Original Article

Clinical Outcomes and Prognostic Features of Angiosarcoma: Significance of Prior Radiation Therapy

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Abstract

Aims: Angiosarcoma is a rare and aggressive malignancy with a poor prognosis. There is limited literature describing prognostic factors and guidelines for treatment. We aim to describe outcomes in angiosarcoma, including the impact of patient-, tumour- and treatment-related factors on prognosis.

Materials and methods: Patients with non-metastatic angiosarcoma diagnosed between 2008 and 2017 were retrospectively reviewed. Univariable and multivariable Cox proportional hazards methods were used to evaluate factors associated with locoregional recurrence, distant failure and overall survival. The Kaplan–Meier method and log-rank statistics were used to compare outcomes among patients with and without a history of prior radiation therapy.

Results: The cohort included 65 patients. The median age at diagnosis was 68 years (35–93). Nineteen patients had a history of receiving prior radiation therapy at the anatomic location of their angiosarcoma. Treatment modalities included surgery (n = 19), surgery + radiation therapy (n = 12), surgery + chemotherapy (n = 8), chemotherapy + radiation therapy (n = 7) and all three modalities (n = 14). The median follow-up was 18 (2–192) months. The 2-year locoregional control, distant control and overall survival were 61.8, 63.6 and 58.9%, respectively. On multivariable analysis, a history of previous radiation therapy was associated with inferior outcomes with respect to locoregional recurrence (hazard ratio 89.67, 95% confidence interval 8.45–951.07, P < 0.001), distant failure (hazard failure 3.74, 95% confidence interval 1.57–8.91, P = 0.003) and overall survival (hazard ratio 3.89, 95% confidence interval 1.56–9.60, P = 0.003). In patients with primary angiosarcoma, the rates of locoregional control, distant control and overall survival were 72.4, 73.4 and 65.1%, respectively, compared with 31.9, 41.1 and 45.1% in patients with radiation therapy-induced angiosarcoma (P = 0.001).

Conclusion: Angiosarcomas that arise as a result of previous radiation therapy have worse outcomes compared with primary angiosarcomas. Although selection bias and compromise of clinical care in radiation therapy-induced angiosarcoma are partially to blame, differences in genomic profiles of the tumours need to be characterised to evaluate the underlying biological differences, as this may guide future treatment management. This study adds to the existing body of literature on angiosarcoma. Results from the current study are presented alongside previously published data to further characterise outcomes and prognostic factors on this rare and aggressive malignancy.

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Introduction

Angiosarcoma is a rare and aggressive malignancy of endothelial origin, making up about 5% of all soft-tissue sarcomas [1,2]. The tumours tend to arise from endothelial cells of blood vessels either sporadically as primary tumours or as secondary tumours in areas of prior radiation therapy. In addition to radiation therapy exposure, other identified risk factors include chronic lymphoedema and a variety of chemical exposures and familial syndromes, supporting the diverse mutational pathogenesis in the development of angiosarcoma [3]. Genetic mutations, such as over-expression of vascular endothelial growth factor, in angiosarcoma are reported, but are not well correlated with clinical and pathological features, and the pathogenesis of angiosarcoma in different clinical settings or anatomic locations has not been well distinguished [3].

Due to the rare nature of this disease, there is little evidence to guide the management of angiosarcoma. However, the overwhelming majority of the retrospective studies conclude that radical resection with negative margins followed by adjuvant radiation therapy is typically the standard of care [4—6]. Additionally, cytotoxic chemotherapy, such as doxorubicin or paclitaxel, is also used, especially in locally advanced or metastatic disease [7,8]. Despite these therapeutic options, the prognosis in patients with angiosarcoma remains very poor. Several retrospective series have aimed to identify prognostic factors in angiosarcoma to better guide treatment management [9,10]. However, due to the inconsistencies that are present in these studies, it remains unknown whether disparities in treatment response and outcomes among angiosarcomas of various risk factor profiles are driven by biological differences or due to the differences in clinical presentation and management.

Here, we aim to add to the current literature describing outcomes in angiosarcoma, including the impact of patient-, tumour- and treatment-related factors on prognosis. We report our institutional experience in treating angiosarcoma and compare these outcomes with existing data in the literature.

