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ORIGINAL ARTICLE – SARCOMA

Disparities in Amputation Rates for Non-metastatic Extremity Soft Tissue Sarcomas and the Impact on Survival

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ABSTRACT

Background. There are no definitive recommendations guiding amputation use in extremity soft tissue sarcomas (STSs). This study explores disparities in amputation rates and survival in patients with non-metastatic adult-type extremity STSs.

Methods. Patients with non-metastatic adult-type extremity STSs were identified from the 1998–2012 National Cancer Database. Factors affecting amputation were examined across all ages and separately in adults (> 40 years), adolescent/young adults (AYA: ages 15–39), and children (age < 15). Impact on 10-year overall survival (OS) was explored.

Results. Of 15,886 patients, 4.65% had an amputation. AYAs had the most amputations (6.4%) compared to children (5.9%) and adults (4.2%) ($p < 0.001$). Patients with public insurance (OR 1.3, CI 1.08–1.58) and from central states (OR 1.5, CI 1.2–1.86) were more likely to undergo amputation, whereas those from high income brackets (OR 0.8, CI 0.62–0.94) and treated at community cancer centers were less likely (OR 0.7, CI 0.62–0.90). Amputation was an independent risk factor for death at 10 years, with the greatest impact in AYAs compared to older adults (HR 1.7, $p < 0.001$). Treatment in eastern or central states, lower income, lack of private insurance, and comorbidities were all associated with decreased OS (all $p < 0.05$). Female gender (HR 0.8, CI 0.78–0.89) and high-volume centers (HR 0.8, CI 0.74–0.94) were associated with improved OS.

Conclusions. Although amputations for extremity STSs are rare, disparities exist across age groups, insurance and geography when it comes to the use of amputation in patients with extremity STSs. Moreover, having an amputation is an independent risk factor for death, with the greatest impact in AYAs.

Soft tissue sarcomas (STSs) represent a rare, yet diverse group of tumors arising from mesenchymal tissue.[1] STSs occur most often in middle aged and older adults, but may occur at any age, and can comprise up to 10% of all pediatric malignancies.[2–5]

Surgical resection with negative margins is the standard of care for most extremity STSs.[6] Although leaving positive microscopic margins may be reasonable in rare cases,[7] macroscopic residual disease is associated with a worse prognosis.[8] As such, surgery is often preceded or followed by local radiation therapy.[6] Results with this approach demonstrate high rates of local control, while optimizing postoperative function.[6] Isolated limb perfusion and chemotherapy have also been explored as preoperative strategies to decrease tumor size in borderline resectable tumors.[9–12] Additionally, modern reconstruction techniques allow for improved tissue coverage after resection and increase feasibility of limb salvage therapy (LST).[13–15] Despite incorporation of multimodality therapies, some cases necessitate formal amputation in order to achieve adequate surgical margins and local disease control.[6] Amputation may also be needed in cases of locally recurrent disease.[6,16,17]

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Currently, there are no definitive recommendations guiding amputation use in extremity soft tissue sarcomas. As a result, the decision to proceed with amputation may be influenced by a variety of factors. The purpose of this study was to evaluate potential disparities in the amputation rate across different demographic factors in patients with non-metastatic extremity STSs. Additionally, we sought to determine factors affecting the likelihood of having an amputation as well as potential factors affecting overall survival (OS).

METHODS

Cohort Selection

The National Cancer Database (NCDB) is a nationwide cancer registry formed by a collaboration of the American College of Surgeons (ACS) and the American Cancer Society. The NCDB database draws from more than 1500 Commission on Cancer-accredited facilities and captures more than 70% of all newly diagnosed malignancies in the United States annually.[18] The de-identified data represented here was obtained from the NCDB Participant User File (PUF). The American College of Surgeons and Commission on Cancer (CoC) have not verified and are not responsible for the analytic or statistical methodology, or the conclusions drawn from these data by the investigators.

