Low Rates of Chemotherapy Use for Primary, High-Grade Soft Tissue Sarcoma: A National Cancer Database Analysis

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ABSTRACT

Background: There is conflicting evidence regarding the role of chemotherapy for high-grade soft tissue sarcoma (STS) in adults. We sought to characterize patterns of chemotherapy use, including multiagent and neoadjuvant chemotherapy, in the United States. **Patients and Methods:** Using the National Cancer Database, we identified 19,969 adult patients who underwent surgical resection for primary high-grade STS from 2004 to 2016. Using logistic regression, we examined factors associated with overall, multiagent, and neoadjuvant chemotherapy use. **Results:** Chemotherapy was administered to 22% (n=4,377) of the study population. Among patients treated using chemotherapy, 85% received multiagent treatment and 47% received neoadjuvant treatment. On multivariate analysis, factors associated with chemotherapy use included tumor size, depth, histology, and primary site; receipt of radiation treatment; younger age; higher patient income; and academic treatment facility. Factors associated with multiagent chemotherapy use included tumor histology, tumor primary site, and younger age. Factors associated with neoadjuvant chemotherapy use included tumor size, depth, margin status, and primary site; receipt of radiation treatment; higher patient income; academic treatment facility type; and distance to treatment facility. Treatment at a high-volume facility was the only factor associated with overall, multiagent, and neoadjuvant chemotherapy use. No significant temporal trend was seen in overall, multiagent, or neoadjuvant chemotherapy use. **Conclusions:** Overall chemotherapy use was low (22%). The variability in chemotherapy use was driven by clinical, patient, demographic, and facility factors. Among patients treated with chemotherapy, the use of multiagent chemotherapy was high (85%), and nearly half received neoadjuvant therapy. There was a discrepancy in the use of chemotherapy—including neoadjuvant and multiagent chemotherapy—between high- and low-volume treatment centers.

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Background

Patients with localized soft tissue sarcoma (STS) are managed with surgery with or without radiation.^{1–3} Despite aggressive local therapy, up to 50% of patients with high-risk (≥ 5 cm, high-grade) primary STS develop metastases, highlighting the critical need for effective systemic therapies.^{4–11} Meta-analyses and prospective clinical trials studying the use of systemic therapies have been limited by the rare and heterogeneous nature of this disease, and provide conflicting evidence regarding the role, number of agents, and timing of chemotherapy for the management of high-risk primary STS in adults.^{12–26}

Most recently, a randomized controlled trial (EORTC-STBSG 62931) comparing treatment with doxorubicin and ifosfamide versus observation showed improved disease-free survival with chemotherapy but no difference in overall survival (OS) between the 2 groups.^{13,14} However, a subsequent analysis examining low-risk and high-risk patients separately showed improved OS with chemotherapy in patients with high-risk disease.^{15,16} In addition, although individual randomized controlled trials have not consistently shown a benefit associated with multiagent chemotherapy, modern meta-analyses have suggested a survival benefit in patients treated with multiagent regimens.^{16,19} There have been no studies to date directly comparing neoadjuvant versus adjuvant chemotherapy, each of which has advantages and disadvantages. Given these data, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for STS and European Sarcoma Networking Group guidelines cite chemotherapy as an option for patients with high-risk disease, although they do not provide more definitive recommendations.^{27,28}

Two prior studies using the SEER registry and the National Cancer Database (NCDB), respectively, have examined patterns of chemotherapy use in the treatment of STS in the United States.^{29–32} However, neither study

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included facility-level factors, such as volume, nor did they examine the timing of chemotherapy or use of single-agent or multiagent chemotherapy. Only 1 study excluded low-grade tumors, for which chemotherapy is not indicated.

Our goal was to determine the rate of chemotherapy, multiagent chemotherapy, and neoadjuvant chemotherapy use in the setting of equivocal evidence for the treatment of adult patients with primary high-grade STS. Furthermore, we sought to characterize the factors associated with the use of each of these treatment regimens at Commission on Cancer (CoC)-accredited facilities in the United States using the NCDB.

Patients and Methods

Data Source and Cohort Definition

In this analysis, we used data from the NCDB from 2004 through 2016. The NCDB is a joint project of the CoC of the American College of Surgeons and the American Cancer Society that includes data from >1,500 CoC-accredited facilities in the United States, and represents >70% of new cancer cases in the United States.³²

Among patients included in the NCDB, we identified those with STS using ICD-O-3.³³ We included patients with undifferentiated pleomorphic sarcoma (UPS), high-grade myxoid liposarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, leiomyosarcoma, liposarcoma, angiosarcoma, fibrosarcoma, fibromyxosarcoma, epithelioid sarcoma, and other undifferentiated or unclassified sarcoma. Exclusion criteria included age <18 years, a diagnosis of high-grade dysplasia, unknown or low-grade disease, and the presence of positive nodes or distant metastases. Furthermore, we excluded patients with sarcoma of the head and neck (because there is a unique set of anatomic, prognostic, surgical, and therapeutic considerations for these tumors) and patients who received palliative treatment, were treated with radiation doses that were unknown or outside the range of 40 to 75 Gy (because these doses suggest that these patients may have had non-localized disease), and who had delays >9 months from diagnosis to start of any treatment. Finally, patients were excluded who did not undergo surgery or whose surgery status was unknown, those whose physicians recommended chemotherapy but who did not receive it due to extensive comorbidities or premature death, those who did not have any histologic confirmation of malignancy, and those who did not have chemotherapy data available, resulting in 19,969 patients in the final cohort.

