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An evaluation of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for retroperitoneal sarcomas using the National Cancer Data Base (NCDB): Does size matter?

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Abstract

Objectives: Retroperitoneal sarcomas (RPS) are often large at diagnosis calling into question the 7th edition AJCC size classification of <5cm (T1) or ≥5cm (T2). The 8th edition expands T stage into 4 categories (T1: ≤5cm, T2: 5<x≤10cm, T3: 10<x≤15cm, T4: >15cm). We evaluated the prognostic ability of the 8th edition using the National Cancer Database (NCDB).

Methods: Patients with RPS treated between 1998–2011 were identified from the NCDB; overall survival (OS) was compared.

Results: Of the 6,427 patients identified, 9% had tumors ≤5 cm (n=580), 19.4% 5<x≤10cm (n=1,246), 20.2% 10<x≤15cm (n=1,298) and 47.4% >15cm (n=3,045). With the 8th edition, stage II patients (G2/3 ≤5cm) have a similar OS to stage IIIA patients (G2/3 5cm<x≤10cm), and patients with larger tumors (stage IIIB, G2/3>10cm) show a decrease in OS. Tumor size as a continuous variable had a modest effect on survival (HR 1.004, p=0.04). On multivariate analysis, higher T-stage was associated with decreased OS (T4 HR 1.3, p<0.001) but high grade and incomplete resection (R2) were stronger prognostic factors. The c-index for both editions were similar (80.13 8th vs 80.08 7th).

Conclusions: The 8th edition AJCC staging system for retroperitoneal sarcoma incorporates larger tumor size parameters that better characterize most patients, but tumor size alone is only a modest predictor of outcome.

Keywords

retroperitoneal sarcoma; staging; survival; AJCC 8th edition

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Introduction

Soft tissue sarcomas comprise a rare and heterogeneous group of cancers, with approximately 13,040 new cases per year and more than 50 different histologic subtypes.[1] Of these, only 10–15% arise in the retroperitoneum, which makes study of retroperitoneal sarcoma (RPS) and the development of a meaningful staging system difficult. Since 1977 the American Joint Committee on Cancer (AJCC) has used available evidence-based literature to construct staging systems for many cancers. In addition to the three variables that comprise the foundation of most cancer staging systems - tumor size (T), nodal status (N), and distant metastases (M) – sarcoma staging has included grade (G) and tumor depth (superficial/deep) since its inception in 1992.[2] Yet even with the incorporation of these additional variables, previous staging systems for sarcoma have been found lacking, and their application to RPS in particular has been questioned.[3–7] Previous staging criteria were based largely on data that included a majority of patients with extremity or trunk sarcomas, which have a tumor biology distinct from RPS.[8,9] Additionally, the T and N categories may be less meaningful for RPS, as nodal disease is prognostic but rare[3,10] and tumor size at the time of diagnosis is often larger than historical staging parameters.[4,6,10–15]

The recently released AJCC 8th edition staging manual addresses some of these concerns. The 8th edition creates a separate staging system specific to the retroperitoneal location, appropriately removes the superficial/deep category formerly used for tumors in non-retroperitoneal locations, and adds two additional T categories to characterize larger tumors.[16] The previous T1 category is preserved (≤5 cm), tumors that are greater than 5 cm but less than or equal to 10 cm are now T2, tumors that are greater than 10 cm but less than or equal to 15 cm are now T3, and tumors that are greater than 15 cm are T4. These changes result in reclassification of patients from the IIB/III groups in the 7th edition to the IIIA/IIIB groups in the 8th edition (Figure 1A-C). The value of the updated AJCC staging classification is unclear.

Recently an analysis using the Surveillance, Epidemiology, and End Results (SEER) database found the predictive accuracy and concordance indices of the AJCC 8th edition staging system to be lower than the previous version, with tumor size having only a limited effect on overall survival (OS) after accounting for other prognostic factors.[17] In contrast to SEER, which is population based, the National Cancer Database (NCDB) collects hospital-based registry data specifically from Commission on Cancer accredited facilities, thus representing an assessment of practice patterns amongst institutions with a specific focus on cancer medicine.[18,19] In the current study, we use the NCDB to evaluate the prognostic value of the AJCC 8th edition staging system for RPS.