Using the NCDB 1998–2012 PUF, all patients with non-metastatic adult-type extremity STSs were identified using the International Classification of Disease for Oncology, 3rd edition (ICD-0-3) by site and histology. Extremity sarcoma cases were identified using site codes C40.0–C41.9 and C49.0–C49.9, and histology codes 8810/3, 8850/3, 9040/3, and 9044/3. Categories of extremity sarcoma included: clear/heme (clear cell sarcoma, angiosarcoma, Kuffer cell sarcoma, hemangioendothelial sarcoma, epithelioid hemangioendothelioma); fibrous (fibrosarcoma, fibromyxosarcoma, periosteal fibrosarcoma, solitary fibrous tumor, malignant fibrous histiocytoma, dermatofibrosarcoma, pigmented dermatofibrosarcoma protuberans, myxosarcoma); lipomatous (liposarcoma, myxoidliposarcoma, pleomorphic liposarcoma, mixed liposarcaoma, fibroblastic liposarcoma, dedifferentiated liposarcoma); synovial (synovial sarcoma NOS, synovial sarcoma spindle cell, synovial sarcoma epithelioid cell, synovial sarcoma biphasic); and adult muscular (leiomyosarcoma, epithelioid leiomyosarcoma, angiomyosarcoma, myosarcoma, myxoid leiomyosarcoma). This study received IRB exemption status after independent regulatory review due to the de-identified nature of the data.

Statistical Analysis

Patients were divided into three cohorts stratified by age: pediatric (< 15 years) adolescent/young adult (AYA: ages 15–39) and older adult (age ≥ 40). Descriptive data including patient sociodemographic, disease, and treatment-related factors were summarized by mean (standard deviation) or median (interquartile range) for continuous, and count (percentage) for categorical data. Comorbidities were classified based upon the Charlson/Deyo score.[19] The Charlson/Deyo score is the scoring system used by the ACS and CoC NCDB dataset. Comorbid conditions as described by Charlson/Deyo are mapped from as many as ten reported ICD-9-CM or ICD-10 secondary diagnosis codes. The Charlson/Deyo value is a weighted score derived from the sum of the scores for each of the comorbid conditions. The range for this value is between 0 and 25. The Charlson-Deyo score is derived from the highest score that is calculated from using either the ICD-9 codes or the ICD-10 codes. Treatment center volume was defined as "high" for centers that treated > 10 extremity sarcomas each year, "moderate" for 5–10 cases, and "low" for < 5 cases/year.

Univariate comparisons were performed using the Fisher exact test for categorical, and t test or non-parametric Kruskal–Wallis test for continuous covariates, followed by multivariable logistic regression to determine independent factors for utilization of amputation.

Overall survival was compared using the Kaplan–Meier method with log-rank test. Multivariable Cox proportional hazards modeling was performed to investigate independent effects of amputation on the risk of death. All tests were two-sided and statistical significance was set at $p < 0.05$. Analyses were performed with SAS, version 9.3 (SAS Institute).

RESULTS

In total, 15,886 patients with non-metastatic adult-type extremity STSs were identified: 81% older adults, 17.5% AYA, and 1.5% pediatric (Table 1). The majority of patients were white (78.9%) with no comorbidities (62.9%) and were treated at high-volume (57.5%), academic (55.5%) centers with private insurance (52.1%). Lower extremity STSs were the most common primary location (74.7%). More patients were treated in the eastern region of the United States (41.8%) compared to the central and west regions.

An amputation was performed in 4.7% of all cases. Amputations were more likely to occur in high-volume centers compared to moderate- and low-volume centers (5.6% vs 3.4% vs 3.3%; $p < 0.001$) as well as academic centers compared to community hospitals (5.4% vs 3.7%;

TABLE 1 Patient characteristics for all patients with non-metastatic extremity STS

