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Synovial sarcoma: The influence of clinicopathological variables on overall survival in a UK population

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ABSTRACT

Introduction: Synovial sarcoma accounts for 5%–10 % of malignant soft-tissue tumours. Curative treatment includes surgery, with radiotherapy and/or chemotherapy. With no specific treatment regimen for synovial sarcoma, the primary aim of this research was to describe the characteristics of a regional synovial sarcoma population in the UK, and to investigate clinicopathological variables associated with overall survival.

Methods: Ninety-four patients with synovial sarcoma from the East Midlands Sarcoma Service database were pseudo anonymised and clinicopathological variables extracted. Kaplan-Meier and Cox regression statistical analyses were used to identify variables affecting overall survival.

Results: Mean age at diagnosis was 42 years (range 8–83 years). Over half (n = 50, 53 %) of patients had a tumour in the lower limb. Thirty-seven (39.6 %) had a tumour size of <5 cm. Sixteen (17 %) patients had local recurrence, and under half (n = 40, 43.5 %) developed metastatic disease. Most patients (n = 63, 63 %) were initially treated with surgery. The majority (n = 58, 61.7 %) had a monophasic subtype, and the overall survival of the whole cohort was 83 months (95 % CI 39.1–127.8). Increasing tumour size and distant recurrence (metastasis) had a significantly negative impact on median overall survival ($p = 0.0001$). Patients who underwent surgery and radiotherapy had a significantly better median overall survival ($p = 0.02$). Multivariable analysis identified adjuvant radiotherapy ($p = 0.039$), lower limb tumour ($p = 0.033$), and tumour size (<5 cm $p = 0.006$, 5–10 cm $p = 0.0001$, >10 cm $p = 0.013$) as significant survival predictors.

Conclusion: Adjuvant radiotherapy is a novel independent prognostic marker for synovial sarcoma.

1. Introduction

There are over 80 subtypes of soft tissue sarcomas (STS), characterised by mesenchymal tissue and divided into groups based on genetics, pathology, anatomical location and clinical behaviour [1]. One such subtype is synovial sarcoma (SS) accounting for 6–9% of soft tissue sarcomas (STS) and despite the name, not derived from synovial tissue. SS commonly presents in the extremity of young adults, with approximately equal prevalence in males and females, and typically seen in the third and fourth decade of life [1]. It presents as a slow growing painful or painless mass, normally found in the extremities, but in rare cases originating in the head, neck, thorax and abdomen [2]. SS can be identified in histological terms as monophasic, biphasic, and poorly differentiated. It is considered to be a high-grade STS [3] characterised by the presence of the pathognomonic t (*X*;18) (p11.2; q11.2) translocation, involving a fusion of the *SS18* (formerly *SYT*) gene on chromosome 18 to one of the SS *X* (*SSX*) genes on chromosome *X* (usually *SSX1* or *SSX2*), seen with more than 90 % of SS resulting in the formation of *SS18* - *SSX* fusion oncogenes [4].

In the past, all STS subtypes were treated with surgery and (neo) adjuvant radiotherapy with little consideration of pathological subtypes [3]. In the treatment of adults with STS *per se*, the aim is to

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completely excise the tumour leaving a margin of normal tissue, preventing local recurrence (LR), minimising morbidity and maximising function [3,5]. This has been the subject of much discussion with no definitive definition of "safe" margin in STS, but in some sarcoma pathologies, for example, myxoid liposarcoma, a planned positive margin with adjuvant radiotherapy had a similar outcome to a negative margin resection, together with a lower rate of recurrence [6,7].

