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Comparative performance of the 7th and the 8th editions of the American Joint Committee on Cancer staging systems for soft tissue sarcoma of the trunk and extremities

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Abstract

Background: The 8th edition AJCC staging for soft tissue sarcomas of the trunk/extremities divides T-stage into 4 categories and upstages nodal disease to stage IV. We used the NCDB to evaluate the prognostic power of the new system.

Methods: 26,144 patients were identified from the NCDB from 2004–2013. Overall survival (OS) was compared using Kaplan-Meier and Cox proportional hazard models.

Results: Including T3 (10cm>x>15cm) and T4 (>15cm) categories resulted in an increased number of patients classified as stage III (5,120 as IIIA[19.6%], 4,280 as IIIB[16.4%] vs. 7,882 [30.1%] previously). There was a small increase in the number of patients classified as stage IV (2,776[10.6%], vs. 2,565[9.8%] previously). In the 7th edition, the HR for death increases with stage, with large incremental increases between stages II-III and III-IV. In the 8th edition, the HR for death demonstrates smaller incremental increases between each stage. Five-year OS for 7th edition T1 and T2 patients was 78.8% and 58.8% (p<0.01), respectively, versus 62.6% T2, 53.5% T3, and 56.1% for T4 patients in the 8th edition (p<0.01). Patients with isolated nodal disease (n=211) had a better 5-year OS than those with distant metastases (33.1% vs 12.4%, p<0.001).

Conclusions: The AJCC 8th edition uses T stage to more accurately stratify overall survival in patients with large, high-grade tumors (T3/4) as compared to those with T2 tumors, which facilitates risk assessment. The distinction between T3 and T4 may not be clinically significant. Patients with metastatic nodal disease have a survival outcome intermediate to those with stage III and stage IV disease.

Keywords

trunk and extremity sarcoma; staging; survival; AJCC 8th edition; nodal metastases

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Introduction

With an annual incidence of approximately 12,390 new cases per year spanning more than 50 distinct histologies, soft tissue sarcomas represent a diverse group of cancers that can arise throughout the body.¹ The rarity and heterogeneity of soft tissue sarcomas makes the development of meaningful staging systems difficult. As such, the American Joint Committee on Cancer (AJCC) has relied heavily upon data from retrospective, single-institution studies to guide its recommendations for staging.

The National Cancer Database (NCDB) collects registry data from more than 1,500 Commission on Cancer (CoC) accredited facilities, representing 70% of newly diagnosed cancer cases nationwide and more than 24 million cancer cases since 1985.^{2,3} Given its breadth, the NCDB represents a rich resource from which to study rare cancers and is particularly useful with regards to the evaluation of staging systems. A successful staging system standardizes communication regarding prognosis for both cancer recurrence and mortality amongst medical professionals and the patient, and allows consideration of relative risk when planning multimodality therapy.

Recently the American Joint Committee on Cancer (AJCC) updated the staging guidelines for soft tissue sarcomas.⁴ Previously, a single staging system was used for all soft tissue sarcomas. In the 8th edition, specific to tumors of the trunk and extremity, the tumor (T) category is divided into 4 subcategories based on tumor size, with new classifications for tumors greater than 10 cm but less than or equal to 15 cm (T3), and for tumors greater than 15 cm (T4). Previously patients with tumors greater than 10 cm were grouped into a single category (T2) without further distinction (Figure 1). The newly designed T-stage results in the creation of two new stage categories (IIIA and IIIB), with the former 7th edition stage IIB patients absorbed into them. In addition, the 8th edition staging system upstages any patient with metastatic nodal disease to stage IV (Figure 1). These changes were largely based on retrospective examination of data from two large single-institution studies.^{5,6} With 5,267 patients treated over an 18-year time period, Maki et al.⁵ demonstrated that local recurrence free survival (LRFS), recurrence free survival (RFS), and disease specific survival (DSS) continued to diminish as tumor size increased. Regarding lymph node status, patients with N1 metastatic disease (regardless of tumor grade) in the absence of distant metastases had survival outcomes inferior to patients with large, high grade tumors without nodal metastases (7th edition stage III), but superior to patients with distant metastatic disease (stage IV), resulting in outcomes intermediate to what are defined as stages III and IV in AJCC 7th edition, a finding which has been shown by other groups.⁷ These data were used to support the designation of N1 metastatic disease as stage IV in the 8th edition. Finally, after controlling for other significant prognostic factors such as age, size, site, and grade, tumor depth was not an independent prognostic factor for DSS, supporting the decision in the 8th edition to remove the superficial/deep classification entirely.^{5,6}

These large retrospective studies^{5,6} summarize extensive experience with trunk and extremity soft tissue sarcoma but reflect the practice patterns of highly specialized centers over long time periods. The NCDB offers a more generalized cross-sectional assessment of practice patterns across the country, while maintaining high cancer-specific standards of

care. The current study uses the NCDB to assess the discriminatory ability of the new AJCC 8th edition staging system.

