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Neoadjuvant Radiotherapy is Associated with R0 Resection and Improved Survival in Extremity Soft Tissue Sarcoma Patients Undergoing Surgery: An NCDB Analysis

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Abstract

Background—Neoadjuvant radiotherapy (RT) is increasingly advocated in the management of soft tissue sarcoma (STS). Therefore, we sought to characterize the impact of neoadjuvant RT on rates of R0 resection and overall survival (OS) in extremity STS patients undergoing surgery.

Methods—From January 2003 to December 2012, we identified patients with a diagnosis of extremity STS from the National Cancer Database. After excluding patients with age < 18 years, not undergoing surgery, metastases at diagnosis, intraoperative RT, and missing/unknown data, we identified 27,969 patients. Using logistic regression and Cox-proportional hazard analysis, we compared rates of R0 resection among preoperative, postoperative and no RT cohorts and determined predictors of R0 resection and OS.

Results—The mean age was 59.5 (±17.1) years, and 45.9% were female. Median tumor size was 10.5cm. 51% of patients did not receive RT, 11.8% received pre-operative RT and 37.2% received post-operative RT. Rates of R0 resection for preoperative RT, postoperative RT, and no RT cohorts were 90.1%, 74.9%, and 79.9%, respectively (P<0.001). Independent predictors of achieving R0 resection included academic facility type (OR 1.36, 95% CI 1.20-1.55), histologic subtype, tumor size (OR 0.99, 95% CI 0.99-0.99), Charlson score (OR 0.92, 95% CI 0.84 – 0.99), and preoperative RT (OR 1.83, 95% CI 1.61-2.07). R0 resection as well as RT (pre-operative or post-operative) was associated with increased OS.

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Synopsis: Using the NCDB, we demonstrate that pre-operative RT independently predicts higher rates of R0 resection in patients with extremity STS undergoing surgical resection. Receipt of RT is also associated with improved OS.

Conclusions—Pre-operative RT independently predicts higher rates of R0 resection in patients with extremity STS undergoing surgical resection. Negative surgical margins and pre-operative or post-operative RT are associated with improved OS.

Keywords

pre-operative radiotherapy; soft tissue sarcoma; surgical margins

Background

Soft tissue sarcomas (STS) are rare tumors of mesenchymal origin, affecting approximately than 12,000 patients per year in the US.[1] The evolution of the treatment of extremity STS has led to the widespread use of limb-sparing surgery as the cornerstone of treatment with curative intent, and radiotherapy (RT) is frequently employed as a key component of these combined modality approaches.[2-5] Important prospective studies, including randomized trials, have demonstrated the impact of adjuvant/ neo-adjuvant RT on increased local control and decreased local recurrence of extremity STS, although these studies did not demonstrate an overall survival (OS) benefit with the addition of RT to surgery. [6-11] Retrospective studies from large databases have suggested that adjuvant RT may improve OS for patients with high grade STS, although the mechanism for this association remains undefined.[12-15]

The timing and dose of RT in combination with surgery has been thoroughly studied in the prospective, randomized SR2 trial which was completed by the National Cancer Institute of Canada.[16] Importantly, although there were significant differences between timing of RT with respect to acute and chronic morbidities of treatment, there was no difference in oncologic outcome between the preoperative and postoperative RT groups. Overall, acute post-surgical complications were higher in the preoperative RT group, while long term complications such as fibrosis, edema and joint stiffness were higher in the post-operative RT group.[16] Yet, there was no significant difference in local recurrence (LR) or OS.[17] Following this study, formal recommendations for the timing of RT with respect to surgery became a patient-specific decision made by multidisciplinary teams at experienced sarcoma centers weighing the risks and benefits.[18]

Since the SR2 trial, neoadjuvant RT has gained increasing acceptance in the multimodality management of primary extremity STS.[4] Proponents of pre-operative RT maintain that the acute morbidities of RT tend to be reversible, while the chronic morbidities tend to be irreversible.[19] Radiation oncologists endorse the smaller treatment fields as well as the well-defined tumor volume. [19-21] In very select situations with specific radiosensitive histologic subtypes, typically myxoid liposarcoma, pre-operative RT can cause appreciable tumor necrosis as measured by the Response Evaluation Criteria in Solid Tumors.[22-24] Finally, the ability to achieve negative surgical margins following preoperative RT is an often cited as a reason to favor neoadjuvant RT, although data in support of this contention are limited.

