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Improved Survival with Radiation Therapy in High Grade Soft Tissue Sarcomas of the Extremities: A SEER Analysis

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Abstract

Purpose—The benefit of radiation therapy in extremity soft tissue sarcomas remains controversial. The purpose of this study was determine the effect of radiation therapy on overall survival among patients with primary soft tissue sarcomas of the extremity who underwent limb sparing surgery.

Patients and Methods—A retrospective study from the Surveillance, Epidemiology, and End Results (SEER) database that included data from January 1, 1988, to December 31st, 2005. A total of 6,960 patients comprised the study population. Overall survival curves were constructed using Kaplan-Meier Method and for patients with low and high grade tumors. Hazard ratios were calculated based on multivariable Cox proportional hazards models.

Results—Of the cohort, 47% received radiation therapy. There was no significant difference in overall survival among patients with low grade tumors by radiation therapy. In high grade tumors, the 3 year overall survival was 73% in patients who received radiation therapy vs. 63% for those who did not receive radiation therapy ($p < 0.001$). On multivariate analysis, patients with high grade tumors who received radiation therapy had an improved overall survival (HR 0.67, 95% CI 0.57-0.79).

In patients receiving radiation therapy, 13.5% received it in a neo-adjuvant setting. The incidence of patients receiving neo-adjuvant radiation did not change significantly between 1988 and 2005.

Conclusions—This is the largest population based study reported in patients undergoing limb sparing surgery for soft tissue sarcomas of the extremities and reports that radiation was associated with improved survival in patients with high grade tumors.

Keywords

Sarcoma; Extremity; Radiation; SEER

Background

Soft tissue sarcomas are rare malignancies that occurred in approximately 9,220 patients in the United States in 2007(1). Approximately half of these present in an extremity (2). These malignancies represent a heterogeneous group of tumors, with many of them posing a high risk of local recurrence and distant metastasis. (3)

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The major therapeutic goals of treating soft tissue extremity sarcomas are to maximize local tumor control using minimal surgery with limb preservation and to improve survival (4). A number of studies show that wide local excision with with pre- or post-operative radiation therapy results in equivalent outcomes regarding local control and overall survival when compared to amputations or more radical excisions (5-9).

For those patients who undergo limb-sparing surgery with wide local excision alone, the addition of radiation provides a local control benefit, but no improvement in overall survival has been demonstrated yet (10). The purpose of this study was to determine whether radiation therapy is associated with improved outcomes among patients with primary soft tissue sarcomas of the extremity who undergo limb sparing surgery.

Methods and Materials

Data and Study population

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute covers 26% of the US population and collects incidence and survival data from 17 population based cancer registries. The database contains information on primary tumor site, histology, stage at diagnosis, first course of treatment, follow-up, and cause of death.

Eligible patients had histologically confirmed invasive extremity soft tissue sarcoma. We identified patients using identified site codes C49.1 and C49.2 of the International Classification of Disease for Oncology, Third Edition. We restricted the analysis to patients aged > 20 years who underwent a limb-sparing surgery between 1988 – 2005. Patients who presented with distant metastasis or underwent amputation were excluded. Detailed information regarding the tumor size and grade were only available in SEER following 1988. Patients with Kaposi's sarcoma were also excluded because the majority of these patients have AIDS which would confound survival outcomes. The final sample size included a total of 6,960 patients.

Variables

Overall survival was the primary study end point. Overall survival was defined as the time from diagnosis to death. Exposure variables included categorical variables for whether patients received radiation therapy and the timing of radiation therapy (neoadjuvant or adjuvant). Information regarding the use of adjuvant chemotherapy, and specific radiation therapy technique (dose, fractionation, beam energy) were not available in the SEER database.

Covariates included in the analysis were all categorical and included: age (20-44 years, 45-59, 60-74, and 75+), sex, SEER registry, year of diagnosis, T stage (T1 ≤ 5cm, T2 > 5cm), nodal stage, grade (low grade = 1-2, high grade = 3-4), location (upper vs. lower), laterality, and histology. Detailed information regarding margin status at time of resection, local control, and performance status was not available in the SEER database.

