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Single institutional experience of radiation therapy for angiosarcoma of the scalp without cervical lymph node metastases: Impact of concurrent chemoradiation with maintenance chemotherapy using taxanes on patient prognosis

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Abstract. Cutaneous angiosarcoma is a rare aggressive malignant tumor. Concurrent chemoradiation (CCRT) with maintenance chemotherapy using taxanes is one of the primary treatments. The aim of the present study was to retrospectively analyze the efficacy of CCRT with maintenance chemotherapy using taxanes in localized angiosarcoma of the scalp without cervical lymph node metastases. A total of 19 patients treated with radiation therapy for localized angiosarcomas of the scalp without cervical lymph node metastases were enrolled. The overall survival (OS), progression-free survival (PFS), and local control (LC) rates were calculated using Kaplan-Meier analysis. Univariate analyses were performed for various potential prognostic factors for OS, PFS, and LC. The median radiation dose was 70 Gy (range, 60-70 Gy), and the fractional dose was 2 Gy. Radiation therapy alone, radiation therapy + interleukin-2, surgery + CCRT with maintenance chemotherapy, CCRT with maintenance chemotherapy, and CCRT without maintenance chemotherapy were administered to 2, 4, 2, 9 and 2 patients, respectively. The 1- and 3-year OS, PFS, and LC rates were 88 and 52%, 47 and 33%, and 74 and 56%, respectively. CCRT with maintenance chemotherapy and surgery were significant prognostic factors for PFS (P=0.036 and 0.025, respectively). Therefore, CCRT with maintenance chemotherapy using taxanes might be effective in treating localized angiosarcomas of the scalp without cervical lymph node metastases.

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Introduction

Cutaneous angiosarcoma is a rare and aggressive malignant tumor with poor prognosis and high risk of hematogenous dissemination (1). It usually develops on the scalp or face of elderly males (1). The scalp is a tumor site associated with poor prognosis (2-4). Angiosarcoma of the scalp is often treated with multimodality treatment, including surgery, radiation therapy, chemotherapy, and immunotherapy (1-14).

Several studies have recently reported the efficacy of taxane chemotherapy for cutaneous angiosarcomas of the scalp (5-7,15-18). In particular, concurrent chemoradiation (CCRT) with taxanes has been reported to be one of the optimal treatment methods for this malignancy (5,6). Moreover, patients receiving CCRT with maintenance chemotherapy using taxanes showed a significant improvement in overall survival (OS) than those receiving CCRT alone (6). In 2006, we established CCRT with maintenance chemotherapy using taxanes (paclitaxel or docetaxel) as the standard treatment strategy for localized angiosarcoma of the scalp without cervical lymph node metastasis. Taxanes were administered as early as possible, followed by maintenance chemotherapy also using taxanes. Maintenance chemotherapy was repeated several times, when possible. Although there were no criteria for administration of concurrent and maintenance chemotherapy, we attempted to administer both concurrent and maintenance chemotherapy, if feasible. Prior to the establishment of this strategy, interleukin-2 (IL-2) was often used in combination with radiation therapy.

This study aimed to retrospectively analyze the efficacy of CCRT with maintenance chemotherapy using taxanes for localized angiosarcomas of the scalp without cervical lymph node metastases. To our knowledge, there have been no studies that have analyzed the efficacy of CCRT and maintenance chemotherapy using taxanes exclusively for localized angiosarcomas of the scalp without cervical lymph node metastases.

Patients and methods

This retrospective study was approved by Okayama University Hospital institutional review board (Approval no. K1610-503), and the need for informed consent was waived owing to the retrospective nature of the study.

Study population. This study included 19 patients with localized angiosarcomas of the scalp without cervical lymph node metastases who received radiation therapy between January 2000 and December 2017 at the Okayama University Hospital. All patients were pathologically diagnosed with angiosarcoma of the scalp. The patients received radiation therapy alone or in combination with surgery, chemotherapy, or immunotherapy.

