Primary Retroperitoneal Sarcoma: A Comparison of Survival Outcomes in Specialist and Non-Specialist Sarcoma Centres

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Abstract

Background: Consensus guidelines outline that patients with primary retroperitoneal sarcoma (RPS) should be managed within specialist sarcoma centres (SSC). There is, however, a paucity of population-based data detailing incidence and outcomes in these patients. Hence, we aimed to evaluate patterns of care among RPS patients in England and compare outcomes for those undergoing surgery in high-volume specialist sarcoma centres (HV-SSC), low-volume SSC (LV-SSC) and non-SSC (N-SSC).

Methods: Data on patients diagnosed with primary RPS between 2013 and 2018 were extracted from NHS Digital's National Cancer Registration and Analysis Service using the national cancer registration dataset. Diagnostic pathways, treatment and survival outcomes were compared between HV- and LV-SSC and N-SSC. Uni- and multivariate analyses were calculated.

Results: Of 1,878 patients diagnosed with RPS, 1,120 (60%) underwent surgery within 12 months of diagnosis, with 847 (76%) operated on at SSC, comprising 432 (39%) in HV-SSC and 415 (37%) in LV-SSC. One- and Five-year estimated OS rates for patients undergoing surgery in N-SSC were 70.6% (95% confidence interval [CI]: 64.8-75.7) and 42.0% (CI: 35.9-47.9), compared to 85.0% (CI: 81.1-88.1) and 51.7% (CI: 46.6-56.6) in LV-SSC ($p<0.01$) and 87.4% (CI: 83.9-90.2) and 62.8% (CI: 57.9-67.4) in HV-SSC, ($p<0.01$). After adjusting for patient- and treatment-related factors, patients treated in HV-SSC were found to have significantly longer OS than those treated at LV-SSC, with an adjusted hazard ratio of 0.78 (CI: 0.62-0.96, $p<0.05$).

Conclusions: Patients with RPS undergoing surgery in HV-SSC have significantly better survival outcomes than those treated in N-SSC and L-SSC.

Introduction

Retroperitoneal sarcoma (RPS) is a rare disease which encompasses a group of different subtypes. Its heterogeneity influences the surgical strategy to be employed and the neo/adjuvant treatments administered [1-3]. Decisions regarding treatment are taken by balancing the oncological risks, the biological behaviour and the patterns of recurrence of the many and varied histotypes [4].

The complexity of the disease, in addition to its rarity, means optimal management of these patients is provided within specialist sarcoma centres (SSC). Although referring patients to SSC is strongly recommended by guidelines [5-7], the number of patients managed outside SSC in England is unknown and no direct comparison of outcomes for primary RPS patients operated on in SSC and non-specialist sarcoma centres (N-SSC) has been formally evaluated. In addition, it is currently unclear whether case-volume within SSC is associated with better survival outcomes.

The aim of this study was to evaluate patterns of care of patients diagnosed with primary RPS in England and compare outcomes for those undergoing surgery in SSC vs N-SSC, as well as to evaluate the association between survival outcomes in high-volume SSC (HV-SSC) and low-volume SSC (LV-SSC).

Methods

Data sources

Data on patients diagnosed with primary RPS between 2013 and 2018 were extracted from the National Cancer Registration Dataset (NCRD) [8].

The patient cohort and histological subtypes included were based on definitions from a previous Transatlantic Australasian Retroperitoneal Sarcoma Working Group publication [4]. Patients with well-differentiated liposarcoma (WDLPS), dedifferentiated/other liposarcoma (DDLPS), leiomyosarcoma (LMS) and "other" sarcoma were included. Other type of tumours, quality issues data, age that fell outside the range 15-99, and patients with multiple tumours were excluded.

Data about comorbidities were available and classified using the Charlson comorbidity index (CCI) [9]. Information about deprivation measures and route of diagnosis was also available [10]. Socioeconomic deprivation (SED) was measured by lower super output areas (LSOAs) of residence based on the income domain score of the English Indices of Multiple Deprivation. LSOAs were grouped into five SED quintiles, each containing 20% of the population of England. The least deprived quintile was labelled 1 and the most deprived 5. Patients were assigned to a socioeconomic deprivation quintile based on their postcode of residence at the time of diagnosis.

Definition and outcomes

In accordance with the 2019 NHS England Sarcoma Service Specification [11], SSC were defined as centres hosting a sarcoma multidisciplinary team (MDT) and providing diagnosis, treatment, and follow-up for sarcoma patients.