Methods

After obtaining Institutional Review Board approval, the NCDB Participant User File for sarcoma was queried for patients age 18 or older with trunk or extremity tumors treated between January 1, 2004 and December 31, 2013, using the International Classification of Disease for Oncology (3rd ed) topography codes C471, C472, C476, C491, C492, and C496.⁸ All histologic subtypes included in the data were individually vetted to exclude non-sarcomatous or mixed histologies. Patients with sarcomas of the retroperitoneum, head and neck, or central nervous system, osteosarcomas, or dermatofibrosarcoma protuberans were excluded. Pediatric patients, patients with significant gaps in their clinical data, patients with less than 90 days of follow-up, and/or patients with inadequate information for tumor, node, and metastasis (TNM) staging for classification according to the AJCC 7th or 8th edition staging were excluded. Due to diagnostic ambiguity, patients who were recorded as having metastatic nodal disease yet had no pathologic assessment of lymph nodes were excluded. Patients with localized disease who did not undergo surgical resection were excluded (inclusions and exclusions summarized in Supplemental Figure).

Overall survival (OS) was compared using Kaplan-Meier curves. Cox proportional hazard models were used to estimate five-year OS. Univariate and multivariate analyses were performed to identify factors associated with OS. Concordance indices (C-index) were calculated to evaluate the discriminatory power of both the 7th and 8th AJCC staging editions. Statistical significance was defined at $p < 0.05$. All analyses were performed using SAS 9.4 (Cary, NC).

Results

Patient Characteristics

Demographics and clinical characteristics of the 26,144 patients with trunk or extremity sarcomas are shown in Table 1. The most common histologies were liposarcoma (n=5,437 20.8%), malignant fibrous histiocytoma (n=3,675 14.1%), leiomyosarcoma (n=3,570 13.7%), fibrosarcoma (n=2,734 10.5%), giant cell sarcoma (n=2,300 8.8%), sarcoma not otherwise specified (n=1,917 7.3%), and synovial sarcoma (n=1,326 5.1%). Between 2004 and 2013, the number of cases per year appeared similar, with 8.1–11.0% of the total number of cases occurring each year. Most patients were treated with surgical resection – either radical resection (n=13,499, 51.6%) or partial resection (n=9,838, 37.6%), with amputation in a minority of the patients (n=1,373, 5.3%). Radiation therapy was administered to 13,249 (50.7%) patients; chemotherapy was administered to 4,525 (17.3%) patients.

Staging

With the addition of T3 and T4 categories in the AJCC 8th edition staging system, stages IIIA and IIIB are comprised of a conglomerate of patients previously staged as either IIB or III, and patients with nodal disease migrated to stage IV (Figure 1B). In the new 8th edition,

stages IA, IB, and II (previously IIA) remained the same. For the 8th edition, there was an increase in the total number of patients comprising stage III (n=9,400, 35.9%), with 5,120 patients in stage IIIA (975 previously IIB and 4,145 previously III) and 4,280 patients in stage IIIB (754 previously IIB and 3,526 previously III). The addition of patients with isolated nodal disease (n=211; previously stage III) to the stage IV category increased the total number of patients with metastatic disease to 2,776 (10.6%).

Overall Survival

Median follow up for the population was 40.8 months. Overall survival for both staging editions are shown in Figure 2A & B. In both systems, the hazard ratio (HR) for death increases and the 5-year OS decreases as stage increases (Table 2). In the 7th edition, a large incremental increase in HR is noted between stages IIB (75.6%) and III (53.3), whereas in the 8th edition, the incremental increases are smaller between each stage (IIIA: 62.4%, IIIB: 50.1%; Table 2). The c-index for the 7th edition staging system (0.72) was comparable to the 8th edition (0.74).