Radiation therapy. Radiation therapy was carried out using electron and X-ray beams, 5 days per week for approximately 2 months. The prescribed dose was 70 or 60 Gy in 2.0-Gy fractions. Up to 60 Gy, the area of the initial irradiation field typically encompassed the tumor with a 5-cm margin from the edges. In cases with residual tumor, immediately before completion of 60 Gy, a 10-Gy boost dose was delivered to the tumor mass. The boost irradiation field typically covered a 2-cm margin from the edge of the tumor mass. The extent of disease was determined by a dermatologist. In post-surgical cases, the irradiation field was conjointly determined by radiation oncologists and dermatologists. Computed tomography (CT) simulation was used to determine the energy of the electron beams and the thickness of bolus applied. The thickness of the bolus was 5 or 10 mm.

Chemotherapy regimens. The weekly paclitaxel or docetaxel schedule comprised 80 mg/m^2 of paclitaxel or 30 mg/m^2 of docetaxel, respectively, on days 1, 8, and 15 of a 28-day cycle. The triweekly paclitaxel or docetaxel schedule comprised 210 mg/m^2 of paclitaxel or 60 mg/m^2 of docetaxel, respectively, on day 1 of a 21-day cycle. Dose reduction and/or extension of the treatment interval was based on the discretion of the dermatologist. A weekly paclitaxel or docetaxel regimen was used concurrently with radiation therapy. The type of chemotherapy regimen depended on the discretion of the dermatologist. Maintenance chemotherapy was defined as the repeated administration of chemotherapy until tumor recurrence.

Other treatments. Prior to the establishment of this CCRT with maintenance chemotherapy treatment strategy, immunotherapy (IL-2) was used in combination with radiation therapy.

Surgery was performed in cases deemed completely resectable by the dermatologist.

Patient and treatment characteristics. The patient and treatment characteristics are shown in Table I. The cohort comprised 14 men and 5 women with a median age of 78 years (range, 34-91 years). Radiation therapy alone, radiation therapy + IL-2, surgery + CCRT with maintenance chemotherapy, CCRT with maintenance chemotherapy, and CCRT without maintenance chemotherapy were administered to 2, 4, 2, 9, and 2 patients, respectively. Data on tumor size was missing for 1 patient, and 17 patients had tumors measuring ≥5 cm.

For radiation therapy, the median radiation dose was 70 Gy (range, 60-70 Gy). Only 1 patient was treated using electron and X-ray beams. All other patients were treated using electron beams only (3-12 MeV). Data on the bolus were missing for 3 patients, but the records indicated that all other patients were treated using a bolus; a 5-mm and 10-mm bolus was applied in 14 and 2 patients, respectively. The planned radiation therapy could not be completed in 1 patient owing to scalp infection. The radiation dose in this patient was 60 Gy. The other patients completed the planned radiation therapy schedule.

Among the 13 patients who received chemotherapy, taxanes (paclitaxel or docetaxel) were concurrently administered with radiation therapy. Weekly paclitaxel and docetaxel regimens were used concurrently with radiation therapy in 11 and 2 patients, respectively; these patients received 2 courses of the treatment. Among the patients who received CCRT, 11 patients subsequently received maintenance chemotherapy with a taxane. The weekly and triweekly paclitaxel maintenance chemotherapy regimens were used in 5 and 3 patients, respectively. Weekly and triweekly maintenance chemotherapy schedules of paclitaxel and docetaxel were used in 1 and 2 patients, respectively. Data regarding the total number of chemotherapy courses were missing for 3 patients; excluding these patients, the median number of courses was 11 (1-58). Among 13 patients treated with CCRT, taxane maintenance chemotherapy was not administered in 2 patients, 1 of whom developed spontaneously resolving elevated blood pressure and arrhythmia during the fourth course of paclitaxel. After this event, we decided to discontinue chemotherapy during and after radiation therapy for that patient. In the other patient, chemotherapy was discontinued approximately 2 months after radiation therapy due to unknown reasons. Overall, 6 of the 19 patients were not administered taxanes. Among them, 4 patients were treated before our treatment strategy of CCRT with maintenance chemotherapy using taxanes was established; the remaining 2 patients were considerably aged (90 and 91 years).

Additionally, 4 patients received immunotherapy using IL-2, and 2 patients underwent surgery before radiation therapy. In 1 patient who underwent surgery, the lesion around the postoperative site was clinically apparent before radiation therapy.

