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Trends in practice patterns and outcomes: A decade of sarcoma care in the United States

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ABSTRACT

Background: Soft tissue sarcomas (STS) represent a rare and heterogeneous group of tumors. We sought to characterize national trends in referral patterns, treatment strategies, and overall survival (OS) over the course of a decade.

Methods: Adult patients with extra-abdominal STS were identified using the National Cancer Database and categorized by diagnosis year (2005–2009 and 2010–2014). High-volume hospitals (HVH) were defined as those > 90th percentile in volume of STS patients treated, and others were defined as low-volume hospitals (LVH). Standard statistical methods were used to compare treatment strategies and OS by diagnosis period.

Results: Of 55,212 patients, 25,469 (46.1%) were diagnosed in 2005–2009 and 29,743 (53.9%) in 2010–2014. Despite increased utilization of neoadjuvant radiation therapy (26.6% vs. 34.8%, P < 0.001), the rate of R0 resections did not change (75.0% vs. 74.8%, P = 0.067). Furthermore, at a national level, OS did not improve over time (HR 0.99, 95% CI 0.96–1.01). When outcomes were stratified by volume, treatment at HVH compared to LVH was associated with improved rates of R0 resection (OR 1.27, 95% CI 1.20–1.35) and OS (HR 0.92, 95% CI 0.89–0.95). Moreover, there was a modest improvement in OS at HVH (HR 0.95, 95% CI 0.91–1.00), but not at LVH (HR 1.01, 95% CI 0.97–1.04). However, referral to HVH did not change over time (40.7% vs. 40.7%, P = 0.91).

Conclusion: OS for STS did not change at a national level over the course of a decade, although it improved at HVH. Further outcome improvements will likely require more effective systemic therapies.

1. Introduction

Soft tissue sarcomas (STS) represent a heterogeneous group of mesenchymal tumors with varying histologies that account for about 1% of malignancies in adults [1]. In 2018, an estimated 13,040 patients were diagnosed with STS in the United States [2]. Survival outcomes of patients diagnosed with STS can be poor with median survival times ranging from 48 months for patients with resectable, localized tumors [3] to only 14–20 months for those with metastatic disease [4]. Age, tumor size and grade, surgical margin positivity, and certain histologic subtypes have been identified as independent prognostic factors [5,6]. Like other cancers with low incidence, survival for STS is typically lower than that for more common malignancies [7]. As such, centers with more experience managing patients with STS have generally been associated with better outcomes [8–10].

The utilization and sequencing of multimodality therapy for STS have evolved over time, but the mainstay of treatment remains surgical resection with negative margins when feasible [11,12]. Radiation for resectable STS has historically been administered in the adjuvant setting, but subsequent studies have demonstrated benefits of neoadjuvant sequencing in improving locoregional control and reducing late radiation morbidity [13–16]. For locally advanced or unresectable STS, guidelines recommend consideration of neoadjuvant radiation prior to reassessment for surgical resection [11,12]. The benefits of systemic treatment, primarily doxorubicin-based chemotherapy, are marginal at best [17], with one Cochrane review demonstrating an absolute

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; HVH, high-volume hospital; IQR, interquartile range; LVH, low-volume hospital; NCDB, National Cancer Database; OR, odds ratio; OS, overall survival; STS, soft tissue sarcoma

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recurrence-free benefit of only 6–10% at 10 years and no significant difference in overall survival (OS) [18].

Despite increased understanding of STS and the use of multimodality therapy, the outcomes of patients treated for STS at one high-volume cancer center did not change over the course of two decades from 1982 to 2001, a sobering statistic highlighting the limitations of conventional treatment modalities [19]. Since 2010, several targeted therapies have demonstrated efficacy against STS [20]. Pazopanib, a multitargeted tyrosine kinase inhibitor, was approved by the US Food and Drug Administration as second-line treatment of advanced STS in 2012 [21]. Survival outcomes in the era of emerging targeted therapies for STS is less well characterized.

The purpose of the current study was to determine the national practice patterns, treatment strategies, and OS of patients diagnosed with extra-abdominal STS over the course of a decade, from 2005 to 2014. Because of the variations in management and outcomes that have previously been observed between high- (HVH) and low-volume hospitals (LVH) for STS, treatment modalities and outcomes were specifically analyzed by hospital volume. We hypothesized that treatment strategies have evolved, but whether these changes have translated into improved OS over time is unclear.

2. Materials and methods

2.1. Data source and patient selection

A retrospective cohort study was performed using the 2015 soft tissue participant use file of the National Cancer Database (NCDB). The NCDB is a collaborative effort between the American College of Surgeons' Commission on Cancer and the American Cancer Society that captures hospital registry data from more than 1500 Commission on Cancer-accredited facilities and represents more than 70% of newly diagnosed cancers [22,23]. All deidentified data are compliant with the Health Insurance Portability and Accountability Act. The study was deemed exempt from review by the Institutional Review Board of the University of Pennsylvania.

Not all facilities currently accredited by the Commission on Cancer contributed to the NCDB every year. In order to analyze data by hospital volume and to determine treatment and outcome trends in a stable group of hospitals, only patients from facilities that contributed to the NCDB every year from 2005 to 2014 were included. From this cohort of patients, those age 18 years or older diagnosed with extra-abdominal, non-cardiac STS were identified using the International Classification of Diseases for Oncology, 3rd edition, topographical and morphological codes. Primary disease sites included the head/neck, extremities, trunk, and overlapping or unspecified sites. Only patients with malignant or locally aggressive STS histologies were included. Patients with incomplete survival data were excluded.

2.2. Variables

The primary outcome of interest was OS as determined by the interval between diagnosis and death (in months), censoring at the time of last contact for patients who were alive. Secondary outcomes analyzed were rates of neoadjuvant administration of radiation therapy and chemotherapy and rates of R0 resection among patients with localized disease who underwent surgical resection of their primary tumor. Analyses of neoadjuvant radiation therapy and chemotherapy were limited to patients for whom sequencing of treatment in relation to surgery was identified in the database. Among patients diagnosed with stage IV STS, receipt of systemic therapy other than conventional chemotherapy, including participation in clinical trials, was analyzed. Of note, only first-course treatments are included in the NCDB. The primary independent variable of interest was diagnosis period: 2005–2009 and 2010–2014.

Additional demographic and hospital-specific variables included for analyses were patient age (< 65 and ≥ 65 years), sex, race (white, black, other), ethnicity (Hispanic, non-Hispanic), Charlson-Deyo score (0, 1, 2, ≥ 3), primary payer (private, government [Medicare, Medicaid, or other government insurance], self-pay/uninsured), income quartile, patient residence (metropolitan, urban, rural), great circle distance between patient residence and hospital location ($\leq 50^{th}$, 51st-75th, 76th-90^{th}, $> 90^{th}$ percentile), hospital type (community, integrated cancer network, academic), and hospital volume. Hospital volume was empirically derived using the NCDB. To limit the influence of fluctuations from a single year's data, hospitals that exceeded the 90^{th} percentile in the number of patients treated per year in 2005 and 2006 were categorized as HVH, and others were identified as LVH.

Tumor characteristics analyzed included primary disease site (head/neck, extremity, trunk, overlapping/not specified), histologic subtype (undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma, others), tumor grade, tumor size, nodal involvement, and American Joint Committee on Cancer (AJCC) 6th or 7th edition cancer stage. Because AJCC stage encompasses tumor size, grade, and regional and distant metastases, stage rather than the individual components was included for multivariable analyses. Besides hospital volume, all other variables were provided by the NCDB. Missing data were included as a separate category for analyses.

2.3. Statistics

Statistical analyses were performed using R for Windows version 3.5.1 [24]. All tests were two-sided. P values < 0.05 were considered statistically significant. Descriptive statistics are presented as frequencies for categorical variables and medians with interquartile ranges (IQR) for continuous variables. Statistical analyses for categorical variables were performed using Pearson's χ^2 or Fisher's exact test, as appropriate. The Wilcoxon rank-sum test was used for continuous variables.