Materials and Methods

The NCDB Participant User File for sarcoma was queried for patients age 18 years or older with retroperitoneal tumors treated at the reporting facility between January 1, 1998 and December 31, 2011, using the International Classification of Disease for Oncology (3rd ed) topography code C480. The histologic subtypes were reviewed and the following histologic

subtypes were excluded: non-sarcomatous or mixed histologies and dermatofibrosarcoma protuberans. Patients with less than 90 days of follow-up, significant gaps in their clinical data, and/or inadequate information for tumor, node, and metastasis (TNM) staging for classification according to the AJCC 7th or 8th edition staging systems were also excluded. Patients with stage T0, tumor size recorded as "0," or discordant classification between pathologic node status and number of nodes assessed (i.e. pathologic node positive and number of nodes assessed = 0) were excluded. Patients with localized disease who did not undergo surgery were excluded (Supplemental Figure).

Kaplan-Meier survival curves and Cox proportional hazard models were used to evaluate 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 the 7th and 8th AJCC staging editions. Analyses were performed using SAS 9.4 (Cary, NC), with statistical significance defined at $p < 0.05$.

Results

Patient Characteristics

Table 1 demonstrates the demographics and clinical characteristics of the 6,427 patients with retroperitoneal sarcoma in the study. Liposarcoma was the most common histology (n=3,304 51.4%), followed by leiomyosarcoma (n=1,892 29.4%), and sarcoma not otherwise specified (NOS, n=354, 5.5%). The median tumor size was 15 cm (range 3–99 cm) with 9% of patients having tumors ≤5 cm (n=580), 19.4% with tumors $5 < x \leq 10$ cm (n=1,246), 20.2% with tumors $10 < x \leq 15$ cm (n=1,298) and 47.4% with tumors >15 cm (n=3,045).

Most patients were treated with surgical resection (radical resection n=3,082, 48.0%; local resection n=2,181, 33.9%; debulking n=309, 4.8%; unknown surgical resection n=265, 4.1%). A small subset of patients received chemotherapy (n=1,146, 17.8%) and/or radiation therapy (n=1,769, 27.5%). The majority of patients underwent an R0/R1 resection (n=3,956, 61.4%); data on concomitant organ resection were not available. As expected, surgical lymph node assessment was uncommon, with 21.3% (n=1,372) undergoing pathologic assessment of at least one node.

Staging

Patients with intermediate grade tumors greater than 5 cm in size who were previously classified as stage IIB in the 7th edition (n=636) were redistributed into either stage IIIA (n=186, 29.2%) or stage IIIB (n=450, 70.8%) according to the 8th edition guidelines depending on tumor size (Figure 1 A-C). Similarly, patients with high grade tumors greater than 5 cm who were previously classified as stage III in the 7th edition (n=2,129) were redistributed into either stage IIIA (n=422, 19.8%) or stage IIIB (n=1,707, 80.2%, Figure 1 A-C).

Overall Survival

Median follow up for the cohort was 36.6 months. Overall survival for both the 7th and the 8th staging editions is shown in Figure 2A & B. In the 7th edition, patients with stage IIB

disease (larger, intermediate grade tumors) had significantly better OS than patients with stage IIA (small intermediate or high grade tumors) disease ($p<0.001$, Table 2). With the 8th edition, patients with stage II disease (previously 7th edition IIA, small intermediate or high grade tumors) have a similar OS to stage IIIA patients (intermediate or high grade tumors $5cm<x\leq10cm$), whereas patients with larger tumors of similar grade (stage IIIB, intermediate or high grade >10cm) show a decrease in OS (Table 2). Stage IIIB also included 106 patients with nodal disease; there was no difference in OS within stage IIIB when stratified by nodal status ($p=0.931$). The c-index for both editions were similar (7th edition: 80.1, 95% CI 77.3-82.7; 8th edition: 80.1, 95% CI 77.3-82.8).

Role of T stage

In the 7th edition, patients with T1 and T2 disease had a 5-year OS of 57.5% and 52.4%, respectively ($p<0.001$). In the 8th edition, 5-year OS based on T stage alone was 57.5%, 55.1%, 51.8%, and 51.5% for T1, T2, T3, and T4 patients, respectively, $p=0.007$ (Figure 2C & D).

