, although the last was not statistically significant ($p=0.1645$).

Conclusion: Definitive RT combined with docetaxel chemotherapy provided an effective approach for treating AFS.

Advances in knowledge: Since patients treated with chemoradiotherapy using docetaxel showed better OS and distant metastasis-free rates than those who did not receive docetaxel, it was warranted to continue use of docetaxel. In chemoradiotherapy at a dose of 70 Gy using docetaxel, 2-year in-field control rate was 67%.

Angiosarcoma is a rare malignant tumour of vascular origin that represents 2% of all soft-tissue sarcomas. It can occur in any region of the body, but most often arises on the face and scalp of elderly people [1]. Several studies have suggested that angiosarcoma of the face and scalp (AFS) forms a distinctive subgroup owing to its extremely poor prognosis [1]. This highly aggressive tumour spreads widely through the skin, recurs locally and metastasises early. The existence of clinically undetectable spread makes radical resection difficult and reconstruction is usually required [2].

In recent years, the treatment of patients with angiosarcoma has changed considerably. For example, the use of more limited surgery followed by multimodal therapy involving radiotherapy (RT) and chemotherapy has increased [3]. It is essential to improve the quality of evidence for this rare AFS disease by accumulating clinical outcomes. This retrospective study was, therefore, performed to summarise data on AFS in our hospital.

MATERIALS AND METHODS

The institutional review board approved the study. All patients provided written informed consent before study entry. The study was conducted in accordance with the Declaration of Helsinki.

Patient characteristics

Between January 1999 and July 2011, a total of 17 patients with AFS underwent curative RT at our hospital. Data on these 17 patients (12 males and 5 females, age range 52–88 years, median age 73 years) were retrospectively analysed. All the tumours were histologically diagnosed as angiosarcoma. Angiosarcomas that developed in previous radiation fields (suggesting radiation-induced angiosarcoma) were not included in this study. Clinical information was obtained by a retrospective review of patient records. The patients' characteristics are presented in Table 1.

The performance status (PS), tumour size, lymph node metastasis status and distant metastasis status were evaluated at the start of treatment. Cervical lymph node metastasis

Table 1. Patient and tumour characteristics

Characteristics	Patients (n)
Age (years)	
<75	10
≥75	7
Gender	
Male	12
Female	5
Performance status	
0	15
1	2
Primary site	
Scalp	16
Face	1
Tumour size (cm)	
<5	2
≥5	15
Lymph node metastasis	
Yes	3
No	14

was recognised in three patients. Distant metastases were not found.

Treatment

Irradiation was performed using 6–12 MeV electron beams for the primary lesion. The prescribed dose was 70 Gy for all patients. Fractions of 2.0–2.5 Gy were given 5 days per week. Irradiation was performed using phantom data. CT simulation was not used. The depth of prescription points for 6-, 9- and 12-MeV electron beams was 14, 22 and 28 mm, respectively. Based on the phantom data, the surface of the brain absorbs 92 and 107% of the prescribed dose for 6- and 12-MeV electrons, respectively. At the depth of 10 mm from the surface of the brain, the absorbed doses were 22 and 101%, respectively. The primary site was irradiated using the extended local fields ($n=10$) or whole-scalp fields ($n=7$; Figure 1). The gross tumour volume (GTV) was the visible lesion marked by dermatologists. In extended local irradiation, the GTV was expanded with margins ≥ 2.5 cm to form the clinical target volume (CTV). The planning target volume (PTV) contained the CTV with a margin of 0.5 cm or more. In whole-scalp irradiation, the PTV contained the skin of whole scalp. The eye bulbs and lacrimal glands were not included in the radiation field. The bolus material was not used. Cervical lymph node metastases were irradiated using 6 MV photons with doses of 60–70 Gy in 30–35 fractions in 3 patients.

Details of the other initial treatments are shown in Table 2. Combined with RT, chemotherapy using docetaxel alone, recombinant interleukin-2 (rIL-2) immunotherapy alone and

Figure 1. Example of whole-scalp irradiation. The planning target volume was irradiated from four directions (parietal, bilateral and occipital) in this patient. Border lines of the radiation fields were shifted from the black arrows to the white arrows at a dose of 34 or 36 Gy.

both of these was performed in 10, 4 and 2 patients, respectively. RT alone was performed in one patient because myelosuppression owing to coexisting myelodysplastic syndrome was observed at the beginning of the treatment.