	Total (N = 15,886)	Amputation (N = 738)	LST (N = 15,148)	P
Age				< 0.0001
Pediatric	239 (1.5%)	14 (5.9%)	225 (94.1%)	
AYA	2781 (17.5%)	178 (6.4%)	2603 (93.6%)	
Adult	12,866 (81%)	546 (4.2%)	12,320 (95.8%)	
Male	8480 (53.4%)	390 (4.6%)	8090 (95.4%)	0.76
Race				< 0.0001
White	12,530 (78.9%)	548 (4.4%)	11,982 (95.6%)	
Black	1589 (10.0%)	85 (5.4%)	1504 (94.7%)	
Asian/PI	390 (5.9%)	11 (2.8%)	379 (97.2%)	
Hispanic	935 (5.9%)	76 (8.1%)	859 (91.9%)	
Other	442 (2.8%)	18 (4.1%)	424 (95.9%)	
Facility volume				< 0.0001
Low	4209 (26.5%)	140 (3.3%)	4069 (96.7%)	
Moderate	2471 (15.6%)	83 (3.4%)	2388 (96.6%)	
High	9206 (57.5%)	515 (5.6%)	8691 (94.4%)	
Facility location				< 0.0001
Central	5883 (37.3%)	334 (5.7%)	5549 (94.3%)	
East	6639 (41.9%)	257 (3.8%)	6382 (96.1%)	
West	2971 (18.7)	130 (4.4%)	2841 (95.6%)	
N/A	393 (2.5%)	17 (4.3%)	376 (95.7%)	
Facility type				< 0.0001
Academic	8811 (55.5%)	473 (5.4%)	8337 (94.6%)	
Community	6648 (41.9%)	248 (3.7%)	6400 (96.3%)	
Other	428 (2.7%)	17 (4.0%)	411 (96.0%)	
Insurance type				0.002
Private	8271 (55.5%)	346 (4.2%)	7925 (95.8%)	
Public/Govt	6490 (40.9%)	326 (5.0%)	6164 (95.0%)	
Uninsured	566 (3.6%)	41 (7.2%)	525 (92.8%)	
Unknown	559 (3.5%)	25 (4.5%)	534 (95.5%)	
Income level				< 0.0001
Comfortable	5303 (33.4%)	177 (3.3%)	5126 (96.7%)	
Moderate	7663 (48.2%)	368 (4.8%)	7295 (95.2%)	
Low	2525 (15.9%)	166 (6.6%)	2359 (93.4%)	
Unknown	559 (3.5%)	27 (6.8%)	368 (93.2%)	
Education level				< 0.0001
High	2488 (15.7%)	152 (6.1%)	2336 (93.9%)	
Moderate	7663 (48.2%)	200 (5.4%)	3520 (94.6%)	
Low	9294 (58.5%)	360 (3.9%)	8934 (96.1%)	
Unknown	384 (2.4%)	26 (6.8%)	358 (93.6%)	
Location				< 0.025
Urban	2184 (13.8%)	125 (5.7%)	2059 (94.3%)	
Metro	12,764 (80.4%)	561 (4.4%)	12,203 (95.6%)	
Rural	254 (1.6%)	15 (5.9%)	239 (94.1%)	
Unknown	4012 (25.2%)	37 (5.4%)	647 (94.6%)	
Charlson/Deyo score				< 0.0001
None	9992 (62.9%)	410 (4.1%)	9582 (95.9%)	
One	1556 (9.8%)	73 (4.7%)	1483 (95.3%)	
Few	326 (2.1%)	29 (8.9%)	297 (91.1%)	

TABLE 1 continued

	Total (N = 15,886)	Amputation (N = 738)	LST (N = 15,148)	P
Unknown	4012 (25.2%)	226 (5.6%)	9582 (94.4%)	
Primary site				0.21
Upper extremity	4017 (25.3%)	172 (2.3%)	3845 (95.7%)	
Lower extremity	11,869 (74.7%)	566 (4.7%)	11,303 (95.3%)	
Histology				< 0.0001
Adult muscular	2597 (16.4%)	99 (3.81%)	2498 (96.2%)	
Clear/heme	374 (2.4%)	75 (20.0%)	299 (80.0%)	
Fibrous	6463 (40.6%)	271 (4.2%)	6192 (95.8%)	
Lipomatous	5033 (31.7%)	109 (2.2%)	4924 (97.8%)	
Synovial	1419 (8.9%)	184 (13.0%)	1235 (87%)	
Tumor grade				< 0.0001
I	3552 (22.4%)	46 (1.3%)	3506 (97.7%)	
II	2614 (16.5%)	110 (4.2%)	2504 (95.8%)	
III	4317 (27.2%)	262 (6.1%)	4055 (93.9%)	
IV	2604 (16.4%)	188 (7.2%)	2416 (92.8%)	
X	2799 (17.6%)	132 (4.72%)	2267 (95.3%)	
Stage				< 0.0001
I	6916 (43.5%)	181 (2.6%)	6735 (97.4%)	
II	4959 (31.2%)	200 (4.0%)	4759 (96.0%)	
III	4011 (25.3%)	357 (8.9%)	3654 (91.1%)	

$p < 0.001$) (Table 1). Additionally, patients with grade IV tumors (7.2%; $p < 0.001$), stage III disease (8.9%; $p < 0.001$), and clear/heme histology (20%, $p < 0.001$) were most likely to receive an amputation ($p \leq 0.001$). Separated by age group, AYA patients had the most amputations (6.4%) compared with pediatric patients (5.9%) and older adults (4.2%) ($p < 0.001$).