Materials and Methods

An Institutional Review Board-approved database was used as a source for this analysis. All consecutive patients with a pathological diagnosis of angiosarcoma diagnosed at a single institution between 2008 and 2017 were accessed in the electronic medical record system. Patients with metastatic disease at the time of initial diagnosis were excluded. The medical records of patients meeting inclusion criteria were reviewed for patient-, tumour- and treatment-specific factors, including age, race, gender, prior radiation therapy to the site of the angiosarcoma, grade, tumour size, anatomic site, nodal stage, surgical margins and treatment modality. The anatomic site of the primary tumour was used to categorise patients into six groups, including scalp, head and neck, breast, trunk, liver and extremity. Tumour size was categorised as less than or equal to 5 cm and greater than 5 cm. Tumours were categorised as superficial if tumour was located exclusively above the superficial fascia, or deep, indicating invasion of the fascia. Not all patients underwent surgery. However, in those patients who did undergo surgery, the aim was to achieve negative margins. A pathologist-assigned tumour grade was used to categorise tumours as low grade (grade 1 or 2) or high grade (grade 3). A negative surgical margin was defined as no tumour cells on the inked edge; a positive margin was defined as the presence of tumour cells on the inked edge. Multimodality therapy was defined as patients receiving more than one of the following treatment modalities: surgery, chemotherapy and radiation.

Time intervals for the analysis were calculated from the date of diagnosis. Locoregional control, distant control and overall survival were estimated using Kaplan—Meier methods. Patients were censored at the time of last known live follow-up if no date of death was recorded in the medical record system. Univariable and multivariable Cox proportional hazards methods were used to evaluate factors associated with locoregional recurrence (LRR), distant failure and overall survival. A backward logistic regression method (with selection criterion $P < 0.10$) was applied to obtain the final multivariable model. Log-rank statistics were then used to compare locoregional control, distant control and overall survival among patients with primary (*de novo*) angiosarcoma, defined as a pathological diagnosis of angiosarcoma with no prior lifetime history of radiation therapy, and patients with a history of prior radiation therapy. The statistical analysis was carried out using SPSS Statistics (Version 25; IBM; Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

In total, 65 patients were included in the final analysis based on the aforementioned inclusion and exclusion criteria. Baseline characteristics of the patient population are shown in Table 1. The median age at diagnosis was 68 years (35—93). Nineteen patients (29.2%) had a history of prior radiation therapy to the site of angiosarcoma. The median time between initial radiation therapy and radiation therapy-induced angiosarcoma was 9 years (range 3—35 years). The median dose of prior radiation therapy was 60 Gy (range 34—60 Gy) delivered in a median of 30 fractions (range 10—30 fractions). The most common anatomic site was breast ($n = 17$), followed by extremity ($n = 12$), scalp ($n = 11$), head and neck ($n = 11$), trunk ($n = 9$) and liver ($n = 5$). With regards to treatment management, the vast majority of patients (81.5%) underwent surgery as part of their treatment management. Single modality therapy was used in 24 patients, which included surgery alone in 19 patients (29.2%), chemotherapy alone in four patients (6.2%) and radiation therapy alone in one patient (1.5%). Twelve patients (18.5%) received a combination of surgery and radiation therapy, eight patients (12.3%) received a combination of surgery and chemotherapy, seven patients (10.8%) received a combination of chemotherapy and radiation therapy and 14 patients (21.5%) received a combination of all three treatment modalities. The groups with and without a history of prior radiation therapy were also compared (Table 1). The baseline characteristics of the two groups were very similar, except for gender, tumour location, tumour size and treatment modality. The median radiation therapy dose was 5400 cGy (3500—6800) in a median of 30 fractions (14—36). Ten patients also received a tumour bed boost of an additional 1000 cGy delivered in five fractions. Of 33 patients who received chemotherapy, 25 patients received single-agent paclitaxel. Other chemotherapy regimens included adriamycin in combination with paclitaxel or ifosfamide.

The median follow-up was 17.9 months (range 2.1—191.7). The median follow-up in patients with primary (*de novo*) angiosarcoma was 22.6 months versus 14.8

months in patients with radiation therapy-induced angiosarcoma. At the time of analysis, 23 patients (35.4%) had experienced LRR, 24 patients (36.9%) had experienced distant failure and 38 patients (58.5%) had died. Two-year locoregional control, distant control and overall survival for the entire cohort were 61.8, 63.6 and 58.9%, respectively (Figure 1).