When analyzed as a continuous variable amongst patients with stage I-III disease, increasing tumor size was significantly associated with decreased OS, although the HR for each centimeter increase was small (HR=1.004, 95% CI: 1.000–1.007, $p=0.04$). When dichotomized at 5 cm intervals for tumors up to 25 cm, a significant effect on OS for each size group was identified starting with tumors > 10 cm (Supplemental Table 1).

Univariate and Multivariate Analyses

Amongst patients with localized disease (stages I-III), univariate analysis identified older age, male sex, government insurance status, treatment at a non-academic facility, debulking resection, incomplete surgical resection, higher T stage, higher grade, presence of nodal disease, chemotherapy administration, and lack of radiation therapy were factors associated with poorer OS. In a multivariate model which included only patients with complete information (n=3,681), T stage remained a weak prognostic factor for OS with a significant difference noted between patients with T4 versus T1 tumors (HR 1.3, 95% CI 1.08–1.57, $p<0.001$, Table 3). A significant association with OS was not observed for patients with T2 or T3 tumors as compared to T1 tumors. High tumor grade, incomplete (R2) resection and debulking procedures were associated with the highest HRs for death (Table 3).

For patients with metastatic disease (n = 749) increasing age, male sex, government insurance status, treatment at a non-academic facility, and high grade tumors were associated with poorer OS, whereas selection for surgery was associated with better OS (Supplemental Table 2).

Discussion

The current study uses the NCDB to evaluate the performance of the 8th edition AJCC staging manual for RPS. Our results suggest that while adding additional T stage categories may more accurately characterize tumor size, the overall outcome with respect to the prognostication for OS among these subgroups is minimal. Other clinicopathologic factors

such as tumor grade and ability to achieve a complete surgical resection are associated with greater differences in patient survival compared to tumor size.

Historically, knowledge regarding the prognostic factors and outcomes for patients with RPS was based on retrospective analyses from single, high-volume institutions.[4,11,20–22] More recently, researchers have utilized regional[23] or national databases,[6,10,24–28] or formed multi-institutional working groups,[15,29] with some spanning multiple countries,[14] to define factors that influence outcomes of patients with RPS. The results with respect to the role of tumor size as a prognostic factor are conflicting. In one of the largest single institution series (n=500), tumor size > 10 cm was associated with decreased OS on multivariate analysis in patients with primary RPS (HR=1.7 95% CI: 1.1 – 2.7, p=0.02) but was not associated with distant metastasis free survival or locoregional recurrence.[20] Others have supported using 10 cm as a prognostic cutpoint,[10] or shown a similar relationship between OS and tumor size using 15 cm as a cutpoint.[4,25,30] Many investigators, however, have not found a relationship between tumor size and outcome at all.[13,15,20,31–33]. In a Surveillance, Epidemiology, and End Results (SEER) analysis spanning 17 years and including 1,365 patients, Nathan et al.[6] was unable to identify an association between tumor size and OS when using tumor size either as a continuous variable or dichotomized at various cutpoints, including 20 cm, 10 cm, as well as the AJCC 7th edition cutpoint of 5 cm. Similarly, Berger et al.[26] did not identify a relationship between tumor size and OS in their analysis of 2,762 patients included in the National Cancer Database treated between 2004 and 2013. Our findings suggest that tumor size, categorized by T stage, is at most a modest prognostic factor for OS, with other variables including high grade, incomplete resection (R2 margin), and presence of nodal disease having a greater impact on OS, which are well accepted within the literature as negative prognostic factors.[10,12,20,21,27,33,34]

One potential explanation for the conflicting data pertaining to tumor size as a prognostic factor is the possibility that the effect is bimodal – i.e. tumor size may be prognostic up to a certain point, but after that larger tumors may demonstrate indolent biology and behavior. In an analysis of 192 patients, Ardoino et al.[11] found that the relative hazard for death after resection of primary nonmetastatic RPS increased with tumor size up to 25 cm, and decreased thereafter, similar to the findings in the current study. This relationship is also captured in two RPS specific nomograms, in which increasing tumor size is associated with a worse prognosis up to 30 cm, and then reverses for tumors larger than 30 cm.[7,35] The current AJCC 8th edition staging system is not structured to capture this relationship.

