Older Age Modifies Oncologic Outcome Following Radiotherapy in Soft-tissue Sarcoma: A Subtype-specific SEER Analysis

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Abstract. *Background: Given the immune-mediated mechanisms of radiotherapy (RT), we hypothesized that age would affect response to RT in patients with soft-tissue sarcoma (STS) undergoing surgery. Materials and Methods: Using the Surveillance, Epidemiology, and End Results Program (1990-2011), we identified 15,380 patients with non-metastatic STS. Stratified by age (≥65 years) and histological subtype, we assessed predictors of overall (OS) and disease-specific survival (DSS). Results: Treatment with RT was associated with improved OS and DSS compared to surgery alone ($p<0.05$). Multivariate analysis also demonstrated that older patients obtained significant improvements in OS following RT, while younger patients did not. Results for DSS were similar, with older patients with leiomyosarcoma, sarcoma not otherwise specified, and myxoid liposarcoma, in particular, showing greater improvements in DSS after RT than younger patients ($p<0.05$). Interaction testing demonstrated an impact of year of diagnosis on outcomes but not receipt of RT. Conclusion: Among patients with STS undergoing surgery, age appears to impact oncological outcomes after RT.*

Soft-tissue sarcomas (STS) are an uncommon and diverse group of tumors (1). There is well-recognized biological heterogeneity, with at least 50 different histological subtypes that occur throughout numerous primary sites. As such, clinical behavior of these tumors can vary greatly, making consensus on treatment guidelines difficult to achieve (2-5). Surgery is the mainstay of treatment for primary STS, with chemotherapy and radiotherapy (RT) frequently implemented as adjuvant therapies (3, 5). RT has been shown to significantly improve local tumor control (6-9). However, randomized clinical trials have failed to show an overall survival benefit for RT in the setting of complete surgical excision (3, 6, 7). Recent population-based studies with large cohorts have demonstrated improved outcomes, including survival, for patients receiving RT in conjunction with surgery (10, 11). Although the reason for these discrepant findings is unclear, recent notable studies have demonstrated the possibility for RT to induce significant systemic, or abscopal, effects on cancer regression at distant sites (12, 13).

Given the diversity of STS tumors, efforts to study the natural history and biology of individual histological subtypes are increasing (14, 15). Tumor histology has been shown to predict survival in patients with STS (14, 16), and individualized approaches to treatment of these tumors are hypothesized to improve outcomes (15). However, although individual histological subtypes, such as myxoid liposarcoma, have been shown to have greater radiosensitivity, there exist limited data evaluating whether patient-related factors such as age modify STS response to RT (17).

Since increasing pre-clinical studies have demonstrated the significant effects of RT on the immune system and antitumor immunity (12, 18), and since immunological responses are known to change naturally with age, we sought to evaluate oncological outcomes following RT in a large cohort of STS patients stratified by age. We hypothesized that overall survival (OS) and disease-specific survival (DSS) following RT would be affected by age, contributing to differences in survival outcomes, and that these age-related effects following RT would remain after stratifying by histology.

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Materials and Methods

We identified 73,951 patients with STS in the Surveillance, Epidemiology, and End Results (SEER) database from 1990 to 2011 using published ICD-03 codes (14). We excluded patients younger than 18 years due to differential treatment of pediatric and adult patients with STS, especially with regards to implementation of chemotherapy and RT (2, 4). We excluded patients with more than one primary tumor, metastatic disease, unconfirmed or unknown histology, surgery not performed, patients who underwent intraoperative radiation, and tumors with primary site in bone, brain, spinal cord or meninges. Patients with incomplete or missing tumor information were also excluded.

We abstracted data on age, sex, race/ethnicity, marital status, year of diagnosis, tumor site, grade, and size. Histological subtypes were categorized using previously published methods (14, 16). Relevant treatment-related data included surgery and use of RT. Patients receiving either adjuvant or neoadjuvant RT were combined into one group for analysis in order to evaluate the overall effect of RT. Survival was reported in months, with cause of death described as due to cancer (DSS) or any cause (OS).

Patients were stratified by age, initially using multiple age cut-offs to define younger and older populations. Although our results were overall similar regardless of age cutoff employed (data not shown), we observed that an age cutoff of 65 years most effectively illustrated the differences in survival, including histologically stratified analyses. Since SEER data are de-identified, this study qualified as being exempt from UC Davis Institutional Review Board review.

