A retrospective review of 145 patients with angiosarcoma: Radiation therapy, extent of resection and chemotherapy are important predictors of survival

ALANNAH SMRKE[1], JEREMY HAMM[2], ANAND KARVAT[3], CHRISTINE SIMMONS[1] and AMIRRTHA SRIKANTHAN[4]

Departments of [1]Medical Oncology and [2]Cancer Surveillance Outcomes, BC Cancer, Vancouver Centre, Vancouver, BC V5Z4E6; [3]Department of Radiation Oncology, BC Cancer-Surrey, Surrey, BC V3V1Z2; [4]Division of Medical Oncology, Ottawa Hospital Cancer Centre, Ottawa, ON K1H8L6, Canada

Received November 4, 2019; Accepted February 24, 2020

DOI: 10.3892/mco.2020.2055

Abstract. Angiosarcoma is a subset of soft-tissue sarcomas with poor 5-year survival rate. Given its rarity, limited large cohort data is available for this disease. Therefore, the present study evaluated data from patients with angiosarcoma treated at a provincial Institution (BC Cancer) to determine potential modifiable predictors of survival. A retrospective review of patients across British Columbia (Canada) was conducted at the Sarcoma Outcome Unit of BC Cancer from January 1, 1969 to September 19, 2017. Cox proportional hazard models were used to calculate hazard ratios (HR) for the overall survival (OS) and progression free survival (PFS) of patients. A total of 145 patients with angiosarcoma were identified, of which 68 were metastatic/unresectable at presentation. Of the 145 patients included, 38 received chemotherapy, with 15 receiving taxane. A single patient received chemotherapy in a neoadjuvant setting. Of the resectable patients, 71 had first line surgery and 38 had curative-intent radiation during their treatment. Of the study cohort, 38 patients received prior radiation for an unrelated cancer and 4 patients had pre-existing chronic lymphedema. Resectable disease (HR, 0.22; P<0.01), first treatment with either surgery (HR, 0.08; P<0.01), radiation (HR, 0.19; P<0.01) or chemotherapy (HR, 0.22; P<0.01) were predictors of improved OS. First line surgery resulted in improved OS (HR, 0.36; P<0.01) and PFS (HR, 0.48; P<0.01). In addition, OS was positively impacted by the extent of surgery [complete (R0) vs. microscopic residual tumor (R1); HR, 0.26; P<0.01; R0 vs. macroscopic residual tumor (R2); HR, 0.08; P<0.01) resection. Extent of surgery and any radiation treatment were determined to be important predictors of OS. The results also revealed that patient outcome was improved following any treatment compared with supportive care alone. In conclusion, multidisciplinary care is critical for the treatment of patients diagnosed with angiosarcoma.

Correspondence to: Dr Amirrtha Srikanthan, Division of Medical Oncology, Ottawa Hospital Cancer Centre, 501 Smyth Road, Ottawa, ON K1H8L6, Canada
E-mail: asrikanthan@toh.ca

Key words: angiosarcoma, anthracyclines, taxanes, soft tissue sarcoma, radiation associated sarcoma

Introduction

Soft tissue sarcomas (STS) are a rare group of mesenchymal origin tumors which represent 1% of all malignancies in adults (1). Angiosarcoma is an uncommon subtype of sarcoma of vascular or lymphatic origin which represents 2% of STS (2). Risk factors include prior radiation therapy to the affected site, chronic lymphedema, and exposures such as vinyl chloride and arsenic (2). Patients are often older, with a median age of 60 years (2), and a significant number (20-45%) present with locally advanced or metastatic disease at diagnosis (3). Angiosarcoma represents an aggressive subtype of sarcoma, with 12% survival at 5 years for unresectable or metastatic disease (3).

The rarity of angiosarcoma precludes large randomized trials. Randomized trials generally group many subtypes of STS to achieve sufficient power for the primary outcomes, however heterogeneity within such trials limits the power for meaningful subgroup analysis of various sarcoma histologies. Thus, retrospective chart reviews have continued to provide the majority of current evidence for treatment and outcomes of rare subtypes of sarcoma (1,2).