While one advantage of an NCDB study is that it represents practice patterns across multiple institutions with cancer-specific standards, the large registry-based nature also results in inevitable heterogeneity of data despite rigorous quality controls. The rarity of RPS, presence of multiple histologic subtypes and grading schema, changes in usage of diagnostic terms over time, and impracticality of central pathologic review when using a large registry further contribute to variability and risk of diagnostic error.[36] Therefore, the current work is limited in its ability to evaluate prognosis based on specific histologic subtype. Large volume single institution or multiple institution studies with central pathologic review are

better suited to evaluate the role of histology on prognosis, and have been used to develop sarcoma specific nomograms incorporating the histologic subtype.[4,7,11,35]

In the 8th edition, the AJCC recognized the need for more personalized prognostic tools across all disease sites and encouraged the use of well validated nomograms. Of the four currently available nomograms specific to RPS,[4,7,11,35] the AJCC endorsed a model designed by Gronchi et al.[7] for patients with RPS undergoing curative intent resection and externally validated in two separate studies.[37,38] The model incorporates tumor size and grade, and also takes into account factors not captured by the AJCC staging manual: seven histologic categories, patient age, multifocality, and extent of resection. Nomograms are exceedingly useful tools for calculating individual patient risk, but cannot replace the need for a common language that can accurately and efficiently describe and compare groups of patients.

Conclusions

The creation of a specific staging system for retroperitoneal sarcoma and the addition of larger T stages is a move towards more accurate description, but the discriminatory power of the AJCC 8th edition staging manual for retroperitoneal sarcoma remains limited. Future staging modifications within the confines of the TNMG system should consider larger T size categories and account for the possibility of a bimodal effect of tumor size on survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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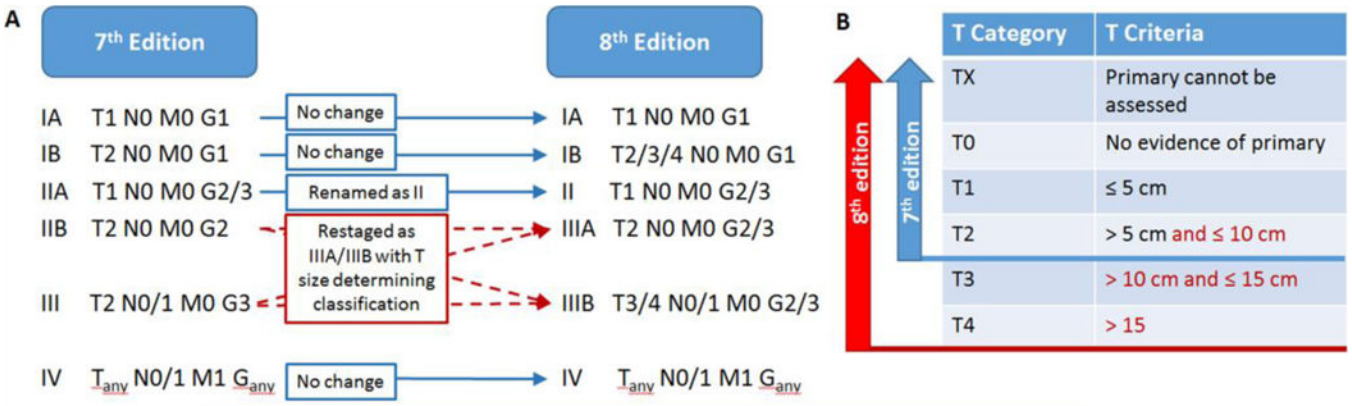

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Changes in Stage between the AJCC 7th and 8th editions (n=6,427)							
AJCC 7th edition	AJCC 8th edition						
	IA	IB	II	IIIA	IIIB	IV	Total
IA	240	0	0	0	0	0	240
IB	0	2,143	0	0	0	0	2,143
IIA	0	0	256	0	0	0	256
IIB	0	0	0	186	450	0	636
III	0	0	0	422	1,707	0	2,129
IV	0	0	0	0	0	1,023	1,023
Total	240	2,143	256	608	2,157	1,023	6,427

Figure 1:

(A) Schema of the changes between the 7th and 8th editions of the American Joint Committee on Cancer staging systems for soft tissue sarcoma of the retroperitoneum, with (B) the updated T definitions (in red), and (C) the resulting changes in stages IIB/III (outlined) within the NCDB study population