Factors associated with neoadjuvant radiation therapy, neoadjuvant chemotherapy, R0 resection, and receipt of other systemic treatments were analyzed by multivariable logistic regression. Patient and clinical factors associated with each treatment by univariable analysis with $P < 0.10$ were included in the multivariable regression. Outputs are described using Odds Ratio (OR) with 95% Confidence Intervals (CI).

OS was estimated using the Kaplan-Meier method and comparisons were made by diagnosis period (2005–2009 and 2010–2014) using the log-rank method. The Cox proportional hazards model was used to analyze factors associated with OS. The multivariable Cox proportional hazards model included all factors with P value < 0.10 with respect to OS or that differed by diagnosis period. Outputs from the Cox proportional hazards analyses are presented as Hazard Ratio (HR) with 95% CI.

3. Results

3.1. Patient and tumor characteristics

A total of 55,212 patients diagnosed with STS met study criteria. Of these, 25,469 (46.1%) were diagnosed in 2005–2009 and 29,743 (53.9%) were diagnosed in 2010–2014. Median follow-up times by diagnosis period were 58.6 (IQR 17.0–93.5) and 29.4 (IQR 14.2–47.7) months, respectively ($P < 0.001$). Demographic and clinicopathologic characteristics are presented in Table 1. Median age increased from 60 (IQR 47–73) to 61 (IQR 48–73) years ($P < 0.001$). Patient comorbidities also increased, with a decline in the proportion of patients with no comorbidities from 83.0% to 80.4% ($P < 0.001$). Patients were also more frequently insured through Medicare, Medicaid, and other government programs (43.9% vs. 47.2%, $P < 0.001$). Median distance traveled by patients to receive treatment increased from 23.2 (IQR 9.3–69.2) to 24.9 (IQR 10.3–72.4) kilometers ($P < 0.001$). Histologic subtypes remained stable over time except for undifferentiated

Table 1
Demographic and clinicopathologic characteristics of 55,212 soft tissue sarcoma patients by diagnosis period, 2005–2014.

Characteristics	2005–2009 N = 25,469 (46.1%) N (%)	2010–2014 N = 29,743 (53.9%) N (%)	P value
Demographics			
Age in years, median (IQR)	60 (47–73)	61 (48–73)	< 0.001
< 65 years	14,987 (58.8)	17,190 (57.8)	0.013
≥65 years	10,482 (41.2)	12,553 (42.2)	
Sex			
Male	13,691 (53.8)	16,290 (54.8)	0.018
Female	11,778 (46.2)	13,453 (45.2)	
Race			
White	21,290 (83.6)	24,686 (83.0)	< 0.001
Black	2763 (10.8)	3376 (11.4)	
Other	972 (3.8)	1336 (4.5)	
Missing	444 (1.7)	345 (1.2)	
Ethnicity			
Hispanic	1756 (6.9)	2251 (7.6)	< 0.001
Non-Hispanic	21,742 (85.4)	26,598 (89.4)	
Missing	1971 (7.7)	894 (3.0)	
Charlson-Deyo score			
0	21,140 (83.0)	23,912 (80.4)	< 0.001
1	3454 (13.6)	4590 (15.4)	
2	687 (2.7)	934 (3.1)	
≥3	188 (0.7)	307 (1.0)	
Primary payer			
Private	12,397 (48.7)	13,604 (45.7)	< 0.001
Government	11,181 (43.9)	14,034 (47.2)	
Self/uninsured	1086 (4.3)	1281 (4.3)	
Missing	805 (3.2)	824 (2.8)	
Income quartile			
≤25th	4261 (16.7)	4874 (16.4)	< 0.001
26th-50th	5718 (22.5)	6515 (21.9)	
51st-75th	6945 (27.3)	7796 (26.2)	
> 75th	8509 (33.4)	10,515 (35.4)	
Missing	36 (0.1)	43 (0.1)	
Patient residence			
Metropolitan county	21,249 (83.4)	24,841 (83.5)	0.18
Urban county	3270 (12.8)	3748 (12.6)	
Rural county	413 (1.6)	455 (1.5)	
Missing	537 (2.1)	699 (2.4)	
Distance traveled in km, median (IQR)	23.2 (9.3–69.2)	24.9 (10.3–72.4)	< 0.001
< 24 km (≤50th percentile)	13,003 (51.1)	14,576 (49.0)	< 0.001
24–72 km (51st-75th percentile)	6246 (24.5)	7721 (26.0)	
72–177 km (76th-90th percentile)	3656 (14.4)	4446 (14.9)	
≥177 km (> 90th percentile)	2564 (10.1)	3000 (10.1)	
Hospital characteristics			
Volume			
Low (≤90th percentile)	15,102 (59.3)	17,651 (59.3)	0.91
High (> 90th percentile)	10,367 (40.7)	12,092 (40.7)	
Hospital type			
Community	7188 (28.2)	7716 (25.9)	< 0.001
Integrated cancer network	2347 (9.2)	2637 (8.9)	
Academic	11,931 (46.8)	14,962 (50.3)	
Missing	4003 (15.7)	4428 (14.9)	
Tumor characteristics			
Primary disease site			
Head/neck	1671 (6.6)	2158 (7.3)	0.005
Extremity	13,183 (51.8)	15,404 (51.8)	
Trunk	9495 (37.3)	10,830 (36.4)	
Overlapping/not specified	1120 (4.4)	1351 (4.5)	
Histology			
Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma	2905 (11.4)	1468 (4.9)	< 0.001
Liposarcoma	3480 (13.7)	4064 (13.7)	
Leiomyosarcoma	3700 (14.5)	4284 (14.4)	
Others	15,384 (60.4)	19,926 (67.0)	
Grade			
Well-differentiated	3943 (15.5)	4324 (14.5)	< 0.001
Moderately differentiated	2747 (10.8)	3610 (12.1)	
Poorly differentiated	6855 (26.9)	7198 (24.2)	
Undifferentiated	4937 (19.4)	5387 (18.1)	
Missing	6987 (27.4)	9224 (31.0)	
Tumor size/T stage			
No primary tumor	34 (0.1)	61 (0.2)	< 0.001
≤5 cm	7086 (27.8)	8540 (28.7)	
> 5 cm	14,518 (57.0)	17,694 (59.5)	
Missing	3831 (15.0)	3448 (11.6)	
N stage			
N0	16,960 (66.6)	25,019 (84.1)	< 0.001
N1	952 (3.7)	1466 (4.9)	
Missing	7557 (29.7)	3258 (11.0)	
AJCC 6th/7th Edition Stage			
I	6181 (24.3)	9458 (31.8)	< 0.001
II	3988 (15.7)	6351 (21.4)	
III	5098 (20.0)	7065 (23.8)	
IV	3245 (12.7)	3832 (12.9)	
Missing	6957 (27.3)	3037 (10.2)	
Treatment characteristics			
Primary site surgery			
No	4663 (18.3)	5708 (19.2)	< 0.001
Yes	20,747 (81.5)	24,000 (80.7)	
Missing	59 (0.2)	35 (0.1)	
Radiation therapy			
No	14,578 (57.2)	17,029 (57.3)	0.59
Yes	10,639 (41.8)	12,445 (41.8)	
Missing	252 (1.0)	269 (1.0)	
Chemotherapy			
No	18,669 (73.3)	21,891 (73.6)	0.55
Yes	5969 (23.4)	6860 (23.1)	
Missing	831 (3.3)	992 (3.3)	
Other systemic treatment/clinical trial			
No	25,383 (99.7)	29,619 (99.6)	0.013
Yes	82 (0.32)	124 (0.42)	
Missing	4 (0.02)	0 (0)	

IQR, Interquartile Range; AJCC, American Joint Committee on Cancer.

pleomorphic sarcoma/malignant fibrous histiocytoma (11.4% vs. 4.9%, P < 0.001), which has largely been more accurately reclassified into other subtypes [25]. A majority of patients presented with tumors > 5 cm in size (57.0% in 2005–2009, 59.5% in 2010–2014).

