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Treatment at Specialized Cancer Centers Is Associated with Improved Survival in Adolescent and Young Adults with Soft Tissue Sarcoma

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Background: Soft tissue sarcomas (STS) are a heterogeneous group of tumors whose management benefits from a multidisciplinary therapeutic approach. Published data suggest that cancer treatment at a specialized cancer center (SCC) can improve survival in other cancers. Therefore, we examined the impact of the location of treatment on survival in children and adolescents and young adults (AYAs) with STS.
Methods: We performed a population-based analysis of children and AYAs hospitalized within 1 year of diagnosis with first primary STS (2000–2014) using the California Cancer Registry linked with hospitalization data. Patients were categorized based on receiving all inpatient treatments at a SCC versus part/none. Multivariable Cox proportional hazards regression identified factors associated with overall and STS-specific survival by age group. Results are presented as adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).
Results: Of the 1,674 patients with STS, 142 were children (0–14) and 1,532 were AYAs (15–39) and 89.4% and 40.4% received all inpatient treatments at a SCC, respectively. Overall, the 5-year survival was improved for patients who received all inpatient care at a SCC (59.8% vs. those who received part/none, 50.7%). Multivariable regression analysis found that having all treatments at a SCC was associated with better overall survival (HR, 0.79, CI: 0.65–0.95) in AYAs, but not in children.
Conclusions: Our findings demonstrate that treatment for STS at a SCC is associated with better survival in AYAs. Eliminating barriers to treatment of AYAs with STS at SCCs could improve survival in this population.

Keywords: AYA, children, soft tissue sarcoma

Introduction

While sarcomas are considered rare tumors, they have a peak incidence in adolescent and young adults (AYA: ages 15–39) with cancer (~9% of all cancers impacting AYAs) and are broadly divided into bone and soft tissue sarcomas (STS). AYA patients with sarcoma continue to have worse survival compared with children.[1–3] Reasons underlying the survival disparity by age are likely multifactorial, including differences in access to care, insurance coverage, access to clinical trials, and response to therapy and complications.[4,5]

Rhabdomyosarcoma is the most common soft tissue sarcoma in young people overall, and clear treatment guidelines have been established in North America by the Children's Oncology Group. In contrast, STS are a very heterogeneous group of sarcomas collectively more common than rhabdomyosarcoma and management benefits from a multidisciplinary approach, particularly for those with high-risk disease.[6,7] Patients with STS are treated at several types of institutions with differing levels of experience treating sarcomas.[8–10] In recent years, research has focused on where patients with cancer obtain their cancer treatment, with studies suggesting that treatment at a specialized cancer center (SCC: defined as Children's Oncology Group [COG] or National Cancer Institute [NCI]-designated cancer center hospitals vs. non-SCC: other hospitals) is associated with better survival outcomes in children and AYA patients with cancer.[11,12] Studies in adults with sarcoma also suggest that

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those treated at specialized or high-volume centers or whose care is guided by a pre-treatment specialized multidisciplinary tumor board have superior outcomes.[13–19]

Much of what is currently known about outcomes of young patients with STS is from clinical trials or single-institution studies that only capture a minority of patients with sarcomas.[6,10,20–26] These studies may not adequately represent a comprehensive ''real-world'' picture of where these patients receive care and the potential impact on survival. This is especially critical for AYAs who are known to have poor clinical trial enrollment[27] and decreased utilization of SCCs.[8,11] In addition, for many patients getting to an SCC is difficult and may be impacted by insurance coverage and socioeconomic status.[28] Patients may need to travel long distances to obtain treatment at a SCC and may receive care for treatment-related complications closer to home.[29] To determine whether children and AYAs with STS benefit from receiving all their inpatient treatment at a SCC, we examined the association of location of cancer care and other potential prognostic factors on survival throughout therapy with the goal of informing education efforts, health care policies, and treatment guidelines to improve survival outcomes in this patient population.

Methods

Study population

This population-based retrospective cohort analysis evaluated all patients in California from 2000 to 2014 with a diagnosis of first primary STS in the California Cancer Registry (CCR) who were hospitalized within 1 year from diagnosis. One year from diagnosis was chosen to capture the duration of upfront therapy inclusive of surgery, chemotherapy, or radiation. Patients with a diagnosis on a death certificate only or with no survival time (i.e., diagnosed at time of death) ($n = 30$), with secondary cancers ($n = 109$) or without inpatient admissions ($n = 270$) were excluded.

Study database

Cases were identified using the CCR linked with the Office of Statewide Health Planning and Development (OSHPD) Patient Discharge Database (PDD). The PDD database contains information on all acute care hospitalizations in California (except federal institutions) and includes discharge date, length of stay, hospital location, and associated ICD-9 codes (primary code and up to 24 secondary codes). The CCR contains information on over 99% of patients diagnosed with invasive cancer in California. It includes information on diagnosis date, tumor characteristics and initial treatment. Each patient has a unique record linkage number, which allows longitudinal tracking of patient hospitalizations in this database.

Covariates

The study variables extracted from these linked databases included: demographic information, diagnosis date, treatment (e.g., chemotherapy, radiotherapy, surgery), stage (nonmetastatic: localized, regional; metastatic: distant), primary anatomic site, health insurance type (private, public, uninsured, unknown), admission date, and hospital name and location (zip code).