Univariable and multivariable analyses of factors predictive of LRR, distant failure and overall survival are shown in Table 2. On univariable analysis, history of prior radiation therapy, tumour location in the liver, tumour size >5 cm and nodal disease were associated with higher rates of LRR. Surgery and multimodality therapy were associated with lower rates of LRR. On multivariable analysis, patients with a history of prior radiation therapy (hazard ratio 89.67, 95% confidence interval 8.45–951.07, $P < 0.001$) and tumour location in the liver (hazard ratio 31.02, 95% confidence interval 2.01–479.44, $P = 0.01$) had higher rates of LRR, whereas patients who underwent surgery (hazard ratio 0.01, 95% confidence interval 0.01–0.09, $P < 0.001$) had lower rates of LRR. Additionally, a trend towards lower LRR was seen in patients who received multimodality therapy (hazard ratio 0.32, 95% confidence interval 0.09–1.09, $P = 0.07$). The rate of locoregional control at 2 years was 72.4% in patients with primary (*de novo*) angiosarcoma versus 31.9% in patients with radiation therapy-induced angiosarcoma (Figure 2A, $P = 0.001$).

On univariable analysis, history of prior radiation therapy, tumour size >5 cm and nodal disease were associated with higher rates of distant failure. On multivariable analysis, history of prior radiation therapy (hazard ratio 3.74, 95% confidence interval 1.57–8.91, $P = 0.003$) and nodal disease (hazard ratio 3.59, 95% confidence interval 1.29–9.97, $P = 0.01$) remained as factors independently associated with distant failure. The rate of distant control at 2 years was 73.4% in patients with primary (*de novo*) angiosarcoma versus 41.1% in patients with radiation therapy-induced angiosarcoma (Figure 2B, $P = 0.001$).

On univariable analysis, history of prior radiation therapy, tumour size >5 cm, deep tumour location and nodal disease were associated with inferior overall survival. Conversely, treatment with surgery was associated with superior survival. On multivariable analysis, patients with a history of prior radiation therapy (hazard ratio 3.89, 95% confidence interval 1.56–9.60, $P = 0.003$) and nodal disease (hazard ratio 3.94, 95% confidence interval 1.37–11.31, $P = 0.01$) had inferior survival, whereas patients who underwent surgery (hazard ratio 0.31, 95% confidence interval 0.08–1.14, $P = 0.08$) had a trend towards improved overall survival. The rate of overall survival at 2 years was 65.1% in patients with primary (*de novo*) angiosarcoma versus 45% in patients with radiation therapy-induced angiosarcoma (Figure 2C, $P = 0.006$).

Discussion

This was a single institutional experience evaluating factors predictive of LRR, distant failure and overall survival in patents with angiosarcoma. This report adds to the very limited body of literature describing this rare malignancy. It further confirms that angiosarcoma is an aggressive malignancy and has poor clinical outcomes, with a 2-year overall survival of only 58.9%. The poor survival is probably driven by both inferior locoregional control (61.8%) and distant control (63.6%). Additionally, the study also shows that angiosarcomas that arise as a result of prior radiation therapy have worse outcomes with respect to locoregional control, distant control and overall survival compared with primary angiosarcomas.

The 2-year locoregional control rate of 61.8% reported here is consistent with the rates observed by others (Table 3), although rates as high as 74% and as low as 38% have also been observed [4,11]. This high risk of local recurrence rationalises the general treatment recommendations of radical surgery with complete resection and wide margins followed by adjuvant radiation therapy [3]. With respect to surgical margins, even the optimal aim of resection is controversial, as resection to an arbitrary measured margin around visible tumour versus up to complete resection of previously irradiated volume in patients with a history of radiation therapy is carried out [12]. The intended aim of resection was not available in the current study. With respect to radiation, although the use of radiation therapy did not show a significant benefit in the current study, a trend towards improved locoregional control was observed on the univariable model with the use of radiation therapy. This may have been related to a lack of statistical power in order to detect a significant difference. Moreover, multimodality therapy did show a trend towards an improved locoregional control on multivariate analysis, suggesting that more than one treatment modality (probably in the form of surgery + radiation therapy or radiation therapy + chemotherapy) is necessary to achieve improved local control. Other studies have confirmed a significant local control and survival benefit with the use of adjuvant radiation therapy in the treatment of angiosarcoma [13–17].