Various factors may impact the survival of patients with angiosarcoma, including type of therapy used. ANGIOTAX was a single arm phase II trial (n=30) which introduced taxanes as first line systemic therapy for unresectable or metastatic angiosarcoma, with response rates of 18-19% at 6 months (3). This result has been confirmed in a number of small retrospective studies (4-8). Beyond taxanes, the majority of other published work includes retrospective reviews of small numbers of patients which suggest equipoise between taxanes and anthracyclines (5,7). Furthermore, previous single institution retrospective reviews have suggested that individuals with

metastasis at presentation, non-cutaneous primary disease, and unresectable disease have a worse prognosis.

In terms of local therapy, complete oncologic resection has been shown to improve overall survival (OS) (6,9). The effect of radiation therapy is less clear (5-7). Retrospective studies have focused on individual sites and endpoints used in analysis have not been consistent (10-12). In retrospective cohort studies, adjuvant radiation for breast angiosarcoma, or for unselected patients with localized disease did not impact recurrence free survival, but the impact on OS was not explored (11-13). For scalp primaries, radiation has been demonstrated to prolong time to local recurrence, and improved OS on univariate analysis (10).

Here we identify a large retrospective series of patients treated within a single institution to understand real world outcomes of patients with angiosarcoma and to establish potential modifiable predictors of outcomes.

Patients and methods

Patients with angiosarcoma from January 1, 1969 to September 19, 2017 were identified using the provincial Sarcoma Outcomes Unit (SARCOU) Database from the institution British Columbia (BC) Cancer in Canada. Central pathology review at the provincial academic centre specializing in sarcoma occurred for all cases at the time of diagnosis. Age at diagnosis, sex, histology, grade, tumor size, tumor location, chemotherapy [type of chemotherapy, no of lines, response as per Response Evaluation Criteria in Solid Tumors (RECIST), duration of therapy], radiotherapy (prior radiation, treatment dose), surgery (extent of resection, R0, R1 or R2), date of death/last encounter was collected for each patient by retrospective chart review. When possible, charts were reviewed for specific radiation planning information to determine if the angiosarcoma arose within a prior radiation field.

Statistical analysis. Descriptive statistical analysis were used and frequency of occurrence and percentage was calculated for each of the independent variables. Progression-free survival (PFS) and OS was calculated for each patient. PFS was measured from the time of diagnosis until disease progression or death from any cause. OS was measured from the time of diagnosis until death from any cause. Kaplan-Meier curves were constructed for PFS and OS to compare taxanes versus any other chemotherapy. Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals (CIs) for OS and PFS. Patients were censored if an event of interest did not occur prior to September 19, 2017 (the end of follow-up). All analyses were performed using SAS software, version 9.4 (SAS Institute Inc.). Statistical significance was defined using a two-tailed P-value of <0.05.

Results

Baseline characteristics. A total of 145 patients with angiosarcoma, 48.2% of which were female, were identified from January 1, 1969 to September 19, 2017 inclusive. Patient and treatment characteristics are summarized in Table I. Median age at diagnosis was 72 years. The majority of patients had resectable disease at presentation (77 patients, 53.1%), the remaining 68 patients had metastatic or unresectable disease. Common sites of primary disease presentation were head and neck (43/145), breast (35/145), and lower extremity (18/145). Rare sites of presentation (1 case/location) included: Cervical spine, colon, thyroid, adrenal gland and spleen.

Table I. Patient and treatment characteristics.

Variables	n=145, n (%)
Median age (years)	72 (19-96)
Sex	
Female	70 (48.2)
Male	75 (51.7)
Site	
Cutaneous (head and neck)	43 (27.7)
Extra cutaneous	102 (70.3)
Stage at presentation	
Resectable	77 (53.1)
Unresectable	42 (29.0)
Metastatic	26 (18.0)
Etiology	
Primary	103 (71.0)
Radiation associated	38 (26.2)
Chronic lymphedema	4 (2.8)
Initial treatment	
Surgery	71 (48.9)
Chemotherapy	11 (7.6)
Radiation	38 (26.2)
Best supportive care	18 (12.4)
Other[a]	7 (4.8)

[a]Concurrent chemo-radiotherapy or tumor embolization.