Regression analysis identified independent factors associated with the likelihood of an amputation being performed for extremity STS across all patients (Table 2). Amputations were more likely to be performed in patients with public insurance, non-lipomatous histology, advanced grade, or being treated in the central states. Conversely, amputations were significantly less likely to be performed in patients with the highest income and those treated at community cancer centers.

In older adults, amputation was significantly less likely in patients with a higher income (OR 0.76, CI 0.60–0.97) and treated at a community facility (OR 0.75, CI 0.61–0.93). Additionally, in this population, higher amputation rates were independently seen in the central states (OR 1.5; CI 1.13–1.99), for Hispanics (OR 1.76, CI 1.19–2.59), and in those with multiple comorbidities (OR 1.87, CI 1.17–3.01).

In the AYA population, logistic regression showed that amputations were significantly less likely in females (OR 0.64, CI 0.44–0.94), but increased in patients with public or government insurance (OR 2.00, CI 1.28–3.14) (Table 2). Interestingly, both AYA (OR 1.76, CI 1.07–2.9) and adult patients (OR 1.5, CI 1.13–1.99) had a higher likelihood of amputation when treated in the central states.

Performing an amputation in patients with extremity STSs was associated with an increased risk of death of 66% at 10 years (Table 3). Low income status (HR 1.13, CI 1.03–1.23), residing in the central (HR 1.18, CI 1.07–1.3) or eastern United States (HR 1.14, CI 1.04–1.25), public insurance (HR 2.01, CI 1.86–2.16), and being uninsured (HR 1.49, CI 1.21–1.83) also significantly increased risk of death at 10 years. Conversely, females (HR 0.83, CI 0.78–0.89) and those treated at higher volume centers (HR 0.83, CI 0.74–0.94) had a decreased risk of death at 10 years. Interestingly, although an amputation increased the risk of death by 50% in the older adult population (HR 1.54, CI 1.34–1.77, $p < 0.001$), the impact of an amputation was much more significant in AYAs (HR 2.62, CI 1.92–3.54, $p < 0.001$) and held no significance in children (HR 0.98, CI 0.13–7.59, $p = 0.98$) (Fig. 1).

DISCUSSION

Current therapy for extremity STSs can achieve limb salvage in 80–90% of cases..[20–24] Despite the substantial success of LST, amputation is still a necessary treatment modality for STSs with certain local characteristics such as neurovascular or bone involvement, local infection, or a resulting non-functional limb.[6,16,17,25] Although our large

TABLE 2 Logistic regression for predictors of amputation

	All				Adult				AYA			
	OR	CI		*p*	OR	CI		*p*	OR	CI		*p*
Facility type												
Academic	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Community	0.74	0.62	0.89	0.002	0.75	0.61	0.93	0.01	–	–	–	–
Other	< 0.001	< 0.001	> 999.99	0.96	< 0.001	< 0.001	> 999.99	0.97	–	–	–	–
Facility location												
West	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Central	1.45	1.15	1.86	0.002	1.50	1.13	1.99	0.005	1.76	1.07	2.90	0.03
East	0.78	0.61	1.0	0.05	0.80	0.60	1.08	0.14	0.84	0.50	1.40	0.49
N/A	> 999.99	< 0.001	> 999.99	0.96	–	–	–	–	0.21	0.06	0.78	0.02
Gender												
Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Female	–	–	–	–	–	–	–	–	0.64	0.44	0.94	0.02
Race												
Asian/PI	–	–	–	–	1.02	0.49	2.10	0.97	–	–	–	–
Black	–	–	–	–	1.22	0.87	1.71	0.24	–	–	–	–
Hispanic	–	–	–	–	1.76	1.19	2.59	0.004	–	–	–	–
Other	–	–	–	–	0.81	0.40	1.62	0.55	–	–	–	–
Insurance												
Private	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Public/Govt	1.3	1.075	1.57	0.01	–	–	–	–	2.00	1.28	3.14	0.003
Uninsured	0.93	0.91	1.98	0.14	–	–	–	–	1.40	0.74	2.65	0.30
Unknown	0.93	0.55	1.56	0.78	–	–	–	–	1.31	0.47	3.67	0.61
Income												
Moderate	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Comfortable	0.76	0.62	0.94	0.01	0.76	0.60	0.97	0.03	–	–	–	–
Low	1.15	0.92	1.44	0.21	1.11	0.85	1.45	0.45	–	–	–	–
Unknown	1.41	0.88	2.25	0.15	1.48	0.87	2.51	0.15	–	–	–	–
Charlson/Deyo												
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Few	1.57	0.92	2.53	0.61	1.87	1.17	3.01	0.01	–	–	–	–
One	1.08	0.81	1.43	0.61	1.13	0.83	1.53	0.45	–	–	–	–
N/A	1.31	1.12	1.71	0.15	1.51	1.19	1.92	0.001	–	–	–	–
Grade												
I	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
II	3.055	2.04	4.58	< 0.001	4.18	2.58	6.77	< 0.001	–	–	–	–
III	2.59	1.70	3.95	< 0.001	3.43	2.07	5.67	< 0.001	–	–	–	–
IV	3.32	2.15	5.12	< 0.001	4.49	2.69	7.49	< 0.001	–	–	–	–
X	2.07	1.37	3.13	0.001	2.30	1.38	3.84	0.002	–	–	–	–
Chemotherapy												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Unknown	1.08	0.62	1.89	0.79	0.82	0.41	1.65	0.58	1.71	0.57	5.11	0.34
Yes	1.62	1.31	2.00	< 0.001	1.35	1.05	1.74	0.02	2.54	1.62	3.98	< 0.001
Histology												
Lipomatous	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Adult muscular	1.53	1.12	2.11	0.009	1.46	1.04	2.05	0.03	1.76	0.65	4.74	0.27
Clear/heme	8.54	5.72	12.77	< 0.001	6.13	3.80	9.89	< 0.001	34.10	14.61	79.55	< 0.001
Fibrous	1.55	1.19	2.02	0.001	1.25	0.94	1.67	0.13	4.57	2.30	9.07	< 0.001