The analysis focused on patients who received surgery, and differences between patient characteristics, route of diagnosis, treatment allocation and survival outcomes were

calculated. The route of diagnosis included: standard GP referrals, emergency presentations, “Two weeks wait” (TWW), other outpatients, and inpatient electives/unknown. The TWW system is a fast-track referral made by the GP to a specific hospital for a suspected cancer, which obliges the hospital to see the referred patient within two weeks from the referral.

The primary outcome was overall survival (OS). SSC were divided according to the volume of surgery performed into HV-SCC, which operated on over 50% of the patients within SSC and the remaining centres as LV-SCC.

This retrospective cohort study was conducted using the “Strengthening the report of observational studies in epidemiology (STROBE)” guidelines [12].

Data for this study were collected and analysed under the National Disease Registries Directions 2021, made in accordance with sections 254(1) and 254(6) of the 2012 Health and Social Care Act. Further ethical approval for this study was not required per the definition of research according to the UK Policy Framework for Health and Social Care Research.

Statistics

Comparisons of cohort characteristics between SCC and N-SCC were performed using Mann-Whitney *U* test for patient age, and Fisher’s exact test for comorbidity, deprivation, route to diagnosis, histology, and sex. For survival analyses, the time at risk began at the date of diagnosis, and ended at death from any cause, with patients being censored after five years of follow-up or the end of the follow-up period on the 31st December 2021. Survival rates

were estimated using Kaplan-Meier curves, with comparisons between operated and non-operated patients, and across types of centre performed using univariate Cox regression models, using the Efron method of tie handling. Univariate analyses were also performed for a range of cohort characteristics, to identify other predictors of OS. A multivariate Cox regression model was then produced, to produce adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the comparison between types of centre. Initially, this treated N-SSC as the reference category; but the model was also repeated treating L-SSC as the reference, to allow comparison by the volume of specialist centres.

Statistical analyses were performed using Stata 15 (Station College, Texas TX; Computing Resource Centre, Santa Monica, CA). All hypothesis tests were two-sided, and conducted at the 5% level of significance.

Results

Patient characteristics

Between 2013 and 2018, 1,878 patients were diagnosed with primary RPS in England; the median age was 67 years (interquartile range [IQR]: 55 - 75). Among these, 1,120 (60%) underwent surgery with curative intent within 12 months of diagnosis, whilst the remaining 758 (40%) did not have surgery within 12 months. Distribution of different treatments according to age is presented in ***Figure 1A***.

Within the whole cohort of operated patients, the median age at the diagnosis was 63 years (IQR: 53-71) of whom 50% were male and 7% had a CCI $\geq$2. The most common histology was DDLPS + other LPS, affecting 429 patients. Patient characteristics are summarized in ***Table 1***

and 2. The majority of patients 847 (76%) received surgery at an SSC **(*Figure 1B*)**. The average number of patients treated with surgery at a SSC was 9 per year (range: 1-46). Over half of the operated patients were treated at one of the three highest-volume SSC (432 patients; 51%), with these centres operating on an average of 24 patients per year. These were all SSC, and were designated HV-SSC for analysis. The other 415 patients operated at SSC were operated on amongst the remaining 12 SSC, which performed an average of 6 cases per year (range: 1-13); these were designated as LV-SSC. The remaining 273 patients were treated at N-SSCs, which performed a mean of <1 resection per year (range: 0-4).

Of the 1,120 patients who underwent surgery, 10 were excluded from the survival analysis: 3 because of data quality issues, 6 because their age fell outside the range (15-99), and 1 because the patient had multiple tumours. Survival analysis was therefore performed on the remaining 1,110 patients, who had a median follow-up of 30 months (IQR: 6 – 66), with Kaplan-Meier estimated OS at one and five years of 82.4% (CI: 80.1-84.6) and 53.6% (CI: 50.5-56.6), respectively. The 758 patients who did not undergo surgery, 14 were excluded from the survival analysis: 3 because of data quality issues, 5 because their age fell outside the range (15-99), and 6 because the diagnosis was made post-mortem. The remaining 744 who did not undergo surgery had significantly shorter OS (p<0.01), with Kaplan-Meier estimated OS at one and five years of 39.8% (CI: 36.3-43.4) and 16.1% (CI: 13.5-18.9%), respectively **(*Figure 2*)**.

Comparison between SSC and N-SSC

There was no significant difference in terms of age (p=0.79), CCI (p=0.89), or deprivation index (p=0.65) between patients who had surgery in SCC and N-SSC. In contrast, the route of

diagnosis differed significantly between the two groups (p<0.01), with SSC having a higher proportion of GP referrals (34% vs. 23%) and a lower proportion of emergency admissions (10% vs. 20%) than N-SSC. Histological subtypes were also distributed differently between groups (p<0.01), with SSCs having a higher proportion of both DDLPS (42% vs. 27%) and WDLPS (15% vs. 3%) than N-SSC. Further details of the cohort are summarized in ***Table 1***.