For the chemotherapy use analysis, all 19,969 patients were included, of whom 4,377 (22%) received chemotherapy. The number of chemotherapy agents used was available for 4,109 patients (94%), and all of these patients were included in the subgroup analysis of

single-agent versus multiagent chemotherapy use. Data regarding the timing of chemotherapy were collected starting in 2006 and were available for 3,699 patients (85%), all of whom were included in the subgroup analysis of neoadjuvant versus adjuvant chemotherapy use (Figure 1). Patients with retroperitoneal sarcoma—which is governed by a unique set of anatomic, prognostic, and therapeutic considerations—are listed in a separate NCDB database and thus were not included in this analysis. The data used in the study were derived from a deidentified NCDB file. The American College of Surgeons and CoC have not verified and are not responsible for the analytic or statistical methodology used or for the conclusions drawn from these data by the investigators.

Analytic Variables

The primary outcome was use of chemotherapy, and we were primarily interested in the demographic, clinical, patient, treatment, and facility factors associated with its use. Secondary outcomes included the use of multiagent versus single-agent chemotherapy and the use of neoadjuvant versus adjuvant chemotherapy.

Annual sarcoma surgical volume was analyzed in the initial NCDB population (n=106,822), before any exclusions, to determine high-volume versus low-volume facilities. The cutoff was the 99th percentile annual surgical case volume (supplemental eFigure 1, available with this article at JNCCN.org), which has been used in prior studies.^{34,35} Distance from patient home to treatment facility was analyzed in the final study population, initially using 10-mile increments (supplemental eFigure 2). Final “distance to treatment facility” groups were based on relatively equal group size and presumed practical relevance.

In addition, we were interested in temporal trends of chemotherapy use over time and in describing time from diagnosis to treatment and duration of treatment.

Statistical Analysis

We performed univariate and multivariate logistic regression analyses to determine factors associated with chemotherapy use. Any factors that were statistically significant in univariate analysis or that are standard covariates in the literature, such as sex and age, were included in the multivariate logistic regression. The category within each covariate with the most patients was defined as the reference category. To evaluate temporal trends of chemotherapy use, we included date of diagnosis in the multivariate regression model (as both a categorical and a continuous variable) and compared chemotherapy rates in each year (using chi-square test). Bonferroni correction was used to account for multiple hypothesis testing, and statistically significant values are noted in the tables. Results are shown as odds ratios with 95% CIs.

Figure 1. CONSORT diagram showing definition of study cohort from NCDB STS database.

Abbreviations: GIST, gastrointestinal stromal tumor; NCDB, National Cancer Database; STS, soft tissue sarcoma; WDLPS, well-differentiated liposarcoma.

*This dataset and subsequent analyses do not include patients with retroperitoneal sarcoma; due to unique anatomic, prognostic, and therapeutic considerations, retroperitoneal sarcoma cases are included in a separate NCDB dataset.

To determine factors associated with multiagent and neoadjuvant chemotherapy use, the analysis was repeated on the relevant subgroups. We included all factors that were used in the initial chemotherapy use logistic regression in each of these subgroup analyses. Statistical analysis was performed using STATA, version 15.1 (StataCorp LLP).

Results

Characteristics of Study Cohort

Overall characteristics of the study cohort are summarized in Table 1. Most patients were white (80%),

carried commercial insurance (45%) or Medicare (44%), were treated at low-volume facilities (76%), and lived <100 miles from the treatment facility (88%). The most common histology was UPS (30%) and the most common primary site was extremity (62%). Compared with the primary study cohort (ie, chemotherapy vs no chemotherapy), patients in the subgroup analyses (ie, single-agent vs multiagent chemotherapy or neoadjuvant vs adjuvant chemotherapy) were more likely to be younger, carry commercial insurance, be treated at high-volume facilities, and have larger-size and/or deep tumors. Results are summarized in supplemental eTable 1.

Table 1. Patient Characteristics

Characteristic	n	%
Sex		
Male	10,620	53.2
Female	9,349	46.8
Age, y		
18–49	4,429	22.2
50–69	8,281	41.5
≥70	7,259	36.3
Race/Ethnicity		
White	16,061	80.4
Black	1,835	9.2
Hispanic	1,173	5.9
Other/Unknown	900	4.5
Insurance status		
Commercial	8,912	44.6
Medicare	8,686	43.5
Medicaid	1,104	5.5
Uninsured	628	3.2
Other government/unknown	639	3.2
Annual income, USD		
≥\$63,333	7,392	37.0
\$50,354–\$63,332	4,691	23.5
\$40,227–\$50,353	4,311	21.6
<\$40,277	3,241	16.2
Unknown	334	1.7
County type		
Metropolitan	16,322	81.7
Urban	2,793	14.0
Rural	336	1.7
Unknown	518	2.6
Facility location		
South	6,151	30.8
East	3,829	19.2
Central	4,728	23.7
West	3,120	15.6
Unknown	2,141	10.7
Facility type		
Nonacademic	8,065	40.4
Academic	9,763	48.9
Unknown	2,141	10.7
Facility volume		
Low	15,194	76.1
High	4,775	23.9
Distance to facility, miles		
0–9	7,632	38.2
10–29	5,785	29.0
30–100	4,207	21.1
>100	2,262	11.3
Unknown	83	0.4

(continued)

Table 1. Patient Characteristics (cont.)