The creation of the National Cancer Database (NCDB) has allowed researchers to examine the outcomes of rare tumors, such as extremity STS, on a larger scale. Moreover, by providing data on key variables such as surgical margin status and timing of RT, investigators are able to examine hypotheses not previously possible with other large data

sets. In this study, we sought to analyze the relationship between pre-operative RT and surgical margin status in a large hospital-based data set, specifically hypothesizing that neoadjuvant RT leads to a higher incidence of R0 resection. We also sought to examine the impact of pre-operative RT and surgical margin status on OS in both low-grade and high-grade patients.

Methods

Using the NCDB, we retrospectively identified a total of 72,457 patients who were diagnosed with STS of the extremity according to the International Classification of Diseases for Oncology, 3rd revision between January 1, 2003 through December 31, 2012. Patients less than 18 years of age, who did not undergo surgery, who had unknown surgical margin status, tumor grade, tumor size, or vital status, and with stage IV disease at diagnosis were excluded. Patients who received a combination of pre- and post-operative RT, intraoperative RT, or had unknown delivery of RT were also excluded. Overall, 27,969 patients were included in the final analysis.

Frequency tables were generated for the 14,263 patients in the no RT group, 3,309 patients in the pre-operative RT group, and 10,397 patients in the post-operative RT group (Table 1). Variables examined included age, sex, race, year of diagnosis, facility type, Charlson-Deyo score, grade, histology, tumor size, surgical margins, receipt of chemotherapy, and chemotherapy-surgery sequence. As shown in Table 1, histologies were grouped into 22 separate subtypes including a grouping for sarcoma NOS. Year of diagnosis and tumor size were grouped into categories for summary statistics. Summary statistics were reported as mean ± standard deviation (SD) with median (range) where appropriate.

We performed standard univariate descriptive analyses. Multivariate Logistic regression was performed to evaluate pre-operative RT as a predictor of R0 resection. Other predictors selected in our model were age, sex, race, facility type, year of diagnosis, histology, grade, tumor size, Charlson-Deyo score, radiation-surgery sequence, and systemic-surgery sequence. Tumor size and year of diagnosis were treated as continuous variables. Histologic subtypes were identical to those described in Table 1.

A Cox-proportional hazard analysis and corresponding Kaplan-Meier curve were generated to evaluate OS. OS was measured as time to last contact or death, in months. Disease-specific survival is not captured in the NCDB dataset. In order to evaluate the impact of the sequencing of RT on OS in patients for whom RT is typically routinely indicated, we also performed a sub-group Cox-proportional hazard analysis for patients with Grade 3 and 4 histologies, comprising a total of 16,511 patients. All statistical analyses were performed using Stata version 14 (StataCorp LP, College Station, TX). Significance was set at $P < 0.05$. All patient information was deidentified and, therefore, exempt from the University of California, Davis, Institutional Review Board approval.

Results

The clinico-pathologic characteristics of the patient cohorts are depicted in Table 1. The mean age for the cohorts was 59.7, 58.9 and 59.6, respectively, and the majority in each

cohort was male. The majority of the patients were also Caucasian, and sarcoma NOS was the most prevalent histologic subtype in each group.

Of the patients who received pre-operative RT, 73.4% had either Grade 3 or Grade 4 histology. Of the patients who received post-operative RT, 69.4% had Grade 3 or Grade 4 histology. Patients not receiving RT were more evenly distributed, with 51.5% having Grade 1 or Grade 2 histology. Patients receiving pre-operative RT also tended to have larger tumors, with 46.8% of patients having tumors larger than 10cm, compared to 31.6% and 27.7% in the no RT and post-op RT groups, respectively ($P < 0.001$).

Of the patients who received pre-operative RT, 90.1% had a subsequent R0 resection compared to 79.9% of patients who did not receive RT and 75.0% of patients who received post-operative RT ($P < 0.001$). Overall, post-operative RT was associated with a 2.5 times greater rate of an R1 or R2 resection (25.0%) compared to pre-operative RT (9.6%, $P<0.0001$).

The results of multivariable logistic regression for predictors of R0 resection are depicted in Table 2. Pre-operative RT was associated with a significantly greater likelihood of obtaining an R0 resection with an odds ratio (OR) of 1.826 (95% CI 1.608-2.073, $P < 0.0001$) compared to an OR of 0.674 (95% CI 0.632 – 0.720, $P < 0.0001$) for post-operative RT, using no RT as reference. An R0 resection was also more likely to be achieved at an academic/research center with an OR of 1.366 (95% CI 1.204 – 1.55, $P < 0.0001$). As shown in Table 2, there were no other variables that were associated with achieving an R0 resection, including receipt of pre-operative chemotherapy.