Statistical Analysis

All data was analyzed using SAS Version 9.1 statistical software package (SAS Institute, Cary, NC). The Pearson's chi-square test was used to determine if associations existed between the use of radiation therapy and the covariates of interest. Estimates of overall survival stratified by the use of radiation therapy were calculated using the Kaplan-Meier method for patients with low and high grade tumors and for the subset of patients with large (>5cm) high grade tumors. The log rank test was used to determine if differences in survival curves were statistically significant. Results were considered significant when $p < 0.05$.

To determine the importance of radiation therapy as an independent predictor of overall and mortality, hazard ratios (HR) and their 95% confidence intervals (CI) were calculated based on multivariable Cox proportional hazards models adjusted for all covariates of interest. Models were run for the full sample, and for subsamples of patients with low and high grade tumors. Additional results were obtained to determine if use and timing of radiation therapy was associated with mortality for patients with high grade, large (> 5cm) tumors.

Results

Among the 6,960 patients in this study, 47% received radiation therapy as a component of their treatment. The categorical variables of sex, year of diagnosis, nodal status, and laterality were not associated with administration of radiation therapy (Table 1). The categorical variables of age, T stage, grade, location, and histology were significant predictors of the administration of radiation therapy. High grade, T2, lower extremity located tumors and certain histologies (fibrohistiocytic, synovial, and rhabdomyosarcomas) were more likely to receive radiation. Osseous and peripheral nerve tumors were less likely to receive radiation.

Univariate Analysis

There was no significant difference in overall survival among patients with low grade tumors by radiation therapy. Among patients with high grade tumors, the three year overall survival was 73% for who received radiation vs. 63% for those who did not receive radiation therapy ($p < 0.001$; Figure 1). Among patients with large (>5cm) high grade tumors, the three year overall survival for those who received radiation was 66% vs. 53% for those who did not receive radiation therapy ($p < 0.001$; Figure 2).

Multivariate Analysis

Among all patients, radiation therapy was associated with significantly improved overall survival, even after adjustment for patient and tumor characteristics. Variables adversely affecting survival on multivariable analysis were increasing age, male sex, higher T stage, higher N stage, and higher grade tumors.

Additional analysis was performed on sub-samples of patients based on tumor grade. Patients with high grade tumors who received radiation therapy had an improved overall survival (HR 0.67, 95% CI 0.57-0.79) and cause specific survival (HR 0.76, 95% CI 0.63-0.91), even after adjustment for all available patient and tumor characteristics (Table 2). Patients with large (>5cm) high grade tumors had significantly improved overall survival (HR 0.63, 95% CI 0.53-0.77) associated with the administration of radiation therapy (Table 3).

Neo-adjuvant Radiation

Of the patients who received radiation therapy, 13.5% received it prior to surgical resection. Of this neo-adjuvant cohort, 75% were high grade lesions, and 78% were T2 lesions. The incidence of patients receiving neo-adjuvant radiation therapy did not change significantly between 1988 and 2005 (Figure 3). There was no difference in overall survival in patients with large (>5cm) high grade lesions who received neo-adjuvant radiation versus post-operative radiation therapy.

Discussion

This large population based cohort study examined the impact of radiation therapy on patients who had undergone a limb sparing surgical resection. This study is the first to report

that radiation resulted in improved survival outcomes, with the greatest benefit seen in patients with large (>5cm) high grade tumors.

Wide local excision (WLE) has a high local failure rate up to 30%, and so adjuvant radiation has been added to bring failure rates <10% (11). Local recurrence was found to be an adverse risk factor by 4.4 times for distant metastasis in a large Scandinavian registry study of 559 patients (12). Intuitively, decreasing local failures and thus distant metastases would improve overall survival, but this has not been proven yet. In the largest prospective study completed at the NCI, 91 patients with soft tissue sarcomas of the extremity were randomized to receive or not receive post-operative radiation therapy after WLE (10). In high grade tumors, there were no local recurrences (0%) in the radiation arm compared to 22% in the no radiation arm. In low grade tumors that received radiation, there was a 4% local recurrence rate compared to 31% in patients who did not receive radiation therapy. Thus, it was found that that radiation decreased recurrences, however there was no survival difference between the two arms in both the high and low grade tumors. With so few patients in the study, this negative finding may have been due to a lack of power.

