Primary and Secondary Soft Tissue Angiosarcomas: Prognostic Significance of Surgical Margins in 43 Patients

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Abstract. *Background: Angiosarcomas are aggressive soft tissue sarcomas. Due to their rarity there is a paucity of data regarding the clinical outcome of patients with non-visceral angiosarcomas of the soft tissues. In particular, the prognostic significance of surgical margins remains controversial. Patients and Methods: We retrospectively assessed the outcome of 43 patients with localised disease suitable for surgical treatment with curative intent. The median follow-up was 7.5 years. Results: The 5-year overall survival (OS) rate was 46.2%. Sixteen patients (37.2%) were diagnosed with secondary, radiation-induced angiosarcomas. Twenty-four patients (55.8%) developed local recurrences and 15 patients (34.9%) distant metastases. Negative surgical margin emerged as the only statistically significant prognostic factor (5-year OS: R0 51.8% vs. R1/R2 17.1%, p=0.036). As indicated in the regression analysis, close and wide negative margins within the R0 subgroup led to similar outcomes. Conclusion: Angiosarcomas have a high risk of local recurrence and metastasis. Surgical resection with negative margins improves the outcome.*

Angiosarcomas are rare and aggressive malignancies accounting for approximately 2% of all adult soft tissue sarcomas (1, 2). They originate from the endothelial cells of blood vessels and lymphatics and, therefore, may occur throughout the body. The most common sites include the soft tissues of the head and neck area, followed by the breast and the extremities (3). Besides the soft tissues, angiosarcomas may also arise in the liver, the spleen, the heart and the bones (1). Angiosarcomas occur either sporadically as primary lesions or secondary to radiation and chronic lymphedema. Notably, the incidence for secondary angiosarcomas is rising due to the increased use of adjuvant radiation in the treatment of breast cancer (2, 4).

Angiosarcomas represent a relatively aggressive soft tissue sarcoma subtype with a high risk of metastasis and poor prognosis. The reported metastasis rates vary from 19 to 50% while the 5-year overall survival (OS) rates range from 31 to 60% (3, 5-11). The distinct variation of reported outcomes reflects the heterogeneity of this disease. Primary and secondary angiosarcomas display only slightly diverging outcomes (11), but angiosarcomas of varying localisations exhibit completely different clinical behaviours (7, 12). Hence, angiosarcomas with different localisations should be considered and analyzed separately when feasible. However, the rarity and heterogeneity of angiosarcomas poses epidemiological challenges and precludes even large retrospective studies to subdivide their patients into more homogenous cohorts that can be analysed with an adequate statistical power. Subsequently, there are only a few studies assessing specifically the impact of surgical margins in the different angiosarcoma subsets.

To date, the standard treatment for localized disease involves surgical resection with wide clear margins although the prognostic significance of surgical margins is still a subject for debate. Large retrospective studies could demonstrate that patients who were suitable for surgical resection have an improved outcome when compared to patients with unresectable tumours. However, most of these studies only assessed the tumour resectability as a prognostic indicator and did not assess the impact of surgical margins (3, 9, 10, 13). Regarding the quality of surgical margins as a prognostic factor, several retrospective studies on heterogeneous cohorts of angiosarcoma patients could establish an association between negative margins and improved OS in patients that presented with localised disease (5-7). Nevertheless, these findings stand also in contradiction to several studies that could not reveal a beneficial prognostic impact of negative margins on OS (8, 11, 14-17). Hence, the role of radical surgery, even in this aggressive sarcoma subtype, remains

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Key Words: Angiosarcoma, recurrence, survival, margin, resection.

controversial and more evidence is needed to better understand the factors that ultimately influence the outcome.

In order to gain greater insight into the clinical behaviour of non-visceral soft tissue angiosarcomas, we reviewed demographic, tumor and treatment characteristics of 43 patients who presented with localized disease in our Institution and underwent surgical treatment with curative intent. We assessed potential prognostic indicators of survival and particularly focused on the effect of surgical margins on disease outcome.