In contrast, several histologic subtypes, including liposarcomas and malignant peripheral nerve sheath tumor, were associated with a lower likelihood of an R0 resection (Table 2). Interestingly, Grade 2 tumors were associated with a lower likelihood of an R0 resection (OR 0.878, 95% CI 0.788-0.978, $P = 0.018$) as was increasing tumor size (OR 0.999 per mm increase in tumor size, 95% CI 0.999- 0.999, $P < 0.0001$). A Charlson-Deyo score of 1 was also negatively associated with an R0 resection (compared to a score of 0), although a score of 2 or greater was not.

As depicted in Table 3, Cox-proportional hazard analysis demonstrated that both pre-operative RT and post-operative RT were associated with increased OS. With a HR of 0.80 (95% CI 0.78 – 0.82, $P < 0.0001$), post-operative RT was associated with a greater likelihood of survival than pre-operative RT (HR 0.94, 95% CI 0.91 – 0.98, $P < 0.001$). As shown in Figure 1, we did observe statistically significant differences in OS between R0 resection and both R1, HR 1.13 (95% CI 1.08 – 1.19, $P < 0.0001$) and R2 resections, HR1.221 (95% CI 1.15 – 1.30, $P < 0.001$), respectively.

We then performed a sub-group Cox-proportional hazard analysis limited to patients with Grade 3 and Grade 4 histology, since these patients are more likely to routinely receive RT as a component of their STS treatment (Table 4). Overall, our results remained consistent, as the hazard ratio for pre-operative RT and OS was 0.89 (95% CI 0.85 – 0.94, $P < 0.001$) and for post-operative RT was 0.76 (95% CI 0.74 – 0.79, $P <0.001$). We also observed a survival benefit to R0 resection compared to R1 and R2 resection, respectively.

Discussion

Using the NCDB, we analyzed the impact of neoadjuvant RT on surgical margins in the largest STS patient cohort to date, to our knowledge. We observed that pre-operative RT was significantly associated with an increased likelihood for negative surgical margins, thereby providing evidence for the underlying hypothesis that preoperative RT allows for sterilization of the surgical margins and increases the likelihood of achieving an oncologically optimal resection. Similar to prior studies, we also observed that R0 resection was associated with superior OS.[25,26] Additionally, we observed a survival benefit with both neoadjuvant and adjuvant RT.

The principal findings of the Canadian NCI SR2 trial showed no difference in progression-free survival or LR between the preoperative and postoperative RT arms. It did show a benefit for pre-operative RT for OS over 3 years.[16] However, their study was not powered to detect differences in this secondary endpoint. Interestingly, in this seminal trial, the rate of margin negativity was comparable between the preoperative and postoperative RT groups at 83% and 85%, respectively. Therefore, despite the comparable OS between the preoperative and postoperative RT groups in our hospital-based analysis, the statistically significant greater rate of R1 and R2 resections in the postoperative RT cohort is a key finding. Although several studies have not observed margin status to be an independent predictor of survival in STS (likely because of the importance of other biological drivers of outcome such as tumor grade, tumor size, and tumor histology),[31-34] there are other benefits to R0 resection, such as the potential effects on function and morbidity from additional operations and higher RT doses after R1/R2 resection, which should also be considered.[25-30,42]

In addition, an R0 resection can be difficult to achieve depending on tumor size and location, and our data seem to support the tendency for clinicians to endorse pre-operative RT in those cases given the higher utilization of pre-operative RT in tumors with larger size and higher rates of grade 3 and 4 histology. However, although neoadjuvant RT can cause tumor necrosis, it is uncommon for it to achieve significant tumor shrinkage or downstaging, and typically the extent of the surgical procedure is not altered by pre-operative RT.[4,19-24] Yet, pre-operative RT has been shown in animal models to thicken the pseudocapsule through hylanization, thus theoretically reducing the potential for disruption and histologically positive margins.[38] As multi-modality treatment recommendations for STS continue to evolve, treatment must be individualized for the patient, and there is wide institutional variation based on local specialty expertise and experience.[2-5] However, when considering treatments options for STS patients, it is important to acknowledge factors influencing outcome which are tumor-specific and which are treatment-related. Two of the tumor-specific factors which merit attention are histologic grade and histologic subtype. We observed that the survival benefit of negative surgical margins was increased in high-grade sarcoma patients. While historically the timing of RT has shown no impact on survival,[16,34-36] including the landmark NCIC trial, retrospective analyses have shown a survival benefit in favor of pre-operative RT.[37] These results may represent the impact of facility type where STS care was rendered, a confounding factor which may also explain our results.