Of the 577 hospitals in the NCDB that treated STS patients, 57 (9.9%) were HVH and 520 (90.1%) were LVH. The 90th percentile for the number of STS patients treated was 17 per year. Although treatment at an academic hospital increased over time (46.8% vs. 50.3%, P < 0.001), there was no change in the proportion of patients treated at HVH (40.7% vs. 40.7%, P = 0.91) (Fig. 1). When stratified by AJCC stage, there was no change for stage I (39.9% vs. 39.7%, P = 0.78), stage II (43.7% vs. 42.6%, P = 0.28), or stage IV (37.2% vs. 37.6%, P = 0.76) patients. Treatment at HVH decreased from 50.2% to 46.4% for patients with stage III disease (P < 0.001).

3.2. Trends in treatment strategies

In total, 34,638 patients diagnosed with stage I-III STS underwent resection of their primary tumor. Among these patients, receipt of radiation therapy increased over time (50.6% vs. 52.7%, P < 0.001). Of patients who received radiation therapy with known treatment sequencing (N = 16,372), there was an increase in neoadjuvant administration (26.6% vs. 34.8%, P < 0.001) (Fig. 2). Chemotherapy administration did not change among all (23.4% vs. 23.1%, P = 0.55) or resected stage I-III (16.2% vs. 15.6%, P = 0.28) patients. Among those for whom the timing of chemotherapy in relation to surgery was known (N = 5101), there was no change the proportion that received

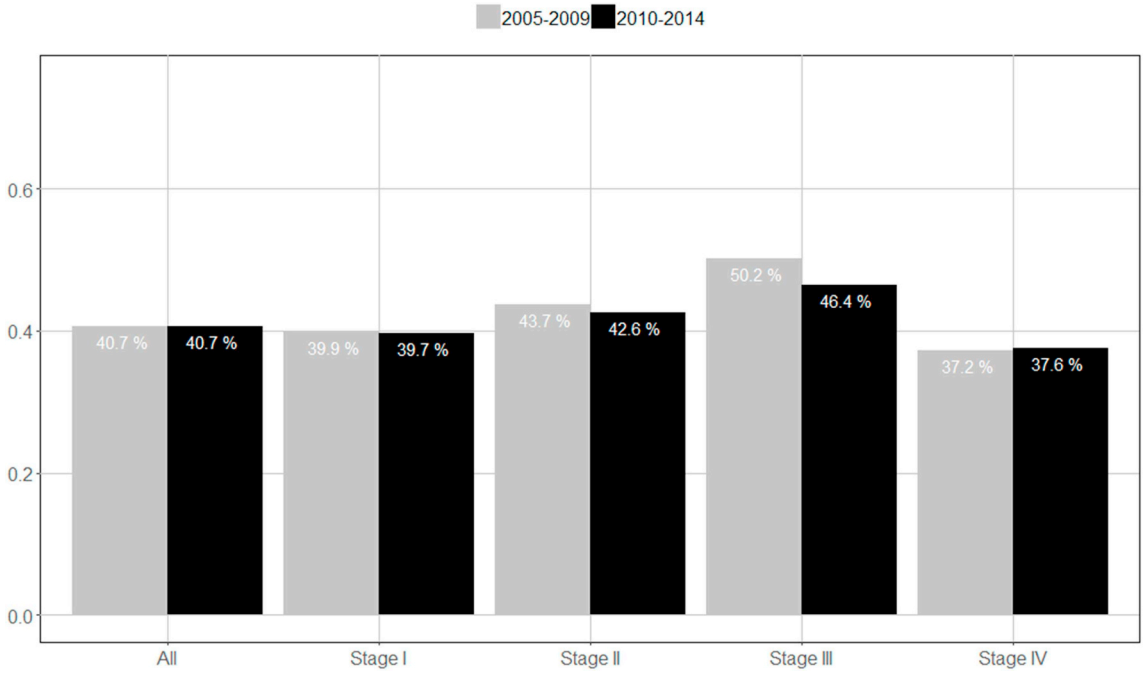

Fig. 1. Proportion of soft tissue sarcoma patients treated at high-volume hospitals by diagnosis period, 2005–2009 and 2010–2014. All patients (P = 0.91), stage I (P = 0.78), stage II (P = 0.28), stage III (P < 0.001), stage IV (P = 0.76).

chemotherapy in the neoadjuvant setting (48.9% vs. 49.1%, P = 0.93). Both neoadjuvant radiation (OR 1.59, 95% CI 1.46–1.72, P < 0.001) and neoadjuvant chemotherapy (OR 1.26, 95% CI 1.13–1.42, P < 0.001) were associated with an R0 resection (Table S1). Despite an increase in neoadjuvant sequencing of radiation therapy over time, there was no change in the rate of R0 resections (75.0% vs. 74.8%, P = 0.067). Among patients with extremity STS who underwent surgical resection (N = 20,347), there was no significant change in the rate of amputation (4.7% vs. 5.0%, P = 0.26).

Receipt of systemic treatments other than conventional chemotherapy was analyzed for patients diagnosed with stage IV STS. Among the 7077 patients diagnosed with stage IV disease, utilization of other treatments as first-line therapy increased from 0.86% in 2005–2009 to 1.36% in 2010–2014 (P = 0.048).

3.3. Treatment strategies by hospital volume

Analyses of treatment strategies in resected stage I-III patients were further stratified by hospital volume. Radiation therapy was more frequently administered in the neoadjuvant setting at HVH than at LVH by both univariable (40.1% vs. 24.4%; OR 2.07, 95% CI 1.94–2.22, P < 0.001) and multivariable (OR 1.33, 95% CI 1.22–1.44, P < 0.001) analyses (Table S2). Similarly, patients treated at HVH were more likely to receive neoadjuvant chemotherapy than those at

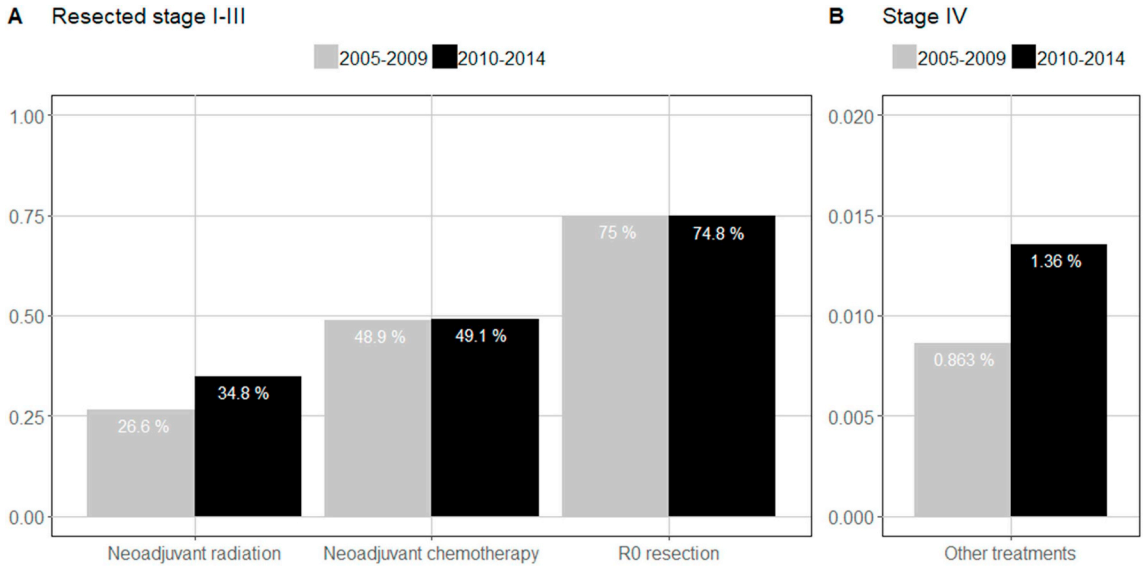

Fig. 2. Treatment strategies for patients diagnosed with soft tissue sarcoma (STS) by diagnosis period, 2005–2009 and 2010–2014.(A) Among patients with resected stage I-III STS, neoadjuvant sequencing for radiation increased (P < 0.001), but did not change for chemotherapy (P = 0.18). Rate of R0 resection did not change (P = 0.067). (B) Among patients diagnosed with stage IV STS, receipt of systemic treatment other than chemotherapy, including participation in clinical trials, increased over time (P = 0.048).