Prior radiation exposure. A total of 38 patients with angiosarcoma had previous radiation, of which 36 had available data on prior radiotherapy plans. Angiosarcoma arose within a prior curative intent radiation therapy field in 28/36 patients: 23/28 adjuvant breast cancer, 3/28 head and neck/skin cancer, 1/28 for prostate cancer. The mean radiation dose prescribed was 48.5 Gy (range 42.5-70 Gy). The median time from curative radiation to development of angiosarcoma was 8 years (range 2-22 years).

Outcomes based on cancer therapy received. The median OS for best supportive care was 2.2 months. Median OS for localized, unresectable non-metastatic and metastatic patients was 47, 5 and 3.0 months, respectively. The median PFS and OS of the entire cohort is illustrated in Fig. 1. In terms of any treatment received, of the 145 patients in the cohort, 55.1% patients underwent surgery, 48.2% received radiation, and 26.2% received chemotherapy (Table I).

Radiation (n=70). Radiation intent was curative in 19 patients (6-neoadjuvant, 13-adjuvant). In addition, 60 patients received

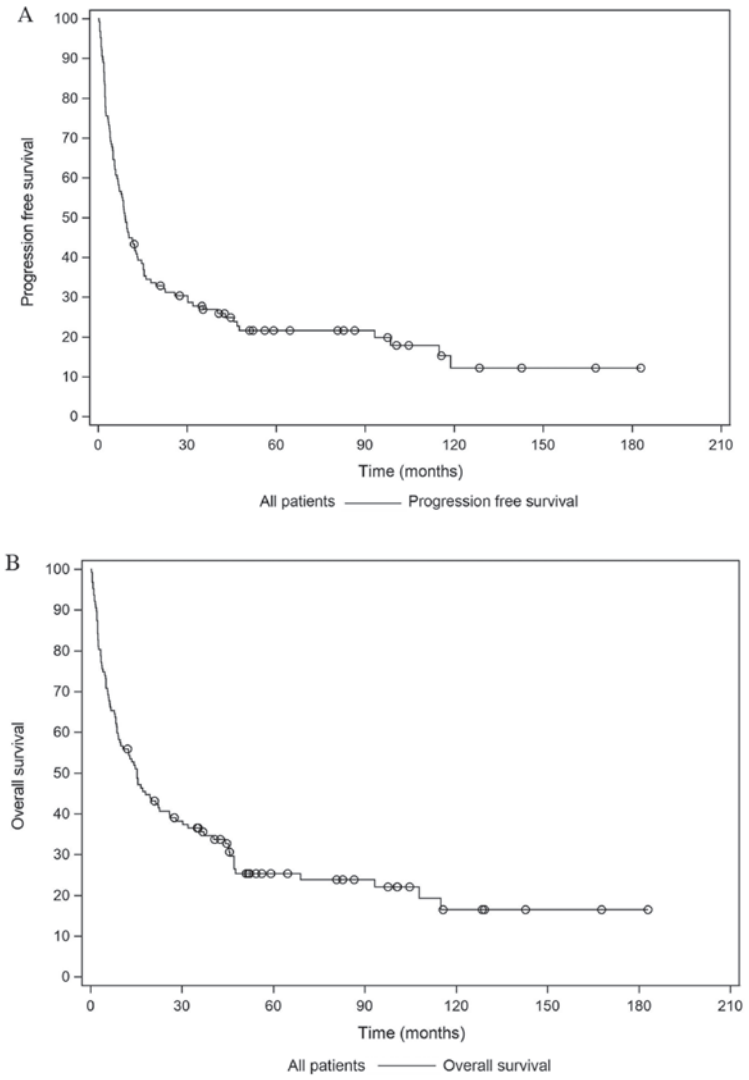

Figure 1. Kaplan-Meier curves for the entire cohort of patients diagnosed with angiosarcoma. (A) Progression free survival and (B) OS were determined.

palliative radiation. Median OS for patients whose first treatment was radiation was 9 months.