In fact, key studies by Yang et al. and Beane et al. in a randomized setting observed no difference in survival when RT was added to limb-sparing surgery in patients with extremity STS.[7,8] Consequently, one explanation of our hospital-based registry data is that they are biased by confounding factors inherent in retrospective analyses such as selection bias. However, it is also important to acknowledge that the results of randomized trials may poorly generalize to the population at large since fewer than 5% of patients in the US participate in randomized trials. There is also a risk of type II error in these randomized studies. Although we are not able to resolve these critical questions, we emphasize that our data are concordant with prior retrospective studies showing an association of receipt of RT with improved STS survival (which some authors have attributed to higher compliance with guideline-based care).

When evaluating the findings of this study, its limitations must be considered. The NCDB does not contain information on local recurrence, a significant topic when considering the impact of RT on overall oncologic outcome. The effectiveness of RT in decreasing rates of LR has been clearly documented.[7,8,25,41] A recent study by Willeumier, et al[43] demonstrated superiority of neoadjuvant RT over adjuvant RT in improving local control. However, because of limitations of the NCDB database, the relationship of margin status to local recurrence cannot be corroborated in our data. Information on LR rates would clearly strengthen this analysis, particularly given the statistically significant differences in rates of R0, R1, and R2 resection among the preoperative, postoperative, and no RT cohorts.

Additionally, retrospective studies are at risk for sources of bias. In this study, pre-operative and post-operative RT were both associated with a survival benefit compared to surgery alone, although the magnitude of the favorable effect was greater for post-operative RT. One explanation for these findings is that the pre-operative RT patients appear to have an imbalance in baseline prognostic factors (tumor size and high grade) which biased these patients to have a worse survival. We attempted to reduce this bias by analyzing solely the Grade 3 and 4 patients, but these associations remained consistent. Given that the findings of O'Sullivan and colleagues showed no difference in key survival endpoints between pre-operative and post-operative RT for extremity STS,[16] the differences in OS we observed between the pre-operative and post-operative RT cohorts may be an artifact of the retrospective nature of our analysis. Ultimately, this important question requires further analysis with more rigorous statistical matching techniques to control for key prognostic factors.

In summary, our analysis of a large NCDB cohort of extremity STS patients reveals that pre-operative RT is associated with a statistically significant higher incidence of R0 resection, and both neoadjuvant and adjuvant RT are associated with improved survival. Therefore, we consider these data further evidence of the benefits of preoperative RT, although we recognize that the sequencing of RT remains a key component of individualized multi-modality STS care which is best provided in the context of an experienced STS referral center.

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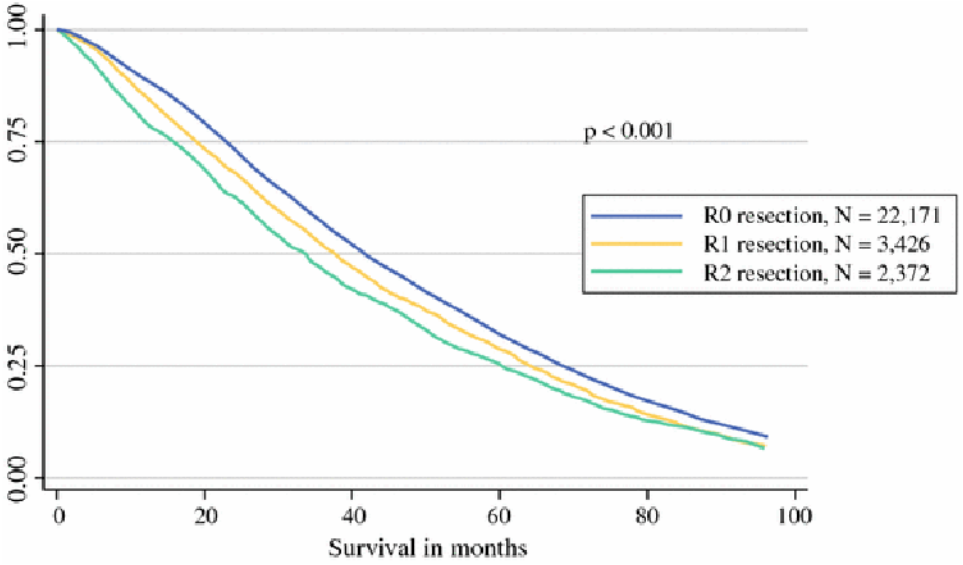

Figure 1.