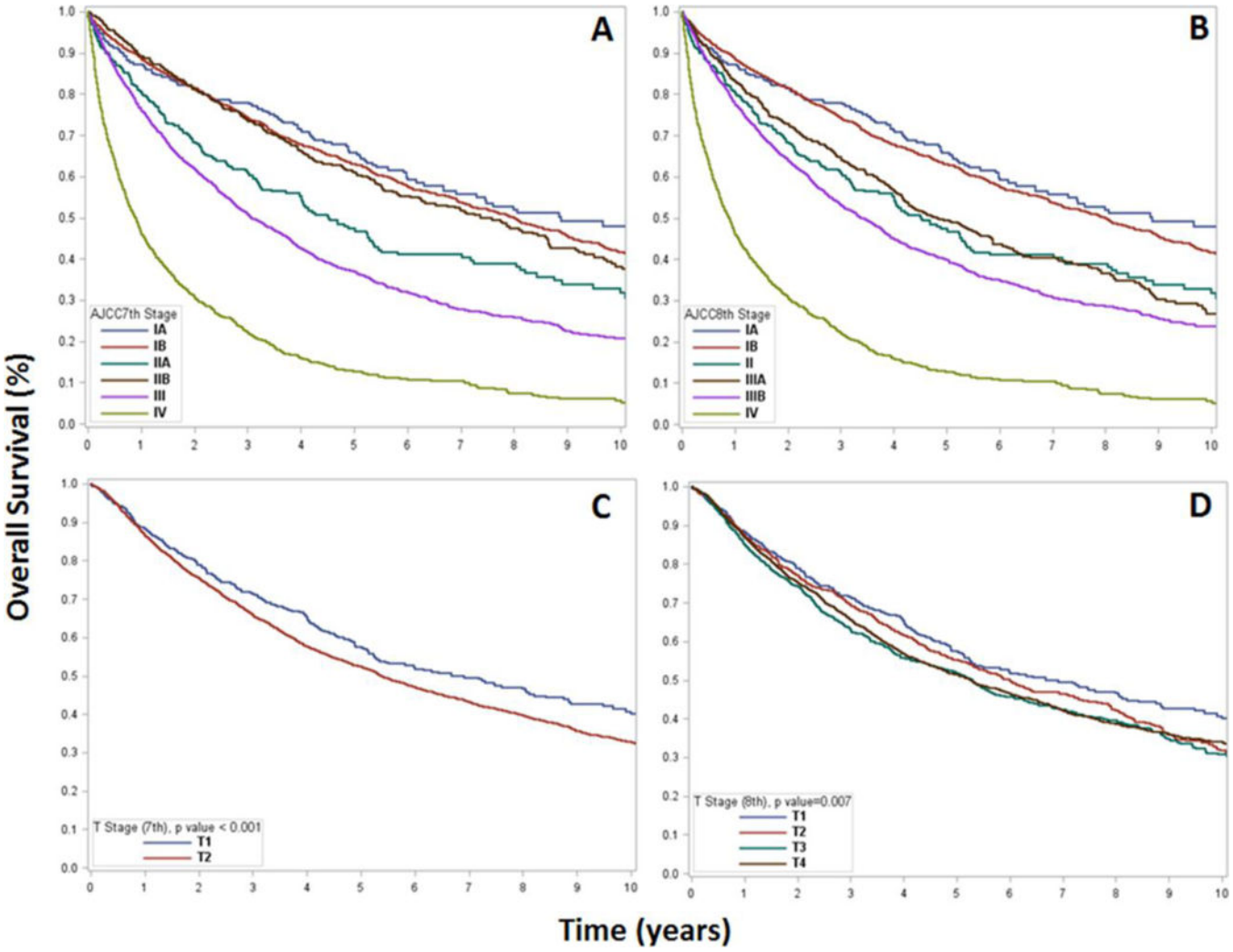

Figure 2:

Overall survival by stage according to the AJCC 7th edition **(A)** and the 8th edition **(B)**; stratified by T stage in the AJCC 7th edition **(C)** and 8th edition **(D)**

Table 1:

Demographic and Clinical Characteristics of Patients with Retroperitoneal Sarcoma in the National Cancer Database (n = 6,427)

	n (%) or median (range)
Age (years)	62 (18–90)
Male sex	3,013 (46.9)
Race	5,052 (78.6)
White	641 (10.0)
Black	400 (6.2)
Hispanic	286 (4.5)
Asian	48 (0.8)
Other/unknown	
Charlson-Deyo Comorbidity Score	3,529 (79.0)
0	745 (16.7)
1	191 (4.3)
2	
Treatment Facility	384 (6.0)
Community Cancer Program	2,441 (38.0)
Comprehensive Community Cancer Program	3,594 (55.9)
Academic/Research Program	8 (0.1)
Other	
Tumor size (cm)	15 (3–99)
Tumor Stage	580 (9.0) *
7^{th} & 8^{th} Ed. T1 (≤5 cm)	5,589 (87.0)
7^{th} Ed. T2 (>5 cm)	1,246 (19.4)
8^{th} Ed. T2 (5 cm > x ≥10 cm)	1,298 (20.2)
8^{th} Ed. T3 (10 cm > x ≥15 cm)	3,045 (47.4)
8^{th} Ed. T4 (>15 cm)	258 (4.0)
Unknown	
Nodal disease	222 (3.5%) **
Metastatic disease	1,023 (15.9)
Grade	2,851 (44.4)
High (G3 or high-GX)	816 (12.7)
Intermediate (G2)	2,760 (42.9)
Low (G1, low-GX, or NOS)	
Resection Margins	3,956 (61.4)
R0/R1	216 (3.4)
R2	590 (9.2)
Metastatic (No surgery on primary)	1,665 (26.0)
Unknown	

Ed.: edition; NOS: not otherwise specified; R1: microscopic positive margin; R2: gross positive margin

* Percent total refers to the total within the respective 7^{th} or 8^{th} edition staging system, with 4.0% unknown in both

** Includes pathologic node positive (n=141) and clinically node positive (n=81)

Table 2:

Cox proportional hazards model for risk of death stratified by stage according to the AJCC 7th and 8th editions (n = 6,427)

	Stage	n	Hazard Ratio for Death		95% CI	5-year Overall Survival (%)
AJCC 7th Edition	IA	240	reference			65.87
	IB	2,143	1.19	0.94	1.50	63.03
	IIA	256	1.89	1.42	2.51	47.26
	IIB	636	1.40	1.09	1.81	60.94
	III	2,129	2.68	2.12	3.38	36.97
	IV	1,023	7.52	5.94	9.52	12.66
AJCC 8th Edition	IA	240	reference			65.87
	IB	2,143	1.19	0.94	1.50	63.03
	II	256	1.88	1.42	2.51	47.26
	IIIA	608	1.84	1.43	2.37	49.46
	IIIB	2,157	2.47	1.96	3.12	39.92
	IV	1,023	7.49	5.92	9.48	12.66

CI: Confidence interval; AJCC: American Joint Committee on Cancer

Table 3:

Prognostic factors associated with impaired overall survival in patients with stage I-III retroperitoneal sarcoma (n = 3,681*)

Prognostic Factor	HR	95% CI		p-value
Age (years)	1.02	1.02	1.03	<0.001
Female sex	0.83	0.75	0.92	<0.001
Insurance status	REF	0.36	1.27	<0.001
Private	0.68	1.11	1.78	
Other government	1.40	1.11	1.47	
Medicaid	1.28	1.18	2.27	
Medicare	1.64			
Uninsured				
Surgery type	REF	0.89	1.10	0.010
Radical	0.99	1.12	1.77	
Local	1.41	0.61	1.12	
Debulking	0.83			
Resection, type unknown				
T stage	REF	0.82	1.23	<0.001
T1	1.00	0.92	1.38	
T2	1.13	1.08	1.57	
T3	1.30			
T4				
N+ disease	1.31	0.91	1.88	0.147
Margin	REF	0.98	1.25	<0.001
R0	1.11	1.59	2.43	
R1	1.97			
R2				
Grade	REF	1.06	1.50	<0.001
Low	1.26	2.22	2.80	
Intermediate	2.50			
High				
Chemotherapy	1.40	1.21	1.62	<0.001
Radiation therapy	0.88	0.79	0.99	0.033

* Patients with missing or unknown data excluded

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