The use of radiotherapy alone in adult STS is unusual, and mainly used for the reduction of large tumours that are considered unresectable. However, neoadjuvant radiotherapy, although associated with an increased likelihood of achieving a negative surgical margin prior to surgery for STS, may not be achieved. Neoadjuvant radiotherapy can also be responsible for post-operative wound complications such as skin atrophy, soft tissue fibrosis and microvascular damage leading to non-healing wounds not amenable to surgical repair [8,9]. Furthermore, chemotherapy used in an adjuvant or induction fashion has yet to be demonstrated as an effective treatment of adult STS [3]. In the UK, chemotherapy is mainly used following multidisciplinary team discussion for individual cases where high grade tumours are considered borderline resectable in the hope of improving negative margins but can also be used in palliative care [4].

Conversely, paediatric and adolescent SS are treated as a chemosensitive, non-rhabdomyosarcomatous tumours with designed treatment protocols [10]. However, the use of radiotherapy can be utilized in the treatment of paediatric SS to reduce the rate of LR if local control cannot be achieved by surgery alone [11].

Despite The European Society for Medical Oncology (ESMO) guidelines [12] suggesting that all adult STS should be managed alike, gaps in research into the treatment of specific histological types of STS remain, and a definitive treatment protocol for the optimal treatment of SS alone has yet to be determined. Therefore, this research aims to determine which clinicopathological variables are associated with local recurrence and overall survival.

2. Methods

A retrospective observational study was undertaken, where 94 patients with SS were identified from the East Midlands Sarcoma Service database, (a clinicopathological database, maintained by the clinicians who run the service) between 1990 and 2018. Variables associated with clinicopathology, treatment and demographics were extracted, coded using SPSS [13] and saved on a secure server. Due to the historical nature of this database, not all data, such as translocation analysis was available for collection, and therefore unable to be included in this research. Ethical approval was gained from the Confidential Advisory Group and the Health Research Authority (project ID 260719). The *Kaplan-Meier* method and the log rank test were used to estimate overall survival (OS) with radiotherapy, chemotherapy, size, initial treatment modality, local recurrence, and distance recurrence as independent variables. For the purposes of reliable statistical analysis, patients who had distant recurrence at diagnosis were excluded from the analysis of radiotherapy. The reason for this is to create credible results due to radiotherapy mainly being used for local control and patients with distant recurrence being treated with a different treatment regime. Moreover, patients presenting with distant recurrence were included in all other analysis of overall survival providing a more accurate and unbiased assessment of survival outcomes in the chosen variables. Wherever multiple comparisons were made in univariate analyses, a Bonferroni correction was performed to avoid Type I error inflation. Missing data, where it occurred was assumed to be missing at random.

Multivariable analysis was used, calculated by Cox Regression to identify the impact of categorical variables: site, size, chemotherapy, radiotherapy, subtype, and local recurrence on OS. The chosen variables were either found to be significant in univariate analysis or, found to be variables of interest based on other research studies, and/or clinical practice. Hazard ratios (HR) and 95 % confidence intervals (95 % CI) were ascertained, and statistical significance, unless otherwise stated, was set at $p < 0.05$. Where three or more multiple comparisons were made, Bonferroni Correction was performed, and the alpha value adjusted to account for the number of comparisons being tested. The data collected were stored in compliance with General Data Protection Regulation (GDPR).

3. Results

3.1. Cohort characteristics

The cohort characteristics are set out in Table 1 and Fig. 1 (due to rounding of percentages, numbers may not always equal 100 %).

Mean follow up was 70 months (SD60.22). Due to low prevalences, the 28 (29 %) patients who had a tumour located in non-extremity extremity sites were grouped together for the statistical analysis. Gender distribution in this cohort was approximately equal, with 45 (49 %) females and 48 (51 %) males. The mean age of the cohort was 42 years (SD20.82). Eighty (85 %) patients were aged between 19 and 90 years, and 11 (12 %) patients aged below 18 years (Fig. 1). Fifty-eight (62 %) patients had a monophasic subtype, which had a higher prevalence than the biphasic subtype (20 patients, 21 %). Two patients (2 %) had a spindle cell (SC) subtype, and three (3 %) patients had a not otherwise specified subtype (NOS).