Definition of recurrence. Local recurrence was defined as recurrence in the scalp and face, while distant recurrence included the cervical lymph nodes. Local control was evaluated using examination and biopsy, whereas distant recurrence was evaluated using CT, magnetic resonance imaging, and positron-emission tomography (PET)-CT. The follow-up protocol was not clearly determined.

Adverse events. Adverse events were evaluated using the Common Terminology Criteria for Adverse Events version 4.0. Adverse events of grades >2 were investigated.

Statistical analyses. OS, progression-free survival (PFS), and local control (LC) rates were calculated using Kaplan-Meier analysis. OS, PFS, and LC were calculated from the initiation of treatment until death, disease progression or death, and local recurrence, respectively. Univariate analyses were performed

Table I. Patient and treatment characteristics.

Characteristic	No. of patients
Age[a], years	
<75	8
≥75	11
Sex	
Male	14
Female	5
Tumor size (n=18)[b], cm	
<5	1
≥5	17
Radiation dose, Gy	
60	3
70	16
Surgery	
Yes	2
No	17
IL-2	
Yes	4
No	15
Concurrent chemotherapy	
Yes	13
No	6
Concurrent and maintenance chemotherapy	
Yes	11
No	8

[a]The median age was 78 years, and the range was 34-91; [b]tumor size was not assessable for 1 patient.

for the various potential prognostic factors for OS, PFS, and LC. Distant metastasis-free survival (DMFS) was also analyzed in the same manner. DMFS was calculated until distant recurrence or death. Multivariate analysis was not performed owing to the small number of patients. Kaplan-Meier analyses and log-rank tests were performed using the JMP 12 statistical software package (SAS Institute, Cary, NC, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Follow-up and outcomes. The median follow-up period was 15 months (range, 3-102 months). During follow-up, local and distant recurrence occurred in 6 and 13 patients, respectively. The first sites of recurrence were only local, only distant, and both local and distant in 5, 8, and 1 patients, respectively. In the 5 cases where the first site of recurrence was only local, all the sites of the first local recurrence were within the radiation field. In the 1 case where the first site of recurrence was local and distant, data on the site of local recurrence was missing. A total of 10 patients who died due to angiosarcoma had distant metastases at the time of death, with the most common site of metastases being the lung (n=7). In 6 patients, death was related to lung metastases. No patient died of other diseases. The rates of 1- and 3-year OS, PFS, and LC were 88 and 52%, 47 and 33%, and 74 and 56%, respectively.

The results of the univariate analyses are shown in Table II. CCRT with maintenance chemotherapy and surgery were significant prognostic factors for PFS (P=0.036, and 0.025, respectively) but not for OS and LC. The results of CCRT with maintenance chemotherapy using taxanes regarding OS, PFS, and LC are shown in Fig. 1. No significant prognostic factors were found for OS and LC. In DMFS, CCRT with maintenance chemotherapy using taxanes and surgery were significant prognostic factors as well (P=0.018, and 0.029). The results of CCRT with maintenance chemotherapy using taxanes with respect to DMFS is shown in Fig. 2.

Adverse events. During radiation therapy, 4 patients treated with CCRT developed hematotoxicity. Both grade 3 leukocytopenia and neutropenia were noted in 2 patients; 1 patient developed both grade 4 leukocytopenia and neutropenia; and 1 patient developed grade 3 neutropenia. However, no patient discontinued chemotherapy because of hematotoxicity. The 6 patients without CCRT did not develop hematotoxicity. All patients developed radiation dermatitis up to Grade 3, but radiation therapy was not suspended due to hematotoxicity or dermatitis. A grade 3 scalp infection occurred in 1 patient that required intravenous antibiotic therapy. Only this patient could not complete the planned radiation therapy schedule, the dose of which was 60 Gy.