Patients and Methods

Patients. A total of 43 patients with non-visceral angiosarcomas of the soft tissues were treated surgically at our Institution between August 1999 and February 2016. Only patients with soft tissue angiosarcomas of the extremities, the breasts, the truncal wall, and the head and neck area were included. We restricted analyses to participants with localised disease at the primary presentation and all patients underwent initial surgical resection with curative intent. Further, we included only patients with full information available on the outcome, histology and surgical margins at the initial procedure. They were assessed and their clinicopathological characteristics are summarized in Table I. Patient follow-up was obtained from our database, medical records and patient correspondence. The study was approved by the local ethics committee.

Treatment. The goal of surgical treatment for all patients was resection of the primary tumour or residual disease with clear margins with curative intent. If necessary, plastic reconstructive surgery involving split thickness skin grafts, local or free flaps were used for the coverage of resulting soft tissue defects. Several patients received adjuvant radiation and/or chemotherapy. The indication for adjuvant radiation or chemotherapy was given at the discretion of the interdisciplinary tumour board of either our institution or the referring institutions.

A total of 10 patients (23.2%) received adjuvant radiotherapy with a median overall dose of 60.0 Gy (range=50.0-765.0Gy). Five (11.6%) patients received anthracycline-based adjuvant chemotherapy after resection of the primary tumour.

Histopathological classification. All tumours were diagnosed and classified using the French Federation of Cancer Centres and the latest World Health Organisation guidelines. All pathology slides and the according surgical margin widths were analysed or reviewed for consensus diagnosis by experienced soft tissue pathologists from our institution.

Statistical analysis. All patients were analyzed retrospectively regarding possible prognostic factors influencing survival (Tables II and III). Overall survival (OS) was defined as the time period from the date of surgery for primary tumour to the date of death from any cause or censored at the date of last follow-up assessment in living patients. The local recurrence-free survival (LRFS) was calculated from the date of surgery for primary disease to the date of first recurrence or censored at the date of last follow-up assessment in recurrence-free patients. Survival rates were estimated according to the Kaplan-Meier method with respective 95% confidence intervals (CIs) and were compared using the log-rank test. Regression analysis on surgical margin width was performed using the Cox proportional hazards model and the Wald test. $p<0.05$ was considered statistically significant. The data analysis was performed using the statistical programme Stata (Version 11.2, StataCorp, College Station, TX, USA).

Table I. *Demographic, tumor and treatment characteristics of 43 patients with angiosarcoma of the soft tissues.*

	All patients N (%)	Patients with primary angiosarcomas N (%)	Patients with secondary angiosarcomas N (%)
Median age (range, years)	65.4 (37.0-89.5)	65.4 (37.0-89.5)	64.9 (49.1-82.5)
Gender			
Female	30 (69.8)	14 (51.9)	16 (100)
Male	13 (30.2)	13 (48.1)	0 (0)
Site			
Extremity	18 (41.9)	18 (66.7)	0 (0)
Breast	19 (44.2)	3 (11.1)	16 (100)
Head/neck	2 (4.7)	2 (7.4)	0 (0)
Truncal wall	4 (9.3)	4 (14.8)	0 (0)
Size			
<5cm	13 (30.2)	6 (22.2)	7 (43.8)
≥5cm	30 (69.8)	21 (77.8)	9 (56.2)
Depth			
Epifascial	30 (69.8)	18 (66.7)	12 (75.0)
Subfascial	13 (30.2)	9 (33.3)	4 (25.0)
Histologic grade			
G1	8 (18.6)	4 (14.8)	4 (25.0)
G2	10 (23.3)	7 (25.9)	3 18.8)
G3	25 (58.1)	16 (59.3)	9 (56.2)
Margin status (Primary tumour)			
R0	34 (79.1)	20 (87.0)	14 (87.5)
R1	4 (9.3)	3 (11.1)	1 (6.25)
R2	5 (11.6)	4 (14.8)	1 (6.25)
Adjuvant radiation (Primary tumour)			
Yes	10 (23.3)	10 (37.0)	0 (0)
No	33 (76.7)	17 (63.0)	16 (100)
Adjuvant chemotherapy (Primary tumour)			
Yes	5 (11.6)	4 (14.8)	1 (6.3)
No	38 (88.4)	23 (85.2)	15 (93.8)
Local recurrence			
Yes	24 (55.8)	11 (40.7)	13 (81.2)
No	19 (44.2)	16 (59.3)	3 (18.8)
Distant metastasis			
Yes	15 (34.9)	10 (37.0)	5 (31.2)
No	28 (65.1)	17 (63.0)	11 (68.8)
Vital status			
No evidence of disease	15 (34.9)	9 (33.3)	6 (37.5)
Alive with local disease	6 (14.0)	6 (22.2)	0
Dead of disease	21 (48.8)	11 (40.7)	10 (62.5)
Dead of other cause	1 (2.3)	1 (3.7)	0