Similarly, the 2-year distant control rate of 63.6% reported here is consistent with the rates observed by other institutions (Table 3), although rates as high as 81.4% and as low as 22.9% have also been reported [3,13]. With these reports, it is clear that patients with angiosarcoma seem to be at a high risk of distant metastases, similar to other soft-tissue sarcomas [18]. As such, the high rate of distant failure raises the question of cytotoxic chemotherapy, although a clear clinical benefit of chemotherapy is yet to be established [19,20]. On univariable analysis, our findings are in agreement with prior literature in that the use of cytotoxic chemotherapy is not associated with improved survival in non-metastatic angiosarcoma. However, future combinations of cytotoxic chemotherapy, anti-angiogenic agents, targeted agents and immunotherapy may provide a solution for the poor distant control observed in this patient population [21–23]. With the combination of such poor distant control and local control, it is no surprise that the long-term overall survival for this disease is poor. The 2-year overall survival of 58.9% in this study is consistent with survival

Table 1
Characteristics of 65 patients with angiosarcoma treated with surgery, radiation therapy and/or chemotherapy

Characteristic	No. patients (%)	No. patients with no prior radiation therapy (%)	No. patients with prior radiation therapy (%)	P-value
Age median (range)	68.0 (35.6–93.1)	67.1 (35.6–88.7)	68.5 (39.4–93.1)	0.45
Race				
White	59 (90.8)	42 (91.3)	17 (89.5)	0.817
African American	6 (9.2)	4 (8.7)	2 (10.5)	
Gender				
Male	29 (44.6)	26 (56.5)	3 (15.8)	0.003
Female	36 (55.4)	20 (43.5)	16 (84.2)	
Prior radiation therapy				
No	46 (70.8)	46 (100)	0 (0)	<0.001
Yes	19 (29.2)	0 (0)	19 (100)	
Tumour location				
Scalp	11 (16.9)	11 (23.9)	0 (0)	0.002
Head and neck	11 (16.9)	10 (21.7)	1 (5.3)	
Breast	17 (26.2)	6 (13.0)	11 (57.9)	
Trunk	9 (13.8)	5 (10.9)	4 (21.1)	
Liver	5 (7.7)	4 (8.7)	1 (5.3)	
Extremity	12 (18.5)	10 (21.7)	2 (10.5)	
Tumour size				
≤5cm	20 (30.8)	17 (45.9)	3 (16.7)	0.04
>5 cm	35 (53.8)	20 (54.1)	15 (83.3)	
Unknown	10 (15.4)	9	1	
Deep tumour				
No	30 (46.2)	22 (50.0)	8 (42.1)	0.595
Yes	33 (50.8)	22 (50.0)	11 (57.9)	
Unknown	2 (3.1)	2	0	
Grade				
Low (grade 1 or 2)	10 (15.4)	9 (28.1)	1 (5.9)	0.13
High (grade 3)	39 (60.0)	23 (71.9)	16 (94.1)	
Unknown	16 (24.6)	14	2	
Nodal disease				
No	55 (84.6)	39 (84.8)	16 (84.2)	0.95
Yes	10 (15.4)	7 (15.2)	3 (15.8)	
Surgical margin				
Negative	37 (56.9)	24 (70.6)	13 (68.8)	0.87
Positive	16 (24.6)	10 (29.4)	6 (31.6)	
No primary surgery	12 (18.5)	12	0	
Surgery				
No	12 (18.5)	12 (26.1)	0 (0)	0.01
Yes	53 (81.5)	34 (73.9)	19 (100)	
Radiation therapy				
No	31 (47.7)	18 (39.1)	13 (68.4)	0.06
Yes	34 (52.3)	28 (60.9)	6 (31.6)	
Chemotherapy				
No	32 (49.2)	23 (50.0)	9 (47.4)	0.85
Yes	33 (50.8)	23 (50.0)	10 (52.6)	
Treatment modality				
Surgery alone	19 (29.2)	13 (28.3)	6 (31.6)	0.01
Chemotherapy alone	4 (6.2)	4 (8.7)	0 (0)	
Radiation Therapy alone	1 (1.5)	1 (2.2)	0 (0)	
Surgery + Radiation Therapy	12 (18.5)	9 (19.6)	3 (15.8)	
Surgery + Chemotherapy	8 (12.3)	1 (2.2)	7 (36.8)	
Chemotherapy + Radiation Therapy	7 (10.8)	7 (15.2)	0 (0)	
Surgery + Chemotherapy + Radiation Therapy	14 (21.5)	11 (23.9)	3 (15.8)	

rates reported by other institutions (Table 3). However, rates as low as 22.1% have previously been reported, confirming the need for novel treatment strategies in angiosarcoma [17].