SCCs were defined as COG member institutions and/or NCI-designated cancer centers, depending on age at diagnosis.[8,11] There are 28 total SCCs in California, including 20 COG member institutions, 4 NCI designated institutions, and 4 combined COG/NCI institutions. A patient was considered to have received care at a SCC if they were ≤ 21 years old and they went to a COG member institution and/or NCI-designated cancer center or if >21 years of age and they went to an NCI designated cancer center. We defined inpatient treatment at a SCC as receipt of all versus part/no treatment at a SCC in the first year after diagnosis, to fully cover the standard length of initial treatment. Patients were still considered to have received all care at a SCC if their initial diagnosis occurred at a non-SCC or if they were hospitalized for complications of cancer treatment (e.g., febrile neutropenia) at non-SCCs.

Neighborhood socioeconomic status (nSES) is based on Census and American Community Survey data at the census tract level.[30] The nSES indices were grouped into quintiles based on the distribution of SES across census block groups and into lower (quintiles 1, 2, 3) and higher nSES (4, 5).[30] Each patient was assigned a nSES category. For health insurance, we analyzed patients with public insurance (e.g., Medicaid) and no insurance together, since many uninsured AYAs obtain public insurance shortly after receiving a cancer diagnosis or during their first admission.[31–33] Comorbidities were determined by the presence of an ICD-9 code included in the enhanced Elixhauser index[34,35] found in hospital admissions up to 2 years before cancer diagnosis or at the first admission during or after cancer diagnosis. We were unable to capture comorbidities diagnosed and recorded in the outpatient setting only. Potential treatment-related complications were determined by ICD-9 codes associated with each hospitalization and occurring within the first year after diagnosis; grouped into cardiac, renal, gastroenterology, neurologic, hematologic, pulmonary, and infectious.

Statistical analyses

Patients with STS were analyzed together and separately by age group (children: 0–14 years and AYA: 15–39 years). Descriptive statistics (e.g., Chi-square tests) were used to characterize the study population. Five-year overall survival was estimated using Kaplan–Meier analysis. Associations between select baseline sociodemographic and clinical characteristics having all treatments (versus part/none) at a SCC to calculate a propensity score for location of care was estimated using multivariable logistic regression. Results are presented as odds ratios (ORs) and 95% CI.

Inverse probability weighted, multivariable Cox proportional hazard models were used to measure the association of treatment at a SCC on overall and sarcoma-specific survival by age group, adjusting for baseline demographic characteristics (age, sex, nSES, health insurance status, race/ethnicity, disease stage, comorbidity, and complications). Propensity scores were calculated based on age, sex, race/ethnicity, neighborhood SES, payment, disease stage, and comorbidities. The standardized mean differences in baseline covariates between patients receiving all versus part/none of their care at a SCC were used to verify the balancing effect of propensity score weighting. Survival time was measured in days from diagnosis to the date of death from all causes for overall survival, and

patients who died from causes other than STS were censored at the time of death in analyses of sarcoma-specific survival. Patients alive at the study end date (12/31/2014) were censored at this time or at the date of last follow-up, whichever occurred first. In these models, the proportional hazards assumption was assessed based on cumulative sums of Martingale residuals and based on inspection of the survival curves [log (− log) of the survival distribution function by log (months)]. Variables that violated this assumption were included in the models as stratifying variables (histology, chemotherapy, surgery) to allow for differences in baseline hazards associated with these variables. The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical analyses were performed using SAS statistical software (version 9.4), and a two-sided P value of <0.05 was considered statistically significant. Ethics approval was obtained by the Institutional Review Board of the University of California, Davis and by the California Committee for the Protection of Human Subjects.

Results

Cohort characteristics

There were 1,674 patients, 142 children (0–14 years) and 1,532 AYA (15–39 years), who were diagnosed with and hospitalized for STS between 2000 and 2014 in California (Table 1). The majority had lower nSES (children: 70.4%; AYA: 60.8%) and private insurance (children 57%; AYA: 65.6%). Additionally, there was a significant difference in the distribution of clinical characteristics among children and AYA patients, including differences in tumor size ($p < 0.0001$) with AYAs having larger tumors and metastatic disease ($p = 0.0203$) at presentation. The majority of children received all their inpatient care at a SCC (89.4%) in contrast to AYA patients (40.4%). Among patients ages 15–21, we found that a slightly higher percentage (54.7%) has all care at a SCC (data not shown). There were also differences in care delivered by location of care with a larger proportion of patients with all care at a SCC receiving radiation (48.9%, $p = 0.0048$), chemotherapy (52%, $p = 0.013$), and surgery (86.9%, $p = 0.028$).

Inpatient admissions in both types of institutions (SCC vs. non-SCC) had potential treatment-associated complications captured. There was a significant difference between location of care across the whole cohort only for gastrointestinal complications ($p < 0.0001$) with higher proportion occurring at SCCs (35.9% vs. 26.2%). Differences in complications across the two age groups were only statistically different for gastrointestinal ($p = 0.0009$) and neurologic ($p = 0.0064$) in AYA patients, with a higher proportion occurring at SCCs.