Results

Patients' characteristics. The median age at the time of primary diagnosis was 65.4 years (range=37.0-89.5) for the entire cohort (Table I). There were 30 female (69.8%) and 13 male (30.2%) individuals. Twenty-seven patients (62.8%) were diagnosed with primary angiosarcoma and 16 (37.2%) with secondary angiosarcoma. All patients with secondary angiosarcomas had a previous history of breast cancer and adjuvant radiation. The median interval between radiation for breast cancer and occurrence of secondary angiosarcoma was 6.8 years (range=4.7-12.9 years).

In the entire cohort, tumours were located in the extremities in 18 patients (41.9%), in the breasts in 19 patients (44.2%), at the truncal wall in 4 patients (9.3%), and in the head and neck area in 2 patients (4.7%). The distribution of the histologic grading was G1 in 8 cases (18.6%), G2 in 10 cases (23.3%) and G3 in 25 cases (58.1%).

A total of 24 patients (55.8%) had at least one local recurrence, whereas 15 patients (34.9%) had two or more local recurrences (range=2-10). Over time, 15 patients (34.9%) developed distant metastases. From these patients, nine (20.9% of the total) had pulmonary metastases, three bone (7.0%) and another three (7.0%) distant soft tissue metastases.

Surgical treatment in one or two steps led to microscopically negative margins (R0) in 34 patients (79.1%), whereas four patients (9.3%) were left with microscopically positive margins (R1) and five (11.6%) with macroscopically positive margins (R2). In patients with positive margins, the tumours were too advanced and widespread for complete re-excision.

Follow-up. As of May 2016 (the cut-off date), reverse Kaplan-Meier estimate of median follow-up after primary diagnosis was 7.5 years (95%CI: 5.4-12-5) (18). At the cut-off date, 15 patients (34.9%) had no evidence of disease, whereas six (14.0%) were alive with localised disease. During the follow-up, 21 patients (48.8%) died from disease and one patient (2.3%) from another cause.

Univariate analysis of LRFS. The 5-year rate of LRFS was 40.2 % (95%CI: 23.3-56-8) for the entire cohort. Patients with primary angiosarcomas tended to have a prolonged LRFS compared to patients with secondary, radiation-induced angiosarcomas (5-year LRFS: 53.2 [27.8-73.2] *vs*. 26.7% [8.3-49.6]), but the difference was not statistically significant in the univariate analysis and only a borderline *p*-value was obtained (p=0.056) (Figure 1, Table II). As all patients with secondary angiosarcomas had breast angiosarcomas, this tumour site also tended to have a diminished LRFS when compared with other localisations. Treatment characteristics such as surgical margins, adjuvant radiation or chemotherapy did not alter the LRFS in a significant manner.

Univariate analysis of OS. In the entire series, the 5-year estimate of the OS rate was 46.2% (95% CI: 29.1-61.8). The median survival time was 4.9 years for patients with primary angiosarcomas and 4.6 years for secondary angiosarcomas. The median survival time after diagnosis of initial metastasis was 1.8 years.