Kaplan-Meier plot for overall survival in all patients stratified by R0, R1, or R2 surgical margin status.

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Table 1

Patient demographics and tumor characteristics

Factor	n, %						
	No Radiation Therapy		Pre-Op Radiation		Post-Op Radiation		p-value
Total	14,263	51.0	3,309	11.8	10,397	31.2	
Age	59.64	17.4	58.91	16.2	59.61	16.9	0.070
Sex							<0.0001
Male	7,468	52.4	1,872	56.6	5,795	55.7	
Female	6,795	47.6	1,437	43.4	4,602	44.3	
Year of Diagnosis							<0.0001
2004-2006	4,195	29.4	789	23.8	3,326	32.0	
2007-2009	4,936	34.6	1,147	34.7	3,585	34.5	
2010-2012	5,132	36.0	1,373	41.5	3,486	33.5	
Race							<0.0001
White	12,027	84.3	2,814	85.0	8,908	85.7	
Black	1,490	10.5	353	10.7	925	8.9	
American Indian, Aleutian or Eskimo	46	0.3	13	0.4	38	0.4	
Asian	250	1.8	43	1.3	263	2.5	
Pacific Islander	85	0.6	18	0.5	80	0.8	
Other	120	0.8	24	0.7	65	0.6	
Unknown	245	1.7	44	1.3	118	1.1	
Histology							<0.0001
Sarcoma, NOS	2,477	17.4	1,036	31.3	2,168	20.9	
Ewing's sarcoma	144	1.0	14	0.4	79	0.8	
Epithelioid sarcoma	126	0.9	27	0.8	109	1.1	
High grade undifferentiated pleomorphic sarcoma	1,470	10.3	499	15.1	1,806	17.4	
Fibrosarcoma	1,330	9.3	291	8.8	1,126	10.8	
Solitary fibrous tumor	121	0.9	17	0.5	58	0.6	
Dermatofibrosarcoma protuberans	271	1.9	6	0.2	62	0.6	
Liposarcoma, NOS	755	5.3	89	2.7	407	3.9	

Factor	n, %						
	No Radiation Therapy		Pre-Op Radiation		Post-Op Radiation		p-value
Liposarcoma, well differentiated	1,784	12.5	70	2.1	383	3.7	
Myxoid liposarcoma	656	4.6	315	9.5	596	5.7	
Round cell liposarcoma	53	0.4	22	0.7	92	0.9	
Pleomorphic liposarcoma	209	1.5	104	3.1	324	3.1	
Dedifferentiated liposarcoma	454	3.2	57	1.7	354	3.4	
Leiomyosarcoma	2,416	16.9	356	10.8	1,319	12.7	
Vascular sarcoma	533	3.7	23	0.7	283	2.7	
Rhabdomyosarcoma	160	1.1	48	1.5	121	1.2	
Synovial sarcoma	411	2.9	195	5.9	455	4.4	
Clear cell sarcoma	54	0.4	2	0.1	18	0.2	
Chondrosarcoma	342	2.4	35	1.1	127	1.2	
Malignant giant cell tumor	21	0.2	1	0.0	11	0.1	
Malignant peripheral nerve sheath tumor	468	3.3	98	3.0	484	4.7	
Alveolar soft part sarcoma	8	0.1	4	0.1	15	0.1	
Grade							<0.0001
Grade 1	4,749	33.3	365	11.0	1,416	13.6	
Grade 2	2,600	18.2	514	15.5	1,737	16.7	
Grade 3	4,123	28.9	1,359	41.1	4,360	41.9	
Grade 4	2,791	19.6	1,071	32.4	2,884	27.7	
Tumor Size							<0.0001
<5 cm	5,276	37.0	421	12.7	3,715	35.8	
5-10 cm	4,508	31.6	1335	40.2	3,817	36.7	
>10-15 cm	2,074	14.6	843	25.4	1,650	16.0	
>15 cm	2,045	17.0	710	21.4	1,215	11.8	
Charlson-Deyo Score							<0.0001
no comorbid conditions	11,604	81.4	2,733	82.6	8,673	83.4	
1 comorbid condition	2,137	15.0	468	14.1	1,425	13.7	
>1 comorbid condition	522	3.7	108	3.3	299	2.9	