TABLE 2 continued

	All				Adult				AYA			
	OR	CI		*p*	OR	CI		*p*	OR	CI		*p*
Synovial	6.44	4.74	8.73	< 0.001	6.24	4.32	9.01	< 0.001	10.07	5.10	19.89	< 0.001
Stage												
1A	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1	1.37	0.89	2.11	0.16	1.33	0.76	2.31	0.32	1.35	0.65	2.82	0.42
2	1.96	1.25	3.08	0.004	2.40	1.39	4.14	0.002	1.28	0.53	3.10	0.59
3	4.24	2.88	6.23	< 0.001	4.58	2.85	7.36	< 0.001	4.55	2.37	8.73	< 0.001

TABLE 3 Risk factors for death at 10 years

	HR	CI		*P*-value
Amputation				
Yes	1.66	1.46	1.88	< 0.001
Facility location				
Central	1.18	1.07	1.30	< 0.001
East	1.14	1.04	1.25	< 0.001
Insurance				
Public/Govt	2.01	1.86	2.16	< 0.001
Uninsured	1.49	1.21	1.83	< 0.001
Income				
Low	1.13	1.03	1.23	0.01
Facility volume				
High	0.83	0.74	0.94	0.003
Gender				
Female	0.83	0.78	0.89	< 0.001
Comorbidities				
Few	1.98	1.64	2.37	< 0.001
One	1.38	1.24	1.54	< 0.001

study does not have this granular information, we found multiple disparities in amputation rates that went beyond local tumor factors. Insurance status, ethnicity, geographic location and age all independently impacted the likelihood of being treated with an extremity amputation. Moreover, having an amputation greatly impacted the 10-year OS for both AYAs and older adults, but not children.

AYAs had the highest rate of amputation of all age groups, and in this age group, the risk of death after an amputation was 2.6 times that of a similar patient that did not get an amputation. These findings are likely a reflection of more aggressive local disease based on tumor factors the database does not capture. They may also be a consequence of differing practice patterns at pediatric and adult institutions with some of the younger AYAs being treated with non-optimal protocols (either a pediatric protocol when the patient should have had an adult protocol or vice versa). To help rectify this, STS trials with expanded age groups have opened to be accessible at both types of institutions.[26] Recently, AYA and adult STSs have been shown to differ in presentation, histology, treatment, and survival; these factors should also be weighed in the development of STS trials and outcomes research.[27] This point is echoed by the fact that AYA STS has not seen the same improvement in survival compared to older adult STS.[28]

As with many types of medical therapy,[29] race and socioeconomic status impacted the likelihood of amputation. Patients with public or no insurance were more likely to have amputation compared to patients with private insurance, which was most profound in AYAs who are most likely to be under- or uninsured.[27] This could result from a clinician assuming a lack of continuing treatment or follow-up ability from these patients, and thus recommending a 'definitive' therapy. It may additionally reflect a lack of access to clinical trials, 'old school' practice at lower volume centers, or other similar access to care issues.[29] Furthermore, in older adults but not in AYAs or children, Hispanics were more likely to have had an amputation compared to other race/ethnic groups (Table 2). Racial treatment disparities could be related to socioeconomic differences. However, it may also be indicative of clinician cultural bias, patient language barriers, or other patient cultural factors involved in decision making.[29,30]