Factors associated with survival

A Kaplan–Meier analysis demonstrated that 5 year overall survival was better for patients who received all inpatient care at a SCC (59.8% ± 1.92%) compared with those who only received part/none of their treatment at a SCC (50.7% ± 1.74%; $p < 0.0001$) (Fig. 1). AYA patients with non-metastatic disease who received all care at a SCC had the best overall survival (71.1% ± 2.3%; $p < 0.0001$) and patients with metastatic disease who received part/none of their care at a SCC had the worst overall survival (15.6% ± 2.4%; $p < 0.0001$) (Fig. 2). There were significant differences in survival by location of care for patients with ($p = 0.0118$) and without ($p = 0.0416$) metastatic disease.

Worse overall survival was associated with increasing age, metastatic disease, and having any complication among children and AYAs. In AYAs, worse overall survival was additionally associated with older age, public/no insurance, body wall, visceral and other primary site, tumor size >5 cm, metastatic disease, and having any comorbidity. Improved survival was associated with receiving all (vs. part/none) of the inpatient care at a SCC for AYAs (HR, 0.79, CI: 0.65–0.95), but this association was not seen in children (Table 2).

Sarcoma-specific survival could only be calculated for AYA patients, as there were not enough events ($n = 21$) in children to perform the analysis. In AYAs with STS, worse sarcoma-specific survival was associated with older age, tumor size >10 cm, remote disease, and having a complication (Table 2). Improved sarcoma-specific survival was not significantly associated with receiving all inpatient care at a SCC (HR, 0.80, CI: 0.63–1.01).

Factors associated with treatment at a SCC

In multivariable logistic regression analysis, having public insurance was the only factor evaluated that was independently associated with being more likely to receive all treatment-related admissions at a SCC (Supplementary Table S1). Age older than 18 years, female sex, NH Black and Hispanic race/ethnicity, and remote stage of disease were all associated with being less likely to receive all inpatient care at a SCC.

Discussion

Non-rhabdomyosarcoma soft tissue sarcoma is a rare group of tumors impacting children and AYA patients. AYAs continue to face worse survival outcomes compared with children, as this study demonstrates, aligning with previous reports in the literature.[3,4] A potentially significant and understudied contributor for this disparity in survival is complications and location of care. We demonstrate that complications captured in the inpatient setting are associated with poor survival. Furthermore, we found that care at a SCC is associated with over a 20% improvement in overall survival for AYA patients with STS. However, utilization of these centers is limited for older AYAs, women, Black, and Hispanic patients with STS.

Management of sarcomas requires intensive multimodality therapy (surgery, chemotherapy, and radiation) that can be associated with therapy-related complications.[36,37] Treatment-related complications, while impacting both age groups, have been associated more often with modifications in therapy (e.g., dose modifications, eliminating drugs, therapy delays) in the AYA age group,[36,37] which could potentially lead to worse survival. This study demonstrated that potential treatment-related complications were associated with worse survival in both age groups, although a more pronounced association with worse survival was noted in AYAs with STS. While complications may contribute to the worse survival experienced by AYAs, it is likely the not only contributor, and further investigation is needed.

This study demonstrates that treatment for cancer at a SCC has the potential to improve outcomes in AYA patients with metastatic and non-metastatic STS. The association with

Table 1. Selected Demographic and Clinical Characteristics of Children and Adolescent and Young Adult Patients with Soft Tissue Sarcoma, California, 2000–2014

	Total cohort			*Children*			*AYA*		
Variables	*All* N = *746* N *(%)*	*Part/None* N = *928* N *(%)*	p *value*	*All* N = *127* N *(%)*	*Part/none* N = *15* N *(%)*	p *value*	*All* N = *619* N *(%)*	*Part/None* N = *913* N *(%)*	p *value*
Age									
0–5	27 (3.6)	<5		27 (21.3)	<5				
6–9	24 (3.2)	<5		24 (18.9)	<5				
10–14	76 (10.2)	11 (1.2)		76 (59.8)	11 (73.3)				
15–20	162 (21.7)	64 (6.9)					162 (26.2)	64 (7.0)	
21–30	199 (26.7)	352 (37.9)					199 (32.1)	352 (38.6)	
>30	258 (34.6)	497 (53.6)	<0.0001			0.5951	258 (41.7)	497 (54.4)	<0.0001
Sex									
Male	413 (55.4)	439 (47.3)		70 (55.1)	7 (46.7)		343 (55.4)	432 (47.3)	
Female	333 (44.6)	489 (52.7)	0.001	57 (44.9)	8 (53.3)	0.5344	276 (44.6)	481 (52.7)	0.0019
Health Insurance Status									
Private	459 (61.5)	627 (67.6)		70 (55.1)	11 (73.3)		389 (62.8)	616 (67.5)	
Public/Uninsured	263 (35.3)	272 (29.3)		54 (42.5)	<5		209 (33.8)	268 (29.4)	
Other/unknown	24 (3.2)	29 (3.1)	0.0316	<5		0.3753	21 (3.4)	29 (3.2)	0.1685
Race/Ethnicity									
NH White	308 (41.3)	332 (35.8)		35 (27.6)	<5		273 (44.1)	328 (35.9)	
Hispanic	289 (38.7)	394 (42.5)		62 (48.8)	7 (46.7)		227 (36.7)	387 (42.4)	
Black	56 (7.5)	88 (9.5)		17 (13.4)	<5		39 (6.3)	87 (9.5)	
Asian/PI	86 (11.5)	109 (11.7)		10 (7.9)	<5		76 (12.3)	106 (11.6)	
Other	7 (0.9)	5 (0.5)	0.1117	<5		0.5572	<5	5 (0.5)	0.0068
Neighborhood SES*									
Low	446 (59.8)	585 (63.0)		91 (71.7)	9 (60.0)		355 (57.4)	576 (63.1)	
High	285 (38.2)	331 (35.7)		33 (26.0)	6 (40.0)		252 (40.7)	325 (35.6)	
Unknown	15 (2.0)	12 (1.3)	0.2524	<5		0.4555	12 (1.9)	12 (1.3)	0.0646
Histologies									
Adipocytic	84 (11.3)	150 (16.2)		<5	<5		81 (13.1)	148 (16.2)	
Fibroblastic/Myofibroblastic	61 (8.2)	82 (8.8)		11 (8.7)	<5		50 (8.1)	78 (8.5)	
Nerve Sheath	103 (13.8)	71 (7.7)		23 (18.1)			80 (12.9)	71 (7.8)	
Smooth Muscle	57 (7.6)	155 (16.7)		<5	<5		55 (8.9)	154 (16.9)	
Uncertain Differentiation	251 (33.6)	251 (27.0)		51 (40.2)	7 (46.7)		200 (32.3)	244 (26.7)	
Undifferentiated	169 (22.7)	152 (16.4)		35 (27.6)	<5		134 (21.6)	151 (16.5)	
Vascular	21 (2.8)	67 (7.2)	<0.0001	<5		0.0152	19 (3.1)	67 (7.3)	<0.0001
Stage									
Non-Metastatic (localized, regional)	547 (73.3)	634 (68.3)		101 (79.5)	13 (86.7)		446 (72.1)	621 (68.0)	
Metastatic	177 (23.7)	254 (27.4)		26 (20.5)	<5		151 (24.4)	252 (27.6)	
Unknown	22 (2.9)	40 (4.3)	0.0587			0.511	22 (3.6)	40 (4.4)	0.2313