Our study did not find an overall survival benefit in the low grade tumors. This seems consistent with a prospective study that suggests that wide local excision alone for low grade, T1 tumors with complete resection margins is acceptable (13). This phase III adjuvant brachytherapy study of 164 patients demonstrated a 5 year local control benefit with radiation for high grade tumors (91% vs 70%), but not of any additional benefit for the low grade tumors. Despite the better local control for high grade tumors with radiation, this study, like the NCI study, also did not show any difference in distant metastasis or disease free survival. Our results confirm that radiotherapy is primarily effective in large high grade lesions and with a cohort of over 6,000 patients, our study also shows an overall survival benefit. (10, 13, 14) Treatment of sarcoma may be analogous to the breast cancer paradigm, where wide local excision and radiation is equivalent to more radical amputation / mastectomy, and the local control benefit of radiation was found to have an overall survival benefit for patients in a larger pooled analysis (15).

This study was limited primarily based on information availability in the SEER database. First, no information on radiotherapy technique (total dose, fraction size, beam energy) was available, so results could not determine if survival varies based on these factors. Second, although some patient characteristics that are potential confounding factors (such as margin or performance status) were not available in this data set, this study adjusted for all available patient and tumor characteristics. It is possible that the use of adjuvant radiation for low grade sarcomas may be justified if there are known, adverse risk factors (eg, incomplete resection, positive margins) not captured by the SEER database. It is possible that adjuvant radiation for these patients improved results to the level of the more favorable, low grade subgroup that would not need radiation according to the prospective wide local excision alone trial (13).

We also cannot comment on the influence of chemotherapy in this study because it was not recorded in SEER. Per NCCN guidelines, chemotherapy is not a standard treatment regardless of histology. We attempted to exclude pediatric tumors with an age eligibility >20 years old. Adjuvant chemotherapy was given to all high grade tumors in the NCI prospective study, but no change in overall survival was seen. A Lancet meta-analysis of 1568 patients from 14 trials using doxorubicine-based regimens failed to find an overall survival advantage (16). Thus, chemotherapy's role for adult sarcoma tissue is controversial and remains uncertain (16-19). Regardless, even if one assumes that adjuvant chemotherapy was preferentially to the radiation arm, the Lancet meta-analysis suggests a small absolute

benefit of 5% at 5-10 years. This study suggests a benefit beyond any chemotherapy effect with an absolute overall survival difference of 10% in high grade lesions.

The majority of patients who received neo-adjuvant radiation in this study were in the large (>5cm) high grade subset but there was no difference in overall survival between patients with neo-adjuvant or post-operative radiation for this group. In regards to neo-adjuvant vs. post-operative radiation treatment preference, a large randomized trial from the NCI Canada Clinical Trial Group initiated in 1994, closed in 1997, and reported in 2002 showed that local recurrence and progression-free survival were similar between either arm (20). However, neo-adjuvant radiotherapy was associated with improved long-term functional outcomes when compared to post-operative radiotherapy (21). Despite these results, we found that the incidence of patients receiving neo-adjuvant radiotherapy nationwide has not changed significantly over the past twenty years.

Conclusions

This is the largest population based study in patients undergoing limb sparing surgery for soft tissue sarcomas of the extremities and our results indicate that radiation therapy was associated with improved survival outcomes in patients with high grade tumors. Furthermore, neo-adjuvant radiation appears equivalent to post-operative radiation therapy in terms of survival outcomes in patients with large high grade tumors. Finally, the rates of neo-adjuvant radiation therapy have not increased significantly over the past several years.

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Figure 1.
Plot of Overall Survival in Patients with High Grade Tumors, Stratified by Radiation Therapy Use.

Figure 2.
Plot of Overall Survival in Patients with Large (>5cm) High Grade Tumors, Stratified by Radiation Therapy Use.

Figure 3.
Proportion of Patients who received Neo-adjuvant Radiation Therapy from 1988-2005.