Characteristic	n	%
Year		
2004–2008	7,287	36.5
2009–2012	5,954	29.8
2013–2016	6,728	33.7
Charlson-Deyo comorbidity score		
0	15,865	79.5
1	3,144	15.7
≥2	960	4.8
Histology		
UPS	6,009	30.1
High-grade myxoid liposarcoma	581	2.9
Synovial sarcoma	1,026	5.1
MPNST	753	3.8
Leiomyosarcoma	3,040	15.2
Liposarcoma	2,067	10.4
Angiosarcoma	723	3.6
Fibrosarcoma	313	1.6
Fibromyxosarcoma	1,595	8.0
Epithelioid sarcoma	260	1.3
Other undifferentiated/ unclassified sarcoma	3,602	18.0
Primary site		
Extremity	12,355	61.9
Heart	153	0.8
Trunk	1,142	5.7
Thorax	1,999	10.0
Abdomen/Pelvis	3,727	18.6
Other	593	3.0
Tumor size, cm		
≤5	5,371	26.9
5.1–10	6,208	31.1
10.1–15	3,106	15.5
>15	2,530	12.7
Unknown	2,754	13.8
Tumor depth		
Deep	9,027	45.2
Superficial	4,908	24.6
Unknown	6,034	30.2
Surgical margins		
Negative	15,169	76.0
Positive	3,525	17.6
Unknown	1,275	6.4
Radiation therapy		
Yes	10,949	54.8
No	9,020	45.2

Abbreviations: MPNST, malignant peripheral nerve sheath tumor; UPS, undifferentiated pleomorphic sarcoma.

Table 2. Factors Associated With Chemotherapy Use

Characteristic	Chemotherapy n (%)	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Age, y					
18–49	1,715 (38.7)	1.83 (1.69–1.97)	<.001	1.47 (1.32–1.64)	<.001
50–69	2,129 (25.7)	Ref		Ref	
≥70	533 (7.3)	0.23 (0.21–0.25)	<.001	0.28 (0.25–0.32)	<.001
Insurance status					
Commercial	2,748 (30.8)	Ref		Ref	
Medicare	960 (11.1)	0.28 (0.26–0.30)	<.001	0.68 (0.61–0.76)	<.001
Medicaid	347 (31.4)	1.03 (0.90–1.18)	.686	0.85 (0.73–0.99)	.033
Uninsured	170 (27.1)	0.83 (0.69–1.00)	.048	0.69 (0.57–0.84)	<.001
Other government/unknown	152 (23.8)	0.70 (0.58–0.84)	<.001	0.82 (0.67–1.00)	.054
Annual income, USD					
≥\$63,333	1,699 (23.0)	Ref		Ref	
\$50,354–\$63,332	1,059 (22.6)	0.98 (0.90–1.07)	.602	0.96 (0.87–1.06)	.450
\$40,227–\$50,353	930 (21.6)	0.92 (0.84–1.01)	.078	0.92 (0.83–1.02)	.131
<\$40,277	630 (19.4)	0.81 (0.73–0.90)	<.001	0.78 (0.69–0.88)	<.001
Unknown	59 (17.7)	0.72 (0.54–0.96)	.024	0.62 (0.43–0.90)	.011
Facility location					
South	1,114 (18.1)	Ref		Ref	
East	648 (16.9)	0.92 (0.83–1.02)	.130	0.85 (0.75–0.96)	.008
Central	1,063 (22.5)	1.31 (1.19–1.44)	<.001	1.29 (1.16–1.43)	<.001
West	665 (21.3)	1.22 (1.10–1.36)	<.001	1.21 (1.07–1.37)	.002
Unknown	887 (41.4)	3.20 (2.87–3.56)	<.001	1.45 (1.24–1.69)	<.001
Facility type					
Nonacademic	1,331 (16.5)	Ref		Ref	
Academic	2,159 (22.1)	1.44 (1.33–1.55)	<.001	1.22 (1.11–1.34)	<.001
Unknown	887 (41.4)	3.58 (3.22–3.97)	<.001	—	—
Facility volume					
Low	3,081 (20.3)	Ref		Ref	
High	1,296 (27.1)	1.46 (1.36–1.58)	<.001	1.32 (1.19–1.45)	<.001
Histology					
UPS	1,121 (18.7)	Ref		Ref	
High-grade myxoid liposarcoma	182 (31.3)	1.99 (1.65–2.40)	<.001	0.94 (0.77–1.15)	.549
Synovial sarcoma	511 (49.8)	4.33 (3.77–4.97)	<.001	2.35 (2.01–2.76)	<.001
MPNST	207 (27.5)	1.65 (1.39–1.96)	<.001	0.79 (0.65–0.96)	.017
Leiomyosarcoma	609 (20.0)	1.09 (0.98–1.22)	.116	0.99 (0.87–1.12)	.825
Liposarcoma	371 (17.9)	0.95 (0.84–1.09)	.475	0.68 (0.59–0.79)	<.001
Angiosarcoma	223 (30.8)	1.94 (1.64–2.31)	<.001	2.59 (2.12–3.18)	<.001
Fibrosarcoma	48 (15.3)	0.79 (0.58–1.08)	.141	0.71 (0.51–0.99)	.047
Fibromyxosarcoma	222 (13.9)	0.71 (0.60–0.82)	<.001	0.72 (0.61–0.86)	<.001
Epithelioid sarcoma	59 (22.7)	1.28 (0.95–1.72)	.104	0.97 (0.70–1.34)	.846
Other undifferentiated/ unclassified sarcoma	824 (22.9)	1.29 (1.17–1.43)	<.001	1.18 (1.05–1.32)	.004

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Table 2. Factors Associated With Chemotherapy Use (cont.)