In univariate analysis, patients older than 60 years at the time point of initial diagnosis tended to have a reduced OS when compared with younger patients (5-year OS: 38.4 [18.9-57.7] *vs*. 59.4% [28.9-74.2; p=0.077]) (Table 3). Patients with G1 lesions had a slightly better OS when compared with patients with G2 and G3 tumours, although this distribution failed to reach statistical significance (p=0.251). Tumour characteristics such as size, depth and localisation did not alter OS. Moreover, primary and secondary angiosarcomas had comparable outcomes.

The surgical margin status was the only factor that reached statistical significance in univariate analysis. Patients with R0 margins had a significantly improved OS when compared to patients left with R1 or R2 margins (5-year OS: 51.8% [32.2-68.3] *vs*. 17.1% [0.8-52.6], p=0.036) (Figure 2). Primary wound closure and plastic surgical soft tissue coverage led to comparable outcomes. Similar to the findings for the LRFS, adjuvant radiation and chemotherapy did not alter the OS significantly.

Regression analysis of non-categorized surgical margin width. In the subgroup of patients with R0 margins, we additionally assessed the impact-negative margin widths. The closest negative margin width could be assessed histologically in our institution for 27 of the 34 patients with R0-resected tumours. We performed a Cox regression analysis to evaluate the prognostic significance of non-categorized clear margin widths within the R0 subgroup. Here, the closest surgical margin width did not influence OS significantly. The hazard ratio for death in the Wald test was 0.77 (95%CI: 0.41-1.43) for wide margins, which failed to reach statistical significance (p=0.403). LRFS was also unaffected by the surgical margin width. The hazard ratio for recurrence was 0.54 (95% CI: 0.25-1.16) for wide margins (p=0.117). Thus, close and wide negative margins led to a similar OS and LRFS.

Discussion

Angiosarcomas represent an aggressive soft tissue sarcoma subtype with a high risk of local recurrence and distant metastasis. The purpose of this study was to describe the outcome of patients with primary and secondary angiosarcomas of the soft tissues. Visceral and bone angiosarcomas were excluded from the present study, as they display completely different outcomes and clinical behaviours (7, 9). The current analysis included 43 patients

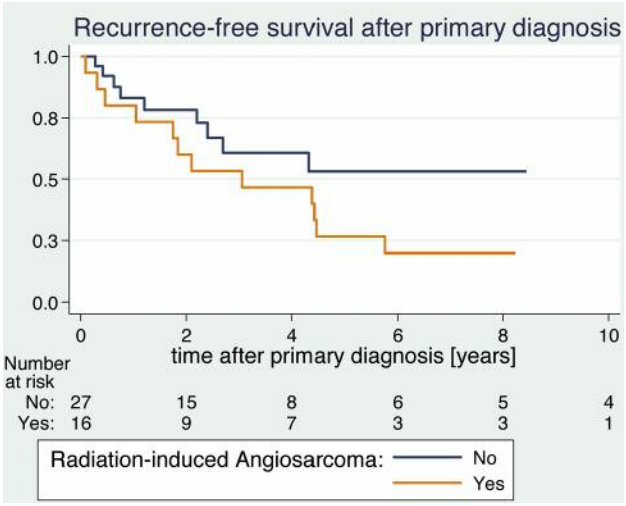

Figure 1. *Estimated local recurrence-free survival curves of primary and secondary, radiation-induced angiosarcomas.*