We used Pearson Chi-square tests to determine the statistical significance in comparison of age-stratified populations. The effects of the predictor variables on OS and DSS were analyzed using multivariable Cox proportional hazards models (19). Hazard ratios (HR) were calculated based on multivariable Cox proportional hazards models adjusting for age, sex, year of diagnosis, marital status, tumor size, grade, site, histological subtype, and RT. Survival estimates using Kaplan–Meier methods were generated. Analyses were conducted using the STATA (StataCorp LP, College Station, TX, USA) and SAS v9.4 (SAS Institute Inc., Cary, NC, USA) statistical software packages. Statistical significance was set at $p<0.05$.

Results

A total of 15,380 patients met our inclusion criteria and were included in our final analysis. The mean age was 56.6±16.8 years, and 33.6% of patients were aged 65 years or more. Overall, 47.9% of patients were female, and 67% were White. Tumors occurred most frequently in the extremities (41.1%) and viscera (22%). High-grade tumors (56%) and tumors 5-10 cm (30.7%) were most prevalent, although there was a wide range. Leiomyosarcoma was the most common histological subtype group (30.1%).

A total of 59.9% of patients were treated with surgery alone. Among the patients treated with surgery only, 47.8% had high-grade tumors, 22.7% low-grade, and 21.3% intermediate-grade. In contrast, 40.1% of patients were treated with either neoadjuvant (6.8%) or adjuvant RT (33.3%). The percentage of patients receiving RT increased over time from 35.6% in 1990-1996 to 40.1% in 2007-2011 ($p<0.05$). Of all patients treated with RT, 68.3% had high-grade tumors ($p<0.05$).

Stratification by age group. A comparison of patients stratified by age group is outlined in Table I. Although there were a greater number of patients <65 years old, the proportion of male and female patients was comparable. Patients 65 years or older were more likely to be White ($p<0.01$), and less likely to be either Hispanic or Black ($p<0.01$). Patients 65 years or older had a greater incidence of high-grade tumors and size >15 cm ($p<0.01$). Patients 65 years or older also had a higher percentage of tumors in the viscera and a lower incidence of genitourinary/gynecological tumors ($p<0.01$). There was variability in the distribution of histological subtypes between age groups, although leiomyosarcoma remained the most common histology in both young and old patients.

Although the magnitude of the differences was small, patients 65 years or older were more frequently treated with surgery alone (61.4% *vs*. 59.1%, $p<0.01$), and had lower rates of both neoadjuvant (6.2% *vs*. 7%, $p<0.01$) and adjuvant (32.4% *vs*. 33.8%, $p<0.01$) RT.

Although the overall percentage of patients receiving RT increased from 1990-1996 to 2007-2011, the magnitude of this increase over time was notably greater in older patients compared to young patients (17.4% *vs*. 10.4%, $p<0.01$).

Predictors of overall survival and disease-specific survival. In all patients and both age-stratified groups, worse OS was predicted by male sex, divorced, separated or widowed marital status, non-extremity tumor site, increasing tumor grade, and larger tumor size ($p<0.05$). Results for multivariable analysis for DSS were similar.

A comparison of RT and histological subtypes as predictors of OS and DSS is outlined in Table II and Table III. Nine out of the 12 major histological subtype groups analyzed demonstrated improved OS in response to RT compared to surgery alone for patients of all ages: Patients with epithelioid [HR=0.45, 95% confidence interval (CI)=0.24-0.85], rhabdomyosarcoma (HR=0.61, 95% CI+0.42-0.90), and synovial sarcoma (HR=0.67, 95% CI=0.51-0.87) had the most improved survival in response to RT for the whole cohort. Seven histological subgroups were associated with improved survival in patients 65 years or older, including leiomyosarcoma (HR=0.84, $p=0.04$), sarcoma not otherwise specified (HR=0.66, $p\leq0.001$), liposarcoma not otherwise specified (HR=0.72, $p=0.05$), myxoid liposarcoma (HR=0.50, $p=0.02$), and rhabdomyosarcoma (HR=0.23, $p\leq0.001$). Patients with epithelioid (HR=0.01, $p<0.01$) and myxoid chondrosarcoma (HR=0.02, $p=0.04$) demonstrated the most dramatic improvements in OS in the older patient subgroup.