Characteristic	Chemotherapy n (%)	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Primary site					
Extremity	2,549 (20.6)	Ref		Ref	Ref
Heart	85 (55.6)	4.81 (3.49–6.63)	<.001	3.10 (2.13–4.50)	<.001
Trunk	184 (16.1)	0.74 (0.63–0.87)	<.001	0.84 (0.70–1.00)	.052
Thorax	479 (24.0)	1.21 (1.08–1.36)	<.001	1.26 (1.11–1.43)	<.001
Abdomen/Pelvis	953 (25.6)	1.32 (1.21–1.44)	<.001	1.11 (1.00–1.23)	.042
Other	127 (21.4)	1.05 (0.86–1.28)	.645	1.00 (0.80–1.25)	.996
Tumor size, cm					
≤5	548 (10.2)	0.36 (0.32–0.40)	<.001	0.34 (0.30–0.38)	<.001
5.1–10	1,501 (24.2)	Ref		Ref	
10.1–15	980 (31.6)	1.45 (1.31–1.59)	<.001	1.55 (1.39–1.72)	<.001
>15	814 (32.2)	1.49 (1.34–1.65)	<.001	1.62 (1.45–1.81)	<.001
Unknown	534 (19.4)	0.75 (0.68–0.84)	<.001	0.77 (0.68–0.88)	<.001
Tumor depth					
Deep	2,391 (26.5)	Ref		Ref	
Superficial	603 (12.3)	0.39 (0.35–0.43)	<.001	0.57 (0.51–0.63)	<.001
Unknown	1,383 (22.9)	0.83 (0.76–0.89)	<.001	0.93 (0.84–1.02)	.114
Surgical margins					
Negative	3,260 (21.5)	Ref		Ref	
Positive	738 (20.9)	0.97 (0.88–1.06)	.469	1.11 (1.00–1.23)	.042
Unknown	379 (29.7)	1.55 (1.36–1.75)	<.001	1.53 (1.33–1.78)	<.001
Radiation therapy					
Yes	2,585 (23.6)	Ref		Ref	
No	1,792 (19.9)	0.80 (0.75–0.86)	<.001	0.82 (0.75–0.88)	<.001

Abbreviations: MPNST, malignant peripheral nerve sheath tumor; OR, odds ratio; UPS, undifferentiated pleomorphic sarcoma.

Factors Associated With Chemotherapy Use

Chemotherapy was administered to 22% (n=4,377) of the study population. On multivariate analysis, factors associated with chemotherapy use included younger age, academic facility type, high-volume facility, larger tumor size, greater tumor depth, positive surgical margins, and receipt of RT (Table 2). Histologies associated with the highest rates of chemotherapy use were synovial sarcoma (50%) and angiosarcoma (31%), whereas fibromyxosarcoma (14%) and liposarcoma (18%) were associated with the lowest rates of chemotherapy use. The primary tumor site associated with the highest rate of chemotherapy use was the heart (56%) and the lowest was the trunk (16%).

Factors Associated With Multiagent Chemotherapy Use

Of the patients included in the multiagent versus single-agent chemotherapy analysis, 85% (n=3,505) received multiagent chemotherapy. On multivariate analysis, factors associated with multiagent chemotherapy use were

younger age, tumor histology, primary site, and treatment at a high-volume facility (Table 3). By histology, multiagent chemotherapy use was lowest in angiosarcoma (49%) and highest in leiomyosarcoma (90%) and synovial sarcoma (90%).

Factors Associated With Neoadjuvant Chemotherapy Use

Of the patients included in the neoadjuvant versus adjuvant chemotherapy analysis, 47% (n=1,734) were treated using neoadjuvant chemotherapy. On multivariate analysis, factors associated with neoadjuvant chemotherapy use included higher income, academic facility type, high-volume facility, greater distance from treatment facility, larger tumor size, and receipt of RT (Table 4). Patients with UPS (53%) were more likely to undergo treatment using neoadjuvant chemotherapy, whereas those with angiosarcoma (27%) were the least likely. Patients with tumors in the extremities (57%) were the most likely to undergo neoadjuvant chemotherapy, whereas those with tumors in the heart (8%) were the least

Table 3. Factors Associated With Multiagent Chemotherapy Use

Characteristic	Multiagent Chemotherapy n (%)	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Age, y					
18–49	1,466 (90.1)	1.44 (1.17–1.77)	.001	1.19 (0.90–1.57)	.227
50–69	1,738 (86.4)	Ref		Ref	
≥70	301 (64.0)	0.28 (0.22–0.35)	<.001	0.31 (0.23–0.42)	<.001
Facility volume					
Low	2,376 (83.2)	Ref		Ref	
High	1,129 (90.1)	1.84 (1.49–2.27)	<.001	1.73 (1.34–2.24)	<.001
Histology					
UPS	886 (84.6)	Ref		Ref	
High-grade myxoid liposarcoma	153 (88.4)	1.39 (0.85–2.28)	.192	1.03 (0.61–1.73)	.905
Synovial sarcoma	448 (92.0)	2.09 (1.45–3.02)	<.001	1.39 (0.93–2.08)	.108
MPNST	175 (88.8)	1.45 (0.90–2.32)	.128	1.03 (0.62–1.71)	.907
Leiomyosarcoma	515 (89.6)	1.56 (1.14–2.14)	.006	1.87 (1.33–2.65)	<.001
Liposarcoma	309 (89.3)	1.52 (1.04–2.22)	.031	1.67 (1.11–2.50)	.013
Angiosarcoma	100 (49.0)	0.17 (0.13–0.24)	<.001	0.20 (0.14–0.29)	<.001
Fibrosarcoma	40 (87.0)	1.21 (0.51–2.90)	.667	1.15 (0.46–2.89)	.766
Fibromyxosarcoma	184 (88.0)	1.34 (0.85–2.10)	.206	1.13 (0.71–1.81)	.607
Epithelioid sarcoma	50 (87.7)	1.30 (0.58–2.91)	.527	1.35 (0.58–3.17)	.490
Other undifferentiated/ unclassified sarcoma	645 (84.0)	0.95 (0.74–1.23)	.712	0.97 (0.74–1.28)	.846
Primary site					
Extremity	2,131 (88.5)	Ref		Ref	
Heart	56 (73.7)	0.36 (0.22–0.62)	<.001	0.90 (0.47–1.74)	.759
Trunk	147 (84.0)	0.68 (0.45–1.04)	.077	0.93 (0.58–1.49)	.761
Thorax	345 (76.5)	0.42 (0.33–0.54)	<.001	0.61 (0.45–0.81)	.001
Abdomen/Pelvis	732 (82.8)	0.63 (0.50–0.78)	<.001	0.56 (0.43–0.72)	<.001
Other	94 (81.7)	0.58 (0.36–0.95)	.030	0.75 (0.44–1.28)	.285