To date, several retrospective series have analysed prognostic factors in angiosarcoma. Patient- and tumour-related factors, including tumour depth and size, patient age and performance status, histological grade, mitotic
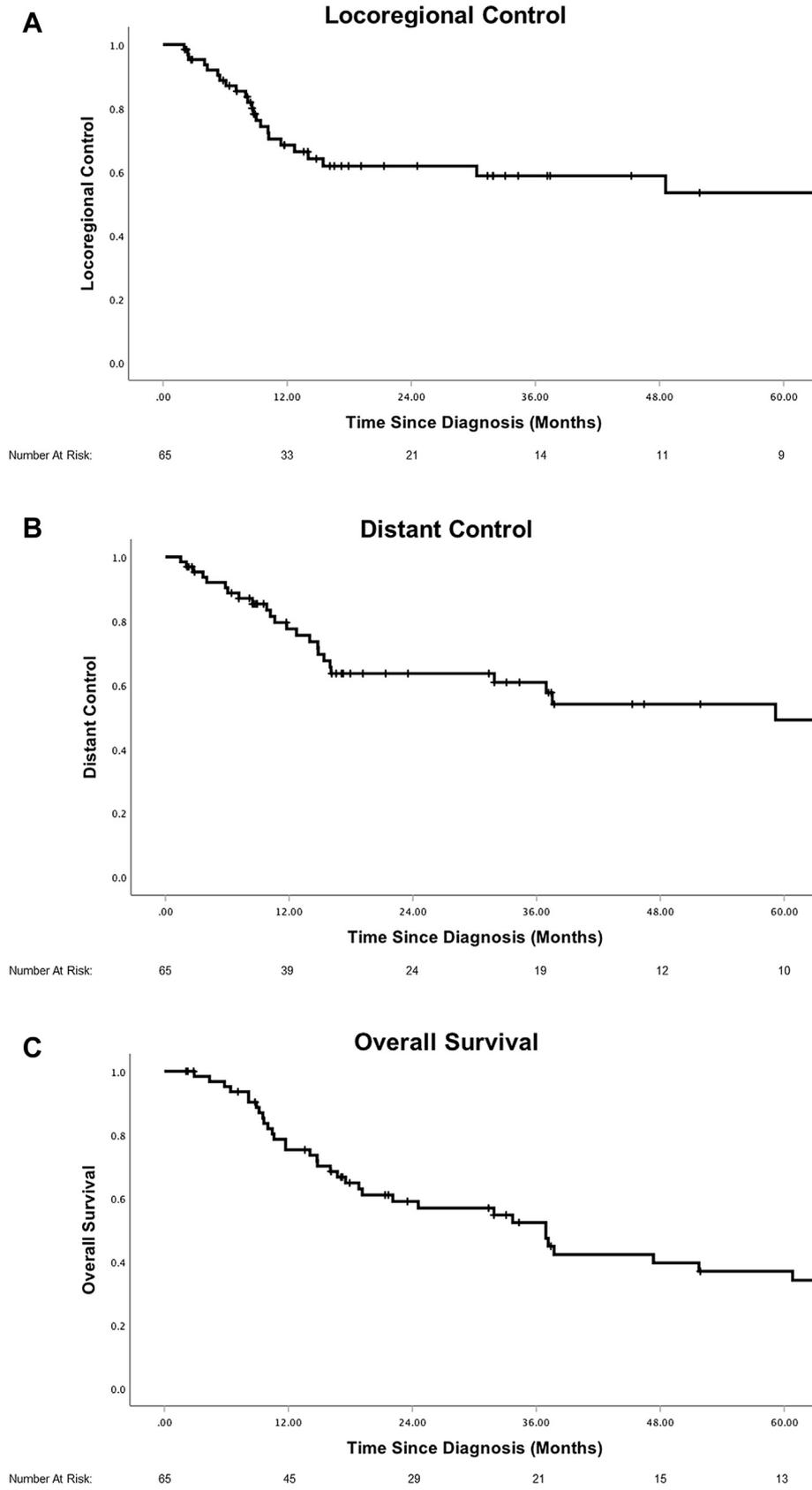
Fig 1. (A) Local control, (B) distant control, (C) overall survival.