Table I. *Patient demographics and tumor characteristics by age group.*

Factor	Age <65 years (n=10,210) n	(%)	Age ≥65 years (n=5,170) n	(%)	*p*-Value
Gender					0.0799
Male	5,374	(52.6)	2,644	(51.1)	
Female	4,836	(47.4)	2,526	(48.9)	
Race					<0.01
White	6,467	(63.3)	3,843	(74.3)	
Spanish-Hispanic-Latino	1,567	(15.4)	474	(9.2)	
Black	1,290	(12.6)	389	(7.5)	
Other[1]	886	(8.7)	464	(9.0)	
Histology					<0.01
Leiomyosarcoma	3,207	(31.4)	1,425	(27.6)	
Malignant fibrous histiocytoma	1,401	(13.7)	1,180	(22.8)	
Sarcoma, NOS	1,053	(10.3)	608	(11.8)	
Liposarcoma, well differentiated	1,012	(9.9)	551	(10.7)	
Liposarcoma, NOS	836	(8.2)	472	(9.1)	
Myxoid liposarcoma	807	(7.9)	213	(4.1)	
Other[2]	649	(6.4)	218	(4.2)	
Dedifferentiated liposarcoma	380	(3.7)	312	(6)	
Synovial Sarcoma	560	(5.5)	75	(1.5)	
Rhabdomyosarcoma	166	(1.6)	75	(1.5)	
Epithelioid	120	(1.2)	35	(0.7)	
Malignant peripheral nerve sheath tumor	19	(0.2)	6	(0.1)	
Site					<0.01
Extremities	4,185	(41)	2,139	(41.4)	
Visceral	2,133	(20.9)	1,252	(24.2)	
Genitourinary/Gynecological	1,769	(17.3)	611	(11.8)	
Trunk	1,560	(15.3)	807	(15.6)	
Head/neck	377	(3.7)	285	(5.5)	
Thoracic	186	(1.8)	76	(1.5)	
Grade					<0.01
Low	2,402	(23.5)	1,092	(21.1)	
Intermediate	2,297	(22.5)	975	(18.9)	
High	5,511	(54)	3,103	(60)	
Size					<0.01
<5 cm	2,696	(26.4)	1,221	(23.6)	
5-10 cm	3,059	(30)	1,664	(32.2)	
>10-15 cm	2,035	(19.9)	975	(18.9)	
>15 cm	2,420	(23.7)	1,310	(25.3)	
Treatment					0.0149
Surgery only	6,038	(59.1)	3,173	(61.4)	
Adjuvant or neoadjuvant radiation	4,172	(40.9)	1,997	(38.6)	

NOS: Not otherwise specified. [1]Asian, Pacific Islander, American Indian, Alaskan Native, or unknown; [2]includes alveolar soft part (0.2%), fibrosarcoma (4.4%), malignant solitary fibrous tumor (0.3%), and myxoid chondrosarcoma (0.8%).

Malignant fibrous histiocytoma was the only histology to be associated with improved survival for the cohort overall (HR=0.79,), and both age groups (<65 years: HR=0.81,; ≥65 years: HR=0.80). Synovial sarcoma (HR=0.73) was the only histology associated with improved survival in the subgroup <65 years old without maintaining improved OS in older patients. Noted exceptions that did not demonstrate improved OS for the overall cohort after RT included well-differentiated liposarcoma (p=0.85), fibrosarcoma (p=0.09) and myxoid chondrosarcoma (p=0.09).