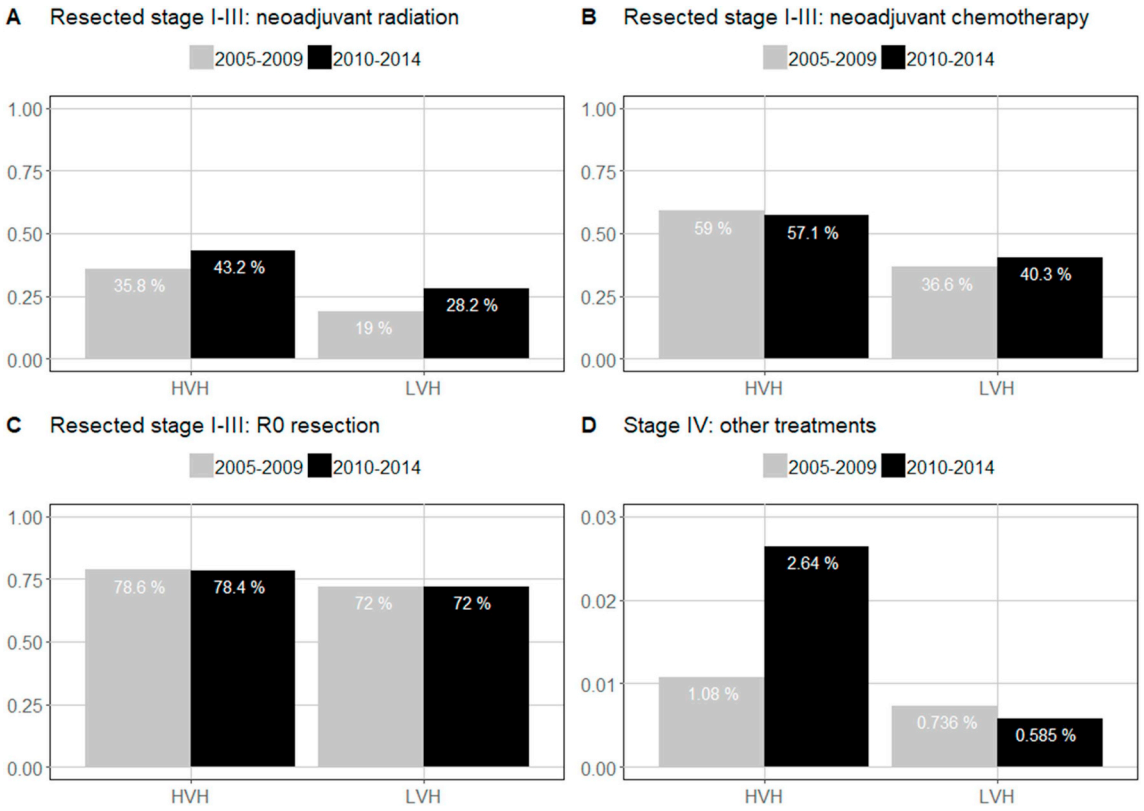

Fig. 3. Treatment strategies for patients diagnosed with soft tissue sarcoma (STS) at high-volume (HVH) and low-volume (LVH) hospitals, 2005–2009 and 2010–2014.(A–C) Treatment trends among resected stage I-III STS patients. (A) Neoadjuvant radiation therapy sequencing increased at both HVH ($P < 0.001$) and LVH ($P < 0.001$). (B) Neoadjuvant chemotherapy sequencing did not change at either HVH ($P = 0.36$) or LVH ($P = 0.086$). (C) Rates of R0 resection did not change at either HVH ($P = 0.18$) or LVH ($P = 0.32$). (D) Among stage IV patients, receipt of systemic treatment other than chemotherapy and participation in clinical trials increased at HVH ($P = 0.003$), but did not change at LVH ($P = 0.58$).

LVH by univariable (57.8% vs. 39.0%; OR 2.15, 95% CI 1.92–2.40, $P < 0.001$) and multivariable (OR 1.55, 95% CI 1.36–1.78, $P < 0.001$) analyses (Table S3). Additionally, the rate of R0 resections was higher at HVH than LVH (78.5% vs. 72.0%, $P < 0.001$), and treatment at HVH was independently associated with an R0 resection (OR 1.27, 95% CI 1.20–1.35, $P < 0.001$).

Comparing 2005–2009 and 2010–2014, utilization of neoadjuvant radiation therapy increased at both HVH (35.8% vs. 43.2%, $P < 0.001$) and LVH (19.0% vs. 28.2%, $P < 0.001$), while neoadjuvant sequencing for chemotherapy did not change at either HVH (59.0% vs. 57.1%, $P = 0.36$) or LVH (36.6% vs. 40.3%, $P = 0.086$) (Fig. 3). Despite increased neoadjuvant sequencing of radiation therapy, rates of R0 resection did not change over time at HVH (78.6% vs. 78.4%, $P = 0.18$) or LVH (72.0% vs. 72.0%, $P = 0.32$).

For patients diagnosed with stage IV STS, treatment at HVH compared to LVH was associated with increased administration of systemic treatments other than conventional chemotherapy (1.9% vs. 0.66%, $P < 0.001$). By multivariable analysis, treatment at HVH was independently associated with other systemic therapies (OR 2.78, 95% CI 1.58–5.05, $P < 0.001$) (Table S4). Furthermore, receipt of other treatments increased over time at HVH (1.1% vs. 2.6%, $P = 0.003$), but did not change at LVH (0.74% vs. 0.59%, $P = 0.58$).

3.4. Overall survival: national trends

Median OS times were 88.4 (95% CI 85.3–91.5) months for patients diagnosed in 2005–2009 and 80.2 (95% CI 78.9 - not reached) months for those diagnosed in 2010–2014. The 3-year OS rates during these time periods were 65.2% (95% CI 64.7–65.8%) and 66.3% (95% CI 65.7–66.9%), respectively. Unadjusted OS did not change significantly over time (log-rank $P = 0.14$) (Fig. 4). Adjusting for patient and clinical factors influencing OS, diagnosis period was not associated with OS (HR 0.99, 95% CI 0.96–1.01, $P = 0.31$) (Fig. 5, Table 2).

Among resected stage I-III patients, median OS times were 135 (95% CI 132 – not reached) months in 2005–2009 and not reached in 2010–2014. The corresponding 3-year OS rates were 78.4% (95% CI 77.7–79.1%) and 77.7% (95% CI 77.1–78.3%), respectively. Unadjusted OS appeared to be slightly better in the earlier diagnosis period by log-rank analysis (log-rank $P = 0.026$). By multivariable analysis, diagnosis period was not associated with OS (HR 1.03, 95% CI 0.99–1.07, $P = 0.19$). Similarly, for stage IV patients, unadjusted OS was slightly better in 2005–2009 (median 12.0, 95% CI 11.3–12.7, months; 3-year OS 21.0%, 95% CI 19.6–22.5%) than in 2010–2014 (median 10.4, 95% CI 9.8–11.0, months; 3-year OS 19.9%, 95% CI 18.6–21.5%, log-rank $P = 0.016$), but survival outcomes did not differ by multivariable analysis (HR 1.02, 95% CI 0.97–1.08, $P = 0.43$).

3.5. Overall survival by hospital volume

When stratified by volume, OS was longer for patients treated at HVH (median 110.1, 95% CI 106.4–114.3, months; 3-year OS 69.5%, 95% CI 68.8–70.1%) than those at LVH (median 77.4, 95% CI 74.2–81.2, months; 3-year OS 63.2%, 95% CI 62.7–63.8%, log-rank $P < 0.001$). Furthermore, treatment at HVH compared to LVH was associated with 8% hazard reduction in all-cause deaths after adjusting for other factors (HR 0.92, 95% CI 0.89–0.95, $P < 0.001$). Taking both volume and academic status into consideration, only volume, and not academic status (academic vs. community, HR 0.99, 95% CI 0.96–1.02, $P = 0.53$), was associated with OS.