Table 1

Predictors of Radiation Therapy Use

	No. of Patients* (n = 6,960)	% Who Received Radiation Therapy† (n = 3,692)	% Who Did Not Receive Radiation Therapy† (n = 3,268)	P-value‡
Overall		47.0	53.1	
Patient characteristics				
Age in years				<.001
20-44 years	1,917	51.4	48.6	
45-59 years	1,774	53.3	46.7	
60-74 years	1,760	57.8	42.2	
75+ years	1,509	49.2	50.8	
Sex				.21
Male	3,680	53.8	46.3	
Female	3,280	52.3	47.7	
Location of SEER registry				<.001
San Francisco	594	61.5	38.6	
Connecticut	489	49.9	50.1	
Detroit	654	51.2	48.8	
Hawaii	218	56.0	44.0	
Iowa	531	53.9	46.1	
New Mexico	192	55.7	44.3	
Seattle	520	60.4	39.6	
Utah	235	57.5	42.6	
Atlanta	356	50.8	49.2	
San Jose	234	60.7	39.3	
Los Angeles	1,011	46.0	54.0	
Alaska	4	25.0	75.0	
Georgia	10	30.0	70.0	
California (other than SF/SJ/LA)	1,011	52.9	47.1	
Kentucky	230	51.3	48.7	
Louisiana	232	52.6	47.4	
New Jersey	439	49.4	50.6	

	No. of Patients* (n = 6,960)	% Who Received Radiation Therapy† (n = 3,692)	% Who Did Not Receive Radiation Therapy† (n = 3,268)	P-value‡
Year of diagnosis				
1988	156	52.6	47.4	.055
1989	155	51.0	49.0	
1990	146	57.5	42.5	
1991	187	57.8	42.3	
1992	244	52.1	48.0	
1993	266	51.9	48.1	
1994	278	60.1	39.9	
1995	278	47.5	52.5	
1996	324	51.5	48.5	
1997	330	48.5	51.5	
1998	257	56.8	43.2	
1999	264	54.6	45.5	
2000	543	58.0	42.0	
2001	617	54.0	46.0	
2002	559	53.5	46.5	
2003	769	50.5	49.5	
2004	810	50.4	49.6	
2005	777	53.4	46.6	
Tumor characteristics				
T stage				<.001
T1	2,437	46.7	53.3	
T2	3,438	63.6	36.4	.87
N status				
N0	6,845	53.1	46.9	<.001
N1	61	54.1	45.9	
Grade				<.001
Low grade (G1/2)	2,317	41.3	58.7	
High grade (G3/4)	2,689	71.2	28.8	<.001
Location				
Upper	1,998	49.1	51.0	

	No. of Patients* (n = 6,960)	% Who Received Radiation Therapy† (n = 3,692)	% Who Did Not Receive Radiation Therapy† (n = 3,268)	P-value‡
Lower	4,962	54.7	45.3	
Laterality				.68
Right	3,402	52.9	47.2	
Left	3,549	53.3	46.7	
Histology				<.001
Fibrohistiocytic tumors	2,350	57.2	42.8	
Liposarcoma	1,758	50.9	49.2	
Leiomyosarcomas	817	38.7	61.3	
Synovial sarcomas	438	67.8	32.2	
Fibrosarcoma	395	50.1	49.9	
Osseous and chondromatous neoplasms of soft tissue	154	40.3	59.7	
Peripheral nerve sheath tumors	142	43.0	57.0	
Blood vessel tumors	73	49.3	50.7	
Rhabdomyosarcoma	64	71.9	28.1	
Other	769	56.8	43.2	

SEER: Surveillance, Epidemiology, and End Result. SF: San Francisco, SJ: San Jose, LA: Los Angeles.

*Due to missing data, n for each variable ranges from 5,006 to 6,960.

†Some percentages do not add to 100 due to rounding

‡P-values from Chi-square test.

Hazard Ratios and 95% Confidence Intervals for Multivariable Models of Overall Mortality, Stratified by Tumor Grade.