(*continued*)

Table 1. (Continued)

Variables	Total cohort			Children			AYA		
	All N = *746* N *(%)*	*Part/None* N = *928* N *(%)*	p *value*	*All* N = *127* N *(%)*	*Part/none* N = *15* N *(%)*	p *value*	*All* N = *619* N *(%)*	*Part/None* N = *913* N *(%)*	p *value*
Tumor size									
0–5 cm	180 (24.1)	195 (21.0)		48 (37.8)	6 (40.0)		132 (21.3)	189 (20.7)	
5.1–10 cm	249 (33.4)	272 (29.3)		44 (34.6)	7 (46.7)		205 (33.1)	265 (29.0)	
>10 cm	208 (27.9)	295 (31.8)		21 (16.5)	<5		187 (30.2)	293 (32.1)	
Unknown	109 (14.6)	166 (17.9)	0.0322	14 (11.0)		0.5134	95 (15.3)	166 (18.2)	0.2368
Primary site									
Body wall	166 (22.3)	210 (22.6)		26 (20.5)	<5		140 (22.6)	208 (22.8)	
Extremity	379 (50.8)	355 (38.3)		56 (44.1)	8 (53.3)		323 (52.2)	347 (38.0)	
Head/neck	64 (8.6)	68 (7.3)		23 (18.1)	<5		41 (6.6)	65 (7.1)	
Visceral	119 (16.0)	250 (26.9)		16 (12.6)	<5		103 (16.6)	248 (27.2)	
Other	18 (2.4)	45 (4.8)	<0.0001	6 (4.7)		0.8543	12 (1.9)	45 (4.9)	<0.0001
Radiation									
Yes	365 (48.9)	390 (42.0)	0.0048	60 (47.2)	5 (33.3)	0.3065	305 (49.3)	385 (42.2)	0.0061
Chemotherapy									
Yes	388 (52.0)	417 (44.9)	0.013	71 (55.9)	7 (46.7)	0.6117	317 (51.2)	410 (44.9)	0.0364
Surgery									
Yes	648 (86.9)	770 (83.0)	0.028	114 (89.8)	15 (100)	0.1936	534 (86.3)	755 (82.7)	0.0603
Comorbidities									
Yes	240 (32.2)	398 (42.9)	<0.0001	37 (29.1)	<5 (26.7)	0.8419	203 (32.8)	394 (43.2)	<0.0001
Complications									
Cardiovascular	9 (1.2)	15 (1.6)	0.4831	<5		0.7302	8 (1.3)	15 (1.6)	0.5798
Renal	45 (6.0)	59 (6.4)	0.7839	<5		0.5474	42 (6.8)	59 (6.5)	0.8026
Gastrointestinal	268 (35.9)	243 (26.2)	<0.0001	57 (44.9)	4 (26.7)	0.1777	211 (34.1)	239 (26.2)	0.0009
Neurologic	88 (11.8)	83 (8.9)	0.0555	6 (4.7)	2 (13.3)	0.1715	82 (13.2)	81 (8.9)	0.0064
Hematologic	108 (14.5)	129 (13.9)	0.7367	19 (15.0)	<5	0.3825	89 (14.4)	128 (14.0)	0.8435
Pulmonary	75 (10.1)	80 (8.6)	0.3147	11 (8.7)		0.2353	64 (10.3)	80 (8.8)	0.2993
Infectious	164 (22.0)	185 (19.9)	0.3051	35 (27.6)	<5	0.5317	129 (20.8)	182 (19.9)	0.6654
Vital Status									
Alive	476 (63.8)	509 (54.8)		94 (74.0)	13 (86.7)		382 (61.7)	496 (54.3)	
Death									
From sarcomas	140 (18.8)	235 (25.3)		18 (14.2)	<5		122 (19.7)	234 (25.6)	
From other causes	130 (17.4)	184 (19.8)	0.0006	15 (11.8)	<5	0.5585	115 (18.6)	183 (20.0)	0.0087

NH, non-Hispanic; SES, socioeconomic status; SCC, specialized cancer center.