The increased risk of death after amputation reported in the present study agrees with more recent literature, which demonstrates that even though amputations have been associated with improved local control, there is a decrease in both disease-specific and OS.[25,28–33] In our study, this increased risk of death after amputation was most

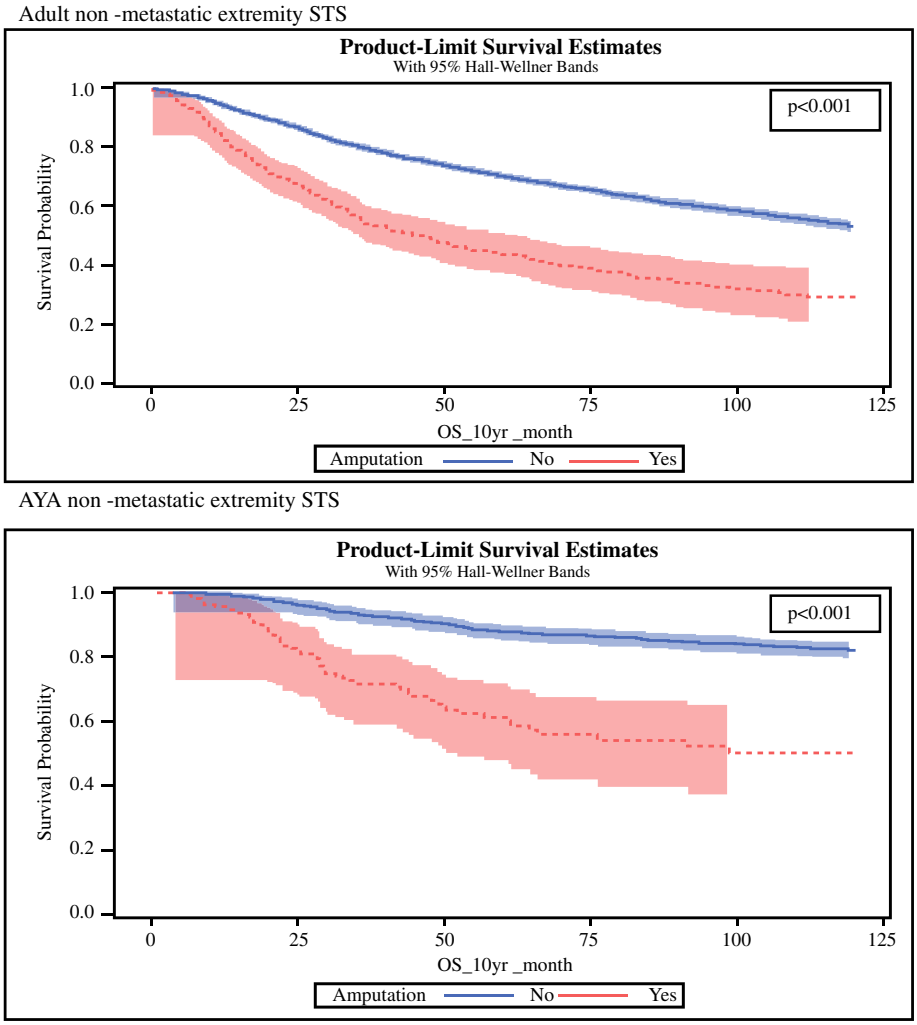

FIG. 1 10-Year survival for adult and AYA non-metastatic extremity STS

pronounced in the younger AYA population. Although this may represent more aggressive tumor biology in this younger cohort which is known to have a large influence on survival, the pediatric cohort did not show a similar increased risk of death after amputation.[34–40] Therefore, other factors related to a decreased and fragmented access to care in this population may be the greater driving force behind this finding. These factors deserve further investigation.

The heterogeneity of amputation rates across a variety of patients with STSs warrants discussion regarding treatment guidelines. While the data presented here should not be viewed as the sole evidence for revising treatment recommendations, it does expose factors influencing amputation that may be modifiable. The effects of ethnicity, income level, and insurance status on amputation rates may be surrogates depicting "access to care" issues.[29,30] Earlier recognition and subsequent treatment of these patients may decrease amputations in these groups. Pairing this recognition with treatment from high-volume centers may be an additional strategy, as treatment at high-volume centers showed better survival, despite having increased amputation rates.