Thirty (37 %) patients had a tumour size less than 5 cm, 29 (31 %) patients had a tumour measuring between 5 and 10 cm, and 25 (26 %) patients had a tumour measuring greater than 10 cm (Fig. 1A).

Surgery was the initial treatment for 63 (63 %) patients. Twenty-

Table 1
– Cohort characteristics.

Characteristics	Number (n)	Percent (%)
Gender		
Male	48	51.1 %
Female	45	47.9 %
Missing data	1	1 %
Subtype		
Monophasic	58	61.7 %
Biphasic	20	21.3 %
Not otherwise specified (NOS)	3	3.2 %
Spindle cell	2	2.1 %
Missing data	11	5.7 %
Site		
Head and neck	5	5 %
Trunk wall	5	5 %
Retroperitoneal	1	1 %
Upper limb	14	14.9 %
Lower limb	50	53.2 %
Thoracic	17	18.1 %
Missing data	2	2.8 %
Size		
<5 cm	37	36.6 %
5–10 cm	29	31.3 %
>10 cm	25	26 %
Missing data	3	1 %
Recurrence		
Local recurrence	16	17 %
Distant recurrence	40	43.5 %
Metastasis at diagnosis	9	9.8 %
Missing data	29	23.7 %
Initial modality of treatment		
Surgery	63	63 %
Chemotherapy	18	19 %
Radiotherapy	09	10 %
Missing data	4	2 %
Peri-surgical treatment		
Adjuvant radiotherapy	25	26.6 %
Induction radiotherapy	14	14.9 %
No radiotherapy	47	50 %
Pre-operative chemotherapy	13	13 %
Post-operative chemotherapy	13	13 %