In terms of adverse events after radiation therapy, 4 patients treated with taxanes developed hematotoxicity. Grade 3 leukocytopenia and neutropenia, grade 3 neutropenia, and grade 4 neutropenia developed in 1 patient each. Grade 3 anemia was observed in 1 patient. Grade 3 and 4 skin ulceration was noted in 1 patient each; 1 patient developed grade 3 cranial bone necrosis with grade 4 skin ulceration. Grade 3 skin ulceration was noted in 1 patient who underwent CCRT (total dose of 60 Gy) with maintenance chemotherapy using a weekly paclitaxel schedule after complete resection. The patient with grade 4 skin ulceration received CCRT (total dose of 70 Gy) with maintenance chemotherapy using a weekly docetaxel schedule during radiation therapy and a triweekly paclitaxel schedule after radiation therapy. Approximately 3 months after radiation therapy, a residual lesion was suspected, and a complete resection was performed. However, pathologically there was no residual tumor. Approximately 7 months after the resection, epidermization was performed for the ulcer at the postoperative site. However, graft failure was observed after epidermization. The patient with grade 3 cranial bone necrosis with grade 4 skin ulceration underwent CCRT (total dose of 70 Gy) with maintenance chemotherapy using a docetaxel schedule after resection and epidermization. In this patient, the cranial bone necrosis was removed, followed by reconstruction using an anterolateral thigh flap and epidermization.

Discussion

In this study, we retrospectively evaluated the efficacy of CCRT with maintenance chemotherapy using taxanes for localized angiosarcomas of the scalp without cervical lymph node metastases. On univariate analyses, CCRT with maintenance

Table II. Results of univariate analysis.

		[a]Overall survival rate			Progression-free survival rate			Local control rate		
Variable	No. of patients	1-year	3-years	P-value	1-year	3-years	P-value	1-year	3-years	P-value
Age (years)				0.175			0.074			0.298
<75	8	100	71		75	60		88	70	
≥75	11	77	34		24	12		59	40	
Sex				0.192			0.670			0.751
Male	14	82	49		41	31		72	54	
Female	5	100	60		60	40		80	60	
Radiation dose, Gy				0.051			0.171			0.224
60	3	100	100		100	100		100	100	
70	16	86	45		39	23		70	46	
Surgery				0.234			0.025			0.236
Yes	2	100	100		100	100		100	100	
No	17	86	45		39	23		70	47	
IL-2				0.919			0.270			0.425
Yes	4	75	50		50	25		75	38	
No	15	91	53		44	35		74	62	
CCRT				0.351			0.080			0.370
Yes	13	100	67		53	42		80	64	
No	6	67	33		33	17		63	42	
CCRT with maintenance chemotherapy				0.160			0.036			0.176
Yes	11	100	75		69	55		90	72	
No	8	73	29		25	13		53	35	

[a]No patients died of other diseases. IL-2, interleukin-2; CCRT, concurrent chemoradiation.

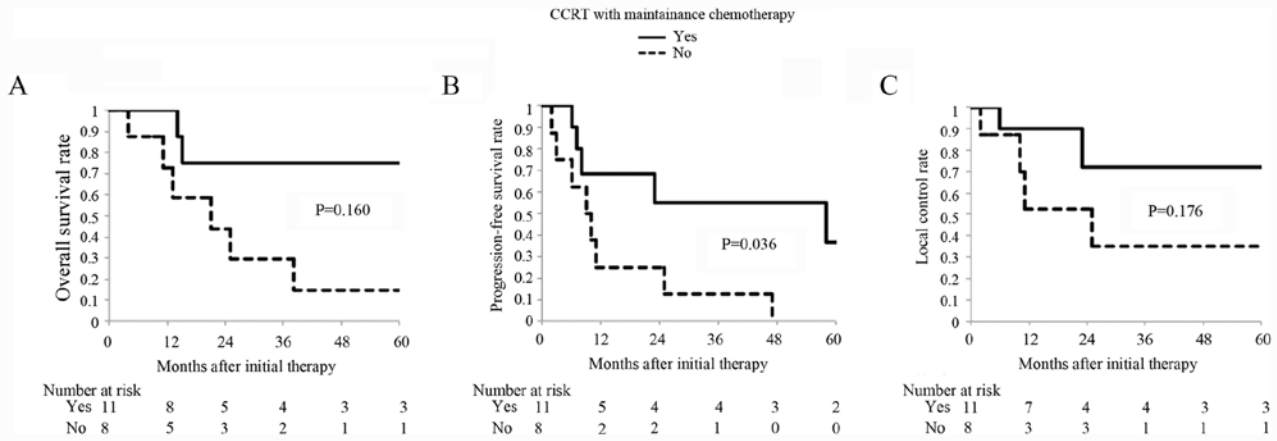

Figure 1. Kaplan-Meier curves of the patients who received (solid line) or did not receive (dashed line) CCRT with maintenance chemotherapy. (A) Overall survival, (B) progression-free survival and (C) local control rate. CCRT, concurrent chemoradiation.