Among patients treated at HVH, unadjusted OS did not change over

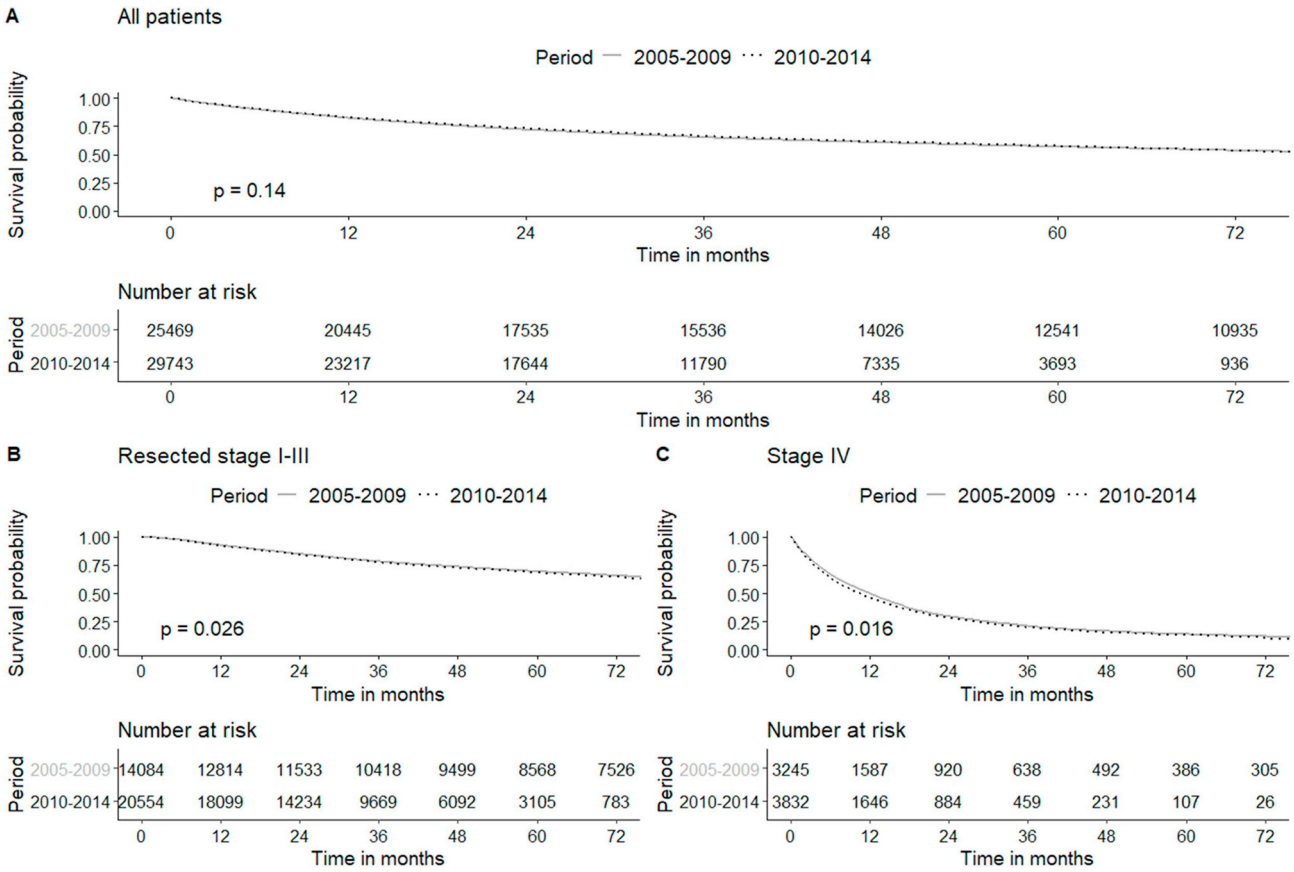

Fig. 4. Kaplan-Meier estimates of unadjusted overall survival of soft tissue sarcoma patients by diagnosis period, 2005–2009 and 2010–2014. (A) All STS patients (N = 55,212). (B) Resected stage I-III patients (N = 34,638). (C) Stage IV patients (N = 7077).

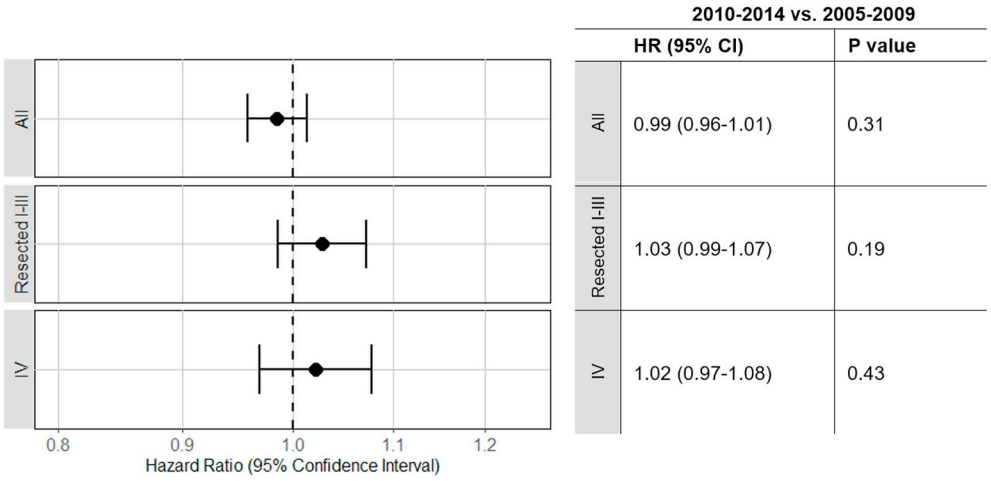

Fig. 5. Multivariable Cox proportional hazards analyses of overall survival (OS) of soft tissue sarcoma patients by diagnosis period, 2010–2014 vs. 2005–2009. OS compared for all, resected stage I-III, and stage IV patients. Hazard ratio (HR) values < 1.0 are favorable and > 1.0 are unfavorable for patients diagnosed in 2010–2014 compared to 2005–2009. Error bars indicate 95% Confidence Intervals (CI).

time (log-rank P = 0.26), but the latter diagnosis period was associated with a modest improvement in OS by multivariable analysis (HR 0.95, 95% CI 0.91–1.00, P = 0.035) (Fig. 6, Fig. 7). OS did not change for patients treated at LVH (log-rank P = 0.35; HR 1.01, 95% CI 0.97–1.04, P = 0.68).

4. Discussion

The relatively low incidence and histologic heterogeneity of STS make it a challenging disease to treat. Over the past few decades, knowledge has substantially improved regarding the varying tumor biology of different STS histologic subtypes and the appropriate utilization of surgical, radiation, and systemic treatment options [13,26]. In the 2010s, tyrosine kinase inhibitors have also emerged as potential targeted therapeutic options for STS, although clinical trials for these agents have not demonstrated an improvement in OS [20,21,27]. This study was performed in order to determine whether an improvement in knowledge regarding tumor biology and treatment options have translated into a change in survival outcomes at a population level for patients diagnosed with STS. Using data from a nationally representative cohort of hospitals that treated STS patients between 2005 and 2014, the current study demonstrated that STS treatment has evolved with increased administration of radiation therapy in the neoadjuvant setting. While there has been no change in

Table 2
Univariable and multivariable Cox proportional hazards analyses of overall survival of patients diagnosed with soft tissue sarcoma (N = 55,212).