Surgery (n=71). A total of 71 of 77 resectable patients at diagnosis underwent surgery. The majority of patients underwent an R0 resection (42/71). A total of 18/71 patients underwent an R1, 5/71 R2 and 6/71 were unknown. Median OS by extent of resection was 93.3, 16 and 3.4 months for R0, R1, R2 resections respectively.

Chemotherapy (N=38). Median OS of patients treated with first line chemotherapy was 13.2 months. Of the 38 patients who received chemotherapy, the intent was palliative in the majority of patients (32 patients, 84.2%). One patient received neoadjuvant chemotherapy (2.6%), 3/38 patients received adjuvant chemotherapy, of which two had concurrent radiation for scalp angiosarcoma (Table II). Most patients receiving chemotherapy received only one line of treatment 21 patients (≥55.3%), 14 patients (36.8%) patients received two lines and three (7.9%) patients received three lines of therapy. More patients were treated with doxorubicin or liposomal doxorubicin (27 patients, 71%) than taxanes (15 patients, 39.5%).

Table II. Chemotherapy Information for 38 patients treated with systemic therapy.

Variables	n=38, n (%)
Chemotherapy lines	
1	21 (14.5)
2	14 (9.7)
3	3 (2.1)
Regimen exposure (any line)	
Taxane	15 (39.5)
Doxorubicin or liposomal doxorubicin	27 (71.0)
Gemcitabine, Sunitinib, Cisplatin/ Doxorubicin, Dacarbazine, Vinorelbine, Pembrolizumab, Doxorubicin/Ifosfamide	1 each (2.6)
Intent	
Neoadjuvent	1 (2.6)
Concurrent with radiation	2 (5.3)
Adjuvant	3 (7.9)
Palliative	32 (84.2)

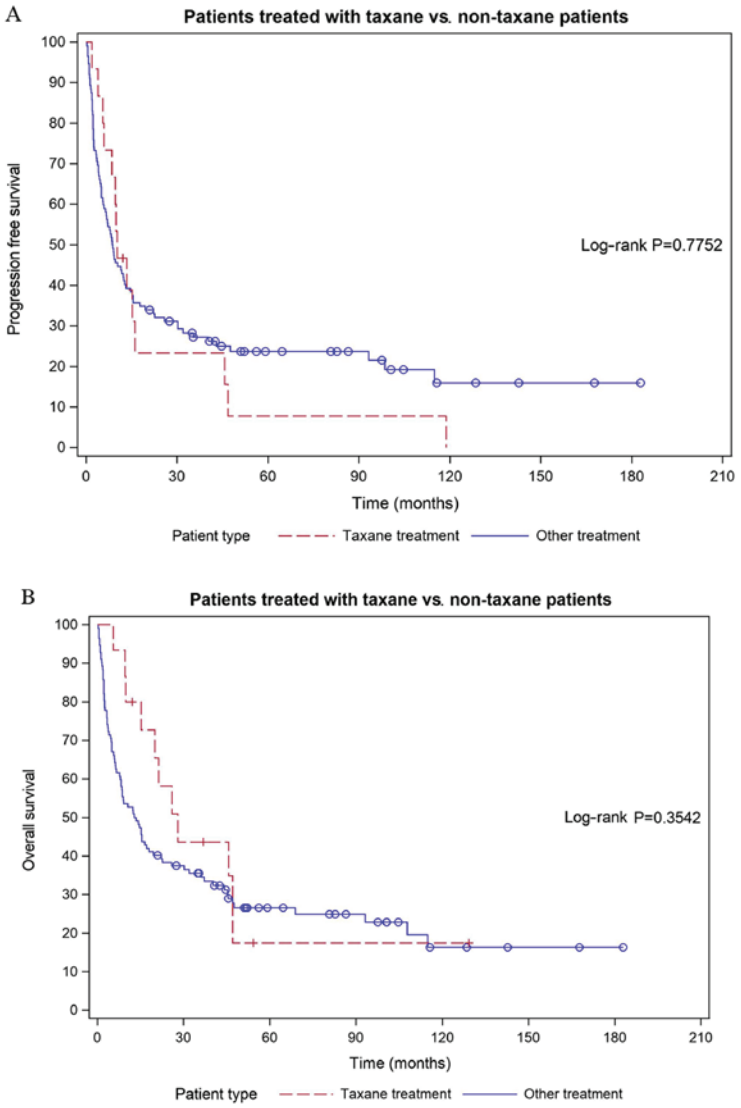

Figure 2. Kaplan-Meier curves for patients with angiosarcoma treated with taxane versus other systemic therapies (Taxane; n=15/38). (A) Progression free survival and (B) OS were determined. Dashed line, taxane treated patients; solid line, non-taxane treated patients.