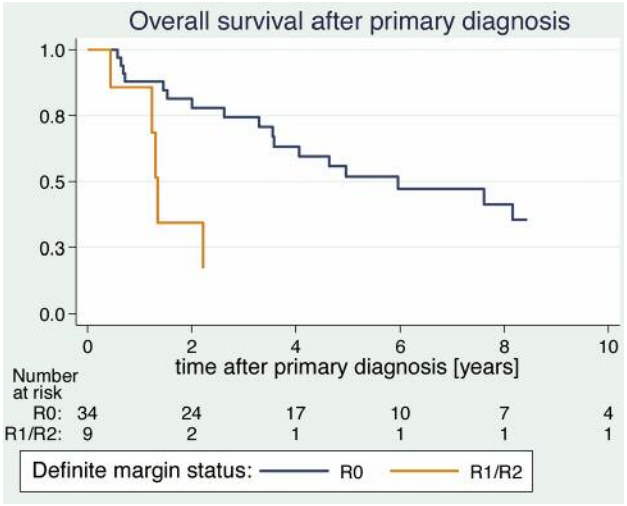

Figure 2. *Effects of surgical margins on overall survival.*

with localised disease at the time point of presentation and all patients underwent surgical treatment with curative intent. The median age at primary diagnosis was 65.4 years (95%CI: 37.0-89.5) and the most common sites included the extremities and the breasts. Primary angiosarcomas occurred equally in male and female patients (48.1% *vs*. 51.9%) while secondary angiosarcomas only presented on the breasts of females that had previously been treated with adjuvant radiotherapy for breast cancer. The median interval between radiation for breast cancer and occurrence of secondary angiosarcoma was 6.8 years in our series while other studies reported intervals between 7 and 9 years (8, 10, 14, 17, 19, 20). In our patient population, the frequency of radiation-induced angiosarcomas was 37.2% which is consistent with the reported rate of 34% by Perez *et al*. (8) who also only analyzed patients with non-visceral angiosarcomas. However, the incidence of secondary radiation-induced angiosarcoma is increasing as more patients undergo breast-conserving surgery and radiation (14).

In the present study, patients with primary and secondary angiosarcomas displayed almost similar outcomes. The median survival time was 4.9 years for patients with primary angiosarcomas and 4.6 years for secondary angiosarcomas. In accordance, several other studies also found no significant survival differences between patients with primary and secondary angiosarcomas. Median survival times for patients with secondary angiosarcomas ranged in those studies from 3.0 to 4.8 years (11, 17, 21). However, local control represents a challenging problem in this subgroup. In our series, 81.2% of all patients with secondary angiosarcomas developed local recurrences during their course of disease. In contrast, only 40.7% of all patients with primary angiosarcomas had local recurrence. These local outcomes are comparable to the findings of Hillebrand *et al*. reporting local recurrence rates of 70% for secondary angiosarcomas and 44% for primary angiosarcomas (11). In the current study, none of the assessed tumour and treatment characteristics had a statistically significant impact on local outcome.

The high metastatic potential of angiosarcomas represents another problem. In the present study, only patients with localised disease at the initial presentation were included and none of them had distant metastases at that time point. Nonetheless, 34.9% of all patients developed distant metastases within the median follow-up period of 7.5 years. The most common sites were the lungs (60%). Survival was diminished rapidly after diagnosis of metastasis with a median survival time of only 1.8 years. Reviewing previous publications, Perez *et al*. presented a quite similar series involving only non-visceral angiosarcomas (8). In this retrospective analysis of 88 patients, distant metastasis occurred in 29% of all patients within a median follow-up of 1.8 years. The 5-year OS rate was 35% for the entire cohort while our patient population displayed a rate of 46.2% (95%CI: 29.1-61.8). Notably, Perez *et al*. also included patients with advanced tumours that were too widespread for surgical treatment at the time of first presentation. The poor outcome of these patients might have led to the reduced OS rate.

Interestingly, Perez *et al*. could only identify the primary tumour size as a statistical significant predictor of OS. Other patient characteristics as well as the surgical margin status failed to reach statistical significance in their study.