Table 2

Univariate and multivariate analysis on factors predictive of locoregional failure, distant failure and overall survival in angiosarcoma

	Locoregional failure				Distant failure				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	0.99 (0.96–1.02)	0.58	NS		0.99 (0.96–1.02)	0.56	NS		1.01 (0.98–1.04)	0.41	NS	
Race												
White	Reference		Reference		Reference		Reference		Reference		Reference	
African American	1.78 (0.52–5.04)	0.36	NS		0.45 (0.60–3.31)	0.43	NS		1.02 (0.32–3.37)	0.96	NS	
Gender												
Male	Reference		Reference		Reference		Reference		Reference		Reference	
Female	1.29 (0.56–2.99)	0.55	NS		1.56 (0.67–3.66)	0.3	NS		0.94 (0.49–1.80)	0.86	NS	
Prior radiation therapy												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	3.98 (1.70–9.31)	0.001	89.67 (8.45–951.07)	<0.001	3.51 (1.56–7.90)	0.002	3.74 (1.57–8.91)	0.003	2.47 (1.26–4.84)	0.008	3.89 (1.56–9.60)	0.003
Tumour location												
Scalp	Reference		Reference		Reference		Reference		Reference		Reference	
Head and neck	1.24 (0.28–5.57)	0.78	NS		0.14 (0.02–1.20)	0.07	NS		0.87 (0.26–2.86)	0.81	NS	
Breast	1.90 (0.49–7.39)	0.35	NS		1.09 (0.36–3.27)	0.88	NS		1.10 (0.38–3.24)	0.86	NS	
Trunk	1.71 (0.34–8.52)	0.51	NS		1.22 (0.29–5.19)	0.78	NS		2.06 (0.65–6.56)	0.22	NS	
Liver	5.40 (1.07–27.19)	0.04	31.02 (2.01–479.44)	0.01	1.35 (0.26–7.04)	0.72	NS		1.87 (0.44–7.92)	0.4	NS	
Extremity	1.02 (0.21–5.06)	0.98	NS		0.74 (0.20–2.74)	0.65	NS		1.21 (0.38–3.83)	0.74	NS	
Tumour size												
≤5cm	Reference		Reference		Reference		Reference		Reference		Reference	
>5 cm	3.34 (1.10–10.10)	0.03	NS		3.64 (1.33–9.90)	0.01	NS		2.59 (1.18–5.69)	0.02		
Deep tumour												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	1.69 (0.72–3.97)	0.23	NS		1.97 (0.84–4.67)	0.12	NS		2.29 (1.14–4.61)	0.02	NS	
Grade												
Low	Reference		Reference		Reference		Reference		Reference		Reference	
High	28.7 (0.20–41.63)	0.19	NS		5.15 (0.69–38.50)	0.11	NS		3.31 (0.78–14.0)	0.1	NS	
Nodal disease												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	2.74 (1.05–7.17)	0.04	NS		3.09 (1.18–8.07)	0.02	3.59 (1.29–9.97)	0.01	3.49 (1.48–8.21)	0.004	3.94 (1.37–11.31)	0.01
Surgical margin												
Negative	Reference		Reference		Reference		Reference		Reference		Reference	
Positive	1.69 (0.58–5.00)	0.34	NS		1.92 (0.75–4.92)	0.17	NS		1.71 (0.74–3.96)	0.21	NS	
Surgery												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	0.30 (0.13–0.73)	0.008	0.01 (0.01–0.09)	<0.001	0.55 (0.20–1.50)	0.24	NS		0.44 (0.20–0.99)	0.047	0.31 (0.08–1.14)	0.08

Table 2 (continued)

	Locoregional failure				Distant failure				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Radiation therapy												
No	Reference		Reference	NS	Reference		Reference	NS	Reference		Reference	NS
Yes	0.45 (0.20–1.05)	0.063	NS		0.94 (0.42–2.09)	0.87	NS		0.70 (0.37–1.34)	0.28	NS	
Chemotherapy												
No	Reference		Reference	NS	Reference		Reference	NS	Reference		Reference	NS
Yes	1.24 (0.54–2.85)	0.61	NS		1.68 (0.74–3.81)	0.22	NS		1.61 (0.83–3.11)	0.16	NS	
Multimodality therapy												
No	Reference		Reference		Reference		Reference	NS	Reference		Reference	NS
Yes	0.45 (0.20–1.01)	0.05	0.32 (0.09–1.09)	0.07	0.96 (0.41–2.24)	0.92	NS		0.67 (0.35–1.29)	0.23	NS	

HR, hazard ratio; CI, confidence interval.

index, necrosis and multifocality, have been associated with patient outcome in these analyses [2–5,7,8,13–15]. The current study did find tumour depth and size to be predictors of poor prognosis on univariate analysis, but both were lost on multivariate analysis, probably due to a lack of statistical power. Here, we showed that nodal disease predicts for increased distant failure and lower overall survival, which is consistent with the findings of other previous studies [24,25].