Comparison between LV- and HV-SSC

The only significant difference between LV- and HV-SSC was tumour histology (p=0.01), with LV-SSC operating on less DDLPS + other LPS, and WDLPS compare to HV-SSC (39% vs 45% and 14% vs 17%, respectively), but more LMS and other (27% vs 24% and 21% vs 14%, respectively). A summary of the results is available in ***Table 2***.

Univariable analysis of outcomes by HV-SSC

Thirty-day crude postoperative mortality was significantly lower among patients who underwent surgery within HV-SSC compared to N-SSC, with rates of 1% vs. 5%, p<0.05, respectively. However, no significant difference was found between HV-SCC and LV-SSC, with the latter having a 30-day postoperative mortality rate of 2% (p=0.17).

Patients operated on at HV-SSC were found to have significantly longer OS, with one- and five-year estimated rates of 87.4% (83.9-90.2) and 62.8% (57.9-67.4) compared to 85.0% (81.1-88.1) and 51.7% (46.6-56.6) for those operated on in LV-SSC and 70.6% (64.8-75.7) and 42.0% (35.9-47.9) for those operated on in N-SSC, yielding a HR of 0.69 (95% CI 0.56-0.85; p<0.01) and 0.50 (95% CI 0.40-0.62; p<0.01), for LV-SSC and HV-SSC respectively when compared to N-SSC (***Figure 3***).

Multivariate analysis of outcomes by HV-SSC

Multivariate analysis was performed to assess whether the type of centre was an independent predictor of patient outcomes, after adjusting for potentially confounding factors. Analysis of OS found increasing age, male sex, morphology other than WDLPS, and emergency presentation to be associated with significantly shorter OS (***Table 3***). After adjusting for these factors, patients treated at SSC were found to have significantly longer OS than those treated a N-SSC, with adjusted HRs of 0.79 (95% CI: 0.63-0.98, $p<0.05$) for LV-SSC and 0.61 (95% CI: 0.48-0.77, $p<0.01$) for HV-SSC, compared to N-SSC. Within the SSC, patients treated at HV-SSC were found to have significantly longer OS than those treated at LV-SSC, with an adjusted HR of 0.78 (95% CI: 0.62-0.96, $p<0.05$).

Discussion

This is the first population-based study comparing outcomes between SSC and N-SSC for patients with primary RPS undergoing surgical resection in England. In addition, to the best of our knowledge, this is the only study analysing the association between case volume within SSC and survival outcomes. Our study demonstrated significantly better survival outcomes for patients who received treatment at SSC compared to N-SSC. Importantly, patients who underwent surgery within HV-SSC had significantly better 5-year OS than those operated on in LV-SCC, with surgery in a HV-SSC found to be an independent predictor of survival on the multivariate analysis.

The importance of managing sarcoma patients in SSC, irrespective of the site of origin, is well known [13,14]. Bonvalot et al. recently demonstrated significantly better oncological outcomes for RPS patients in France treated within SSC compared to those treated outside the NetSarc network [15]. Data from the European rare cancer initiative (Rare Cancer Europe) found patients managed within multidisciplinary tumour boards had better local recurrence and recurrence-free survival rates, and there was better compliance with clinical practice guidelines [16]. Given the rarity of RPS and the spectrum of biological behaviour within this tumour population, it is evident that the understanding of the disease provided by SSC, and the complexity of skills available within a specialist multidisciplinary team, will lead to improved outcomes for patients with RPS [17,18].

Other studies have analysed the association between survival outcomes in RPS patients and hospital case volume, using the latter as a surrogate to define SSC [19,20]. With the purpose of identifying a threshold to define a high-volume centre, Villano et al [21] identified 13 cases per year as a minimum threshold after which negligible survival benefits were observed. However, the demographics and treatment of patients differed significantly between the <13 and 13+ volume groups. In particular, the higher volume centres had more patients with higher grade/more undifferentiated tumours, which was likely to act as an important confounder, with potentially poorer outcomes in large centres that operated on the more complex/higher risk cases. In England, where over 50% of surgical resections were undertaken in the three largest centres with an average of 24 patients per year, a significantly better survival rates were observed compared to the 12 LV-SSC, with an average of 6 resections per year.