Table II. *Results of univariate analyses to determine factors predictive of local recurrence-free survival in 43 patients with angiosarcoma of the soft tissues.*

	N	Number of patients with local recurrence	Estimated 1-year OS (95%-CI)	Estimated 2-year OS (95%-CI)	Estimated 5-year OS (95%-CI)	*p*-Value (log-rank)*
Age (years)						
≤60	16	8	85.1 (52.3-96.1)	77.4 (44.9-92.1)	52.2 (22.7-75.3)	
>60	27	16	80.7 (59.6-91.5)	67.2 (44.6-82.2)	33.0 (13.4-54.3)	0.111
Radiation-induced						
No	27	11	83.0 (60.7-93.3)	78.1 (54.9-90.3)	53.2 (27.8-73.2)	
Yes	16	13	80.0 (50.0-93.1)	60.0 (31.8-79.7)	26.7 (8.3-49.6)	0.056
Tumor site						
Extremity	18	6	86.5 (55.8-96.5)	78.7 (47.0-92.7)	53.9 (19.6-79.2)	
Head/Neck	2	1	100 (-)	100 (-)	(-)	
Breast	19	16	77.8 (51.1-91.0)	61.1 (35.3-79.2)	27.8 (10.1-48.9)	
Truncal wall	4	1	75.0 (12.8-96.1)	75.0 (12.8-96.1)	75.0 (12.8-96.1)	0.086**
Grading						
G1	8	4	100 (-)	100 (-)	62.5 (22.9-86.1)	
G2	10	8	80.0 (40.9-94.6)	60.0 (25.3-82.7)	40.0 (12.3-67.0)	
G3	25	12	76.2 (51.6-89.4)	63.5 (37.4-81.0)	28.2 (6.2-56.1)	0.181**
Margin status						
R0	34	20	84.9 (67.5-93.4)	74.9 (55.8-86.6)	40.8 (22.5-58.3)	
R1/R2	9	4	60.0 (12.6-88.2)	40.0 (5.2-75.3)	40.0 (5.2-75.3)	0.446
Wound closure						
Primary closure	24	17	77.8 (54.6-90.1)	64.1 (40.8-80.2)	39.6 (19.3-59.4)	
Non-primary closure (plastic surgical tissue transfer)	19	7	87.8 (59.5-96.8)	80.5 (50.6-93.3)	41.4 (13.7-67.7)	0.457
Adjuvant radiation						
No	33	19	79.8 (60.3-90.4)	64.9 (44.4-79.4)	39.3 (20.6-57.5)	
Yes	10	5	88.9 (43.3-98.4)	88.9 (43.3-98.4)	45.7 (11.0-75.7)	0.458
Adjuvant chemotherapy						
No	38	22	80.0 (62.6-90.0)	67.1 (48.2-80.3)	38.2 (21.0-55.3)	
Yes	5	2	100 (-)	100 (-)	50.0 (0.6-91.0)	0.161

*Log-rank test for equality of survivor functions; **global log-rank test for trend of survivor functions. OS, Overall survival; CI, confidence interval.

Nonetheless, surgical margin status emerged as the only significant predictive factor in our series. Similar observations were also made in the multi-center based series of Fayette *et al*. in which patients with localised angiosarcoma had more favourable outcomes when the primary tumours were resected with R0 margins (7). The single-institutional analyses by Fury *et al*. and Lindet *et al*. also determined that negative margins were associated with an improved OS. However, the survival benefit was only moderate in these studies and they did not assess the potential impact of margin widths. In our series, patients with negative margins had a remarkably better OS than patients that could only be resected with positive margins (5-year OS: 51.8% [32.2–68.3] *vs*. 17.1% [0.8-52.6]). Although the compared groups were relatively small, the distribution was found to be statistically significant due to the distinct differences in OS (p=0.036). Notably, the negative margin width had no influence on OS as assessed in the subgroup analysis of patients with R0 margins. Hence, close and wide negative margins led to similar outcomes.

Taken together, these findings might initially suggest an aggressive surgical approach with the goal of attaining negative margins to improve survival. However, we cannot retrospectively conclude whether it was the R0 resection itself or the factor "R0 resectability" that led to the improved outcome. It is also probable that tumours which cannot be completely resected had more aggressive biological features than completely resectable tumours and, thus, impaired the outcome more substantially. More specifically, it might be the inherent aggressiveness of the tumour itself that dictates both the surgically attainable margin status and the final outcome. Subsequently, a positive margin status might be rather a result than a cause of biological aggressiveness, and it may not influence the outcome directly. A similar relation between the attainable margin status and tumour biology could be established in primary and locally recurrent soft tissue sarcomas (22-24).