chemotherapy using taxanes was a significant prognostic factor for PFS and DMFS. All 10 patients who died had distant metastases at the time of death, and 7 of them had lung metastases. Moreover, in 6 of these 10 patients, death was related to lung metastases. We therefore speculated that CCRT with maintenance chemotherapy may improve OS by preventing distant metastases. However, in this study, CCRT with maintenance chemotherapy using taxanes was not a significant prognostic factor for OS.

There are several reports on the importance of CCRT with maintenance chemotherapy (5-7). Miki *et al* (5) reported that patients treated with docetaxel, including those with lymph node metastasis, showed significantly better OS (P=0.0477)

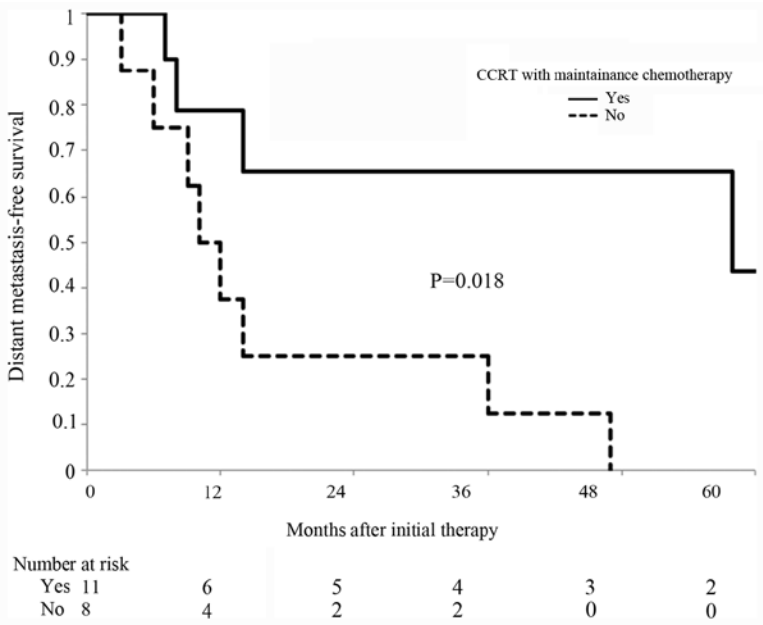

Figure 2. Kaplan-Meier curves for distant metastasis-free survival rate of the patients who received (solid line) or did not receive (dashed line) CCRT with maintenance chemotherapy. CCRT, concurrent chemoradiation.

and distant metastasis-free rates (P=0.0063) than those who did not receive docetaxel. In their study, docetaxel was concurrently administered with radiation therapy. Fujisawa *et al* (6) reported that the 5-year OS rate of patients receiving CCRT with docetaxel or paclitaxel was significantly higher than that of those receiving postoperative radiation therapy (56 vs. 8%, respectively; P<0.01). Moreover, patients who received CCRT followed by maintenance chemotherapy showed a significant improvement in OS than those receiving CCRT alone (P<0.01). Their study included patients with limb lesions and with lymph node metastases. Regarding maintenance chemotherapy, Ito *et al* (7) also reported that maintenance chemotherapy with taxanes substantially affected survival. Patients administered maintenance chemotherapy with taxanes had prolonged disease-specific survival (DSS) and event-free survival (EFS) compared with those who did not receive it (3-year DSS: 77.0 vs. 39.2%, 5-year DSS: 57.0 vs. 19.6%, median survival: 62.2 vs. 17.7 months, P=0.0049; 3-year EFS: 52.4 vs. 22.5%, 5-year EFS: 34.9 vs. 5.6%, median survival: 46.7 vs. 12.4 months, P=0.0024). Moreover, multivariate analysis revealed that maintenance chemotherapy with taxanes was an independent prognostic factor for DSS and EFS (P=0.046 for both). Their study included patients with lymph node metastases and other distant metastases. Treatments for primary lesions included radiation therapy, surgery, and chemotherapy. Collectively, the findings of these studies support our hypothesis that CCRT with maintenance chemotherapy might improve OS. The retrospective design, small population, and short follow-up period of our study may explain the lack of any significant impact of CCRT with maintenance chemotherapy on OS.