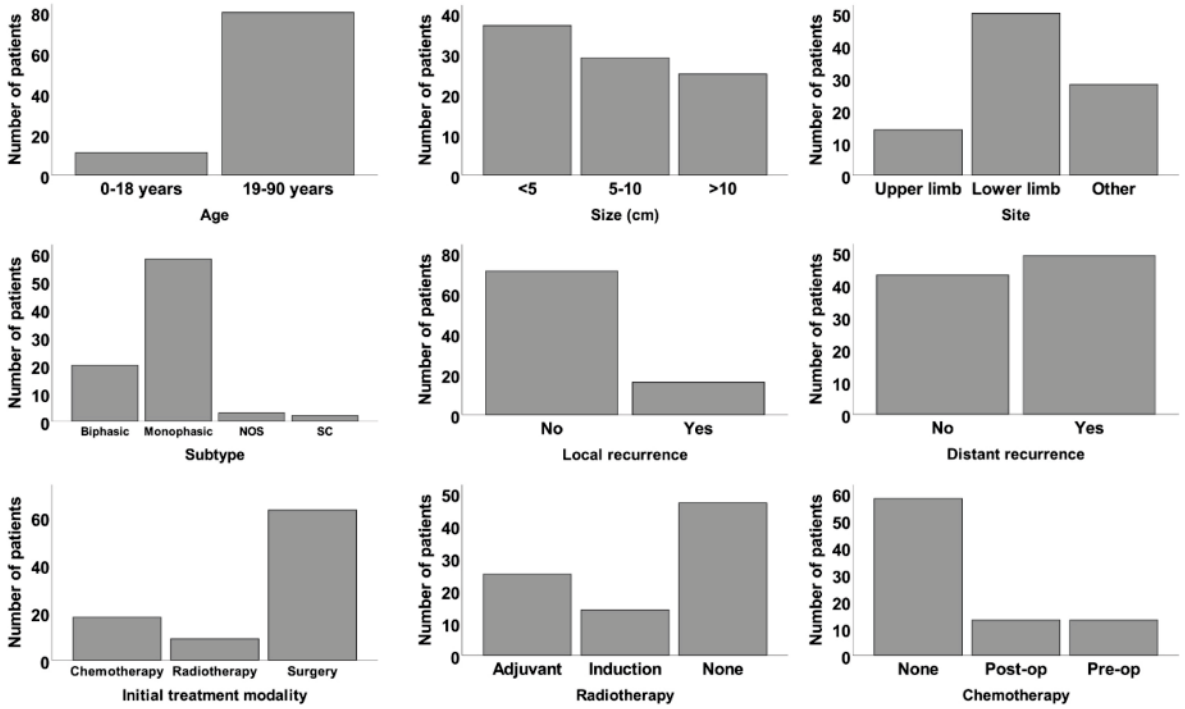

Fig. 1. Bar charts illustrating cohort characteristics including treatment modalities and patients with local or distant recurrence.

seven (29 %) patients had either chemotherapy (n = 18, 19 %), or radiotherapy (n = 9, 10 %) as their initial treatment (Fig. 1). Twenty-six (28 %) patients had peri-surgical chemotherapy, with 13 (14 %) patients receiving pre-operative and 13 (14 %) receiving post-operative chemotherapy. Thirty-nine (42 %) patients underwent radiotherapy, with fourteen (15 %) receiving induction radiotherapy, and twenty-five (27 %) receiving adjuvant radiotherapy (Fig. 1).

A total of 16 (17 %) patients had a local recurrence (LR), with mean time to local recurrence being 42 months (SD51.50). Six patients had a LR (38 %) in the lower limb, four (25 %) upper limb, five (31.3 %) thoracic region, and one (6.3 %) in the head and neck. Distant recurrence occurred in 48 (44 %) patients. Nine (10 %) of these had a distant recurrence at diagnosis. The mean time to distant recurrence was 26 months (SD43.21). Half (n = 8, 50 %) of all patients that had LR received adjuvant radiotherapy. Three (19 %) patients received induction radiotherapy, and five (31 %) patients did not receive any radiotherapy. Most patients (n = 12, 75 %), who had a LR did not receive chemotherapy, whilst two (13 %) patients underwent post-operative chemotherapy, and one (6 %) patient underwent pre-operative chemotherapy. Out of the 16 (17 %) patients who had a LR, eight (50 %) had a monophasic subtype, three (19 %) had a biphasic subtype, and two patients (13 %) had a NOS subtype. Six (38 %) patients who had a LR had a tumour size <5 cm, five patients (31 %) had a tumour size >10 cm, and four (25 %) had a tumour measuring between 5 and 10 cm in size (Fig. 1).

The median overall survival of the whole cohort was 83 months (95 % CI 39.1–127.8, Fig. 2). The probability of survival at five years (60 months) was approximately 55 % and the probability of survival at ten years (120 months) approximately 35 %. Overall, our descriptive analysis shows that our regional UK cohort is congruent with other published datasets [14,15].

3.2. The role of clinicopathological variables on overall survival

Univariate Kaplan-Meier survival analysis was performed using the clinical variables: induction radiotherapy, adjuvant radiotherapy, chemotherapy; initial treatment, size of tumour, and local and distant recurrence. These variables are known from clinical practice and/or the literature to effect survival and were used to further validate our cohort (Fig. 3).

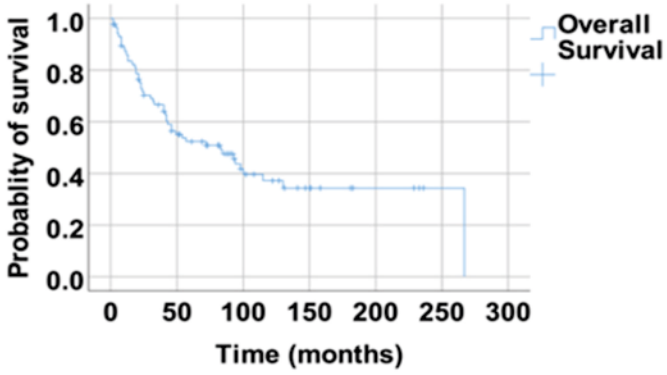

Fig. 2. Overall survival of the cohort. The median overall survival of the whole cohort was 83 months (95 % CI 39.1–127.8, Fig. 2). The probability of survival at five years (60 months) was approximately 55 % and ten years (120 months) approximately 35 %.