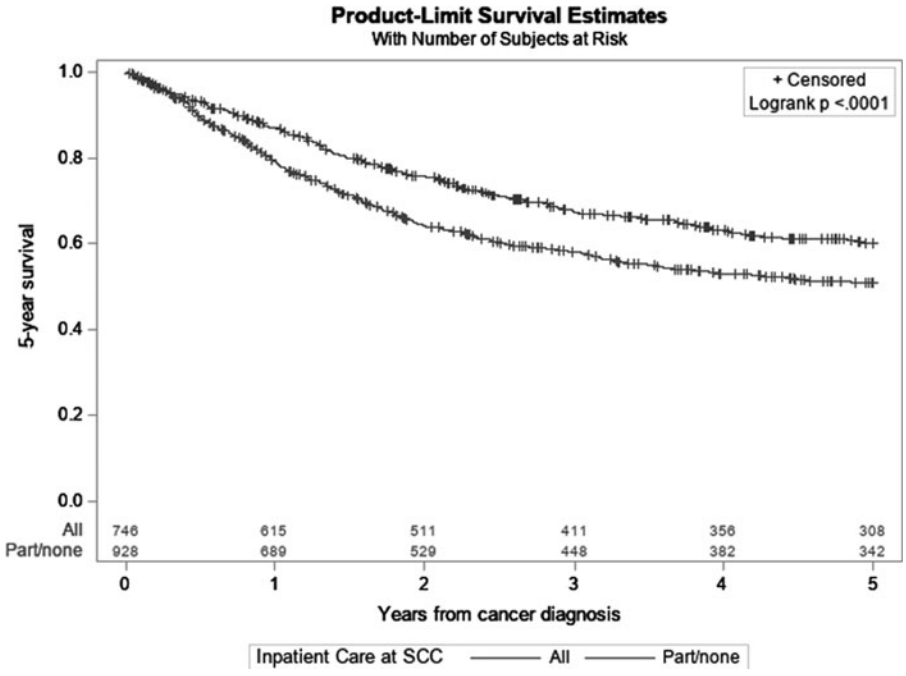

FIG. 1. Kaplan–Meier analysis of 5-year overall survival in children and adolescents and young adults with soft tissue sarcoma hospitalized within 1 year from diagnosis by location of inpatient treatment at a SCC. SCC, specialized cancer center.

improved survival in AYAs is consistent with what has been documented in the literature for other cancers, including leukemia, Hodgkin lymphoma, and central nervous system tumors.[11,12,38] Given the complexity of treatment of STS, especially in patients with metastatic or unresectable disease, this finding is not surprising. While a similar finding was not demonstrated for children, this may be associated with the small sample size in this rare group of tumors. The potential positive impact of receiving all inpatient treatment at a SCC on survival for the AYA age group is substantial. We have hypothesized that the improved survival may be secondary to access to multimodal therapy, adherence to published care guidelines,[18] multidisciplinary expertise,[17] clinical trials,[4] and treatment of complications. However, complications do not appear to explain the survival differences by location of care. In AYAs, there was noted to be higher prevalence of admissions associated with both gastrointestinal and neurological complications for those who received all inpatient care at a SCC. It is difficult to determine though if these complications were a result of treatment at a SCC or if patients who have complications may be more likely to receive care at a SCC than a non-SCC. Exact reasons for the differences in survival based on location of care remain largely unknown. Future work is needed to identify why