Factor	n, %						
	No Radiation Therapy		Pre-Op Radiation		Post-Op Radiation		p-value
Margins							<0.0001
R0	11,395	79.9	2,981	90.1	7,795	75.0	
R1	1,636	11.5	190	5.7	1,600	15.4	
R2	1,232	8.6	138	4.2	1,002	9.6	
Chemo							<0.0001
Not given	12,342	86.5	2,247	67.9	8,353	80.3	
Given	1,503	10.5	998	30.2	1,771	17.0	
Unknown	418	2.9	64	1.9	273	2.6	
Facility Type							<0.0001
Community Cancer Program	744	5.2	79	2.4	685	6.6	
Comprehensive Community Cancer Program	3,876	27.2	608	18.4	3,279	31.5	
Academic/Research Program	6,725	47.2	2,021	61.1	4,402	42.3	
Integrated Network Cancer Program	828	5.8	141	4.3	638	6.1	
Other specified types of cancer program	0	0.0	0	0.0	0	0.0	
Unknown	2,090	14.7	460	13.9	1,393	13.4	

Table 2
Multivariable Predictors of R0 Resection

	Odds Ratio	p-value	[95% Conf. Interval]	
Age	0.9815	0.001	0.9790	0.9840
Sex				
Male	Reference			
Female	0.9583	0.166	0.9023	1.0178
Race				
White	Reference			
Black	0.9783	0.680	0.8815	1.0858
American Indian, Aleutian or Eskimo	1.1315	0.655	0.6584	1.9446
Asian	0.8965	0.299	0.7296	1.1017
Pacific Islander	0.9725	0.882	0.6727	1.4060
Other	0.7649	0.119	0.5460	1.0717
Unknown	0.8063	0.079	0.6342	1.0253
Facility Type				
Community Cancer Program	Reference			
Comprehensive Community Cancer Program	1.1402	0.047	1.0019	1.2976
Academic/Research Program	1.3665	0.000	1.2042	1.5508
Integrated Network Cancer Program	0.9659	0.679	0.8195	1.1385
Unknown	0.9747	0.769	0.8209	1.1572
Year of Diagnosis	1.0022	0.798	0.9855	1.0192
Histology				
Sarcoma, NOS	Reference			
Ewing's sarcoma	0.7723	0.14	0.5477	1.0889
Epithelioid sarcoma	0.9648	0.835	0.6883	1.3524
High grade undifferentiate pleomorphic sarcoma	1.0420	0.459	0.9346	1.1617
Fibrosarcoma	0.8749	0.029	0.7763	0.9861
Solitary fibrous tumor	0.7840	0.182	0.5484	1.1209
Dermatofibrosarcoma protuberans	0.9739	0.869	0.7109	1.3341
Liposarcoma, NOS	0.5138	0.000	0.4422	0.5969
Liposarcoma, well differentiated	0.4023	0.000	0.3495	0.4630
Myxoid liposarcoma	1.0372	0.660	0.8814	1.2207
Round cell liposarcoma	1.3610	0.181	0.8668	2.1372
Pleomorphic liposarcoma	0.9586	0.694	0.7767	1.1831
Dedifferentiated liposarcoma	0.3888	0.000	0.3324	0.4547
Leiomyosarcoma	1.1024	0.082	0.9876	1.2306
Vascular sarcoma	0.9389	0.496	0.7829	1.1258
Rhabdomyosarcoma	1.0013	0.993	0.7444	1.3470
Synovial sarcoma	1.0419	0.676	0.8593	1.2632