The median OS for patients without a LR was 94 months (95 % CI 35.4–153.6), for patients with a LR it was 83 months (95 % CI 38.2–128.2). Although not significant in this cohort, it should be noted the proportional hazard assumption is violated ($p = 0.603$) (Fig. 3A). The mean time to local recurrence was approximately 42 months, after which the Kaplan-Meier curves separate, indicating a worse prognosis for those with a local recurrence. As predicted, patients who had a distant recurrence, had a significantly poorer median OS time of 40 months compared to those who did not (95 % CI 19.2–61.1, $p = 0.0001$, Fig. 3B), with the mean time to distant recurrence being approximately 24 months. Patients had a significantly declining probability of survival with increasing size of tumour ($p = 0.0001$, Fig. 3C). Patients also had a significantly greater probability of survival when surgery was the initial treatment with a median OS of 94 months (CI 63.3–125.7, $p = 0.011$, Fig. 3D). This is quite likely due to the fact that the patients with distant

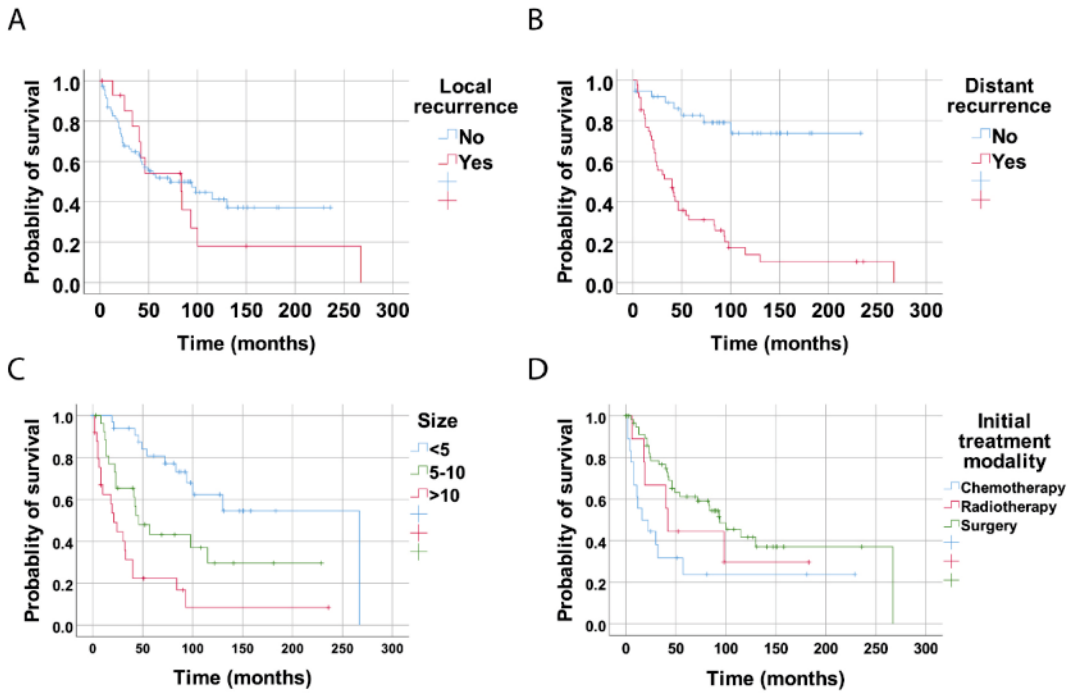

Fig. 3. Probability of survival of patients with(A) local recurrence, (B) distant recurrence, (C) size of lesion and (D) initial treatment modality. When comparing three or more groups, Bonferroni correction was made where $\alpha = 0.017$.