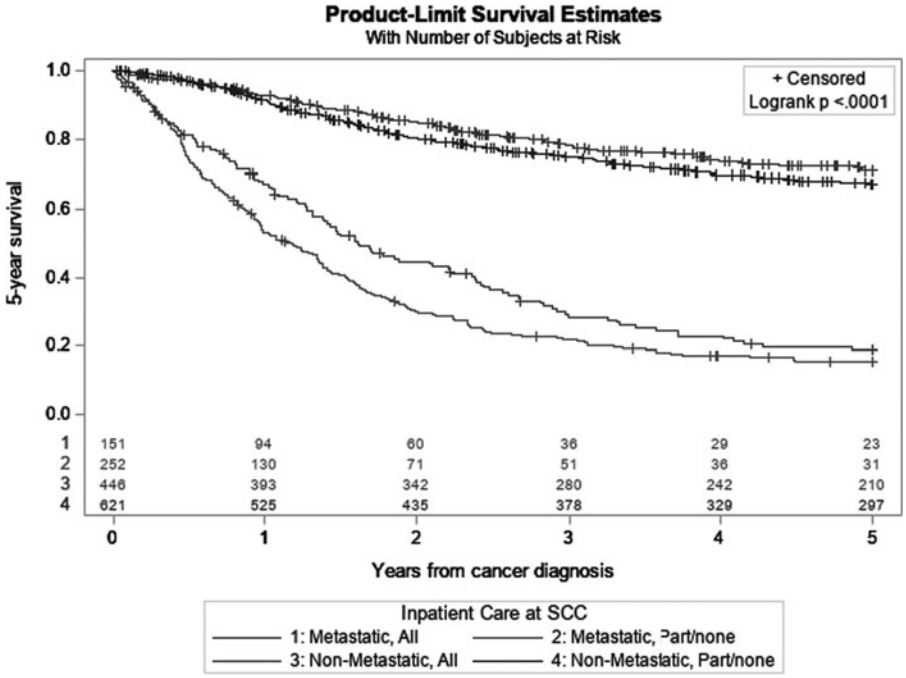

FIG. 2. Kaplan–Meier analysis of overall 5-year survival in adolescent and young adult patients with soft tissue sarcoma hospitalized within 1 year from diagnosis by metastatic disease status and location of inpatient treatment at a SCC.

Table 2. Characteristics Associated with Survival Among Hospitalized Children and Adolescent and Young Adult Patients with Soft Tissue Sarcoma California, 1991–2014

	Total cohort		*Children AYA*		
	Overall HR (CI)	*STS Specific HR (CI)*	*Overall HR (CI)*	*Overall HR (CI)*	*STS Specific HR (CI)*
Age					
0–5	Reference	Reference	Reference		
6–9	1.24 (0.31–4.99)	0.85 (0.13–5.68)	1.84 (0.04–92.54)		
10–14	1.24 (0.44–3.43)	1.04 (0.28–3.90)	2.59 (0.27–25.01)		
15–20	2.20 (0.85–5.71)	1.83 (0.53–6.28)		Reference	Reference
21–30	2.89 (1.12–7.44)	2.79 (0.82–9.48)		1.18 (0.92–1.53)	1.41 (1.02–1.96)
> 30	3.50 (1.36–9.01)	3.05 (0.90–10.33)		1.44 (1.11–1.87)	1.52 (1.09–2.13)
Sex					
Male	Reference	Reference	Reference	Reference	Reference
Female	0.78 (0.65–0.93)	0.74 (0.59–0.93)	0.77 (0.21–2.79)	0.81 (0.68–0.96)	0.78 (0.63–0.97)
Health insurance status					
Private	Reference	Reference	Reference	Reference	Reference
Public/Uninsured	1.44 (1.20–1.73)	1.35 (1.06–1.72)	2.50 (0.49–12.66)	1.43 (1.19–1.71)	1.29 (1.02–1.62)
Race/ethnicity					
NH White	Reference	Reference	Reference	Reference	Reference
Asian/PI	1.05 (0.79–1.40)	1.13 (0.80–1.60)	9.29 (0.41–212.13)	1.04 (0.79–1.36)	1.15 (0.82–1.60)
Hispanic	0.99 (0.81–1.22)	0.83 (0.64–1.08)	2.16 (0.20–22.82)	0.98 (0.80–1.19)	0.85 (0.66–1.10)
NH Black	1.29 (0.96–1.75)	1.30 (0.89–1.89)	10.70 (0.42–272.15)	1.26 (0.94–1.70)	1.30 (0.89–1.88)
Neighborhood SES					
Low	Reference	Reference	Reference	Reference	Reference
High	0.86 (0.71–1.04)	0.85 (0.67–1.09)	1.63 (0.35–7.72)	0.81 (0.68–0.98)	0.88 (0.70–1.11)
Tumor size					
0–5	Reference	Reference	Reference	Reference	Reference
5.1–10 cm	1.72 (1.28–2.32)	1.71 (1.18–2.50)	2.36 (0.35–16.02)	1.46 (1.09–1.95)	1.45 (1.00–2.09)
> 10 cm	2.07 (1.53–2.80)	2.08 (1.42–3.06)	0.32 (0.02–4.26)	1.86 (1.38–2.51)	1.85 (1.27–2.69)
Unknown	1.79 (1.30–2.46)	1.39 (0.91–2.11)	6.12 (0.58–64.01)	1.70 (1.25–2.33)	1.40 (0.93–2.11)
Comorbidities					
No	Reference	Reference	Reference	Reference	Reference
Yes	1.40 (1.17–1.67)	1.30 (1.04–1.63)	3.40 (0.39–29.64)	1.36 (1.14–1.62)	1.33 (1.07–1.66)
Complications					
No	Reference	Reference	Reference	Reference	Reference
Yes	3.03 (2.46–3.72)	3.15 (2.41–4.10)	6.14 (1.04–36.36)	2.92 (2.38–3.57)	2.78 (2.15–3.60)
Cancer treatment at an SCC					
Part/None	Reference	Reference	Reference	Reference	Reference
All	0.80 (0.66–0.97)	0.83 (0.65–1.05)	0.31 (0.01–14.94)	0.79 (0.65–0.95)	0.80 (0.63–1.01)

*Additionally adjusted for primary site; stratified by stage, histology, chemotherapy, and surgery.
NH, non-Hispanic; SCC, specialized cancer center.

survival is improved at SCCs to inform intervention to optimize the care delivered to this population in non-SCC settings as well. However, regardless of the reasons behind improved survival associated with SCC, we advocate that AYA patients with these rare tumors be treated at SCCs.