Kaplan–Meier overall survival analysis. Figure 1 demonstrates the impact of age on OS following RT for patients with leiomyosarcoma. For patients aged <65 years (Figure 1A), there was no significant difference in OS among patients treated with or without RT (p=0.12). However, for

Table II. *Association of radiotherapy with overall survival by histological subtype, stratified by age.*

Histology	Age <65 years (n=10,210)			Age ≥65 years (n=5,170)		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Leiomyosarcoma	0.94	(0.84-1.05)	0.29	0.84	(0.71-0.99)	0.04
Malignant fibrous histiocytoma	0.81	(0.68-0.97)	0.02	0.80	(0.68-0.94)	0.01
Sarcoma, NOS	0.86	(0.70-1.06)	0.17	0.66	(0.52-0.84)	<0.001
Liposarcoma, well-differentiated	0.59	(0.35-1.00)	0.05	1.39	(0.85-2.27)	0.19
Liposarcoma, NOS	0.87	(0.65-1.17)	0.36	0.72	(0.52-1.00)	0.05
Myxoid liposarcoma	0.79	(0.54-1.16)	0.23	0.50	(0.28-0.88)	0.02
Dedifferentiated liposarcoma	0.77	(0.51-1.17)	0.21	0.74	(0.51-1.05)	0.09
Fibrosarcoma	1.57	(0.95-2.58)	0.08	1.00	(0.49-2.05)	0.99
Synovial sarcoma	0.73	(0.54-0.98)	0.04	0.49	(0.22-1.10)	0.09
Rhabdomyosarcoma	0.72	(0.44-1.20)	0.21	0.23	(0.09-0.57)	<0.001
Epithelioid	0.72	(0.35-1.50)	0.38	0.01	(0.00-0.01)	0.01
Myxoid chondrosarcoma	0.30	(0.07-1.26)	0.10	0.02	(0.00-0.80)	0.04

HR: Hazard ratio; CI: confidence interval; NOS: not otherwise specified.

Table III. *Association of radiotherapy with disease-specific survival by histological subtype, stratified by age.*

Histology	Age <65 years (n=10,210)			Age ≥65 years (n=5,170)		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Leiomyosarcoma	0.96	(0.85-1.08)	0.50	0.86	(0.71-1.04)	0.12
Malignant fibrous histiocytoma	0.78	(0.63-0.96)	0.02	0.90	(0.73-1.10)	0.30
Sarcoma, NOS	0.94	(0.75-1.17)	0.57	0.72	(0.55-0.96)	0.02
Liposarcoma, well-differentiated	0.44	(0.19-1.02)	0.05	1.45	(0.57-3.66)	0.43
Liposarcoma, NOS	0.89	(0.65-1.23)	0.48	1.03	(0.66-1.61)	0.89
Myxoid liposarcoma	0.78	(0.51-1.2)	0.26	0.47	(0.23-0.95)	0.04
Dedifferentiated liposarcoma	0.83	(0.52-1.31)	0.42	0.72	(0.48-1.07)	0.10
Fibrosarcoma	1.39	(0.76-2.53)	0.29	2.27	(0.87-5.96)	0.10
Synovial sarcoma	0.72	(0.53-0.98)	0.04	0.53	(0.21-1.31)	0.17
Rhabdomyosarcoma	0.61	(0.36-1.03)	0.06	0.23	(0.08-0.64)	0.01
Epithelioid	0.71	(0.33-1.50)	0.37		n/a	
Myxoid chondrosarcoma	0.57	(0.14-2.37)	0.44		n/a	

HR: Hazard ratio; CI: confidence interval; NOS: not otherwise specified. n/a: insufficient number of events.

patients ≥65 years (Figure 1B), there was a significant difference in OS when comparing RT- and non-RT-treated subgroups (p=0.04). Similar results were observed for several other histological subtypes (data not shown).

Discussion

We analyzed a large national database of patients with STS to evaluate the effect of age on oncological outcomes after RT. We observed a statistically significant improvement in OS and DSS in all patients receiving RT compared to surgery alone across the majority of histological subgroups. More importantly, there was no significant improvement in younger patients compared to a significant improvement in older patients, suggesting that survival benefits in response to RT are significantly affected by age-related differences.

The characteristics of our patient cohort are comparable to previous population-based and observational studies evaluating STS outcomes. For example, Koshy *et al.* (10) studied a SEER population with 47% of patients receiving RT from 1988 to 2005. These authors observed an improvement in 3-year OS for patients with high-grade tumors receiving RT compared to