	Odds Ratio	p-value	[95% Conf. Interval]	
Clear cell sarcoma	0.9419	0.852	0.5019	1.7675
Chondrosarcoma	1.0734	0.585	0.8323	1.3843
Malignant giant cell tumor	1.1670	0.754	0.4440	3.0672
Malignant peripheral nerve sheath tumor	0.6464	0.000	0.5481	0.7624
Alveolar soft part sarcoma	0.8970	0.843	0.3058	2.6309
Grade				
Grade 1	Reference			
Grade 2	0.8779	0.018	0.7879	0.9781
Grade 3	1.0651	0.231	0.9608	1.1808
Grade 4	1.0612	0.294	0.9498	1.1857
Tumor Size	0.9992	0.000	0.9990	0.9994
Charlson-Deyo Score				
no comorbid condition	Reference			
1 comorbid condition	0.9174	0.042	0.8441	0.9971
>1 comorbid condition	0.9879	0.884	0.8391	1.1631
Radiation-Surgery Sequence				
No radiation therapy	Reference			
Radiation therapy before surgery	1.8257	0.000	1.6075	2.0734
Radiation therapy after surgery	0.6746	0.000	0.6321	0.7200
Systemic Surgery Sequence				
No systemic therapy	Reference			
Systemic therapy before surgery	1.0583	0.530	0.8867	1.2632
Systemic therapy after surgery	0.5581	0.000	0.4957	0.6284
Systemic therapy before and after surgery	1.0705	0.699	0.7583	1.5111
Systemic therapy given, sequence unknown	1.1080	0.535	0.8013	1.5322
Unknown	1.0106	0.849	0.9065	1.1266

Table 3

Predictors of Overall Survival

	Hazard Ratio	p-value	[95% Conf Interval]	
Age	1.0105	0.000	1.0094	1.0115
Sex				
Male		Reference		
Female	0.9311	0.000	0.9092	0.9535
Race				
White		Reference		
Black	1.0681	0.001	1.0260	1.1118
American Indian, Aleutian or Eskimo	1.1644	0.135	0.9535	1.4221
Asian	1.1191	0.009	1.0284	1.2179
Pacific Islander	1.0792	0.306	0.9327	1.2486
Other	1.2171	0.005	1.0613	1.3957
Unknown	0.8870	0.017	0.8039	0.9786
Facility Type				
Community Cancer Program		Reference		
Comprehensive Community Cancer Program	0.9622	0.172	0.9104	1.0169
Academic/Research Program	0.9982	0.948	0.9459	1.0534
Integrated Network Cancer Program	0.9692	0.385	0.9031	1.0401
Unknown	1.2379	0.000	1.1556	1.3262
Histology				
Sarcoma, NOS		Reference		
Ewing's sarcoma	0.9604	0.553	0.8403	1.0976
Epithelioid sarcoma	1.0373	0.564	0.9159	1.1749
High grade undifferentiate				
pleomorphic sarcoma	0.7603	0.000	0.7292	0.7927
Fibrosarcoma	0.9256	0.001	0.8833	0.9699
Solitary fibrous tumor	0.9190	0.249	0.7961	1.0609
Dermatofibrosarcoma protuberans	1.0397	0.496	0.9296	1.1629
Liposarcoma, NOS	0.8076	0.000	0.7570	0.8616
Liposarcoma, well differentiated	0.8506	0.000	0.8019	0.9023
Myxoid liposarcoma	0.8806	0.000	0.8304	0.9338
Round cell liposarcoma	0.7276	0.000	0.6232	0.8496
Pleomorphic liposarcoma	0.8395	0.000	0.7732	0.9114
Dedifferentiated liposarcoma	0.9385	0.086	0.8730	1.0091
Leiomyosarcoma	0.8876	0.000	0.8518	0.9248
Vascular sarcoma	1.2166	0.000	1.1305	1.3092
Rhabdomyosarcoma	0.9758	0.669	0.8720	1.0919
Synovial sarcoma	0.9581	0.219	0.8949	1.0257

	Hazard Ratio	p-value	[95% Conf Interval]	
Clear cell sarcoma	1.0107	0.928	0.8028	1.2723
Chondrosarcoma	0.8556	0.001	0.7798	0.9387
Malignant giant cell tumor	0.6312	0.008	0.4482	0.8891
Malignant peripheral nerve sheath tumor	1.0179	0.604	0.9519	1.0884
Alveolar soft part sarcoma	0.7108	0.083	0.4829	1.0462
Grade				
Grade 1		Reference		
Grade 2	1.1095	0.000	1.0639	1.1570
Grade 3	1.3232	0.000	1.2716	1.3769
Grade 4	1.3475	0.000	1.2910	1.4064
Tumor Size	1.0003	0.000	1.0002	1.0004
Charlson-Deyo Score				
no comorbid conditions		Reference		
1 comorbid condition	1.1577	0.000	1.1190	1.1979
>1 comorbid condition	1.4249	0.000	1.3335	1.5226
Radiation-Surgery Sequence				
No radiation therapy		Reference		
Radiation therapy before surgery	0.9444	0.005	0.9075	0.9828
Radiation therapy after surgery	0.8025	0.000	0.7814	0.8243
Chemotherapy				
No chemotherapy		Reference		
Received chemotherapy	0.9798	0.271	0.9448	1.0161
Unknown	0.8271	0.000	0.7688	0.8897
Margin Status				
R0		Reference		
R1	1.1438	0.000	1.1024	1.1869
R2	1.2412	0.000	1.1889	1.2957