Regarding adverse events, patients treated with CCRT tended to develop severe hematotoxicity compared with those treated without CCRT. In addition, 1 patient did not complete the planned radiation therapy because of scalp infection. However, all the other patients treated with CCRT completed the planned radiation therapy and continued the chemotherapy. Therefore, the severity of these acute adverse events during CCRT is acceptable. Similarly, the toxicity associated with maintenance chemotherapy was also acceptable. None of the patients were required to discontinue the maintenance chemotherapy because of adverse events; the 3 patients with skin ulceration also continued maintenance chemotherapy.

Regarding prognostic factors other than CCRT with maintenance chemotherapy, surgery was a significant risk factor for PFS and DMFS in this study. In their systematic review and meta-analysis, Shin *et al* (4) reported that surgery was the most effective treatment for improving the survival rate. However, we believe that in our study, the impact of surgery was unclear. This is because only 2 patients underwent surgery; they also underwent CCRT with maintenance chemotherapy, which may have affected the outcome. Age was not a significant risk factor for OS in this study; this was similar to the findings of previous studies (2,5,6,8-12). However, some other studies have reported that age is a significant factor for survival (4,7,13,14). To date, the association between age and survival remains unclear. Tumor size has also been reported to be a prognostic factor for survival (4,8,11,13), with previous studies using a cut-off value of 5 cm. Conversely, other previous studies have reported that tumor size is not a significant factor affecting survival (2,3,5-7,9,10,12,14). Tumor size was not included in our univariate analyses because data on the tumor size of 1 patient were missing and only 1 patient had a tumor measuring <5 cm. Therefore, the prognostic impact of tumor size could not be determined in our study.

Regarding radiation therapy, the appropriate prescribed doses, irradiation fields, and radiotherapy techniques have not yet been determined. In previous reports, various prescribed doses, irradiation fields, and radiotherapy techniques were used. Bernstein *et al* (2) reported median preoperative, postoperative, and definitive radiotherapy doses of 52, 53, and 56 Gy, respectively, delivered using megavoltage photons, electrons, or intensity-modulated radiotherapy. The median dose per