Improved survival outcomes in HV-SSC may be related to lower rates of R2 resection and tumour rupture, as previously demonstrated [22-24]. Another factor that may have contributed to better survival outcomes in SSC is the lower rate of postoperative mortality, which usually accounts for approximately 2% [25,26]. Our study showed that postoperative mortality was twice as high for patients treated at N-SSC compared to LV-SSC, and lower for patients treated within HV-SSC. This may be related to a higher percentage of patients presented as an emergency in N-SSC as well as surgeons' inexperience and worse management of elderly and frail patients [27]. Importantly, there was no significant difference in 30-day mortality between HV-SSC and LV-SSC. This may be related to a better failure-to-rescue in LV-SSC compared to N-SSC. In contrast, the improved long-term outcomes seen in the HV-SSC when compared to the LV-SSC may be attributable to a higher rate of recurrent disease in the latter with a histology driven, tailored oncological approach adopted in the HV-SSC likely to contribute to improved long term outcomes.

Despite guidelines and service specification' recommendations, up to 24% of patients are still managed outside SSC in England. Our results may suggest that when patients are referred to a N-SSC from a GP they may not be referred on to a SSC despite there being a clear mandate for this in national guidance. A proportion of patients however, likely unavoidably, underwent surgery in N-SSC after being admitted as an emergency. Nevertheless, it is important to highlight that the number of patients managed within SSC in England, thanks to the National Healthcare System and NICE-guidance, is probably one of the highest in the world.

Noticeably, 40% of patients did not receive radical surgery within a year of diagnosis, with a resultant very poor 5-year survival outcomes. A significant proportion of patients who did not undergo surgery were aged 75+ (***Figure 1***) and had more comorbidities (***Table 1***), with surgery undertaken in only 36% of cases in this specific subgroup. In addition, although staging data was not available, it is likely that a proportion of patients who did not receive surgery presented with metastatic disease. Nevertheless, it is also possible that some patients did not receive surgery because they were deemed inoperable at N-SSC or even at SSC. Further analysis is required to determine reasons for patients not undergoing curative resection, particularly to evaluate inequalities in care.

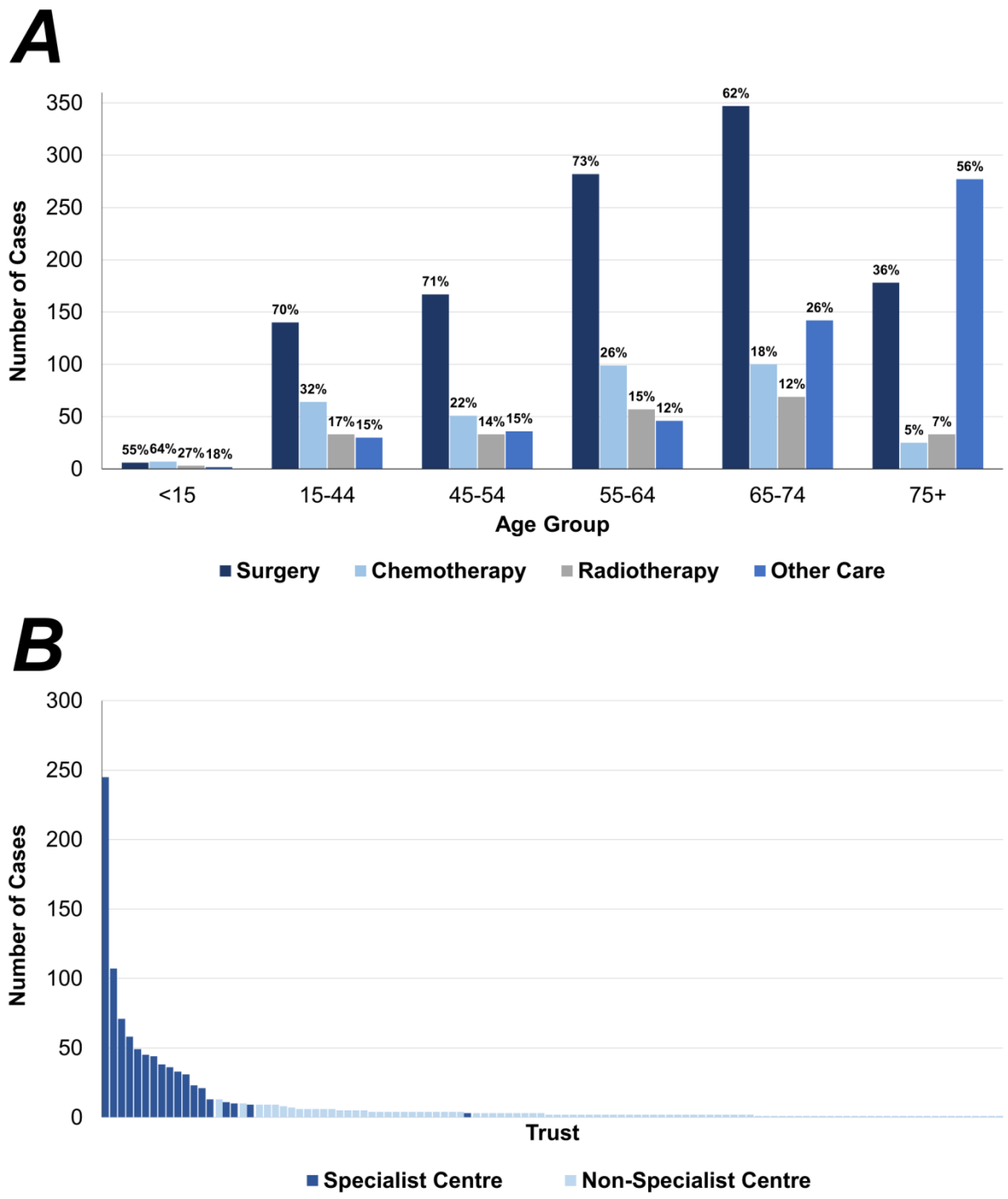
Several limitations must be acknowledged. First, it is a retrospective analysis. Second, data on stage and grade of tumours were not available and these have a significant impact on outcome. Other important data, such as rate of R2 resection, number of organs resected, and tumour rupture, were also unavailable, making our conclusions less robust. Nevertheless, the major strength of the study is the large sample size, due to the capability of the national cancer registration dataset to capture data for most patients with RPS with a high level of completeness and accuracy. It is important to highlight that our results are not necessarily generalizable to countries with a different healthcare system or patient demographic.