Additionally, an inferior outcome in patients with a history of prior radiation therapy was observed in this study compared with patients with no prior history of radiation therapy, with respect to locoregional control, distant control and overall survival. Existing literature provides conflicting reports regarding the prognosis in patients with radiation therapy-induced angiosarcoma, otherwise referred to as secondary angiosarcoma in some literature, versus primary angiosarcoma. Studies by Yin *et al.* [25] and Abraham *et al.* [4] are consistent with our findings of inferior survival in radiation therapy-induced angiosarcoma compared with primary angiosarcoma. However, other studies report superior outcomes in patients with secondary angiosarcomas [26,27]. With conflicting existing data with respect to clinical outcomes, additional studies are needed to confirm our data showing inferior local control, distant control and overall survival in radiation therapy-associated angiosarcoma. The differences in outcomes between primary and secondary angiosarcomas are probably driven by differences in the genomic profiles of the tumours. For example, high levels of MYC and FLT4 amplifications have previously been observed in secondary angiosarcomas but not in primary angiosarcoma [28,29]. Additional genomic differences between radiation therapy-induced angiosarcoma and primary angiosarcoma need to be characterised to evaluate the underlying biological differences, which may guide future treatment management in these patients. Alternatively, it should be acknowledged that factors other than genomic differences in tumour pathogenesis between primary and secondary angiosarcoma may contribute to disparities in clinical outcomes. For example, the use of radiation therapy is often limited in patients who have received prior radiation therapy in the treatment field, limiting the definitive local therapy these patients receive. Despite accounting for differences in the treatment groups using multivariable analysis, selection bias is probably present, as patients who have received radiation therapy for prior malignancy are probably older and have greater medical comorbidities.

Given the retrospective nature of this analysis, there are several limitations in this study. First, the small cohort of only 65 patients may limit the power to detect significant predictors of prognosis, although this remains a relatively large cohort given the rarity of this disease. Also, details of therapy, including chemotherapy agents used, were not analysed in this study, due to the heterogeneity of the treatments the patients received. Radiation doses and fractionations were also not evaluated due to the heterogeneity of the dose and fractionation schemes used in this cohort. As such, selection bias plays a big role, as evidenced by the heterogeneity in treatment
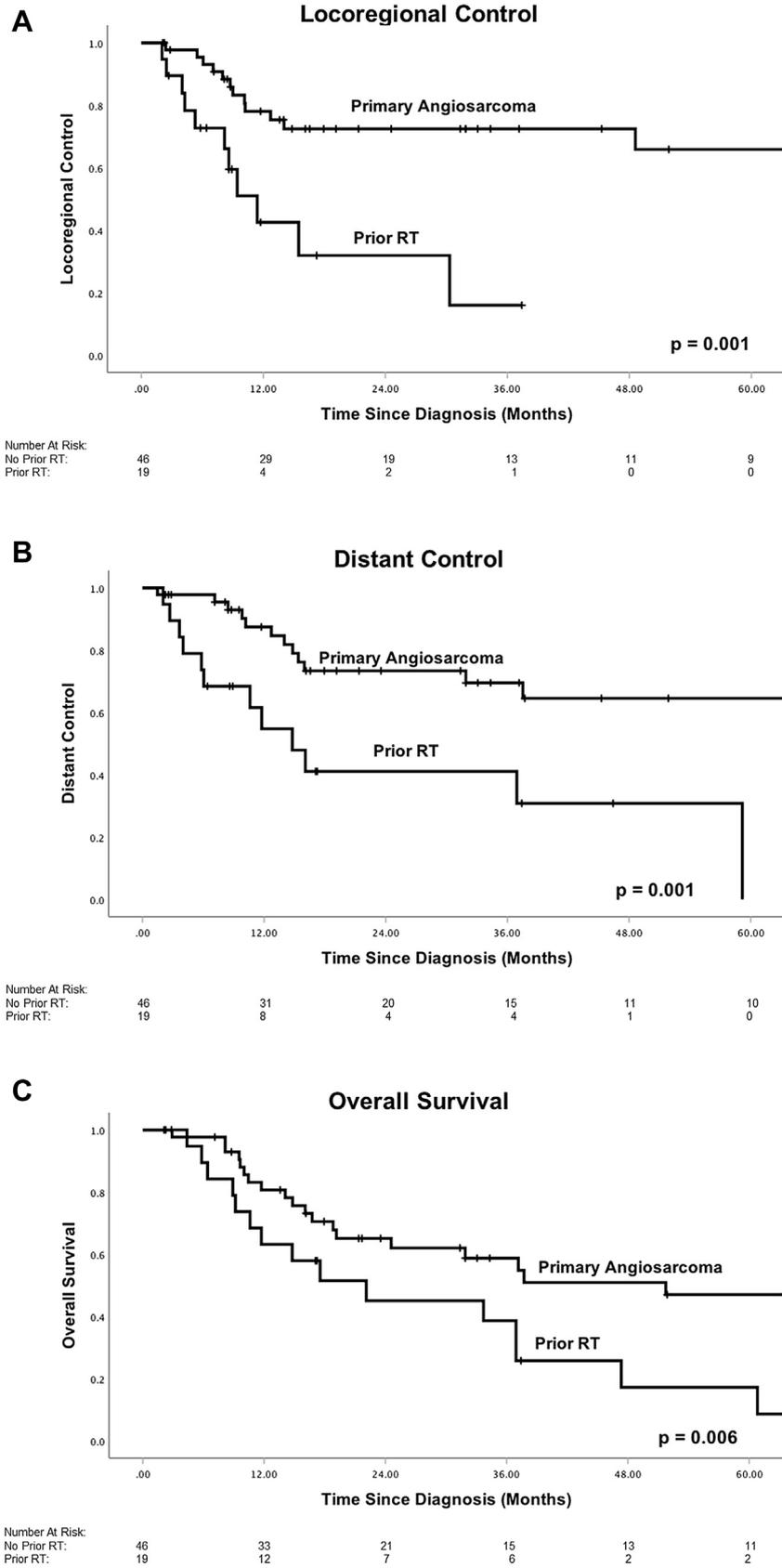
Fig 2. (A) Locoregional control, (B) distant control and (C) overall survival in patients with and without a history of prior radiation.