In the last five patients, docetaxel was administered at a dose of 25 mg m^{-2} per week in a cycle of 3 weeks on and 1 week off. The timing was adjusted such that docetaxel was concurrently administered with RT only for the first or last week of the RT course to avoid severe acute toxicity. In another seven patients, docetaxel was administered at a dose of 20–72 mg per week for 2–6 weeks during RT in accordance with patient status.

rIL-2 immunotherapy was given to six patients at a daily dose of 35×10^4 – 80×10^4 units and a total dose of 40×10^4 – 2450×10^4 units. Three patients received rIL-2 via systemic administration, one via intratumoural injection, one via trans-catheter arterial administration and one via both intratumoural injection and systemic administration. 3 of 17 patients (18%) underwent tumour resection before RT.

Table 2. Therapies in addition to RT

Treatment method	Patients (n)
Immunotherapy or chemotherapy during RT	
Docetaxel alone	10
rIL-2 alone	4
Docetaxel+rIL-2	2
Nothing	1
Surgery	
Yes	3
No	14

RT, radiotherapy; rIL-2, recombinant interleukin-2.

Evaluations and statistical analysis

The Response Evaluation Criteria in Solid Tumours (RECIST) v. 1.1 were used for the response assessment [4]. Acute tissue reactions to the treatment were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 [5].

The overall survival (OS), in-field control and distant metastasis-free rates were calculated from the start of RT using the Kaplan–Meier method. CT scans were used to assess the presence of metastasis. The generalised Wilcoxon test was used for statistical analyses. To identify prognostic factors for OS, univariate analyses were performed using age (<75, ≥75 years), gender, PS, tumour size, lymph node metastasis, surgery, radiation field (whole scalp or local), rIL-2 immunotherapy and docetaxel chemotherapy. *p*-values <0.05 were regarded as statistically significant. All statistical analyses were performed using GraphPad Prism v. 5 (GraphPad Software, La Jolla, CA).

RESULTS

All patients completed RT without an interval for more than 1 day. The follow-up time ranged from 11 to 67 months (median 18 months).

The response rate was 82% (9 with complete response and 5 with partial response). The remaining three patients had stable disease.

The median OS was 26 months. Locoregional relapse alone, distant metastasis alone and both of these were confirmed in 4, 5 and 4 patients, respectively. The sites of distant metastasis included the lung in seven patients, the liver in two patients, the bone marrow in one patient and the stomach in one patient. When locoregional relapse was divided according to radiation field, in-field relapse developed in six patients and out-field relapse in one patient.

Table 3 summarises the prognostic factors. Lymph node metastasis, rIL-2 immunotherapy and surgery were significantly worse prognostic factors. By contrast, patients treated with docetaxel showed significantly better OS (*p*=0.0477) and distant metastasis-free rates (*p*=0.0063). These patients also showed better in-field control (*p*=0.1645), but this was not statistically significant. The 2-year in-field control rate was 67% in patients treated with docetaxel.

Table 3. Univariate analysis of potential prognostic variables and survival times of scalp angiosarcoma patients

Variable	Patients (<i>n</i>)	Overall survival	
		MST (months)	<i>p</i> -value
Age (years)			
<75	10	45.76	0.8932
≥75	7	23.08	
Gender			
Male	12	33.65	0.6291
Female	5	24.52	
PS			
0	15	25.59	0.0824
1	2	36.55	
Tumour size (cm)			
<5	2	33.65	0.329
≥5	15	23.45	
LN metastasis			
Yes	3	7.072	0.0008
No	14	33.65	
Radiation field			
Extended local	10	25.59	0.5571
Whole scalp	7	34.61	
Docetaxel			
Yes	12	33.65	0.0477
No	5	22.7	
rIL-2			
Yes	6	18.65	0.015
No	11	33.65	
Surgery			
Yes	3	14.61	0.0106
No	13	33.65	

CTV, clinical target volume; LN, lymph node; MST, median survival time; PS, performance status; rIL-2, recombinant Interleukin-2.

Radiation dermatitis was observed in all 17 patients (6 patients with Grade 1 CTCAE toxicity criteria, 9 with Grade 2 and 2 with Grade 3). All patients healed uneventfully. Two patients treated with combined chemotherapy developed Grade 3 haematotoxicity. These patients recovered by modifying the dose of combined chemotherapy. No patient developed bone necrosis, brain necrosis or other late reactions.