In conclusion, HV-SSC had significantly better survival outcomes compared to LV-SSC and N-SSC. The NHS England National Service Specification for Sarcoma recommends that centres should aim to perform at least 24 radical resections for primary RPS per annum [11] and our results provide evidence to fully support this recommendation. We acknowledge significant

challenges to implementing changes to NHS services, however, engagement with NHS England with input from the Regional Expert Advisory Groups is required to optimize the way care for RPS is organised.

Figures and tables

Figure 1 – A) Treatment received by patients with retroperitoneal sarcoma within the first 12 months from diagnosis according to age; B) Number of retroperitoneal sarcoma patients who underwent surgery by Trust from 2013 to 2018.



Data of patients who received chemo and/or radiotherapy in the preoperative setting or as a palliative treatment were not available and the use of chemo and/or radiotherapy was not mutually exclusive.

Table 1 – Patient Cohort characteristics and comparison between patient' characteristics in SSC and N-SSC

Factor	Non-Operated patients		Operated patients				
	N	Statistic	N	SSC	N	N-SSC	p-value
Age at Diagnosis (Years)	758	71 (IQR 60-80)	847	64 (IQR 53-71)	273	62 (IQR 52-72)	0.79
Sex (% Male)	396	52%	431	51%	124	45%	0.13
Ethnicity	758		847		273		0.58
White		662 (87%)		753 (89%)		239 (88%)	
BAME		96 (13%)		94 (11%)		34 (12%)	
Indices of Multiple Deprivation (IMD)	758		847		273		0.35
1 – most deprived		118 (16%)		121 (14%)		42 (15%)	
2		143 (19%)		143 (17%)		55 (20%)	
3		153 (20%)		201 (24%)		50 (18%)	
4		166 (22%)		192 (23%)		66 (24%)	
5 – least deprived		178 (23%)		190 (22%)		60 (22%)	
Charlson Comorbidity Index	758		847		273		0.80
0		595 (79%)		718 (85%)		229 (84%)	
1		69 (9%)		73 (9%)		27 (10%)	
≥ 2		94 (12%)		56 (7%)		17 (6%)	
Tumour Histology	758		847		273		**<0.001**
DDLPS + other LPS		205 (27%)		354 (42%)		75 (27%)	
WDLPS		37 (5%)		131 (15%)		7 (3%)	
LMS		185 (24%)		214 (25%)		101 (37%)	
Other		331 (44%)		148 (17%)		90 (33%)	
Route to Diagnosis	758		847		273		**<0.001**
GP referral		184 (24%)		287 (34%)		63 (23%)	
Emergency presentation		195 (26%)		86 (10%)		55 (20%)	
TWW		119 (16%)		206 (24%)		64 (23%)	
Other outpatient		71 (9%)		88 (10%)		40 (15%)	
I/P elective, unknown		189 (25%)		181 (21%)		51 (19%)	