Our study is subject to the limitations of a retrospective database design and encompasses the risk of retrospective selection bias. Diagnoses, staging, and treatment evaluation were susceptible to coding errors that are inherent with retrospective database analysis. Factors influencing the decision to perform amputation are not known, and it is not possible to compare the amputation rates of individual surgeons and/or multidisciplinary teams. Additionally, many younger AYAs have historically been treated at pediatric hospitals, and many independent children's hospitals are not part of the CoC and therefore do not contribute cases to the NCDB. Additionally, the NCDB does not capture the granular information of neurovascular or bone involvement, local infection, or non-functional limb status, which would all be tumor factors favoring amputation.

CONCLUSION

Although amputation for non-metastatic adult-type extremity STSs is rare, disparities exist across age groups, insurance and geography when it comes to the use of amputation in patients with extremity STSs. Moreover, having an amputation is an independent risk factor for death, with the greatest impact in AYAs. The lack of defined guidelines and standardized protocols for STS amputation likely leads to the variability across geography, hospitals, and ages. However, high-volume centers appear to have improved survival rates across all ages for extremity STSs.

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REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin*. 2007;57(1):43–66.
2. Albritton K, Bleyer WA. The management of cancer in the older adolescent. *Eur J Cancer*. 2003;39(18):2584–99.
3. Birch JM, Alston RD, Quinn M, Kelsey AM. Incidence of malignant disease by morphological type, in young persons aged 12–24 years in England, 1979–1997. *Eur J Cancer*. 2003;39(18):2622–31.
4. Geraci M, Birch JM, Alston RD, Moran A, Eden TOB. Cancer mortality in 13 to 29-year-olds in England and Wales, 1981–2005. *Br J Cancer*. 2007;97(11):1588–94.
5. Ferrari A, Bleyer A. Participation of adolescents with cancer in clinical trials. *Cancer Treat Rev*. 2007;33(7):603–8.
6. Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas. *Clin Sarc Res.* 2016;6(1):20.
7. Gerrand CH, Wunder JS, Kandel RA, O'Sullivan B, Catton CN, Bell RS, Griffin AM, Davis AM. Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. *J Bone Joint Surg Br*. 2001;83(8):1149–55.
8. Alektiar KM, Velasco J, Zelefsky MJ, Woodruff JM, Lewis JJ, Brennan MF. Adjuvant radiotherapy for margin-positive high-grade soft tissue sarcoma of the extremity. *Int J Radiat Oncol Biol Phys*. 2000;48(4):1051–8.
9. LeGrange F, Cassoni AM, Seddon BM. Tumour volume changes following pre-operative radiotherapy in borderline resectable limb and trunk soft tissue sarcoma. *Eur J Surg Oncol*. 2014;40(4):394–401.
10. Roberge D, Skamene T, Nahal A, Turcotte RE, Powell T, Freeman C. Radiological and pathological response following pre-operative radiotherapy for soft-tissue sarcoma. *Radiother Oncol*. 2010;97(3):404–7.
11. Eggermont AMM, de Wilt JHW, ten Hagen TLM. Current uses of isolated limb perfusion in the clinic and a model system for new strategies. *Lancet Oncol*. 2003;4(7):429–37.
12. Smith HG, Cartwright J, Wilkinson MJ, Strauss DC, Thomas JM, Hayes AJ. Isolated limb perfusion with melphalan and tumour necrosis factor α for in-transit melanoma and soft tissue sarcoma. *Ann Surg Oncol*. 2015;22(Suppl 3):356–61.
13. Lohman RF, Nabawi AS, Reece GP, Pollock RE, Evans GR. Soft tissue sarcoma of the upper extremity: a 5-year experience at two institutions emphasizing the role of soft tissue flap reconstruction. *Cancer*. 2002;94(8):2256–64.
14. Barner-Rasmussen I, Popov P, Bohling T, Tarkkanen M, Sampo M, Tukiainen E. Microvascular reconstruction after resection of soft tissue sarcoma of the leg. *Br J Surg*. 2009;96(5):482–9.
15. Agrawal N, Wan D, Bryan Z, Boehmler J, Miller M, Tiwari P. Outcomes analysis of the role of plastic surgery in extremity sarcoma treatment. *J Reconstr Microsurg*. 2013;29(2):107–11.
16. Clark MA, Thomas JM. Amputation for soft-tissue sarcoma. *Lancet Oncol*. 2003;4:335–42.
17. Ferrone ML, Raut CP. Modern surgical therapy: limb salvage and the role of amputation for extremity soft-tissue sarcomas. *Surg Oncol Clin N Am.* 2012;21:201–13.
18. Winchester DP, Stewart AK, Bura C, Jones RS. The National Cancer Data Base: a clinical surveillance and quality improvement tool. *J Surg Oncol.* 2004;85(1):1–3.
19. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45(6):613–9.
20. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomized trial. *Lancet*. 2002;359:2235–41.
21. Haas RL, Delaney TF, O'Sullivan B, et al. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? *Int J Radiat Oncol Biol Phys*. 2012;84:572–80.
22. Eggermont AM, Schraffordt Koops H, Lienard D, et al. Isolated limb perfusion with high-dose tumor necrosis factor-alpha in combination with interferon-gamma and melphalan for nonresectable extremity soft tissue sarcomas: a multicenter trial. *J Clin Oncol*. 1996;14:2653–65.
23. Hoven-Gondrie ML, Gastiaannet E, van Ginkel RJ, et al. TNF dose reduction and shortening of duration of isolated limb perfusion for locally advanced soft tissue sarcoma of the extremity is safe and effective in terms of patient outcome. *J Surg Oncol.* 2001;103:648–55.
24. Bhangu A, Broom L, Nepogodiev D, et al. Outcomes of isolated limb perfusion in the treatment of extremity soft tissue sarcoma: a systemic review. *Eur J Surg Oncol*. 2013;39:311–9.
25. Stevenson MG, Musters AH, Geertzen JH, et al. Amputations for extremity soft tissue sarcoma in the era of limb salvage treatment: local controls and survival. *J Surg Oncol.* 2018;117:434–42.
26. Kauffman M. Selinexor in advanced liposarcoma (SEAL). Clinicatrials.gov identifier NCT02606461. 2015. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02606461.
27. Keegan TH, Ries LA, Barr RD, et al., National Cancer Institute Next Steps for Adolescent and Young Adult Oncology Epidemiology Working Group. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. *Cancer*. 2016;122:1009-16.
28. Kasper B, Ouali M, van Glabbeke M, et al. Prognostic factors in adolescents and young adults (AYA) with high risk soft tissue sarcoma (STS) treated by adjuvant chemotherapy: a study based on pooled European Organisation for Research and Treatment of