While this study has demonstrated the importance of treatment at a SCC for AYA patients with STS, we know that there is a distinct group of patients not being seen at SCCs, including older AYAs. This group of patients is less likely to enroll on clinical trials that are often only accessible at SCCs and that this can have a negative impact on survival.[4,27,39] Hispanic and Black race/ethnicity was associated with being less likely to be seen at a SCC even when accounting for neighborhood SES and insurance status. The reasons for this are likely multifactorial and may include referral patterns, issues with insurance, and fear of medical experimentation at hospitals offering clinical trials. In addition, women are less likely to be seen at a SCC. To our knowledge that has not been previously described. One could speculate that young women may be primary caregivers and may be more likely to receive care where it is most convenient, even if it is not at a SCC. These disparities in utilization of SCCs are problematic especially with the mounting evidence of the improved outcomes associated with SCCs. Identifying reasons why utilization to SCCs is lower in this population and potential solutions to improve utilization for older AYAs, women, and Hispanic and Black patients are critical to ensuring equitable access not only to expert, multidisciplinary care but to improved survival.

A limitation of this study is that we focus on patients with inpatient admissions and lack information on outpatient visits, which is especially important for those patients with

localized disease or who do not receive chemotherapy and are less likely to be hospitalized. However, a majority of patients with STS, especially metastatic STS, have inpatient admissions, allowing us to identify their location of inpatient care. Lacking outpatient data also may result in underreporting of treatment-associated complications in our study. In addition, the number of children in this study is small, limiting the power to determine the impact of location of care on children with STS. However, this study is a large population-based study evaluating a large cohort of children and AYA patients with STS, providing a real-world picture of factors impacting their survival, including location of care.

The superior survival experienced by AYA patients receiving inpatient care at a SCC may be secondary to improved access to expertise in the treatment of STS and clinical trials. However, there continues to be a distinct group of people that are not utilizing or have access to SCCs, including older AYAs, women, Black, and Hispanic patients with STS. While identifying which patients benefit most from care at a SCC is a critical first step toward improving outcomes, optimizing access to and utilization of care at SCCs with the current standard therapies for STS significantly improving survival in this patient population, especially in those patients who are currently less likely to receive treatment at a SCC.

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No competing financial interests exist.

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Supplementary Material

Supplementary Table S1

References

1. Ferrari A, Trama A, De Paoli A, et al. Access to clinical trials for adolescents with soft tissue sarcomas: enrollment in European pediatric Soft tissue sarcoma Study Group (EpSSG) protocols. Pediatr Blood Cancer. 2017;64(6):26348.
2. Barr RD, Ferrari A, Ries L, et al. Cancer in adolescents and young adults: A narrative review of the current status and a view of the future. JAMA Pediatr. 2016;170(5):495–501.
3. Keegan TH, Ries LA, Barr RD, et al. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. Cancer. 2016;122(7):1009–16.
4. van der Graaf WTA, Orbach D, Judson IR, et al. Soft tissue sarcomas in adolescents and young adults: a comparison with their paediatric and adult counterparts. Lancet Oncol. 2017;18(3):e166–75.
5. Westermann C, Weller J, Pedroso F, et al. Socioeconomic and health care coverage disparities in children, adolescents, and young adults with sarcoma. Pediatr Blood Cancer. 2020;67(12):e28708.
6. Spunt SL, Million L, Chi YY, et al. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. Lancet Oncol. 2020; 21(1):145–61.
7. Ferrari A, Sultan I, Huang TT, et al. Soft tissue sarcoma across the age spectrum: a population-based study from the Surveillance Epidemiology and End Results database. Pediatr Blood Cancer. 2011;57(6):943–9.
8. Alvarez E, Keegan T, Johnston EE, et al. Adolescent and young adult oncology patients: disparities in access to specialized cancer centers. Cancer. 2017;123(13):2516–23.
9. Wolfson JA, Sun CL, Wyatt LP, et al. Impact of care at comprehensive cancer centers on outcome: results from a population-based study. Cancer. 2015;121(21):3885–93.
10. Ferrari A, Merks JHM, Chisholm JC, et al. Outcomes of metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) treated within the BERNIE study: a randomised, phase II study evaluating the addition of bevacizumab to chemotherapy. Eur J Cancer. 2020;130:72–80.
11. Wolfson J, Sun CL, Wyatt L, et al. Adolescents and Young Adults with Acute Lymphoblastic Leukemia and Acute Myeloid Leukemia: impact of Care at Specialized Cancer Centers on Survival Outcome. Cancer Epidemiol Biomarkers Prev. 2017;26(3):312–20.
12. Alvarez EM, Malogolowkin M, Hoch JS, et al. Treatment Complications and Survival Among Children and Young Adults With Acute Lymphoblastic Leukemia. JCO Oncol Pract. 2020;16(10):e1120–e1133.
13. Martin-Broto J, Hindi N, Moura DS. Which goals should we pursue in each line of treatment for advanced soft tissue sarcoma? Future Oncol. 2019;15(26s):17–23.
14. Blay JY, Honore C, Stoeckle E, et al. Surgery in reference centers improves survival of sarcoma patients: a nationwide study. Ann Oncol. 2019;30(7):1143–1153.
15. Venigalla S, Carmona R, VanderWalde N, et al. Disparities in perioperative radiation therapy use in elderly patients with soft-tissue sarcoma. Int J Radiat Oncol Biol Phys. 2018;102(1):155–65.
16. Lazarides AL, Kerr DL, Nussbaum DP, et al. Soft Tissue Sarcoma of the Extremities: What Is the Value of Treating at High-volume Centers? Clin Orthop Relat Res. 2019; 477(4):718–27.
17. Blay JY, Soibinet P, Penel N, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. Ann Oncol. 2017;28(11):2852–59.
18. Collignon C, Carton M, Brisse HJ, et al. Soft tissue sarcoma in children, adolescents and young adults: outcomes according to compliance with international initial care guidelines. Eur J Surg Oncol. 2020;46(7):1277–1286.
19. Cheraghlou S, Li H, Judson BL. Association of facility and system factors with survival among pediatric patients with