There was no difference in PFS and OS for patients treated with a taxane versus non-taxane (Fig. 2), PFS for taxane treated patients 10.2, vs. 8.7 months for non-taxane treated patients (P=0.78). OS for taxane treated patients was 28 months, compared to 13.2 months for non-taxane treated patients (P=0.35). A total of 13 patients who received an anthracycline in the first line went on to have second line chemotherapy, while 3 patients who received a taxane went onto second line treatment.

Predictors of OS. OS was significantly improved for female patients, who had resectable disease (HR=0.22, P<0.01) and surgery with no residual disease (R0 vs. R1, HR=0.26, P<0.01, R0 vs. R2 HR=0.07, P<0.01). Patients who received any of chemotherapy, radiation or surgery versus best supportive care had significantly improved OS (chemotherapy HR=0.21, radiation HR=0.19, surgery HR 0.08, P<0.01). Surgery (HR=0.10, P=0.02) significantly improved PFS, but chemotherapy and radiation did not (chemotherapy HR 0.21, P=0.13, radiation HR=0.19, P=0.12) (Table III).

OS and PFS was significantly improved if the first treatment was surgery compared to radiation (PFS HR 0.49, P<0.01, OS HR=0.41, P<0.01) or chemotherapy (PFS HR 0.23, P<0.01, OS HR=0.37, P<0.01). There was no difference in PFS or OS if chemotherapy or radiation was given first.

Discussion

Unresectable and metastatic angiosarcoma remains a subtype of soft tissue sarcoma with poor prognosis. Data from our provincial institution over 48 years demonstrated that adequate upfront surgical resection remains the most significant predictor of survival. For those with incurable disease, systemic therapy or radiation therapy offer a meaningful improvement in survival compared to best supportive care. No difference in survival was identified with respect to which modality is used first (radiation or chemotherapy) and type of systemic therapy used (taxane vs. non-taxane).

The median age of our cohort, 72 years, was slightly older than previously published studies (57.4-67 years) (3-8)

Table III. HRs for PFS and OS variable.

	HR for PFS	P-value	HR for OS	P-value
Sex (F vs. M)	0.70	<0.01[a]	0.715	<0.01[a]
Non cutaneous vs. cutaneous	0.71	0.07	0.76	0.16
Tumor size (per cm)	1.05	<0.01[a]	1.01	0.27
Age at diagnosis (per year)	1.00	0.26	1.01	0.11
Resectable disease	0.10	0.15	0.22	<0.01[a]
Extent of Surgery (R0 vs. R1)	0.30	<0.01[a]	0.26	<0.01[a]
Extent of Surgery (R0 vs. R2)	0.14	<0.01[a]	0.07	<0.01[a]
Extent of Surgery (R1 vs. R2)	0.47	0.14	0.29	0.03[a]
First treatment surgery vs. chemotherapy	0.23	<0.01[a]	0.37	<0.01[a]
First treatment surgery vs. radiation	0.49	<0.01[a]	0.416	<0.01[a]
First treatment surgery vs. best supportive care	0.10	0.02[a]	0.08	<0.01[a]
First treatment radiation vs. chemotherapy	0.83	0.85	0.88	0.72
First treatment radiation vs. best supportive care	0.19	0.12	0.19	<0.01[a]
First treatment chemotherapy vs. best supportive care	0.21	0.13	0.21	<0.01[a]

[a]P<0.05. HR, hazard ratio; PFS, progression free survival; OS, overall survival; F, female; M, male.