Cancer (EORTC) clinical trials 62771 and 62931. *Eur J Cancer.* 2013;49:449–56.
29. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J Clin*. 2004;54:78–93.
30. Freeman H. Cancer in the socioeconomically disadvantaged. *CA Cancer J Clin*. 1989;39:266–88.
31. Stojadinovic A, Jaques DP, Leung DH, et al. Amputation for recurrent soft tissue sarcoma of the extremity: indications and outcome. *Ann Surg Oncol*. 2001;8:509–18.
32. Ghert MA, Abudu A, Driver N, et al. The indications for and the prognostic significance of amputation as the primary surgical procedure for localized soft tissue sarcoma of the extremity. *Ann Surg Oncol.* 2005;12:10–7.
33. Williard WC, Hajdu SI, Casper ES, Brennan MF. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. *Ann Surg.* 1992;215:269–75.
34. Collin CF, Friedrich C, Godbold J, et al. Prognostic factors for local recurrence and survival in patients with localized extremity soft-tissue sarcoma. *Semin Surg Oncol.* 1988;4:30–7.
35. McKee MD, Liu DF, Brooks JJ, et al. The prognostic significance of margin width for extremity and trunk sarcoma. *J Surg Oncol.* 2004;85:68–76.
36. Coindre JM, Terrier P, Bui NB, et al. Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. *J Clin Oncol*. 1996;14:869–77.
37. Potter BK, Adams SC, Qadir R, et al. Fungating soft-tissue sarcomas: treatment implications and prognostic importance of malignant ulceration. *J Bone Joint Surg Am.* 2009;91:567–74.
38. Mann GB, Lewis JJ, Brennan MF. Adult soft tissue sarcoma. *Aust N Z J Surg.* 1999. 69;336–343.
39. Shiu MH, Castro EB, Hajdu SI. Surgical treatment of 297 soft tissue sarcomas of the lower extremity. *Ann Surg.* 1975;182:597–602.
40. Collin C, Godbold J, Hajdu S, Brennan M. Localized extremity soft tissue sarcoma: an analysis of factors affecting survival. *J Clin Oncol*. 1987;5:601–12.