Table 2

		All Patients (n=4,322)		Low grade (n=1,942)		High grade (n=2,380)	
		HR	95% CI	HR	95% CI	HR	95% CI
Radiation therapy*							
No radiation		1.0	Reference	1.0	Reference	1.0	Reference
Radiation therapy		0.78	(0.69, 0.89)	1.00	(0.79, 1.27)	0.67	(0.57, 0.79)
Patient characteristics							
Age in years		1.0	Reference	1.0	Reference	1.0	Reference
20-44 years		1.31	(1.05, 1.64)	1.41	(0.91, 2.19)	1.29	(0.99, 1.68)
45-59 years		2.39	(1.94, 2.94)	4.25	(2.87, 6.30)	1.90	(1.49, 2.43)
60-74 years		5.30	(4.32, 6.51)	12.65	(8.57, 18.68)	3.82	(2.99, 4.87)
75+ years							
Sex		1.0	Reference	1.0	Reference	1.0	Reference
Male		0.75	(0.66, 0.85)	0.81	(0.64, 1.02)	0.72	(0.63, 0.84)
Female							
Tumor characteristics							
T stage		1.0	Reference	1.0	Reference	1.0	Reference
T1		1.70	(1.48, 1.96)	1.20	(0.91, 1.58)	1.97	(1.67, 2.33)
T2							
N status		1.0	Reference	1.0	Reference	1.0	Reference
N0		2.40	(1.39, 4.14)	1.06	(0.14, 8.21)	3.00	(1.68, 5.38)
N1							
Grade		1.0	Reference	NA	NA	NA	NA
G1/2		2.35	(2.02, 2.73)	NA	NA	NA	NA
G3/4							
Location		1.0	Reference	1.0	Reference	1.0	Reference
Upper		1.03	(0.89, 1.18)	1.11	(0.84, 1.46)	1.03	(0.87, 1.22)
Lower							
Laterality		1.0	Reference	1.0	Reference	1.0	Reference
Right		0.97	(0.86, 1.09)	1.09	(0.87, 1.37)	0.94	(0.82, 1.09)
Left							

Histology	All Patients (n=4,322)			Low grade (n=1,942)			High grade (n=2,380)		
	HR	95% CI	Reference	HR	95% CI	Reference	HR	95% CI	Reference
Fibrohistiocytic tumors	1.0	Reference		1.0	Reference		1.0	Reference	
Liposarcoma	0.70	(0.59, 0.83)		0.58	(0.42, 0.80)		0.78	(0.63, 0.98)	
Leiomyosarcomas	1.11	(0.90, 1.37)		0.88	(0.58, 1.34)		1.16	(0.91, 1.48)	
Synovial sarcomas	1.38	(0.97, 1.95)		2.06	(1.09, 3.90)		1.01	(0.65, 1.55)	
Fibrosarcoma	0.80	(0.56, 1.14)		0.73	(0.43, 1.23)		0.76	(0.46, 1.25)	
Osseous and chondromatous neoplasms of soft tissue	1.09	(0.73, 1.64)		0.51	(0.23, 1.10)		1.56	(0.96, 2.52)	
Peripheral nerve sheath tumors	1.49	(0.99, 2.23)		0.71	(0.30, 1.67)		1.86	(1.17, 2.97)	
Blood vessel tumors	1.65	(1.01, 2.71)		0.67	(0.16, 2.84)		2.05	(1.21, 3.48)	
Rhabdomyosarcoma	1.31	(0.75, 2.30)		--	--		1.43	(0.81, 2.52)	
Other	1.13	(0.93, 1.37)		0.68	(0.42, 1.11)		1.20	(0.97, 1.48)	

HR: Hazard Ratio. CI: Confidence Interval. NA: not applicable. ---: too few events to calculate results. Values in bold are significant at the p= .05 level.

Table 3
Hazard ratios in Univariate and Multivariable Models of Overall Mortality, for Patients with High Grade T2 Tumors

	Overall Survival			
	Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI
Radiation therapy				
Did not receive radiation therapy	1.0	Reference	1.0	Reference
Received neo-adjuvant radiation therapy	0.59	(0.44, 0.78)	0.68	(0.50, 0.94)
Received postoperative radiation therapy	0.59	(0.49, 0.72)	0.61	(0.49, 0.75)

HR: Hazard Ratio. CI: Confidence Interval. Values in bold are significant at the p=.05 level.