DISCUSSION

In previous studies, RT alone has not produced satisfactory outcomes for AFS [1]. This is the reason that combinations with surgery, chemotherapy or immunotherapy have been tried and recommended so far [3,6]. As a combined chemotherapy, doxorubicin-based

regimens were a standard for metastatic or unresectable angiosarcoma, which yielded progression-free survival of only up to 3.7–5.4 months [7]. However, the clinical advantage of paclitaxel or docetaxel has been suggested in recent studies [8–10]. Considering that the origin of angiosarcoma is the endothelial cell, it is conceivable that the antiangiogenic behaviour of paclitaxel or docetaxel may account for such an antitumour effect on angiosarcoma [11]. However, these two agents differ somewhat in their *in vivo* and *in vitro* behaviours in cell lines and in human cancer specimens. Docetaxel has demonstrated a greater ability to inhibit tumour cell growth than paclitaxel [12]. Furthermore, docetaxel is well known as having a radiosensitising effect [13]. In this context, docetaxel was used in as many as 12 patients of 17 in the present study.

In the present study, the significantly higher metastasis-free rate of the docetaxel group might correspond to the assumed anti-angiogenic behaviour, and the favourable in-field control rate might correspond to the assumed radiosensitising effect. These results were comparable with previous reports (Table 4; [1–3,6,14–16]).

Recently, Ohguri et al [16] performed curative RT plus rIL-2 immunotherapy and achieved a median OS of 36.2 months, which was an improvement over previous reports. However, in

the present study, the prognosis of six patients treated with rIL-2 immunotherapy was significantly poor. A possible explanation is that all three of the patients with lymph node metastasis were included in this group. When this bias is taken into account, the role of rIL-2 immunotherapy is not denied.

Owing to its diffuse clinically undetectable spread, it is difficult to completely resect angiosarcoma. Even when wide surgical excision was performed, outcomes were not satisfactory [3]. Therefore, the use of more limited surgery is a trend. In the present study, only three patients underwent surgery and two patients with lymph node metastasis were included in this patient group. Although they showed significantly poor prognoses, the role of surgery was not clarified in the present study.

Radiation doses and radiation fields were relatively homogeneous in the present study although the number of patients was not large. When RT with a dose of 70 Gy combined with docetaxel chemotherapy was performed, the 2-year in-field control rate was 67%, and locoregional relapse developed out of the field in only one patient. There is no indication from the present results that the radiation dose should be increased or the safety margins should be enlarged.

Table 4. Previous reports on results of RT for angiosarcoma

Authors (year)	Site	Patients (n)	Therapy (number of patients)	Radiation dose (Gy)	Overall survival
Hodgkinson et al (1979) [1]	Scalp and face	13	RT (3)	Not documented	Two patients alive >2 year
			RT+S (5)		
			S (5)		
Maddox and Evans (1981) [14]	Scalp and face	17	RT (3)	Not documented	MST 18 months
			RT+S (11)		
			C (3)		
Holden et al (1987) [2]	Scalp and face	72	RT (69)	44–66	MST 15 months
			RT+S (5)		
Sasaki et al (2002) [15]	Scalp and face	24	RT±rIL-2+S (6)	30–100	MST 7 months
			RT±rIL-2 (18)		
Pawlik et al (2003) [3]	Scalp	29	RT (1)	60–72	MST 28.4 months
			RT+S±C (23)		
			S±C (5)		
Ohguri et al (2005) [16]	Scalp	20	RT+rIL-2±S±C (20)	63.4–77.2	MST 36.2 months
Ogawa et al (2012) [6]	Scalp and face	48	RT (5)	26.0–71.6	MST 13.4 months
			RT+S±C±rIL-2 (17)		
			RT±C±rIL-2 (20)		
			rIL-2±S±C (6)		
Our study	Scalp and face	17	All patients	70	MST 26.0 months
			RT±S±rIL-2 (5)		MST 22.7 months
			RT±rIL-2+docetaxel (11)		MST 33.7 months

C, chemotherapy; MST, median survival time; rIL-2, recombinant interleukin-2; RT, radiotherapy; S, surgery.

Patients treated with docetaxel showed significantly better OS and distant metastasis-free rates than those who did not receive docetaxel. Patients treated with docetaxel had a better in-field control rate, but this finding was not statistically significant. However, these statements were not

fully reliable since cervical lymph node metastasis was observed to bias the treatments, unfortunately. At a minimum, it was warranted to continue use of docetaxel. Further accumulation of data would improve the reliability of these findings.

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