Abbreviations: MPNST, malignant peripheral nerve sheath tumor; OR, odds ratio; UPS, undifferentiated pleomorphic sarcoma.

likely. Patients with positive surgical margins were more likely to receive adjuvant than neoadjuvant chemotherapy.

Temporal Trends of Chemotherapy, Neoadjuvant Chemotherapy, and Multiagent Chemotherapy Use

Trends of chemotherapy use, timing, and multiagent therapy are shown in supplemental eFigure 3 and eTable 2. No meaningful change in the use of chemotherapy over time was noted.

Discussion

The results of our analysis show the patterns of chemotherapy use, including multiagent and neoadjuvant chemotherapy, for patients with primary high-grade STS treated with primary surgery across CoC-accredited facilities in the United States. The overall rate of chemotherapy use was 22%; in young (aged <50 years), healthy (Charlson-Deyo comorbidity condition [CDCC] score of

0) patients with high-risk disease (high-grade, >10 cm), use rates reached 45%.

Even in the setting of equivocal data, these rates may be lower than anticipated. However, our findings regarding overall chemotherapy use are consistent with prior literature.¹¹ Factors associated with higher rates of chemotherapy use included larger tumor size and deep tumors, consistent with earlier findings that these patients preferentially benefit from chemotherapy.^{11,15,36–38} Facility-level variables were also associated with increased chemotherapy use, including high-volume and academic type. The primary tumor site that was associated with the highest rate of chemotherapy use was the heart. This is consistent with prior literature, which has shown both high rates of chemotherapy use and improved survival associated with chemotherapy for this rare tumor type.^{39–42}

Table 4. Factors Associated With Neoadjuvant Chemotherapy Use

Characteristic	Neoadjuvant Chemotherapy n (%)	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Annual income, USD					
≥\$63,333	681 (46.9)	Ref		Ref	
\$50,354–\$63,332	424 (47.7)	1.03 (0.87–1.22)	.702	0.94 (0.78–1.13)	.505
\$40,227–\$50,353	394 (50.3)	1.14 (0.96–1.36)	.134	0.97 (0.80–1.19)	.801
<\$40,277	209 (39.6)	0.74 (0.60–0.91)	.004	0.65 (0.51–0.83)	<.001
Unknown	26 (54.2)	1.34 (0.75–2.38)	.325	0.86 (0.43–1.71)	.661
Facility type					
Nonacademic	402 (35.9)	Ref		Ref	
Academic	998 (54.4)	2.13 (1.83–2.48)	<.001	1.42 (1.17–1.72)	<.001
Unknown	334 (44.8)	1.45 (1.20–1.75)	<.001	—	—
Facility volume					
Low	1,086 (41.4)	Ref		Ref	
High	648 (60.4)	2.16 (1.87–2.50)	<.001	1.50 (1.25–1.79)	<.001
Distance to treatment, miles					
0–9	474 (37.7)	Ref		Ref	
10–29	527 (46.2)	1.42 (1.20–1.67)	<.001	1.26 (1.05–1.51)	.013
30–100	427 (51.8)	1.77 (1.48–2.11)	<.001	1.50 (1.22–1.84)	<.001
>100	300 (64.1)	2.95 (2.36–3.67)	<.001	2.33 (1.79–3.03)	<.001
Unknown	6 (66.7)	3.30 (0.82–13.26)	.092	2.87 (0.58–14.12)	.195
Year					
2004–2008	444 (44.0)	Ref		Ref	
2009–2012	616 (46.7)	1.12 (0.95–1.32)	.188	1.28 (1.06–1.55)	.011
2013–2016	674 (49.2)	1.23 (1.05–1.45)	.011	1.48 (1.20–1.82)	<.001
Primary site					
Extremity	1,211 (56.5)	Ref		Ref	
Heart	—	—	—	0.18 (0.07–0.44)	<.001
Trunk	61 (38.1)	0.48 (0.34–0.66)	<.001	0.56 (0.39–0.80)	.002
Thorax	158 (38.2)	0.48 (0.38–0.59)	<.001	0.66 (0.51–0.84)	.001
Abdomen/Pelvis	269 (33.7)	0.39 (0.33–0.46)	<.001	0.57 (0.46–0.69)	<.001
Other	—	—	—	0.44 (0.27–0.70)	.001
Tumor size, cm					
≤5	145 (32.8)	0.63 (0.50–0.79)	<.001	0.73 (0.57–0.94)	.014
5.1–10	549 (43.6)	Ref		Ref	
10.1–15	455 (55.7)	1.63 (1.36–1.94)	<.001	1.62 (1.33–1.97)	<.001
>15	374 (54.2)	1.53 (1.27–1.85)	<.001	1.68 (1.36–2.08)	<.001
Unknown	211 (43.1)	0.98 (0.79–1.21)	.847	1.11 (0.87–1.42)	.389
Tumor depth					
Deep	1,022 (47.9)	Ref		Ref	
Superficial	228 (43.1)	0.82 (0.68–1.00)	.046	0.98 (0.79–1.22)	.871
Unknown	484 (46.6)	0.95 (0.82–1.10)	.489	1.52 (1.26–1.83)	<.001
Surgical margins					
Negative	1,469 (53.5)	Ref		Ref	
Positive	191 (29.9)	0.37 (0.31–0.45)	<.001	0.46 (0.37–0.56)	<.001
Unknown	74 (23.7)	0.27 (0.21–0.36)	<.001	0.43 (0.32–0.58)	<.001
Radiation therapy					
Yes	1,224 (55.3)	Ref		Ref	
No	510 (34.4)	0.42 (0.37–0.49)	<.001	0.53 (0.45–0.62)	<.001