and similar to a recent large Dutch cohort (14). Incidence was similar between males and females, although prior studies demonstrated slightly increased incidence in females (55-65%) (3,6,7,14). The most common site was cutaneous (head and neck) at 27.7% which is a similar proportion to other large cohorts (5,9). The majority were primary angiosarcomas, however, 28 patients (19.3%) had angiosarcoma arise in a previous curative intent radiation field. Our proportion of radiation associated angiosarcomas is similar to previously reported incidence which ranges from 17-34% (3-7,14), and similar time to development as reported previously for a cohort of radiation induced breast angiosarcomas (12,14). Chronic lymphedema was an identified risk factor in 2.8% of patients, which is less than reported rates of 4-13% (3,6,14).

Our study offers a large cohort of 145 patients treated for angiosarcoma, comparable to other published series (5,7,8,14). However, the OS for metastatic patients in our cohort is lower than previously reported studies (3 vs. 7.3-16 months) (6,7,11,14). This anomaly may be explained by the comparatively lower use of chemotherapy in our cohort and the poor OS of patients who received best supportive care alone. The OS for any chemotherapy was 13.2 months, comparable to the survival rates that have been reported in other cohorts (3,14). The OS with best supportive care (BSC) was also similar to previously published data (3,7) at 2.2 months. Interestingly, patients who were female had improved PFS and OS, which is discordant with previous cohorts (14).

Local therapies such as surgery and radiation continue to impact survival. Appropriate upfront resection remains the most significant predictor of OS in our study and others (6,9,14). The OS benefit for complete resection is consistent across multiple studies that highlight the importance of complete resection in soft tissue sarcoma management (15-17). This further highlights the importance of multi-disciplinary review with experienced surgeons for even a borderline resectable case.

Radiation therapy use in this cohort is higher than previously published reports (19.8-41%) (6,14). In our cohort, radiation use led to an improved PFS and OS for those treated versus best supportive care in the non-curative setting. Previous large single institution data of localized and metastatic cohorts have seen reduction in local recurrence (11,13) or only seen a trend towards OS benefit with radiation (47 vs. 10 months) (6). Our results are congruent with a recently published large cohort which found radiation treatment correlated with improved OS (14). Importantly, in our cohort, the impact of radiation on OS met significance (9 vs. 2.2 months) for patients whose first treatment for metastatic disease was radiation. This difference may have been due to local control of the primary to improve symptoms enabling systemic treatment to be delivered, or simply good local control for a prolonged period delaying reduction in performance status.

Our study identified lower rates of chemotherapy usage (26%) in the incurable setting compared to most other published cohorts. Apart from a large Dutch cohort reporting a 13% chemotherapy usage rate (14), previous retrospective cohorts demonstrate higher rates of chemotherapy use, ranging from 40-89.8% (7,9,14,18). Notably, previous published cohorts were either from a single academic centre (9) or from a group of Specialized Sarcoma Centres (7), while in BC, patient care can be geographically disparate, and not all patients were treated in an academic center with sarcoma expertise. This coupled with slightly older baseline age of our cohort may have led to less chemotherapy being prescribed. Importantly, in our cohort, OS was significantly improved if any chemotherapy was used versus best supportive care (13.2 vs. 2.2 months) consistent with reports that angiosarcoma is chemosensitive (7). However, this overall difference may be driven by the poor survival of patients treated with best supportive care and must be interpreted carefully. The specific reason for chemotherapy not being prescribed is unknown, however could be related to baseline comorbidities or

performance status of patients in our cohort. Thus, ongoing advocacy and education may be required to increase systemic therapy uptake and its tolerability in patients.

Although not statistically significant, OS was higher among patients treated with first line taxane versus first line doxorubicin by 18 months. However, this difference must be interpreted with caution given the small number of patients treated with chemotherapy in this cohort. Additionally, more than half of taxane treated patients (8/15) had cutaneous angiosarcoma, for which higher response rates to paclitaxel have been reported (5,19). The equipoise between taxanes and anthracyclines seen in our cohort is reflected in previously published retrospective series (5,7,9). Due to smaller than expected number of patients treated with chemotherapy, we were unable to confidently determine the impact of sequencing systemic therapy on outcome (i.e. PFS2). Future studies of large cohorts of patients treated with chemotherapy across multiple institutions could evaluate the impact of first line treatment on subsequent chemotherapy responsiveness (PFS2). Such studies would be helpful to determine if there is an optimal first line treatment for angiosarcoma.