Variable	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
Diagnosis period				
2005–2009	Reference		Reference	
2010–2014	0.98 (0.95–1.01)	0.14	0.99 (0.96–1.01)	0.31
Hospital volume				
Low volume (≤90th percentile)	Reference		Reference	
High volume (> 90th percentile)	0.80 (0.77–0.81)	< 0.001	0.92 (0.89–0.95)	< 0.001
Hospital type				
Community	Reference		Reference	
Integrated cancer network	0.84 (0.80–0.88)	< 0.001	0.96 (0.92–1.01)	0.16
Academic	0.81 (0.79–0.84)	< 0.001	0.99 (0.96–1.02)	0.53
Sex				
Male	Reference		Reference	
Female	0.92 (0.90–0.94)	< 0.001	0.91 (0.89–0.94)	< 0.001
Age				
< 65 years	Reference		Reference	
≥65 years	2.05 (2.00–2.10)	< 0.001	1.54 (1.48–1.60)	< 0.001
Race				
White	Reference		Reference	
Black	1.08 (1.04–1.13)	< 0.001	1.00 (0.95–1.04)	0.83
Other	0.83 (0.78–0.90)	< 0.001	0.85 (0.79–0.92)	< 0.001
Ethnicity				
Non-Hispanic	Reference		Reference	
Hispanic	0.84 (0.79–0.88)	< 0.001	0.82 (0.78–0.87)	< 0.001
Charlson-Deyo score				
0	Reference		Reference	
1	1.45 (1.40–1.50)	< 0.001	1.25 (1.21–1.30)	< 0.001
2	2.06 (1.94–2.20)	< 0.001	1.60 (1.50–1.71)	< 0.001
≥3	2.82 (2.54–3.14)	< 0.001	1.96 (1.76–2.18)	< 0.001
Primary payer				
Private	Reference		Reference	
Government	2.13 (2.07–2.19)	< 0.001	1.36 (1.31–1.41)	< 0.001
Self-pay/uninsured	1.51 (1.41–1.62)	< 0.001	1.27 (1.18–1.36)	< 0.001
Income quartile				
≤25th	Reference		Reference	
26th-50th	0.92 (0.89–0.96)	< 0.001	0.97 (0.93–1.01)	0.13
51st-75th	0.88 (0.84–0.91)	< 0.001	0.96 (0.92–1.00)	0.030
> 75th	0.75 (0.72–0.78)	< 0.001	0.84 (0.81–0.88)	< 0.001
Patient residence				
Metropolitan	Reference		Reference	
Urban county	1.11 (1.06–1.15)	< 0.001	1.06 (1.01–1.11)	0.010
Rural county	1.13 (1.03–1.25)	0.014	1.05 (0.94–1.16)	0.38
Distance traveled				
< 24 km (≤50th percentile)	Reference		Reference	
24–72 km (51st-75th percentile)	0.92 (0.89–0.95)	< 0.001	1.00 (0.97–1.04)	0.86
72–177 km (76th-90th percentile)	0.95 (0.92–0.99)	0.010	1.00 (0.96–1.05)	0.96
≥177 km (> 90th percentile)	0.85 (0.82–0.90)	< 0.001	0.96 (0.91–1.02)	0.17
Primary disease site				
Head/neck	Reference		Reference	
Extremity	0.62 (0.59–0.66)	< 0.001	0.76 (0.72–0.80)	< 0.001
Trunk	1.06 (1.01–1.12)	0.021	0.98 (0.93–1.04)	0.54
Overlapping/not specified	1.63 (1.52–1.74)	< 0.001	0.98 (0.91–1.05)	0.58
Histology				
Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma	Reference		Reference	
Liposarcoma	0.62 (0.59–0.66)	< 0.001	0.74 (0.70–0.78)	< 0.001
Leiomyosarcoma	1.01 (0.95–1.06)	0.81	0.85 (0.80–0.89)	< 0.001
Others	0.98 (0.93–1.02)	0.30	0.98 (0.94–1.03)	0.49
AJCC stage				
I	Reference		Reference	
II	1.57 (1.49–1.64)	< 0.001	1.61 (1.53–1.69)	< 0.001
III	2.90 (2.78–3.02)	< 0.001	2.83 (2.70–2.95)	< 0.001
IV	8.93 (8.55–9.32)	< 0.001	5.09 (4.85–5.35)	< 0.001
Primary site surgery				
No	Reference		Reference	
R1/2	0.30 (0.29–0.31)	< 0.001	0.43 (0.41–0.45)	< 0.001
R0	0.18 (0.18–0.19)	< 0.001	0.29 (0.28–0.30)	< 0.001
Radiation therapy				
No	Reference		Reference	
Yes	0.83 (0.81–0.85)	< 0.001	0.81 (0.79–0.84)	< 0.001
Chemotherapy				
No	Reference		Reference	
Yes	0.85 (0.78–0.92)	< 0.001	0.98 (0.95–1.01)	0.20
Other systemic treatment/clinical trials				
No	Reference		Reference	

(*continued on next page*)

Table 2 (*continued*)

Variable	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
Yes	1.93 (1.63–2.30)	< 0.001	1.07 (0.90–1.27)	0.44

HR, Hazard Ratio; CI, Confidence Interval; AJCC, American Joint Committee on Cancer.

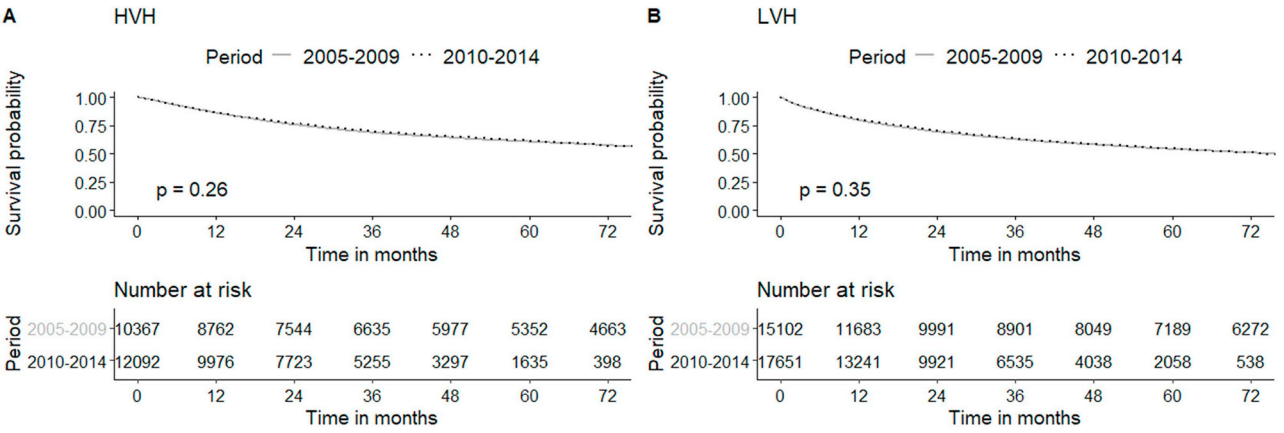

Fig. 6. Kaplan-Meier estimates of unadjusted overall survival of soft tissue sarcoma patients treated at high-volume (HVH) and low-volume hospitals (LVH) by diagnosis period, 2005–2009 and 2010–2014. (A) HVH (N = 22,459). (B) LVH (N = 32,753).

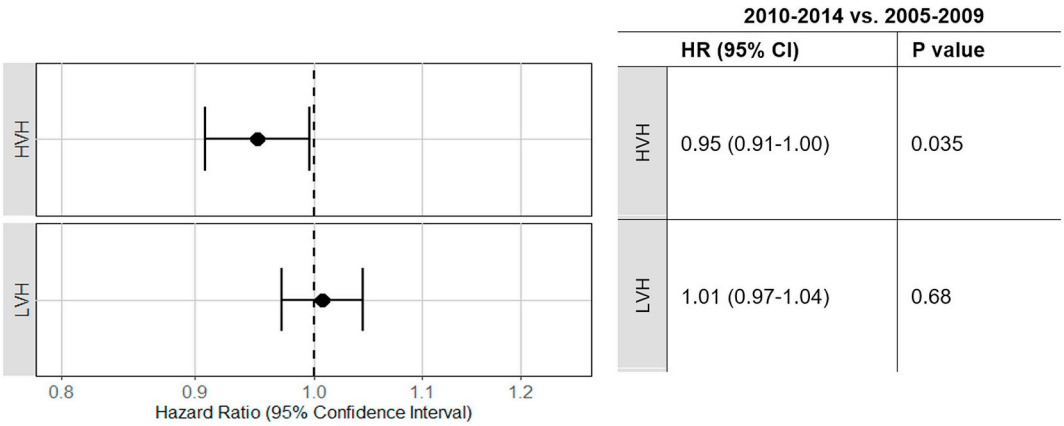

Fig. 7. Multivariable Cox proportional hazards analyses of overall survival of soft tissue sarcoma patients treated at high-volume (HVH) and low-volume hospitals (LVH) by diagnosis period, 2005–2009 vs. 2010–2014. Hazard ratio (HR) values < 1.0 are favorable and > 1.0 are unfavorable for patients diagnosed in 2010–2014 compared to 2005–2009. Error bars indicate 95% Confidence Intervals (CI).