Abbreviation: OR, odds ratio.

Among patients receiving chemotherapy, multiagent chemotherapy was commonly used (85%). Although there are no definitive guidelines regarding the use of multiagent chemotherapy, available data have shown the benefits of multiagent regimens.¹⁶ Therefore, this high rate of use noted in our study may be an expected finding. Notably, older age (≥ 70 years) was associated with decreased rates of multiagent chemotherapy use, possibly due to concern related to treatment morbidity, given that patients in this age group had the highest rates of CDCC scores of ≥ 2 (7.7% vs 1.5% in patients aged 18–49 years and 4.1% in patients aged 50–69 years; $P < .001$). However, whether the morbidity of multiagent chemotherapy outweighs the benefits in an older age group deserves further study. Furthermore, the lowest rates of multiagent chemotherapy use were in patients with angiosarcoma. A prior phase II study examining patients with metastatic or unresectable angiosarcoma showed a survival benefit with the use of paclitaxel, a single-agent regimen.⁴³ The results of that trial may explain the high use of single-agent regimens observed in our study.

The overall rate of neoadjuvant chemotherapy use was 47%, which reflects the equivocal nature of the current data on timing of chemotherapy for primary high-grade STS. Although neoadjuvant chemotherapy provides an opportunity to evaluate treatment response and for downstaging, the availability of surgical pathology in the adjuvant setting may result in more refined patient selection. In our cohort, neoadjuvant chemotherapy use was more frequent in patients with larger tumors, presumably for the potential downstaging impact.⁴⁴

High facility volume was associated with increased chemotherapy use, including both multiagent and neoadjuvant, and was the only variable associated with use rates in all 3 cohorts. Facility volume correlates with increased compliance with oncologic treatment guidelines,^{45,46} and treatment at high-volume facilities has been associated with improved survival in multiple cancer types, including sarcoma.^{47–50}

Two prior studies, using data from NCDB and SEER, examined chemotherapy use in patients with sarcoma.^{29,31} Notable differences were that our study examined the factors associated with multiagent and neoadjuvant chemotherapy use in addition to overall chemotherapy use. Finally, facility-level variables, including facility volume, were not included in the prior studies.

This study has limitations. First, our study was limited to CoC-accredited facilities in the United States.

In general, CoC facilities tend to be larger, are more frequently located in urban areas, have higher surgical volume, and more frequently treat patients with cancer compared with non-CoC-accredited facilities.^{51,52} Second, although the NCDB is fairly comprehensive, it only represents approximately 70% of new cancer diagnoses annually.³² Together, these factors may limit the generalizability of our findings. Third, although this study is retrospective and hypothesis-generating, causal links cannot be established. Fourth, there are no data regarding referral patterns or patient preferences in the NCDB. Therefore, there may be factors associated with care at high-volume centers that were not captured in these data. In addition, there may be variability in how various centers code clinical data, particularly what is considered chemotherapy versus systemic therapy.

Conclusions

We observed low rates of chemotherapy use in this population of patients with high-risk STS. Among patients receiving chemotherapy, the preference for multiagent chemotherapy and the balanced use of neoadjuvant and adjuvant chemotherapy reflected the nature of the existing clinical data. Treatment at a high-volume facility was the only variable associated with the use of chemotherapy, multiagent chemotherapy, and neoadjuvant chemotherapy, suggesting a preference for these approaches at more experienced treatment centers.