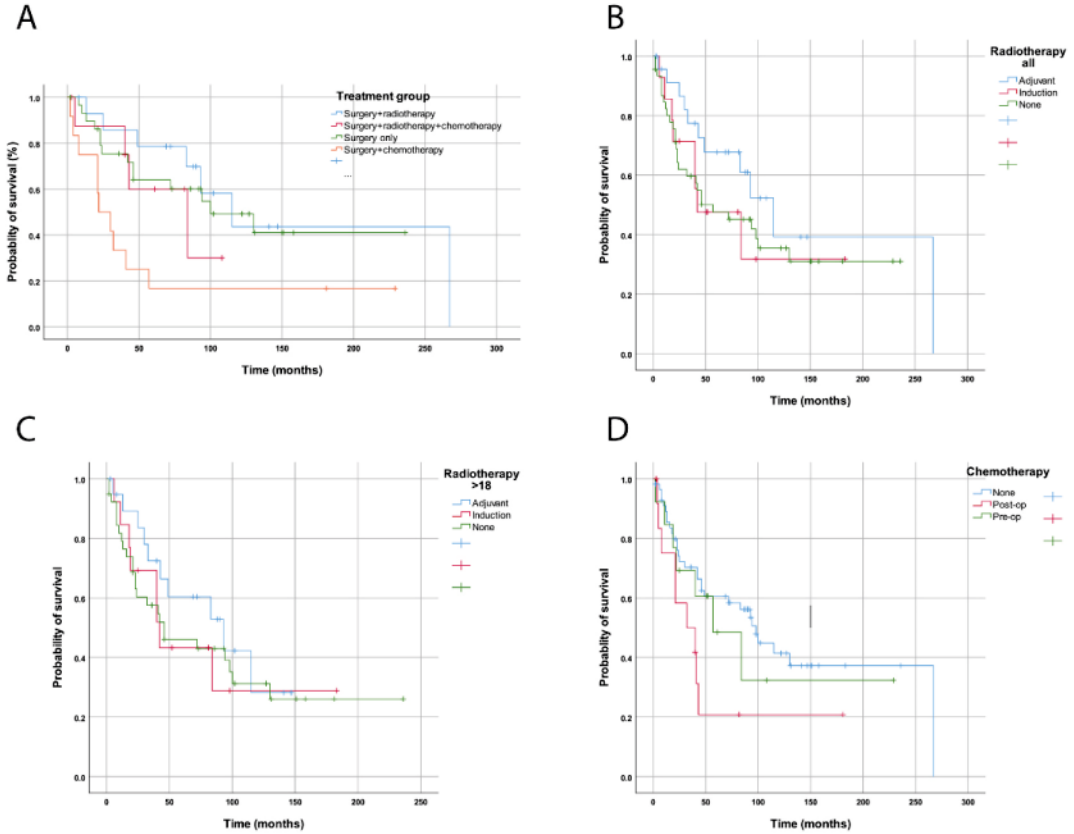

Fig. 4. Probability of survival of (A) – the different treatment groups within our cohort ($p = 0.020$). (B) All patients receiving radiotherapy ($p = 0.367$). C – patients >18 years receiving radiotherapy ($p = 0.630$). D- patients receiving chemotherapy ($p = 0.093$). When comparing three or more groups, Bonferroni correction was made where $\alpha = 0.017$ (three groups) or $\alpha = 0.0125$ (four groups).

recurrence and larger tumours are the patients who are most likely to receive chemotherapy and/or preoperative radiotherapy. Overall, these findings support the current clinical best practice to initially surgically treat STS; however, a more nuanced analysis of synovial sarcoma treatment modalities is warranted given the lack of literature and consensus on treatment for specific STS subtypes.