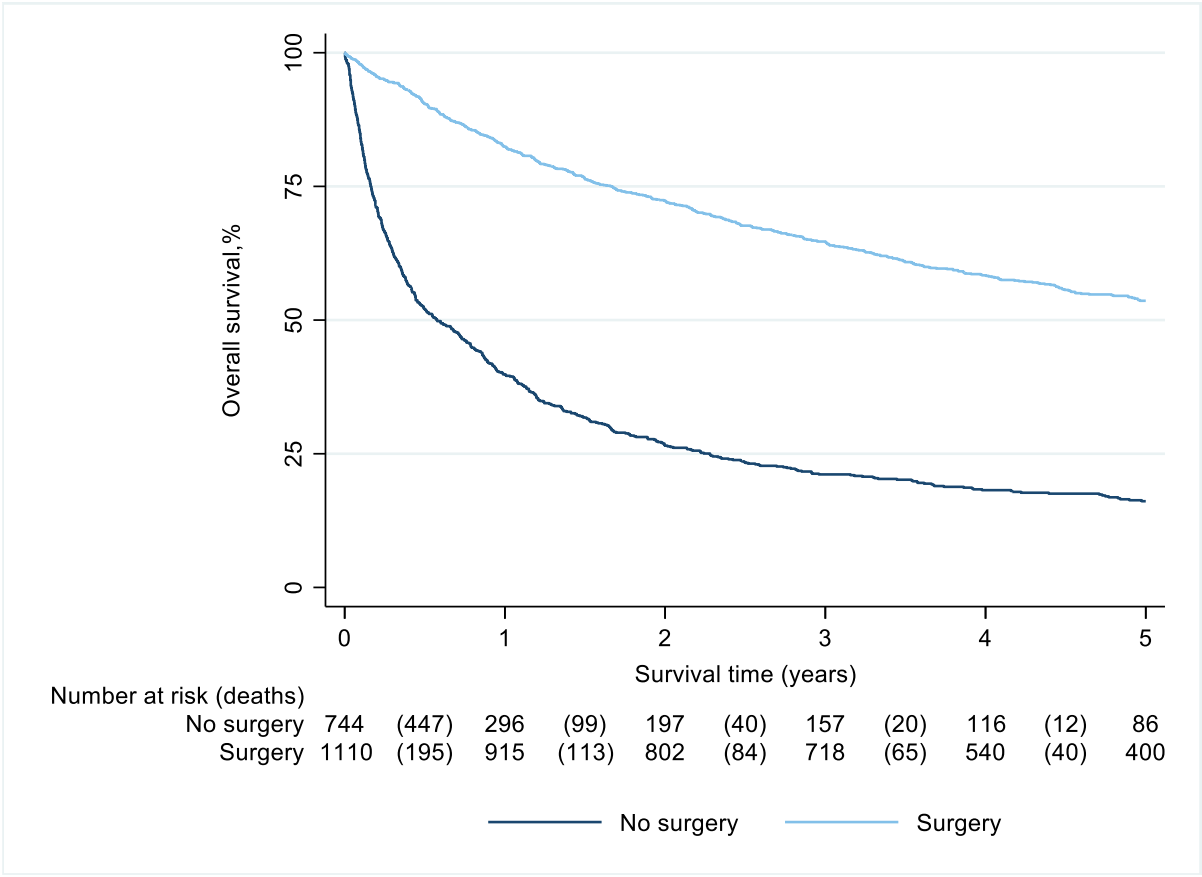
Data are reported as median (interquartile range; IQR), with p-values from Mann-Whitney U tests, or as N (%), with p-values from Fisher's exact tests, as applicable. p-Values are for comparisons between the SCC vs. N-SCC groups, and bold p-values are significant at $p<0.05$. Abbreviations: DDLPS: dedifferentiated liposarcoma; WDLPS: well-differentiated liposarcoma; LMS: leiomyosarcoma; SCC: specialist sarcoma centre; N-SSC: non-specialist sarcoma centre; TWW: two weeks wait; I/P: in patient elective; IMD: Indices of Multiple Deprivation.