OS nationally, there has been a modest improvement in OS at HVH.

Early randomized trials of limb-sparing surgery in patients diagnosed with extremity STS examined wide excision and postoperative radiation therapy and found no difference in local recurrence or OS compared to amputation [28]. The only randomized trial comparing neoadjuvant and adjuvant radiation therapy was conducted by the National Cancer Institute of Canada between 1994 and 1997 [29]. Initial outcomes after a median follow-up of 3.3 years demonstrated improved survival in the neoadjuvant compared to adjuvant cohort, but there was no difference in local control or survival at 5 years [30]. Neoadjuvant radiation therapy, however, was associated with lower rates of late radiation morbidity, including fibrosis, joint stiffness, and edema [16]. Subsequent multicenter observational studies and meta-analyses have further associated neoadjuvant radiation therapy with improved local control for patients with resected STS in comparison to the adjuvant approach [13–15]. The benefits of systemic chemotherapy are less clear, with large meta-analyses of trial results demonstrating only a slight improvement in recurrence-free survival and no effect on OS [17,18]. Guidelines recommend consideration of neoadjuvant radiation therapy and/or chemotherapy for patients with locally advanced STS [11,12]. As the current study shows, neoadjuvant sequencing of radiation therapy appears to have increased according to guideline recommendations, but neoadjuvant administration of chemotherapy remains unchanged.

The lack of significant survival improvements at a national level over the course of a decade highlights the limitations of conventional treatment options. OS for patients in the current study are consistent with survival outcomes reported in the literature [7]. As has previously been observed, a positive resection margin, older age, and increasing AJCC stage were inversely associated with OS [5,6,31,32]. In addition to tumor and treatment factors, there has been extensive literature reporting better outcomes for patients treated at specialized STS centers compared to their counterparts at non-specialized centers. When patients are not managed at STS centers, only 21.3% receive optimal diagnostic workup and 60.0% receive adequate treatment [8]. Patients treated at inexperienced centers are also more likely have positive margins on initial excision, require multiple operations, and experience higher rates of local recurrence and decreased survival [9,10]. Bagaria

et al. showed that high-volume centers were more likely to adhere to treatment guidelines, which was significantly associated with improved OS [33].

Rather than reiterate the volume-outcomes relationship for STS, the current study specifically focused on treatment and survival trends stratified by hospital volume. Adjusting for patient and clinicopathologic factors, neoadjuvant administration of radiation therapy and chemotherapy occurred more frequently at HVH than at LVH. Interestingly, patients with stage IV STS treated at HVH were more likely than those treated at LVH to receive non-conventional systemic therapy and to participate in clinical trials as a part of first-line treatment. Furthermore, the proportion of patients receiving other treatments at HVH increased from 1.1% in 2005–2009 to 2.6% in 2010–2014 (P = 0.003). The specific types of treatments received could not be evaluated due to limitations of the NCDB, but this category likely includes the novel targeted therapies for STS. Consistent with the outcomes of the clinical trials for pazopanib and regorafenib, which demonstrated longer progression-free survival, but not improved OS, in the treatment of non-adipocytic, metastatic STS, receipt of other treatments was not independently associated with improved OS in the current study [21,27]. More effective agents, perhaps targeting specific histologies, are needed in order to achieve further survival improvements for patients with STS.

In the current study, a modest improvement in adjusted OS was observed at HVH, but not at LVH. In a study of stage IV STS patients treated at tertiary cancer centers in France, Italiano et al. reported improved OS from a median time of 12.3 months for patients diagnosed in 1987–1991 to 18 months for patients diagnosed in 2002–2006 (log-rank P = 0.029) [4]. The observed outcome improvement was attributed to increased utilization of additional lines of chemotherapy, participation in clinical trials, as well as increased metastasectomy and use of other locoregional treatment options for metastatic disease. More aggressive treatment of metastatic disease, enrollment in clinical trials, and multidisciplinary decision-making occur more frequently at high-volume, tertiary care centers, and may explain the difference in survival trends at HVH and LVH observed in the current study [34–36].

Despite the outcome difference between high- and low-volume centers, however, referral to HVH did not increase over time. Similarly, Keung et al. did not observe an increase in the treatment of retroperitoneal STS at HVH between 1998 and 2011 [37], while centralization has occurred for other cancer types, such as esophageal and pancreatic cancers [38,39]. Although there are valid concerns regarding centralization, including patient access to care [38,40], the benefits of appropriate referral may outweigh the disadvantages for a relatively rare malignancy like STS. In fact, European guidelines specifically recommend treatment of STS at experienced centers [12].

There are several study limitations that should be acknowledged. This was a retrospective, observational study in which no randomization of patients to specific facilities or treatments occurred. Therefore, as with any retrospective study design, causal relationships cannot be inferred. While the NCDB encompasses a broad range of hospitals, they are all Commission on Cancer-accredited facilities. Treatment and outcome trends at other hospitals in the United States may differ and cannot be defined using available data. The study of only Commission on Cancer-accredited facilities may in fact have overestimated the proportion of patients treated at high-volume STS centers nationally. Furthermore, the NCDB data are based on records submitted by participating facilities and may reflect differences and inconsistencies in data reporting, as well as underlying differencing in the management of STS. For each variable, there is also a small percentage of missing data that makes interpretation of results more challenging. In order to provide the most comprehensive data on national outcomes, however, patients with missing data were not excluded. Additionally, the median follow-up times for the two cohorts of patients in the current study differed significantly by virtue of the time period during which each cohort was diagnosed. However, using time-to-event statistical methods (Kaplan-Meier and Cox proportional hazards) minimizes bias based on differences in follow-up time. Finally, the NCDB provides only first-course treatments and lacks information on treatment complications, functional outcomes, locoregional and distant recurrence patterns, and disease-specific survival, all of which are important in the evaluation of cancer outcomes. Despite these limitations, however, the NCDB provides valuable insight on the patterns of treatment and survival at a national level for a relatively rare malignancy.

5. Conclusions

STS represents a heterogenous group of malignancies that requires multimodal therapy and multidisciplinary care. Over a decade from 2005 to 2014, treatment patterns for STS have evolved with increased utilization of neoadjuvant radiation therapy for patients diagnosed with resectable disease, but the rate of R0 resections remains unchanged. Patients with stage IV STS treated at HVH are more frequently offered non-chemotherapy systemic treatments and participation in clinical trials, although this continues to represent a small proportion of patients diagnosed with advanced STS. While there has been a modest improvement in OS at HVH, there has been no change at LVH. Optimizing the referral of complex STS patients to experienced centers represents an area for improvement. More importantly, however, molecular targeted therapies for STS are just emerging, and the development of more effective agents is needed.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.05.018.