3.3. The role of synovial sarcoma treatment modalities on overall survival

A more nuanced analysis of the different treatment regimens used within our cohort was undertaken to gain further insight into the prognostic factors of synovial sarcoma. Patients treated with surgery and radiotherapy had a median OS of 115 months (95 % CI 66.0–165.1) (Fig. 4). This is greater than for patients treated with surgery alone (n = 30, 32 %), (OS of 100 months, 95 % CI 38.2–162.8). Patients treated with surgery, radiotherapy, and chemotherapy (n = 9, 10 %) had a median OS of 84 months (95 % CI 22.2–146.1). For patients who had surgery and chemotherapy (n = 12, 13 %) the median OS was poor at 22 months (95 % CI 6.8–37.2) (Fig. 4).

Patients treated with induction, or no radiotherapy had a similar probability of survival (Fig. 4B). Patients who underwent adjuvant radiotherapy (n = 25, 27 %) may have improved survival outcomes when compared to patients who underwent induction (n = 14, 15 %) or no radiotherapy (n = 47, 50 %); median OS 115 months (95 % CI 72.8–157.3), compared with 42 months (95 % CI .00–92.0) and 57 months (95 % CI 5.8–108.2) respectively ($p = 0.367$). Although this finding was not significant in this cohort ($p = 0.367$), further evaluation with a larger cohort is recommended. Eleven patients aged <18 years were subsequently excluded from statistical analysis which determined that the treatment results with adjuvant radiotherapy remained consistent (Fig. 4C). Patients receiving no, or pre-operative chemotherapy had a higher median OS (98 months (95 % CI 76.2–120.8) than patients receiving post-operative, probably palliative chemotherapy (Fig. 4D).

3.4. Multivariable analysis – analysing overall survival

Size of tumour and distant recurrence (significant in univariate analysis) were used in multivariable analysis together with other factors pertinent from the literature (chemotherapy, radiotherapy, tumour site, local recurrence and subtype). In Table 2, the first group listed for a variable was the baseline comparator. For tumour size, the '5–10 cm' group was chosen because this group could have had *all* treatments, surgery, radiotherapy and chemotherapy. The multivariable analysis revealed adjuvant radiotherapy ($p = 0.039$), *tumour* size ($p = 0.0001$), lower limb (site of tumour) ($p = 0.033$)and *other* (sites of tumour) ($p = 0.039$) as significant independent prognostic factors for synovial sarcoma (Table 2).

Table 2
Multivariable analysis of the cohort.

Variable	Sub-variable	Sig.	Exp (B) (95 % CI)
Radiotherapy	none	.087	–
	adjuvant	.039	.341 (.123–.947)
	induction	.208	.392 (.092–1.682)
Chemotherapy	none	.564	–
	Pre op	.933	.946 (.259–3.455)
	Post-op	.446	1.599 (.477–5.356)
Local recurrence		.448	.657 (.222–1.944)
Subtype	monophasic	.123	.264 (.049–1.437)
	biphasic	.130	.197 (.024–1.611)
	Other	.290	–
Site	Upper limb	.402	.613 (.195–1.927)
	Lower limb	.033	2.425 (1.077–5.463)
	other	.039	.341 (.123–.947)
Size	5–10 cm	.000	- -
	<5 cm	.006	.257 (.098–.676)
	>10 cm	.013	4.120 1.344–12.631)

4. Discussion

Our results show that tumour site, size, distant recurrence are negative prognostic factors, whilst adjuvant radiotherapy and the treatment of surgery and radiotherapy positively influence the OS of patients with SS. The OS of this cohort was comparable to other research, therefore validating the findings [14,15]. In this cohort, the mean age of diagnosis was 42 years, comparable to previous research [16–19]. Increasing age has previously shown to be a predictor of poor OS so was not included in this analysis [4,20–24]. Gender did not show a clear impact on OS, and the lack of data on fusion type precluded this being addressed in detail. However, it did determine that the monophasic subtype was more commonly found [25,26]. Significant findings in both univariate and multivariable analysis, illustrate a declining probability of survival with increasing size of tumour, with the lower limb being the most common site of tumour, validating the results in keeping with previous research [1,15,18,19,22,24,25,27–29].