fraction was 2 Gy. The radiation fields covered the primary site with generous margins, and some patients received total scalp radiotherapy. Ward *et al* (3) reported doses that ranged from 45 to 75.6 Gy in once daily, twice daily, and thrice daily fractions of 1.8, 1.2 to 1.5 Gy, and 1.0 Gy, respectively. Radiation therapy was administered to the primary site with generous margins. Miki *et al* (5) reported a prescribed dose of 70 Gy for all patients in 2.0-2.5 Gy fractions; docetaxel was administered concurrently in some patients and extended local or whole-scalp fields were used. For extended local fields, the gross tumor volume was expanded with margins of ≥2.5 cm to form the clinical target volume. The planning target volume contained the clinical target volume with a margin of at least 0.5 cm. Radiation was delivered to the primary lesion using 6-12 MeV electron beams. Fujisawa *et al* (6) reported a typical radiotherapy dose between 60 and 70 Gy, with a median dose of 70 Gy. Docetaxel or paclitaxel was administered concurrently in some patients. The irradiation fields encompassed a 2-3 cm margin from either the tumor or surgical margin. Ito *et al* (7) reported a radiotherapy dose of 45-85 Gy (mean 67.5 Gy). Sasaki *et al* (8) reported a radiotherapy dose of 30-100 Gy (median 68 Gy). The radiation fields were determined on the basis of tumor extension, with a safety margin of ≥3 cm. Electron, X-ray, or telecobalt beams were used. Ohguri *et al* (9) reported a median radiation dose of 70.3 Gy with fractions of 2 or 3 Gy. Radiation was delivered using 6-12 MeV electron beams. In most patients, a radiation dose of 50-60 Gy was administered using various techniques to encompass the tumor extension with a safety margin of >3 cm; a 10-20 Gy boost dose was also delivered to the tumor. Ogawa *et al* (10) reported a total radiation dose of 26-71.6 Gy (median 60 Gy), with daily fractions of 1.8-2.0 or 3-4 Gy. The planning target volume included 3-5 cm margins for the clinical target volume. Radiotherapy was delivered using 6-12-MeV electron or 4-MV X-ray beams. None of the 14 patients who received ≥70 Gy had in-field recurrences. Perez *et al* (11) reported a strategy that administered preoperative radiation doses of 50 Gy, postoperative doses of 60 Gy, and doses to bulky disease between 66 and 70 Gy. Patel *et al* (12) reported doses of 40-70 Gy (median 60 Gy) in 10-35 fractions. Radiotherapy was delivered by electrons or megavoltage photons. Pawlik *et al* (13) reported total scalp radiotherapy using electron beams at a total dose of 60-72 Gy. Suzuki *et al* (14) reported a total dose of 60-100 Gy (median 70 Gy) and a median dose per fraction of 2.0 Gy. The primary tumor and all satellite lesions were included with a 3-5 cm margin. Radiotherapy was delivered using 5-9 MeV electron beams. In our study, the prescribed dose was 60 or 70 Gy in 2.0-Gy fractions. Although we cannot propose the optimal radiation dose, we believe that doses of 60 to 70 Gy are acceptable and relatively well tolerated by patients. Total scalp radiotherapy was sometimes used in accordance with several previous reports (2,13). Bernstein *et al* (2) reported that total scalp radiotherapy was not a significant factor for locoregional control, recurrence-free survival, and OS. Miki *et al* (5) also reported that whole-scalp fields were not a significant factor for OS. In our study, in cases where the first site of recurrence was only local, all the sites of the first local recurrence were within the radiation field. We speculate that total scalp radiotherapy may be unnecessary in cases where adequate margins are taken around the tumor, and when dermatologists are able to clearly define the extent of disease.

The present study has several limitations. First, it was a retrospective study conducted in a single institution, and the relatively short median follow-up period of 15 months may have been inadequate to accurately detect local tumor progression and late adverse events. Second, the number of patients was small. Therefore, we could not perform a multivariate analysis. Moreover, patients who received CCRT with maintenance chemotherapy may have had better physical status than those who did not receive CCRT with maintenance chemotherapy. This might have influenced the PFS, OS, LC, and DMFS. Third, the heterogeneity of the treatment may have influenced the generalizability of the results. Fourth, the effects of surgery and IL-2 were not properly investigated because only a small number of patients received them (only 2 patients underwent surgery and 4 received IL-2). Finally, several new drugs such as pazopanib and pembrolizumab have been recently developed (19,20); the impact of these new drugs on angiosarcoma was not evaluated in our study because only 1 patient received pazopanib. This patient was initially treated with paclitaxel during and after the radiation therapy, but was switched over to docetaxel after recurrence of lung metastases. Subsequently, pazopanib was used because docetaxel was ineffective. The patient died of angiosarcoma approximately 5 months after the initiation of pazopanib.

In conclusion, CCRT with maintenance chemotherapy using taxanes may be effective in treating localized angiosarcomas of the scalp without cervical lymph node metastases; this may be particularly useful for preventing distant metastases. Further prospective multicenter studies are required to validate our findings and determine the optimal treatment modalities for localized angiosarcomas of the scalp.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

HI contributed to the study design, data collection, analysis and interpretation, and writing the manuscript. HI, KK, TW and NK were responsible for radiation therapy. TK, TM and OY performed the patient follow-up and were responsible for conducting the other treatments including chemotherapy scheduling. HM contributed to the study design, and data analysis and interpretation. MK, SM, and SK contributed to the study design and reviewing the manuscript. All authors read and approved the manuscript.

Ethics approval and consent to participate

The present study was approved by Okayama University Hospital Institutional Review Board (approval no. K1610-503), and the requirement for informed consent was waived owing to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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