In total, using the strength of a large provincial database over several decades, our study supports that multi-disciplinary care is key to improved survival of patients with angiosarcoma. In our cohort, surgery, chemotherapy, and importantly, radiation therapy all improve OS. This data encompasses multiple treating centers (academic and community) within a province providing universal health care and access to evidence-based therapies.

This study has limitations. As a retrospective cohort over several decades, pathological expertise and diagnosis of angiosarcoma improved over time, as such there is potential for under-reporting of angiosarcoma from earlier decades. Fortunately, BC conducts a central pathology review and all of our cases were reviewed at the time of diagnosis. The presence of a central pathology review report on the electronic medical record confirms a sarcoma expert reviewed each case. Additionally, usage of chemotherapy and radiation therapy was first noted in 1992 for our cohort, thus our results remain valid for the impact of systemic and radiotherapy. As a passive cancer registry, the registry may not identify all cancer cases, as non-registry personnel may not be familiar with all reporting criteria. Lastly, we were unable to capture all individuals treated with agents funded by mechanisms other than BC Cancer, such as private drug insurance and self-pay options. A manual chart review of all cases was undertaken to identify systemic therapy accessed through non-public mechanisms to address this limitation. Finally, given the limited sample size and the number of variables of interest, a multivariate analysis was not performed as it was unlikely that we would be able to control for confounding factors without over fitting the model. Despite these limitations, the impact on our final results are minimal and we anticipate no changes in our outcomes.

In conclusion, this study identified that upfront surgical resection remains the most important predictor of OS in patients affected by angiosarcoma. Unlike other published cohorts, both radiotherapy and chemotherapy statistically improved OS compared to best supportive care. There was equipoise between outcomes of patients treated taxanes versus non taxane chemotherapy within our cohort. Though challenging, more research is needed with large cohorts of patients to better understand the sequencing of taxanes and anthracyclines in this population.

Acknowledgements

Not applicable.

Funding

The present study was supported by institutional funds provided by the BC Cancer, for maintenance of the Sarcoma Outcomes Unit.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ASm, and ASr conceived the present study. ASm collected the data. AK collected the data and reviewed cases of radiation-induced angiosarcoma to determine if they arose with a previously irradiated field. ASm, ASr and JH designed the statistical analysis. ASm, ASr wrote the manuscript. JH performed statistical analysis. ASm, AK, CS, ASr interpreted the data and revised the manuscript for intellectual content. All authors read and approved the manuscript.

Ethics approval and consent to participate

The British Columbia Cancer Agency Ethics Board and Privacy Office approved the present study prior to commencement (University of British Columbia, BC Cancer Research Ethics Board; approval no. H17-02826). Consent was not obtained from individual patients; however, all patient information was anonymized and de-identified by the investigators for analysis.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Linch M, Miah AB, Thway K, Judson IR and Benson C: Systemic treatment of soft-tissue sarcoma-gold standard and novel therapies. Nat Rev Clin Oncol 11: 187-202, 2014.
2. Young RJ, Brown NJ, Reed MW, Hughes D and Woll PJ: Angiosarcoma. Lancet Oncol 11: 983-991, 2010.
3. Penel N, Bui BN, Bay J-O, Cupissol D, Ray-Coquard I, Piperno-Neumann S, Kerbrat P, Fournier C, Taieb S, Jimenez M, *et al*: Phase II trial of weekly paclitaxel for unresectable angiosarcoma: The ANGIOTAX Study. J Clin Oncol 26: 5269-5274, 2008.
4. Schlemmer M, Reichardt P, Verweij J, Hartmann J, Judson I, Thyss A, Hogendoorn PC, Marreaud S, Van Glabbeke M and Blay JY: Paclitaxel in patients with advanced angiosarcomas of soft tissue: A retrospective study of the EORTC soft tissue and bone sarcoma group. Eur J Cancer 44: 2433-2436, 2008.