References

[1] J.R. Toro, L.B. Travis, H.J. Wu, et al., Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978-2001: an analysis of 26,758 cases, Int. J. Cancer 119 (2006) 2922–2930, https://doi.org/10.1002/ijc.22239.
[2] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, CA A Cancer J. Clin. 68 (2018) 7–30, https://doi.org/10.3322/caac.21442.
[3] A. Stojadinovic, D.H.Y. Leung, P. Allen, et al., Primary adult soft tissue sarcoma: time-dependent influence of prognostic variables, J. Clin. Oncol. 20 (2002) 4344–4352, https://doi.org/10.1200/JCO.2002.07.154.
[4] A. Italiano, S. Mathoulin-Pelissier, A. Le Cesne, et al., Trends in survival for patients with metastatic soft-tissue sarcoma, Cancer 117 (2011) 1049–1054, https://doi.org/10.1002/cncr.25538.
[5] P.W.T. Pisters, D.H.Y. Leung, J. Woodruff, et al., Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities, J. Clin. Oncol. 14 (1996) 1679–1689, https://doi.org/10.1200/JCO.1996.14.5.1679.
[6] M.W. Kattan, D.H.Y. Leung, M.F. Brennan, Postoperative nomogram for 12-year sarcoma-specific death, J. Clin. Oncol. 20 (2002) 791–796, https://doi.org/10.1200/JCO.2002.20.3.791.
[7] G. Gatta, R. Capocaccia, L. Botta, et al., Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study, Lancet Oncol. 18 (2017) 1022–1039, https://doi.org/10.1016/S1470-2045(17)30445-X.
[8] R. Clasby, K. Tilling, M.A. Smith, C.D.M. Fletcher, Variable management of soft tissue sarcoma: regional audit with implications for specialist care, Br. J. Surg. 84 (1997) 1692–1696.
[9] M.T.L. Tan, S.R. Thompson, D. Schipp, et al., Patterns of care of superficial soft tissue sarcomas: it is not always just a lump, Asia Pac. J. Clin. Oncol. (2018), https://doi.org/10.1111/ajco.12823.
[10] J.C. Gutierrez, E.A. Perez, F.L. Moffat, Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients, Ann. Surg. 245 (2007) 952–958, https://doi.org/10.1097/01.sla.0000250438.04393.a8.
[11] M. von Mehren, R.L. Randall, R.S. Benjamin, et al., Soft tissue sarcoma, version

2.2018. Clinical practice guidelines in Oncology, J. Natl. Compr. Cancer Netw. 16 (2018) 536–563.
[12] P.G. Casali, N. Abecassis, S. Bauer, et al., Soft tissue and visceral sarcomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 29 (2018) 51–67, https://doi.org/10.1093/annonc/mdy321.
[13] C. Shah, V. Verma, R. Takiar, et al., Radiation therapy in the management of soft tissue sarcoma: a clinician's guide to timing, techniques, and targets, Am. J. Clin. Oncol. 39 (2016) 630–635, https://doi.org/10.1097/COC.0000000000000319.
[14] E. Al-Absi, F. Farrokhyar, R. Sharma, et al., A systematic review and meta-analysis of oncologic outcomes of pre- versus postoperative radiation in localized resectable soft-tissue sarcoma, Ann. Surg. Oncol. 17 (2010) 1367–1374, https://doi.org/10.1245/s10434-009-0885-7.
[15] S. Sampath, T.E. Schultheiss, Y.J. Hitchcock, et al., Preoperative versus postoperative radiotherapy in soft-tissue sarcoma: multi-institutional analysis of 821 patients, Int. J. Radiat. Oncol. Biol. Phys. 81 (2011) 498–505, https://doi.org/10.1016/j.ijrobp.2010.06.034.
[16] A.M. Davis, B. O'Sullivan, R. Turcotte, et al., Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma, Radiother. Oncol. 75 (2005) 48–53.
[17] N. Pervaiz, N. Colterjohn, F. Farrokhyar, et al., A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma, Cancer 113 (2008) 573–581, https://doi.org/10.1002/cncr.23592.
[18] Sarcoma Meta-analysis Collaboration, Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Sarcoma Meta-analysis Collaboration (SMAC), Cochrane Database Syst. Rev. 2 (2000) CD001419.
[19] J. Weitz, C.R. Antonescu, M.F. Brennan, Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time, J. Clin. Oncol. 21 (2003) 2719–2725, https://doi.org/10.1200/JCO.2003.02.026.
[20] K. Nakano, S. Takahashi, Current molecular targeted therapies for bone and soft tissue sarcomas, Int. J. Mol. Sci. 19 (2018) E739, https://doi.org/10.3390/ijms19030739.
[21] W.T.A. Van der Graaf, J.Y. Blay, S.P. Chawla, et al., Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial, Lancet 379 (2012) 1879–1886, https://doi.org/10.1016/S0140-6736(12)60651-5.
[22] K.Y. Bilimoria, A.K. Stewart, D.P. Winchester, C.Y. Ko, The national cancer data base: a powerful initiative to improve cancer care in the United States, Ann. Surg. Oncol. 15 (2008) 683–690, https://doi.org/10.1245/s10434-007-9747-3.
[23] About the National Cancer Database, National cancer Database n.d. https://www.facs.org/quality-programs/cancer/ncdb/about , Accessed date: 1 October 2018.
[24] R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2018.
[25] L.A. Doyle, Sarcoma classification: an update based on the 2013 World Health Organization classification of tumors of soft tissue and bone, Cancer 120 (2014) 1763–1774, https://doi.org/10.1002/cncr.28657.
[26] J.-Y. Blay, M. Brahmi, I. Ray-Coquard, European Journal of Cancer's biennial report on soft tissue and visceral sarcomas or the rapid evolution of treatment concepts in sarcomas, Eur. J. Cancer 70 (2017) 83–86, https://doi.org/10.1016/j.ejca.2016.07.028.
[27] V. Berry, L. Basson, E. Bogart, et al., REGOSARC: regorafenib versus placebo in doxorubicin-refractory soft-tissue sarcoma-A quality-adjusted time without symptoms of progression or toxicity analysis, Cancer 123 (2017) 2294–2302, https://doi.org/10.1002/cncr.30661.
[28] S.A. Rosenberg, J. Tepper, E. Glatstein, et al., The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy, Ann. Surg. 196 (1982) 305–315.
[29] B. O'Sullivan, A.M. Davis, R. Turcotte, et al., Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial, Lancet 359 (2002) 2235–2241.
[30] B. O'Sullivan, A.M. Davis, R. Turcotte, et al., Five-year results of a randomized phase III trial of pre-operative vs post-operative radiotherapy in extremity soft tissue sarcoma, J. Clin. Oncol. 22 (2004) 9007, https://doi.org/10.1200/jco.2004.22.14_suppl.9007.
[31] A. Stojadinovic, D.H.Y. Leung, A. Hoos, et al., Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas, Ann. Surg. 235 (2002) 424–434.
[32] I.C. Dickinson, D.J. Whitwell, D. Battistuta, et al., Surgical margin and its influence on survival in soft tissue sarcoma, ANZ J. Surg. 76 (2006) 104–109, https://doi.org/10.1111/j.1445-2197.2006.03615.x.
[33] S.P. Bagaria, Y.-H. Chang, R.J. Gray, et al., Improving long-term outcomes for patients with extra-abdominal soft tissue sarcoma regionalization to high-volume centers, improved compliance with guidelines or both? Sarcoma (2018), https://doi.org/10.1155/2018/8141056.
[34] E.K. Bartlett, K.D. Simmons, H. Wachtel, et al., The rise in metastasectomy across cancer types over the past decade, Cancer 121 (2015) 747–757, https://doi.org/10.1002/cncr.29134.
[35] A. Du Bois, J. Rochon, C. Lamparter, J. Pfisterer, Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer, Int. J. Gynecol. Cancer 15 (2005) 183–191, https://doi.org/10.1111/j.1525-1438.2005.15202.x.
[36] B.W. Lamb, K.F. Brown, K. Nagpal, et al., Quality of care management decisions by multidisciplinary cancer teams: a systematic review, Ann. Surg. Oncol. 18 (2011) 2116–2125, https://doi.org/10.1245/s10434-011-1675-6.
[37] E.Z. Keung, Y.-J. Chiang, J.N. Cormier, et al., Treatment at low-volume hospitals is associated with reduced short-term and long-term outcomes for patients with retroperitoneal sarcoma, Cancer 124 (2018) 4495–4503, https://doi.org/10.1002/cncr.31699.
[38] K.B. Stitzenberg, E.R. Sigurdson, B.L. Egleston, et al., Centralization of cancer surgery: implications for patient access to optimal care, J. Clin. Oncol. 27 (2009) 4671–4678, https://doi.org/10.1200/JCO.2008.20.1715.
[39] P.A. Learn, P.B. Bach, A decade of mortality reductions in major oncologic surgery: the impact of centralization and quality improvement, Med. Care 48 (2010) 1041–1049, https://doi.org/10.1097/MLR.0b013e3181f37d5f.
[40] J.B. Liu, K.Y. Bilimoria, K. Mallin, D.P. Winchester, Patient characteristics associated with undergoing cancer operations at low-volume hospitals, Surgery 161 (2017) 433–443, https://doi.org/10.1016/j.surg.2016.07.027.