Role of T stage

When stratified by T stage, 5-year OS for T1 and T2 patients as staged in the 7th edition was 78.8% and 58.8% (p<0.01), respectively. In the 8th edition, 5-year OS improved for T2 patients (62.6%, p<0.01), with T3 and T4 patients demonstrating similar 5-year OS of 53.5% and 56.1% (p=0.52), respectively (Figure 2C & D).

Role of nodal disease

In the 8th edition, patients with N1 disease are grouped with patients with distant metastases and classified as stage IV. Five-year OS for patients with nodal disease without distant metastases was significantly longer than patients with distant metastases (33.1% vs 12.4%, p<0.001; Table 2 & Figure 2E) but worse than for patients with localized disease (IIIA: 62.4%, IIIB: 50.1%, p<0.01).

Univariate and Multivariate Analyses

Stratified analyses were performed to assess the impact of T and N stage on survival (Table 3) when controlling for known prognostic factors. As patients with metastatic disease at diagnosis are generally treated with systemic therapy rather than surgical resection, separate multivariate analyses were constructed for patients with localized disease and metastatic disease. On multivariate analysis amongst patients with localized disease (M0; n = 23,579), older age, race, positive margin status, lymph node positive disease (N1), and high grade were associated with poorer OS, whereas radiation therapy was protective (Table 3). Although T stage remained an independent predictor of OS, little difference was noted between patients with T3 tumors versus T4 tumors (HR 2.12 vs 2.19, Table 3).

For patients with metastatic disease (n = 2,565) older age, increasing T stage, nodal disease, and high grade tumors correlated with decreased OS on multivariate analyses, although the overall impact was less than for those with localized disease. In addition, receipt of chemotherapy or radiation therapy were associated with improved outcomes (Supplemental Table).

Conclusions

The current study uses the NCDB to evaluate the prognostic power of the 8th edition of the AJCC staging system for extremity and trunk soft tissue sarcoma. The additional T stage categories and the resultant restaging of patients with large, intermediate or high grade tumors stratifies patients into more distinct categories than the 7th edition. Larger tumor size correlated with OS, although no difference between T3 and T4 tumors was detected. Patients with metastatic nodal disease have a prognosis that is intermediate to those without nodal disease and those with distant metastases, and perhaps should be reclassified into a unique staging category (ie IIIC or M1a).

It is interesting that in this study using a large, US hospital-based database, the addition of the T3 category adds prognostic power, but there is little to no additional discriminatory power among patients with T3 and T4 tumors, suggesting that tumor size correlates well with OS only up to a finite tumor size. These findings are similar to those reported by Maki et al.⁵ in which disease specific survival was equivalent for patients with tumors between 10 and 15 cm and greater than 15 cm, although the authors showed inferior local disease-free survival for patients with tumors larger than 15 cm, forming the basis for the T stage groups used in the 8th edition of AJCC. The current study was not able to assess for local disease-free survival or disease-specific survival as these events are not captured in the NCDB. Our findings and those of Maki et al.⁵ support the current 8th edition staging system that groups together T3 and T4 tumors into the same stage - either low grade (IB) or intermediate/high grade (IIIB). Future work should examine prognostic factors for survival solely amongst large tumors.

The role of nodal status in the staging of soft tissue sarcoma is controversial. Nodal metastases are rare, with an incidence between 0.9% - 16.4% of patients in series specific to soft tissue sarcomas of the trunk and extremity,⁹⁻¹² although higher rates are observed amongst specific histologies.^{12,13} Although rare, nodal disease is a significant adverse prognostic factor for survival, and in a recent SEER analysis was the strongest prognostic factor for OS after excluding distant metastases (HR 5.1, 95% CI 3.5 – 7.6, p<0.001).¹⁰ In the 6th edition of the AJCC staging system, patients with nodal disease were classified as stage IV, as in the current 8th edition. Because of several studies suggesting that patients with isolated nodal metastases fare better than patients with distant metastatic disease,^{7,14,15} the 7th edition AJCC staging system downstaged patients with nodal disease in the absence of distant metastases to stage III. However, these patients had survival outcomes inferior to those patients with large high grade tumors without nodal metastases (also included in stage III).^{5,10} In our study, metastatic nodal disease was the strongest prognostic factor for decreased OS in the absence of distant metastases. Patients with nodal disease without distant metastases had survival intermediate to that of the current stage IIIB and IV patients, adding support to the concept that patients with isolated nodal metastases comprise a unique group. Consideration should be given to creating a separate classification (ie IIIC or M1a) that denotes these patients' distinct outcomes.