Table 3
Review of literature on outcomes of angiosarcoma

Study	No. patients	Site of disease	Follow-up (months)	Local control	Distant control	Overall survival
Present study	65	Scalp, face, breast, trunk, liver and extremity	17.9	61.8%	63.6%	58.9%
Miki et al. [24]	17	Scalp and face	18	52.9%	47.0%	N/A
Sher et al. [30]	69	Breast	40	71.0%	73.9%	61.0%
Scott et al. [27]	41	Any	44.4	64.0%	N/A	54.0%
Scow et al. [31]	41	Breast	27.6	65.9%	48.8%	51.0%
Guadagnolo et al. [32]	70	Scalp and face	25.2	43.0%	55.0%	43.0%
Fayette et al. [5]	161	Any	97	58.7%	N/A	43.0%
Hillenbrand et al. [26]	28	Any	N/A	60.0%	46.4%	42.9%
Pawlik et al. [14]	29	Scalp	18.2	41.4%	72.4%	41.4%
Abraham et al. [4]	46	Any	N/A	74.0%	56.5%	41.3%
Buehler et al. [9]	81	Any	13	63.0%	81.4%	40.0%
Lindet et al. [16]	107	Any	24.2	62.1%	65.5%	38.4%
Patel et al. [11]	55	Scalp and face	N/A	38.0%	N/A	38.0%
D'Angelo et al. [33]	74	Breast	N/A	55.0%	46.0%	35.0%
Fury et al. [6]	125	Any	22.8	59.3%	N/A	31.0%
Ogawa et al. [17]	48	Scalp and face	13.7	46.3%	22.9%	22.1%

management in the cohort. Additionally, the performance status of the patients was not available due to the retrospective nature of this study. Strengths of the current study include a relatively modern cohort pathologically reviewed and treated at a single institution. This study adds to the existing body of literature on this rare and aggressive malignancy. The compilation of institutional data clarifies outcomes in angiosarcoma, which can guide both clinical management and future prospective trials. In conclusion, angiosarcoma continues to be a difficult tumour to control locally and distantly and is therefore associated with poor outcomes. Patients who received prior radiation therapy have an unfavourable prognosis. Additional factors that may also be associated with improved outcomes include surgical management as well as the use of multimodality therapy. Further studies evaluating genomic differences between radiation therapy-induced angiosarcoma and primary angiosarcoma are necessary to develop novel treatment strategies to improve outcomes in this disease.

Conflict of Interest:

The authors have no conflict of interests to disclose for this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.01.006.

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