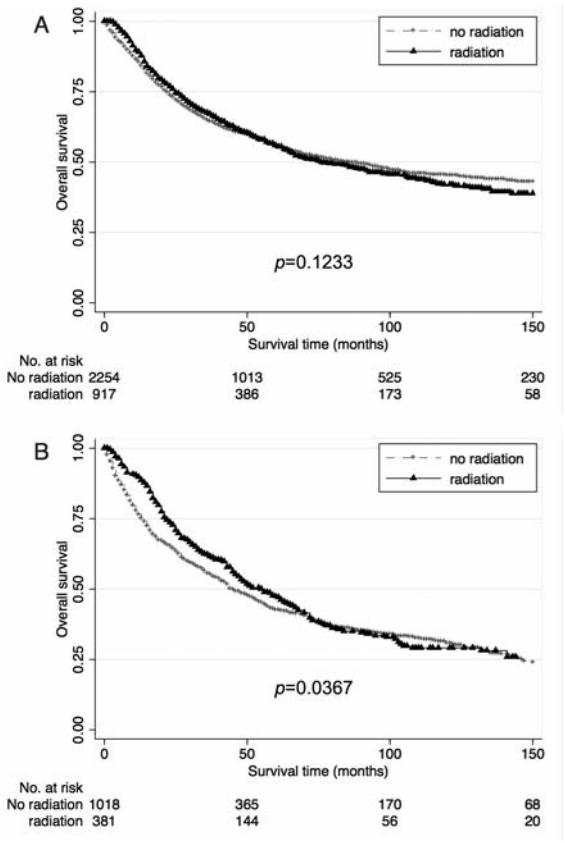

Figure 1. *Kaplan–Meier curve depicting overall survival among patients <65 years (A) (N=3,171) and ≥65 years (B) (N=1,399) with leiomyosarcoma undergoing surgical resection stratified by receipt of radiation therapy.*

surgery alone. Schreiber *et al*. (11) studied a SEER cohort of 46% female and 85% White patients with STS from 1988 to 2006, finding an improvement in 3-year OS following adjuvant RT for tumors greater than 5 cm. Our findings reinforce these authors' observations of improved oncologic outcome in STS patients receiving RT after surgery (10, 11).

Two prospective randomized trials have previously demonstrated statistically significant improvements in local control following adjuvant RT and limb-sparing surgery for extremity STS without significant differences in OS (6, 8). However, using SEER data, we and others (10, 11) have demonstrated that RT is associated with significant improvements in OS and DSS among patients with STS, suggesting a possible association of improved survival with improved local control when patient outcomes are analyzed in aggregate with larger sample sizes outside the context of a clinical trial.

Although we acknowledge that the association of RT with improved OS and DSS in STS may represent the impact of unmeasured confounding factors in a retrospective registry, one of the strengths of our study is the large number of patients with STS available for analysis. Furthermore, the SEER database is highly representative of the general US population and thus allows greater extrapolation and generalizability of our data, tha a recognized limitation of single-institution studies and randomized trials (20-22). It is well documented that fewer than 5% of the US population enrolls in clinical trials, and elderly patients are particularly under-represented, offering less insight into their treatment-related outcomes. Studies have also suggested that patient fragility may discourage implementation of RT in the elderly (23). These factors further highlight the importance of population-based data from sources such as SEER.

To our knowledge, this is the first study to analyze histological subtype-specific outcomes in STS following RT when stratified by age. The reproducible nature of our findings across multiple STS histologies highlights our impression that older patients may stand to benefit more than previously appreciated from the inclusion of RT in combined modality therapy for STS.

It is important to acknowledge the limitations of our study. The SEER database does not include data on surgical margin status, which has been shown to impact both OS and DSS in STS (although only weakly as an independent variable) (24, 25). SEER also lacks important information on the use of chemotherapy which is known to affect oncological outcome, especially for specific histological subtypes such as rhabdomyosarcoma and possibly synovial sarcoma.

Given the retrospective nature of our study design, there is a risk that RT was preferentially implemented in a healthier subpopulation of older patients, introducing selection bias. However, this does not *a priori* explain the age-related differences we observed, since presumably the same selection bias would have applied to younger patients receiving RT. Finally, we acknowledge that there are no categorical biological changes that occur at the age of 65 years, although we observed similar results using multiple age cutoffs, as well as when analyzing age as a continuous variable.

Despite these limitations, this study is the first comprehensive population-based analysis to examine the effects of age and histology on survival in patients with STS undergoing RT and surgery. While implementation of RT may seem more challenging in the elderly population, our data suggest that this approach deserves greater attention.

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