The mean time to local recurrence was 3.5 years [19]. Distant recurrence was found to be significant in univariate analysis with time to distant recurrence being 2 years with a significant negative impact on OS. Nine patients had distant recurrence at diagnosis, a predictive factor of poor outcome [19]. Sixteen patients had a local recurrence, and half of those patients had received adjuvant radiotherapy, possibly to reduce surgical margins [30,31] although this data was not collected.

Analysis in this research showed a declining probability of survival with both local and distant recurrence after resection, in line with other research [19,6,32,33]. One omission was the lack of information available for collection on the status of surgical margin. The significance of a suitable surgical margin has previously been debated [6,7,34], and this could have facilitated further in-depth statistical analysis and implications on both local and distant recurrence on survival.

The use of chemotherapy in STS in adults remains controversial due its toxicity and limited impact on survival. Some research suggests a benefit of chemotherapy for OS of local and distant recurrence [1,27,35,36,13]. The current research shows the median OS for patients who had no, or pre-operative chemotherapy was 60 % at 5 years, better than patients who had post-operative chemotherapy whose median OS was only 20 %. Specific chemotherapy drug regimens were not collected as part of the data collection. Further data could be collected and analysed for significance across larger multi-regional cohorts.

Surgery, as an initial treatment of SS, was a significant finding in univariate analysis. Further analysis into the outcome of specified treatment groups for SS, 'surgery' alone, 'surgery and radiotherapy', 'surgery, chemotherapy and radiotherapy' and 'surgery and chemotherapy' were not significant when Bonferroni correction was used. Further research using a larger sample size may clarify this further.

As far back as the 1950's, adjuvant radiotherapy was shown to be useful in the treatment of SS [37]. The use of adjuvant radiotherapy was a significant finding in multivariable analysis, comparable to previous research [27,32,38]. Moreover, the shift from adjuvant to preoperative radiotherapy is due to a better focusing of treatment and a reduced dose to avoid late complications. However, this does not reduce early wound complications, which are more frequent after preoperative radiotherapy [39]. Reduced toxicity of pre-operative radiotherapy may be of more benefit to the patient due to late radiation toxicity of post-operative radiotherapy [40].

The margin status, specific doses of radiotherapy or chemotherapy, and information on translocation was not available for data collection, which could have facilitated further comprehensive analysis. Moreover, a larger cohort could have facilitated multivariate logistic regression analysis to build a predictive model (nomogram) to be used in practice [41]. However, the findings from our research providing the first multivariable analysis of such variables in a UK population reveals that adjuvant radiotherapy is a significant independent prognostic marker in

the treatment of SS, alongside the site and size of tumour.

Despite much discussion of the benefits and disadvantages of adjuvant radiotherapy, and variety of inconsistent conclusions thus far, there is still no definitive treatment of SS, and therefore further research is needed with a larger cohort to validate these findings.

5. Conclusion

Our regional UK cohort is synonymous with other reported SS cohorts. We confirm that the site and the size of the tumour are determiners of OS. Local and distant recurrence also decrease OS in patients with SS. However, our most interesting and novel finding is that adjuvant radiotherapy, even in comparison with induction radiotherapy, is an independent prognostic marker for SS.

CRediT authorship contribution statement

Bill Robertson-Smith: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jackie Campbell:** Writing – review & editing, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Karen Anthony:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Thomas A. McCulloch:** Writing – review & editing, Visualization. **Robert U. Ashford:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Data statement

Due to ethical issues, the data underpinning this publication cannot be made openly available.

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