Table 2 - Comparison between high- and low-volume specialist centre and non-specialist sarcoma centre

	Surgery		
	LV-SSC	HV-SSC	p-value
Patient No (%).	415 (49)	432 (51)	-
Age at Diagnosis (Years); median (IQR)	64 (54-71)	63.5 (53-71)	0.93
Sex - Male (%)	202 (47)	229 (53)	0.22
Ethnicity			0.13
White	376 (91%)	377 (87%)	
BAME	39 (9%)	55 (13%)	
Indices of Multiple Deprivation (IMD)			0.60
1 - most deprived	65 (16%)	56 (13%)	
2	75 (18%)	68 (16%)	
3	97 (23%)	104 (24%)	
4	88 (21%)	104 (24%)	
5 - least deprived	90 (22%)	100 (23%)	
Charlson Comorbidity Index			0.08
0	348 (84%)	370 (86%)	
1	32 (8%)	41 (10%)	
≥ 2	35 (8%)	21 (5%)	
Tumour Histology			**0.01**
DDLPS + other LPS	160 (39%)	194 (45%)	
WDLPS	56 (14%)	75 (17%)	
LMS	111 (27%)	103 (24%)	
Other	88 (21%)	60 (14%)	
Route to Diagnosis			0.15
GP referral	127 (31%)	160 (37%)	
Emergency presentation	46 (11%)	40 (9%)	
TWW	112 (27%)	93 (22%)	
Other outpatient	39 (9%)	49 (11%)	
I/P elective, unknown	91 (22%)	90 (21%)	

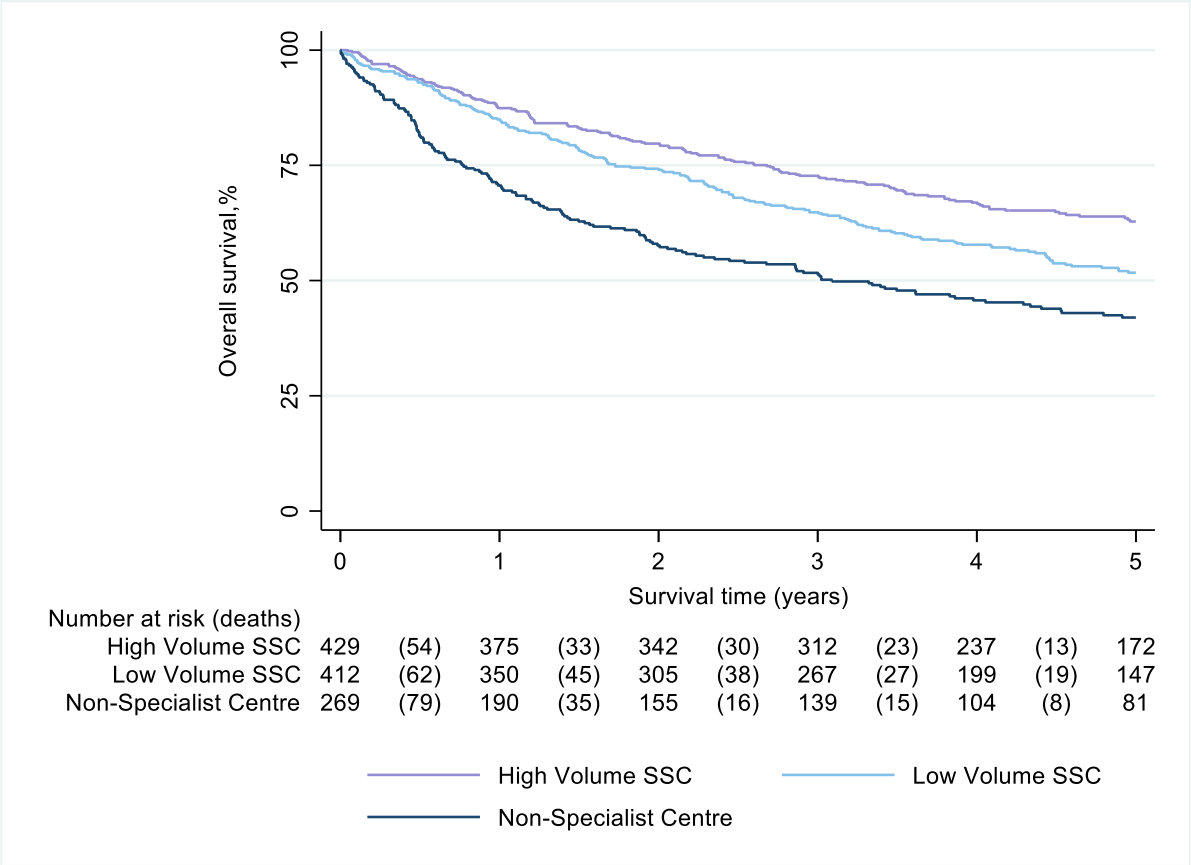
Data are reported as N (%); median (interquartile range).
Abbreviations: DDLPS: dedifferentiated liposarcoma; WDLPS: well-differentiated liposarcoma; LMS: leiomyosarcoma; HV-SCC: high-volume specialist sarcoma centre; LV-SCC: low-volume specialist sarcoma centre; N-SSC: non-specialist sarcoma centre; TWW: two weeks wait. IMD: Indices of Multiple Deprivation

Figure 2 – Kaplan-Meier curves showing survival outcomes between operated and non-operated patients



The analysis was based on N=1854, after excluding 14 patients in the no surgery group since 3 patients had data quality issues, 5 fell outside the range (15-99), and 6 because the diagnosis was made post-mortem. In the surgery group 10 patients were excluded because 3 because of data quality issues, 6 because their age fell outside the range (15-99), and 1 because the patient had multiple tumours. Abbreviations: Haz. Ratio: hazard ratio; L/UCI: lower/upper 95% confidence interval.