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Supplemental online content for:

Low Rates of Chemotherapy Use for Primary, High-Grade Soft Tissue Sarcoma: A National Cancer Database Analysis

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eFigure 1: Analysis of Annual Sarcoma Surgical Case Volume

eFigure 2: Distance From Patient Residence to Treatment Facility

eFigure 3: Trends in Chemotherapy Use, Multiagent Chemotherapy Use, and Neoadjuvant Chemotherapy Use

eTable 1: Study Cohort Characteristics

eTable 2: Analysis of Temporal Trend of Chemotherapy Use

eFigure 1. Analysis of annual sarcoma surgical case volume (by facility) in the National Cancer Database (soft tissue sarcoma database, n=106,822) from 2004 to 2016. Facilities in the 99th percentile performed >55 sarcoma surgeries per year. One facility performed 160 sarcoma surgeries per year, and the next-highest-volume facility performed 99 sarcoma surgeries per year. In the final study population, 19 centers (4.9%) were categorized as high volume and 367 (95.1%) were categorized as low volume. A total of 15,194 (76.1%) patients were seen at low-volume centers, whereas 4,775 patients (23.9%) were seen at high-volume centers.

eFigure 2. Distance from patient residence to treatment facility for adult patients with primary high-grade soft tissue sarcoma in the National Cancer Database from 2004 to 2016.

eFigure 3. Trends in (A) chemotherapy use, (B) multiagent chemotherapy use, and (C) neoadjuvant chemotherapy use in adult patients with primary high-grade soft tissue sarcoma in the National Cancer Database from 2004 to 2016.

eTable 1. Study Cohort Characteristics

Characteristic	Yes vs No Chemotherapy		Single-Agent vs Multiagent Chemotherapy		Neoadjuvant vs Adjuvant Chemotherapy	
	n (%)	P Value	n (%)	P Value	n (%)	P Value
Total, n	19,969		4,109		3,699	
Sex		.626		.861		<.001
Male	10,620 (53.2)		2,204 (53.6)		1,970 (53.3)	
Female	9,349 (46.8)		1,905 (46.4)		1,729 (46.7)	
Age, y		<.001		<.001		.328
18–49	4,429 (22.2)		1,627 (39.6)		1,427 (38.6)	
50–69	8,281 (41.5)		2,012 (49.0)		1,819 (49.2)	
≥70	7,259 (36.3)		470 (11.4)		453 (12.2)	
Race/Ethnicity		<.001		.124		.284
White	16,061 (80.4)		3,206 (78.0)		2,855 (77.2)	
Black	1,835 (9.2)		416 (10.1)		382 (10.3)	
Hispanic	1,173 (5.9)		306 (7.5)		296 (8.0)	
Other/Unknown	900 (4.5)		181 (4.4)		166 (4.5)	
Insurance status		<.001		<.001		.739
Commercial	8,912 (44.6)		2,594 (63.1)		2,297 (62.1)	
Medicare	8,686 (43.5)		876 (21.3)		844 (22.8)	
Medicaid	1,104 (5.5)		332 (8.1)		300 (8.1)	
Uninsured	628 (3.2)		165 (4.0)		149 (4.0)	
Other government/unknown	639 (3.2)		142 (3.5)		109 (3.0)	
Annual income, USD		<.001		.083		.003
≥\$63,333	7,392 (37.0)		1,592 (38.7)		1,451 (39.2)	
\$50,354–\$63,332	4,691 (23.5)		983 (23.9)		888 (24.0)	
\$40,227–\$50,353	4,311 (21.6)		886 (21.6)		784 (21.2)	
<\$40,277	3,241 (16.2)		592 (14.4)		528 (14.3)	
Unknown	334 (1.7)		56 (1.4)		48 (1.3)	
County type		.032		.608		.077
Metropolitan	16,322 (81.7)		3,399 (82.7)		3,074 (83.1)	
Urban	2,793 (14.0)		539 (13.1)		472 (12.8)	
Rural	336 (1.7)		78 (1.9)		70 (1.9)	
Unknown	518 (2.6)		93 (2.3)		83 (2.2)	
Facility location		<.001		<.001		.061
South	6,151 (30.8)		1,008 (24.5)		958 (25.9)	
East	3,829 (19.2)		617 (15.0)		537 (14.5)	
Central	4,728 (23.7)		1,013 (24.7)		901 (24.3)	
West	3,120 (15.6)		624 (15.2)		557 (15.1)	
Unknown	2,141 (10.7)		847 (20.6)		746 (20.2)	
Facility type		<.001		<.001		<.001
Nonacademic	8,065 (40.4)		1,213 (29.5)		1,119 (30.2)	
Academic	9,763 (48.9)		2,049 (49.9)		1,834 (49.6)	
Unknown	2,141 (10.7)		847 (20.6)		746 (20.2)	

(continued on next page)

eTable 1. Study Cohort Characteristics (cont.)