5. Italiano A, Cioffi A, Penel N, Levra MG, Delcambre C, Kalbacher E, Chevreau C, Bertucci F, Isambert N, Blay JY, *et al*: Comparison of doxorubicin and weekly paclitaxel efficacy in metastatic angiosarcomas. Cancer 118: 3330-3336, 2012.
6. Buehler D, Rice SR, Moody JS, Rush P, Hafez GR, Attia S, Longley BJ and Kozak KR: Angiosarcoma outcomes and prognostic factors: A 25-year single institution experience. Am J Clin Oncol 37: 473, 2014.
7. Penel N, Italiano A, Ray-Coquard I, Chaigneau L, Delcambre C, Robin YM, Bui B, Bertucci F, Isambert N, Cupissol D, *et al*: Metastatic angiosarcomas: Doxorubicin-based regimens, weekly paclitaxel and metastasectomy significantly improve the outcome. Ann Oncol 23: 517-523, 2011.
8. Fury MG, Antonescu CR, Van Zee KJ, Brennan ME and Maki RG: A 14-year retrospective review of angiosarcoma: Clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J 11: 241-247, 2005.
9. Skubitz KM and Haddad PA: Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. Cancer 104: 361-366, 2005.
10. Pawlik TM, Paulino AF, Mcginn CJ, Baker LH, Cohen DS, Morris JS, Rees R and Sondak VK: Cutaneous angiosarcoma of the scalp: A multidisciplinary approach. Cancer 98: 1716-1726, 2003.
11. Abraham JA, Hornicek FJ, Kaufman AM, Harmon DC, Springfield DS, Raskin KA, Mankin HJ, Kirsch DG, Rosenberg AE, Nielsen GP, *et al*: Treatment and outcome of 82 patients with angiosarcoma. Ann Surg Oncol 14: 1953-1967, 2007.
12. Sher T, Hennessy BT, Valero V, Broglio K, Woodward WA, Trent J, Hunt KK, Hortobagyi GN and Gonzalez-Angulo AM: Primary angiosarcomas of the breast. Cancer 110: 173-178, 2007.
13. Mark RJ, Poen JC, Tran LM, Fu YS and Juillard GF: Angiosarcoma: A report of 67 patients and a review of the literature. Cancer 77: 2400-2406, 1996.
14. Weidema ME, Flucke UE, van der Graaf WTA, Ho VKY, Hillebrandt-Roeffen MHS; Dutch Nationwide Network and Registry of Histo- and Cytopathology (PALGA)-Group, Versleijen-Jonkers YMH, Husson O and Desar IME: Prognostic factors in a large nationwide cohort of histologically confirmed primary and secondary angiosarcomas. Cancers (Basel) 11: E1780, 2019.
15. Bonvalot S, Rivoire M, Castaing M, Stoeckle E, Le Cesne A, Blay JY and Laplanche A: Primary retroperitoneal sarcomas: A multivariate analysis of surgical factors associated with local control. J Clin Oncol 27: 31-37, 2009.
16. Le Cesne A, Ouali M, Leahy MG, Santoro A, Hoekstra H, Hohenberger P, Van Coevorden F, Rutkowski P, Van Hoesel R, Verweij J, *et al*: Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: Pooled analysis of two STBSG-EORTC phase III clinical trials. Ann Oncol 25: 2425-2432, 2014.
17. Gronchi A, Vullo SL, Colombo C, Collini P, Stacchiotti S, Mariani L, Fiore M and Casali PG: Extremity soft tissue sarcoma in a series of patients treated at a single institution: Local control directly impacts survival. Ann Surg 251: 506-511, 2010.
18. Young R, Natukunda A, Litière S, Woll P, Wardelmann E and Van Der Graaf W: First-line anthracycline-based chemotherapy for angiosarcoma and other soft tissue sarcoma subtypes: Pooled analysis of eleven European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trials. Eur J Cancer 50: 3178-3186, 2014.
19. Fata F, O'Reilly E, Ilson D, Pfister D, Leffel D, Kelsen DP, Schwartz GK and Casper ES: Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer 86: 2034-2037, 1999.