The identification of reliable and consistent prognostic factors for patients with soft tissue sarcoma of the trunk and extremities has been hindered by both the rarity of the disease and

the retrospective nature of available reports within the literature. In addition to tumor size and tumor grade,^{5,6,16,17} large retrospective series have reported age (either as a continuous variable^{5,6} or age greater than 50 years^{16,17}), microscopically positive margins,^{6,17} specific histologic subtypes,^{6,17} anatomic site,^{5,16,17} nodal disease⁵ and recurrence at time of presentation^{6,17} as adverse prognostic factors for local recurrence, distant recurrence, and disease specific survival. The Memorial Sloan Kettering Cancer Center sarcoma specific nomogram predicts the risk of sarcoma-specific death within 12 years of curative intent surgical treatment using age, tumor size, depth, tumor site, histology, and grade (low/high),^{18,19} with others adapting the model to a three-grade system.²⁰ Although we were unable to examine specific histologic subtypes, our data similarly support the role of tumor size, nodal disease, grade, age, and margin status as prognostic factors for survival. Predicting survival is likely to be most accurate when based on a large number of homogeneous patients, including those with similar histologies. Histologic subtype is an accepted prognostic factor for survival,²¹ but with more than 50 subtypes of sarcoma accounting for each in a single staging system is not practical. In addition to staging systems, nomograms offer a valuable method of conveying patient-specific prognostic information and their continued refinement and use is encouraged.

The current study has several limitations, many of which stem from the use of a large registry that draws information from multiple providers and coding personnel across multiple institutions. One advantage of the NCDB is that the Committee on Cancer requires multiple quality reviews and direct assessment of the data at each institution to maintain accreditation. Variability within the data remains, as evidenced by the small proportion of cases in the current study with conflicting grade and histology. With more than 50 different histologic subtypes, soft tissue sarcomas comprise a diverse group of pathologies at high risk for diagnostic error.²² Sarcoma in particular represents a field that has used multiple different grading schema and specific diagnostic terms have gained or lost popularity over time (for example, malignant fibrous histiocytoma was declassified as a diagnostic term in 2002 by the World Health Organization, and replaced by undifferentiated pleomorphic sarcoma²¹), in addition to having multiple categories of “not-otherwise-specified.” Additionally, there is inherent ambiguity related to the use of multiple grading systems, and the NCDB cannot distinguish which one was used. Although a limitation, the current work does not prognosticate based on individual histologies and therefore the histologic ambiguity innate to any large database may be less significant with regard to the current findings.

The current study examines the prognostic power of the new 8th edition AJCC staging system for trunk and extremity soft tissue sarcomas, and shows that the additional T stages (>10 cm) identify discrete groups with respect to prognosis, particularly for those patients with intermediate to high grade tumors. The distinction between T3 and T4 tumors may not be clinically relevant; future studies should examine prognostic factors specific to this population. The inclusion of patients with metastatic nodal disease in the metastatic/stage IV category requires continued evaluation, as these patients have an overall survival that is substantially better than their counterparts with distant metastases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis:

The 8th edition AJCC staging system for trunk/extremity soft tissue sarcomas was evaluated using the NCDB. Adding tumor categories that better characterize size aids in predicting survival, but classifying patients with nodal disease as stage IV may not be appropriate.

Figure 1:

(A) Schema of the changes from the 7th and 8th editions of the American Joint Committee on Cancer staging systems for soft tissue sarcoma of the trunk and extremities, with (B) the TNM definitions (changes in red) and (C) the resulting changes in stages IIIA, IIIB, and IV within the NCDB study population (outlined)

Figure 2:

Overall survival by stage according to the AJCC 7th edition (A) and 8th edition (B); stratified by T stage in the AJCC 7th edition (C) & 8th edition (D); and with the 8th edition further divided into patients with isolated nodal metastases (blue line) and distant metastases (green line) (E)

Table 1:

Demographic and Clinical Characteristics of Patients with Trunk/Extremity Sarcoma in the National Cancer Database (n = 26,144)

	n (%) or median (range)
Age (years)	60.0(18.0–90.0)
Male sex	14,188(54.3)
Race	
White	20,416(78.1)
Black	2,699(10.3)
Hispanic	1,707(6.5)
Asian	732 (2.8)
Other/unknown	590(2.3)
Charlson-Deyo Comorbidity Score	
0	21,716(83.1)
1	3,588(13.7)
2	840 (3.2)
Treatment Facility	
Community Cancer Program	1,276(4.9)
Comprehensive Community Cancer Program	6,408 (24.5)
Academic/Research Program	12,016(46.0)
Integrated Network Cancer Program	2,502 (9.6)
Other	3,942(15.1)
Tumor size (cm)	7.7 cm (0–99.9, mean 14.7)
Tumor Stage	
7 th & 8 th Ed. TO	2 (0.01) *
7 th & 8 th Ed. T1 (<5 cm)	9,791 (37.5)
7 th Ed. T2 (>5 cm)	15,908(60.9)
8 th Ed. T2(5cm>x>10cm)	7,672 (29.4)
8 th Ed. T3(10cm>x>15cm)	4,109(15.7)
8 th Ed. T4(>15cm)	4,127(15.8)
Unknown	443(1.7)
Nodal disease (clinical)	279(1.1) **
Nodal disease (pathologic)	298(1.1) **
Isolated nodal disease (no distant metastases)	211 (0.8)
Metastatic disease (clinical)	2,565 (9.8) #
Grade	
High(G3orGX)	14,626(55.9)
Intermediate (G2)	3,572(13.7)
Low(G1, GX, orNOS)	7,946 (30.4)
Margin positive	
R1	2,505 (9.6)

	n (%) or median (range)
R2	222 (0.9)
No surgery on primary	1,227(4.7)
Unknown	3,112(11.9)

Ed.: edition

* Percent total refers to the total within the respective 7th or 8th edition staging system, with 1.7% unknown in both.

** Missing = 456, 1.7%;

Missing=1,080, 4.1%

Table 2:Cox proportional hazards model for risk of death stratified by stage according to the AJCC 7th and 8th editions

	Stage	n	Hazard Ratio for Death	95% CI	5-year Overall Survival (%)
AJCC 7th Edition	IA	2,796	reference		85.3
	IB	4,551	1.2	1.1–1.3	83.0
	IIA	6,441	1.4	1.3–1.6	79.0
	IIB	1,729	1.6	1.4–1.9	75.6
	III	7,882	3.6	3.3–4.0	52.3
	IV	2,565	14.1	12.7–15.6	12.4
AJCC 8th Edition	IA	2,976	reference		85.3
	IB	4,551	1.2	1.1–1.3	83.0
	II	6,441	1.4	1.3–1.6	79.0
	IIIA	5,120	2.6	2.4–2.9	62.4
	IIIB	4,280	4.0	3.6–4.4	50.1
	IV – overall	2,776	14.1	12.7–15.6	13.9
	IV – N+/M–	211	6.2	5.1–7.6	33.1
	IV – M+	2,565	15.3	13.8–16.9	12.4

CI: Confidence interval; AJCC: American Joint Committee on Cancer; N+: node positive; M+: distant metastases

Table 3:

Prognostic factors associated with impaired overall survival in patients with localized extremity & trunk sarcoma (n = 23,579)

Prognostic Factor	HR	95% CI		P-value
Age (years)	1.04	1.03	1.04	<0.001
Race (Ref White)				<0.001
Black	1.19	1.10	1.29	
Hispanic	1.03	0.92	1.15	
Asian	0.90	0.76	1.07	
Other	0.93	0.78	1.10	
T stage (Ref T1)				<0.001
T2	1.58	1.49	1.68	
T3	2.12	1.97	2.28	
T4	2.19	2.04	2.36	
Unknown	0.82	0.40	1.67	
N1 disease	3.31	2.76	3.97	<0.001
High grade	2.34	2.21	2.47	<0.001
Margin (Ref R0)				
R1/R2	1.20	1.11	1.29	<0.001
Unknown	1.25	1.16	1.34	
Chemotherapy	1.19	1.11	1.28	<0.001
Radiation therapy	0.78	0.74	0.82	<0.001

HR: hazard ratio; CI: confidence interval; Ref: reference value; N1: node positive; R0: negative microscopic margins, R1: positive microscopic margins; R2: positive gross margins