Figure 3 – Kaplan-Meier curves showing survival outcomes between high-volume specialist sarcoma centre, low-volume specialist sarcoma centre, and non-specialist sarcoma centre



The analysis was based on N=1110, after excluding N=10, for the reasons described in the results section
Abbreviations: HV-SCC: high-volume specialist sarcoma centre; LV-SCC: low-volume specialist sarcoma centre; N-SSC: non-specialist sarcoma centre

Table 3 – Uni- and Multi-variate analysis of overall survival for patients treated with surgery

	Univariate analysis				Multivariate analysis			
	Haz. ratio	LCI	UCI	p-value	Haz. ratio	LCI	UCI	p-value
Age at Diagnosis (Years)								
15-44	1.00	-	-	-	1.00	-	-	-
45-54	0.78	0.52	1.15	0.21	0.90	0.61	1.34	0.61
55-64	1.24	0.89	1.73	0.20	1.41	1.01	1.98	**<0.05**
65-74	1.50	1.10	2.06	**0.01**	1.86	1.33	2.58	**<0.01**
75+	2.06	1.47	2.89	**<0.01**	2.26	1.60	3.21	**<0.01**
Sex								
Males	1.00	-	-	-	1.00	-	-	-
Females	0.81	0.68	0.96	**<0.05**	0.82	0.69	0.99	**<0.05**
Charlson comorbidity score								
0	1.00	-	-	-	1.00	-	-	-
1	1.06	0.78	1.44	0.71	1.04	0.76	1.42	0.79
≥2	1.36	0.98	1.89	0.07	1.24	0.88	1.75	0.22
Tumour Histology								
Well differentiated liposarcoma	1.00	-	-	-	1.00	-	-	-
Liposarcoma (Dedifferentiated/Other)	2.61	1.73	3.93	**<0.01**	2.34	1.54	3.54	**<0.01**
Leiomyosarcoma	2.78	1.83	4.22	**<0.01**	2.61	1.70	4.00	**<0.01**
Other Morphology	5.74	3.79	8.70	**<0.01**	5.05	3.30	7.74	**<0.01**
Ethnicity								
White	1.00	-	-	-	1.00	-	-	-
BAME	0.85	0.64	1.15	0.30	0.90	0.68	1.23	0.51
Indices of multiple deprivation								
1 - most deprived	1.00	-	-	-	1.00	-	-	-
2	1.15	0.84	1.56	0.38	1.01	0.74	1.38	0.93
3	1.05	0.78	1.41	0.76	0.98	0.72	1.32	0.88
4	0.89	0.65	1.20	0.43	0.85	0.62	1.16	0.31
5 - least deprived	0.93	0.69	1.26	0.66	0.92	0.68	1.26	0.61
Route to Diagnosis								
TWW	1.00	-	-	-	1.00	-	-	-
GP referral	0.88	0.69	1.12	0.31	0.96	0.75	1.22	0.72
Other outpatient	0.87	0.62	1.21	0.40	0.88	0.62	1.23	0.45
Emergency presentation	2.28	1.74	2.99	**<0.01**	2.06	1.56	2.72	**<0.01**
Inpatient / unknown	1.04	0.79	1.36	0.80	1.09	0.82	1.43	0.56
Type of centre*								
N-SSC	1.00	-	-	-	1.00	-	-	-
LV-SSC (vs. N-SSC)	0.69	0.56	0.85	**<0.01**	0.79	0.63	0.98	**<0.05**
HV-SSC (vs. N-SSC)	0.50	0.40	0.62	**<0.01**	0.61	0.48	0.77	**<0.01**
HV-SSC (vs. L-SSC)	0.72	0.58	0.89	**<0.01**	0.78	0.62	0.96	**0.02**

*Initially, all factors were entered into separate univariate Cox regression models. All factors were then entered into a multivariate Cox regression model. Bold p-values are significant at p<0.05. *The models originally treated N-SSC as the reference category for Specialist Involvement; however, models were additionally repeated with LV-SSC as the reference category, to allow for a comparison between HV-SSC vs. LV-SSC.*

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