Table 4
Multivariable Predictors of Survival- Grade 3 and 4

	Hazard Ratio	p-value	[95% Conf Interval]	
Age	1.0120	0.000	1.0106	1.0134
Sex				
Male		Reference		
Female	0.9321	0.000	0.9036	0.9614
Race				
White		Reference		
Black	1.0960	0.001	1.0391	1.1559
American Indian, Aleutian or Eskimo	1.1396	0.298	0.8910	1.4576
Asian	1.1148	0.057	0.9968	1.2467
Pacific Islander	1.1473	0.181	0.9382	1.4031
Other	1.1983	0.072	0.9836	1.4598
Unknown	0.9130	0.188	0.7973	1.0455
Facility Type				
Community Cancer Program		Reference		
Comprehensive Community Cancer Program	0.9748	0.483	0.9079	1.0467
Academic/Research Program	1.0254	0.477	0.9569	1.0989
Integrated Network Cancer Program	0.9861	0.763	0.9005	1.0799
Unknown	1.2577	0.000	1.1475	1.3785
Histology				
Sarcoma, NOS		Reference		
Ewing's sarcoma	1.0035	0.961	0.8738	1.1524
Epithelioid sarcoma	1.0887	0.241	0.9446	1.2547
High grade undifferentiated pleomorphic sarcoma	0.7654	0.000	0.7310	0.8014
Fibrosarcoma	0.9112	0.003	0.8561	0.9698
Solitary fibrous tumor	0.9660	0.765	0.7696	1.2124
Dermatofibrosarcoma protuberans	0.7368	0.014	0.5783	0.9389
Liposarcoma, NOS	0.7990	0.000	0.7158	0.8918
Liposarcoma, well differentiated	0.8663	0.427	0.6080	1.2344
Myxoid liposarcoma	0.7606	0.000	0.6817	0.8486
Round cell liposarcoma	0.7114	0.000	0.5917	0.8554
Pleomorphic liposarcoma	0.8079	0.000	0.7405	0.8815
Dedifferentiated liposarcoma	0.8865	0.004	0.8164	0.9626
Leiomyosarcoma	0.8588	0.000	0.8162	0.9036
Vascular sarcoma	1.1261	0.007	1.0324	1.2282
Rhabdomyosarcoma	0.9454	0.351	0.8403	1.0637
Synovial sarcoma	0.9688	0.443	0.8933	1.0506
Clear cell sarcoma	1.0210	0.880	0.7797	1.3371

	Hazard Ratio	p-value	[95% Conf	Interval]
Chondrosarcoma	0.9042	0.234	0.7658	1.0675
Malignant giant cell tumor	0.5523	0.006	0.3630	0.8402
Malignant peripheral nerve sheath tumor	1.0622	0.147	0.9789	1.1525
Alveolar soft part sarcoma	0.6916	0.110	0.4397	1.0877
Grade				
Grade 3		Reference		
Grade 4	1.0136	0.402	0.9821	1.0460
Tumor Size	1.0004	0.000	1.0003	1.0005
Charlson-Deyo Score				
no comorbid conditions		Reference		
1 comorbid condition	1.1577	0.000	1.1190	1.1979
>1 comorbid condition	1.4249	0.000	1.3335	1.5226
Radiation-Surgery Sequence				
No radiation therapy		Reference		
Radiation therapy before surgery	0.8936	0.000	0.8519	0.9373
Radiation therapy after surgery	0.7649	0.000	0.7395	0.7911
Chemotherapy				
No chemotherapy		Reference		
Received chemotherapy	0.9868	0.518	0.9479	1.0273
Unknown	0.8417	0.000	0.7654	0.9255
Margin Status				
R0		Reference		
R1	1.2057	0.000	1.1472	1.2671
R2	1.3518	0.000	1.2776	1.4303