Regarding adjuvant treatment modalities, radiation did not significantly improve LRFS and OS in patients with primary angiosarcomas. Patients treated with adjuvant radiation

Table III. *Results of univariate analyses to determine factors predictive of overall survival in 43 patients with angiosarcomas of the soft tissues*

	N	Number of deaths	Estimated 1-year OS (95%-CI)	Estimated 2-year OS (95%-CI)	Estimated 5-year OS (95%-CI)	*p*-Value (log-rank)*
Age (years)						
≤60	16	5	92.9 (59.1-99.0)	85.7 (53.9-96.2)	59.4 (27.4-81.1)	
>60	27	17	84.1 (63.1-93.7)	66.4 (43.8-81.7)	38.4 (18.9-57.7)	0.077
Gender						
Female	30	16	88.9 (69.4-96.3)	80.8 (59.8-91.5)	46.7 (26.1-64.9)	
Male	13	6	83.3 (48.2-95.6)	58.3 (27.0-80.1)	46.7 (16.8-72.2)	0.783
Radiation-induced						
No	27	12	87.7 (66.4-95.8)	70.1 (47.3-84.5)	43.9 (22.3-63.7)	
Yes	16	10	86.7 (56.4-96.5)	79.4 (48.8-92.9)	50.6 (23.3-72.7)	0.711
Tumor size						
≤5 cm	13	7	92.3 (56.6-98.9)	92.3 (56.6-98.9)	50.3 (21.1-73.9)	
>5 cm	30	15	84.7 (64.3-94.0)	64.6 (42.9-79.8)	45.2 (24.4-64.0)	0.529
Tumor depth						
Epifascial	30	17	86.2 (67.3-94.6)	79.0 (59.1-90.0)	49.2 (29.6-66.1)	
Subfascial	13	5	90.9 (50.8-98.7)	56.8 (21.3-81.3)	42.6 (11.3-71.7)	0.512
Tumor site						
Extremity	18	7	93.8 (63.2-99.1)	72.1 (41.5-88.6)	44.0 (15.8-69.3)	
Head/Neck	2	1	50.0 (0.6-91.0)	50.0 (0.6-91.0)	50.0 (0.6-91.0)	
Breast	19	12	88.9 (62.4-97.1)	77.0 (49.7-90.7)	47.4 (23.2-68.3)	
Truncal wall	4	2	75.0 (12.8-96.1)	75.0 (12.8-96.1)	50.0 (5.8-84.5)	0.777**
Grading						
G1	8	4	100 (-)	100 (-)	62.5 (22.9-86.1)	
G2	10	6	80.0 (40.9-94.6)	60.0 (25.3-82.7)	50.0 (18.4-75.3)	
G3	25	12	86.1 (62.9-95.3)	70.0 (44.7-85.3)	37.0 (14.8-59.6)	0.251**
Margin status						
R0	34	17	87.9 (70.9-95.3)	81.4 (63.1-91.2)	51.8 (32.2-68.3)	
R1/R2	9	5	85.7 (33.4-97.9)	34.3 (4.8-68.5)	17.1 (0.8-52.6)	0.036
Wound closure						
Primary closure	24	13	91.1 (68.8-97.7)	76.7 (52.7-89.6)	46.5 (24.3-66.0)	
Non-primary closure (plastic surgical tissue transfer)	19	9	82.4 (54.7-93.9)	69.7 (41.7-86.1)	45.7 (19.2-69.0)	0.989
Adjuvant radiotherapy						
No	33	17	83.3 (64.5-92.7)	69.4 (49.4-82.8)	49.0 (29.1-66.2)	
Yes	10	5	100 (-)	87.5 (38.7-98.1)	37.5 (8.7-67.4)	0.964
Adjuvant chemotherapy						
No	38	22	85.9 (69.3-93.9)	70.5 (52.1-83.0)	41.7 (24.7-57.8)	
Yes	5	0	100 (-)	100 (-)	100 (-)	0.088