surgically treated head and neck sarcomas. JAMA Otolaryngol Head Neck Surg. 2018;144(5):455–456.
20. Ferrari A, Casanova M, Collini P, et al. Adult-type soft tissue sarcomas in pediatric-age patients: experience at the Istituto Nazionale Tumori in Milan. J Clin Oncol. 2005; 23(18):4021–30.
21. Spunt SL, Poquette CA, Hurt YS, et al. Prognostic factors for children and adolescents with surgically resected nonrhabdomyosarcoma soft tissue sarcoma: an analysis of 121 patients treated at St Jude Children's Research Hospital. J Clin Oncol. 1999;17(12):3697–705.
22. Spunt SL, Hill DA, Motosue AM, et al. Clinical features and outcome of initially unresected nonmetastatic pediatric nonrhabdomyosarcoma soft tissue sarcoma. J Clin Oncol. 2002;20(15):3225–35.
23. Pratt CB, Pappo AS, Gieser P, et al. Role of adjuvant chemotherapy in the treatment of surgically resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: A Pediatric Oncology Group Study. J Clin Oncol. 1999;17(4): 1219.
24. Pratt CB, Maurer HM, Gieser P, et al. Treatment of unresectable or metastatic pediatric soft tissue sarcomas with surgery, irradiation, and chemotherapy: a Pediatric Oncology Group study. Med Pediatr Oncol. 1998;30(4):201–9.
25. Pappo AS, Devidas M, Jenkins J, et al. Phase II trial of neoadjuvant vincristine, ifosfamide, and doxorubicin with granulocyte colony-stimulating factor support in children and adolescents with advanced-stage nonrhabdomyosarcomatous soft tissue sarcomas: a Pediatric Oncology Group Study. J Clin Oncol. 2005;23(18):4031–38.
26. Weiss AR, Chen YL, Scharschmidt TJ, et al. Pathological response in children and adults with large unresected intermediate-grade or high-grade soft tissue sarcoma receiving preoperative chemoradiotherapy with or without pazopanib (ARST1321): a multicentre, randomised, open-label, phase 2 trial. Lancet Oncol. 2020;21(8):1110–22.
27. Bleyer A, Budd T, Montello M. Adolescents and young adults with cancer: the scope of the problem and criticality of clinical trials. Cancer. 2006;107(7 Suppl):1645–55.
28. Finlayson SR, Birkmeyer JD, Tosteson AN, et al. Patient preferences for location of care: implications for regionalization. Med Care. 1999;37(2):204–9.
29. Alvarez E, Chamberlain LJ, Aftandilian C, et al. Pediatric Oncology Discharges With Febrile Neutropenia: variation in Location of Care. J Pediatr Hematol Oncol. 2017;39(1): e1–e7.
30. Yost K, Perkins C, Cohen R, et al. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. Cancer Causes Control. 2001;12(8): 703–11.
31. Rosenberg AR, Kroon L, Chen L, et al. Insurance status and risk of cancer mortality among adolescents and young adults. Cancer. 2015;121(8):1279–86.
32. Keegan THM, Parsons HM, Chen Y, et al. Impact of health insurance on stage at cancer diagnosis among adolescent and young adults. J Natl Cancer Inst. 2019;111(11): 1152–60.
33. Parsons HM, Maguire FB, Morris CR, et al. Impact of insurance type and timing of Medicaid enrollment on survival among adolescents and young adults with cancer. Pediatr Blood Cancer. 2020;67(9):e28498.
34. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Med Care. 1998; 36(1):8–27.
35. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130–9.
36. Gupta AA, Anderson JR, Pappo AS, et al. Patterns of chemotherapy-induced toxicities in younger children and adolescents with rhabdomyosarcoma: a report from the Children's Oncology Group Soft Tissue Sarcoma Committee. Cancer. 2012;118(4):1130–7.
37. Gupta AA, Chi YY, Anderson JR, et al. Patterns of chemotherapy-induced toxicities and outcome in children and adolescents with metastatic rhabdomyosarcoma: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2017;64(9):26479.
38. Wolfson J, Sun CL, Kang T, et al. Impact of treatment site in adolescents and young adults with central nervous system tumors. J Natl Cancer Inst. 2014;106(8):dju166.
39. Parsons HM, Harlan LC, Seibel NL, et al. Clinical trial participation and time to treatment among adolescents and young adults with cancer: does age at diagnosis or insurance make a difference? J Clin Oncol. 2011;29(30): 4045–53.

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