Characteristic	Yes vs No Chemotherapy		Single-Agent vs Multiagent Chemotherapy		Neoadjuvant vs Adjuvant Chemotherapy	
	n (%)	P Value	n (%)	P Value	n (%)	P Value
Facility volume		<.001		<.001		<.001
Low	15,194 (76.1)		2,856 (69.5)		2,626 (71.0)	
High	4,775 (23.9)		1,253 (30.5)		1,073 (29.0)	
Distance to treatment, miles		<.001		.042		<.001
0–9	7,632 (38.2)		1,403 (34.2)		1,256 (34.0)	
10–29	5,785 (29.0)		1,242 (30.2)		1,141 (30.8)	
30–100	4,207 (21.1)		917 (22.3)		825 (22.3)	
>100	2,262 (11.3)		530 (12.9)		468 (12.7)	
Unknown	83 (0.4)		17 (0.4)		9 (0.2)	
Year		.001		.023		.040
2004–2008	7,287 (36.5)		1,548 (37.7)		1,010 (27.3)	
2009–2012	5,954 (29.8)		1,249 (30.4)		1,319 (35.7)	
2013–2016	6,728 (33.7)		1,312 (31.9)		1,370 (37.0)	
Charlson-Deyo comorbidity score		<.001		<.001		.045
0	15,865 (79.5)		3,492 (85.0)		3,113 (84.1)	
1	3,144 (15.7)		506 (12.3)		480 (13.0)	
≥2	960 (4.8)		111 (2.7)		106 (2.9)	
Histology		<.001		<.001		<.001
UPS	6,009 (30.1)		1,047 (25.5)		923 (25.0)	
High-grade myxoid liposarcoma	581 (2.9)		173 (4.2)		149 (4.0)	
Synovial sarcoma	1,026 (5.1)		487 (11.8)		442 (12.0)	
MPNST	753 (3.8)		197 (4.8)		160 (4.3)	
Leiomyosarcoma	3,040 (15.2)		575 (14.0)		515 (13.9)	
Liposarcoma	2,067 (10.4)		346 (8.4)		319 (8.6)	
Angiosarcoma	723 (3.6)		204 (5.0)		186 (5.0)	
Fibrosarcoma	313 (1.6)		46 (1.1)		41 (1.1)	
Fibromyxosarcoma	1,595 (8.0)		209 (5.1)		198 (5.4)	
Epithelioid sarcoma	260 (1.3)		57 (1.4)		48 (1.3)	
Other undifferentiated/unclassified sarcoma	3,602 (18.0)		768 (18.7)		718 (19.4)	
Primary site		<.001		<.001		<.001
Extremity	12,355 (61.9)		2,408 (58.6)		2,145 (58.0)	
Heart	153 (0.8)		76 (1.8)		73 (2.0)	
Trunk	1,142 (5.7)		175 (4.3)		160 (4.3)	
Thorax	1,999 (10.0)		451 (11.0)		414 (11.2)	
Abdomen/Pelvis	3,727 (18.6)		884 (21.5)		799 (21.6)	
Other	593 (3.0)		115 (2.8)		108 (2.9)	
Tumor size, cm		<.001		<.001		<.001
≤5	5,371 (26.9)		506 (12.3)		442 (12.0)	
5.1–10	6,208 (31.1)		1,411 (34.4)		1,260 (34.1)	
10.1–15	3,106 (15.6)		919 (22.4)		817 (22.1)	
>15	2,530 (15.5)		774 (18.8)		690 (18.6)	
Unknown	2,754 (13.8)		499 (12.1)		490 (13.2)	

(continued on next page)

eTable 1. Study Cohort Characteristics (cont.)

Characteristic	Yes vs No Chemotherapy		Single-Agent vs Multiagent Chemotherapy		Neoadjuvant vs Adjuvant Chemotherapy	
	n (%)	P Value	n (%)	P Value	n (%)	P Value
Depth		<.001		.005		.134
Deep	9,027 (45.2)		2,274 (55.3)		2,132 (57.6)	
Superficial	4,908 (24.6)		565 (13.8)		529 (14.3)	
Unknown	6,034 (30.2)		1,270 (30.9)		1,038 (28.1)	
Surgical margins		<.001		<.001		<.001
Negative	15,169 (76.0)		3,076 (74.9)		2,748 (74.3)	
Positive	3,525 (17.6)		687 (16.7)		639 (17.3)	
Unknown	1,275 (6.4)		346 (8.4)		312 (8.4)	
Radiation therapy		<.001		.002		<.001
Yes	10,949 (54.8)		2,468 (60.1)		2,215 (59.9)	
No	9,020 (45.2)		1,641 (39.9)		1,484 (40.1)	

Abbreviations: MPNST, malignant peripheral nerve sheath tumor; UPS, undifferentiated pleomorphic sarcoma.

eTable 2. Analysis of Temporal Trend of Chemotherapy Use

Year	OR (95% CI)	P Value
Temporal trend of chemotherapy use 2004–2016		
2004	Ref	
2005	0.98 (0.83–1.17)	.858
2006	1.01 (0.85–1.20)	.902
2007	0.86 (0.72–1.02)	.087
2008	0.88 (0.74–1.04)	.142
2009	0.86 (0.73–1.03)	.098
2010	0.86 (0.72–1.02)	.086
2011	0.89 (0.75–1.06)	.198
2012	1.00 (0.84–1.20)	.960
2013	0.75 (0.63–0.90)	.002
2014	0.87 (0.74–1.04)	.120
2015	0.90 (0.76–1.07)	.245
2016	0.69 (0.58–0.83)	<.001
Temporal trend of multiagent chemotherapy use 2004–2016		
2004	Ref	
2005	1.68 (1.01–2.78)	.044
2006	0.97 (0.62–1.52)	.902
2007	1.25 (0.78–2.01)	.356
2008	0.93 (0.59–1.45)	.735
2009	1.16 (0.73–1.82)	.533
2010	0.72 (0.46–1.11)	.140
2011	0.99 (0.63–1.57)	.973
2012	1.10 (0.70–1.73)	.689
2013	0.90 (0.57–1.42)	.648
2014	0.90 (0.59–1.38)	.640
2015	0.82 (0.54–1.26)	.368
2016	0.73 (0.47–1.13)	.155
Temporal trend of neoadjuvant chemotherapy use 2006–2016		
2006	Ref	
2007	1.14 (0.84–1.55)	.390
2008	1.20 (0.89–1.62)	.241
2009	1.22 (0.91–1.65)	.188
2010	1.08 (0.79–1.48)	.620
2011	1.23 (0.90–1.68)	.189
2012	1.43 (1.06–1.94)	.020
2013	1.34 (0.98–1.83)	.068
2014	1.27 (0.95–1.71)	.110
2015	1.45 (1.08–1.94)	.014
2016	1.43 (1.05–1.95)	.022

Abbreviation: OR, odds ratio.