*Log-rank test for equality of survivor functions; **global log-rank test for trend of survivor functions. OS, Overall survival; CI, confidence interval.

tended to have a slightly prolonged LRFS, but this benefit was only restricted to the first two years and failed to reach statistical significance. Nevertheless, these findings have to be interpreted with caution, because of the relatively small number of patients treated with adjuvant radiation. In the present series, 37.0% of all patients with primary angiosarcomas received adjuvant radiation, while patients with secondary angiosarcomas did not undergo further radiation. The latter have already received the maximum dose of radiation due to their predisposing disease. However, adjuvant radiation has been determined to control local disease in patients with localised, primary angiosarcoma (6, 10, 25). Given the diminished local outcome of patients with primary angiosarcoma, it, therefore, seems reasonable to include adjuvant radiation, especially in cases of positive margins and high histologic grade.

The present study included only patients with localized angiosarcomas that were surgically approachable with curative intent. Although adjuvant chemotherapy did not influence survival in this study, systemic chemotherapy remains an important modality in the treatment of metastatic or unresectable angiosarcomas. Here, doxorubicin and paclitaxel have proven to be reasonable and appropriate choices for monotherapy (26, 27). As indicated in a large retrospective analysis by Italiano *et al*., doxorubicin and weekly paclitaxel seem to have similar efficacy in metastatic angiosarcomas

(28). Nonetheless, cutaneous and soft tissue angiosarcomas exhibited higher response rates when treated with paclitaxel. Moreover, weekly paclitaxel is very well tolerated and, therefore, emerges as a first-line chemotherapeutic agent for disseminated angiosarcomas in several treatment center (29-31). An alternative option to conventional cytotoxic agents represents molecular targeted therapy in the form of vascular endothelial growth factor receptor (VEGFR) inhibitors. Here, sorafenib and pazopanib seem to be promising agents (32). Several case reports demonstrated complete or partial remissions of primary and recurrent angiosarcomas after treatment with pazopanib (33-35). However, further prospective studies are needed to elucidate the effects of novel VEGFR inhibitors on angiosarcomas.

In the current study, we also tried to assess the prognostic significance of tumour size and histologic grade. In contrast to several other studies (3, 6, 8, 10), tumour size did not influence the outcome in our series. As expected, patients with G3 lesions tended to have a diminished OS compared to patients with G1 and G2 tumors, but this distribution failed to reach statistical significance in the univariate analysis due to the small number of cases. Finally, the reservation must be made that the present study is primarily descriptive and included only patients who were suitable for surgical treatment with curative intent and, therefore, did not involve patients with tumours which could not be approached surgically because of rapid disease progression or extensive dissemination. Consequently, our analyses on survival were restricted to the selected group of patients where further surgical treatment was possible and not to all patients with angiosarcomas. Patients with less favourable outcome, including those in palliative situations, were not assessed in this study. This implies a study selection bias that has to be acknowledged.

In conclusion, this single-institutional study provides data that may help clinicians estimate the prognosis of patients with angiosarcomas of the soft tissues. We observed that the optimal surgical treatment of localised angiosarcomas was R0 resection which was also the major parameter correlated to OS. Due to the retrospective nature of this study, we cannot conclude whether it was the R0 resection itself or the R0 resectability that led to improved outcome. However, given the diminished outcome of patients left with positive margins, surgical efforts should aim at function-sparing resections when feasible with negative margins. Here, close negative margins appeared to be adequate. When the goal of achieving negative margins requires major functional impairment or amputation, the postoperative consequences should be clearly discussed with each patient, as this can be highly subjective. The ultimate decision should be made in each case based on tumour progression, the health status of the patient and the decision of the informed patient.

Conflicts of Interest

The Authors declare that they have no potential conflicts of interest.

Acknowledgements

This work was supported by the FoRUM grant (K090-15) of the Ruhr-University Bochum, Germany.

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Received June 6, 2016
Revised July 4, 2016
Accepted July 6, 2016