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Long-term Oncologic Outcomes After Neoadjuvant Radiation Therapy for Retroperitoneal Sarcomas

Daniel P. Nussbaum, MD*, Paul J. Speicher, MD*, Brian C. Gulack, MD*, Asvin M. Ganapathi, MD*, Brian R. Englum, MD*, David G. Kirsch, MD, PhD^{†,‡}, Douglas S. Tyler, MD*, and Dan G. Blazer III, MD*

*Department of Surgery, Duke University, Durham, NC

[†]Department of Radiation Oncology, Duke University, Durham, NC

[‡]Department of Pharmacology and Cancer Biology, Duke University, Durham, NC

Abstract

Objective—To evaluate long-term survival among patients undergoing radiation therapy (RT), followed by surgical resection of retroperitoneal sarcomas (RPS).

Background—Despite a lack of level 1 evidence supporting neoadjuvant RT for RPS, its use has increased substantially over the past decade.

Methods—The 1998–2011 National Cancer Data Base was queried to identify patients who underwent resection of RPS. Subjects were grouped by use of neoadjuvant RT. Perioperative variables and outcomes were compared. Multivariable logistic regression was performed to assess predictors of neoadjuvant RT. Groups were propensity matched using a 2:1 nearest neighbor algorithm and short-term outcomes were compared. Finally, long-term survival was evaluated using the Kaplan-Meier method, with comparisons based on the log-rank test.

Results—A total of 11,324 patients were identified. Neoadjuvant RT was administered to 696 patients (6.1%). During the study period, preoperative RT use increased from 4% to nearly 15%. Male sex, tumor size larger than 5 cm, treatment at an academic/research program, and higher tumor grade all predicted neoadjuvant RT administration. After propensity matching, the only difference in baseline characteristics was the use of neoadjuvant chemotherapy. Although neoadjuvant RT was associated with a higher rate of negative margins (77.5% vs 73.0%; $P = 0.014$), there was no corresponding improvement in 5-year survival (53.2% vs 54.2%; $P = 0.695$).

Conclusions—Despite the increasing use of neoadjuvant RT for patients with RPS, the survival benefit associated with this treatment modality remains unclear. Continued investigation is needed to better define the role of RT among patients with RPS.

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Reprints: Daniel P. Nussbaum, MD, Department of Surgery, Duke University Medical Center, Box 3443, Durham, NC 27710. daniel.nussbaum@duke.edu.

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Keywords

neoadjuvant; preoperative; radiation therapy; radiotherapy; retroperitoneal sarcoma; sarcoma

Retroperitoneal sarcomas (RPSs) require multidisciplinary care, yet they often represent a therapeutic dilemma because of the heterogeneous nature of their biology, behavior, and natural history. Characterized by multiple histologic subtypes—the most common being liposarcoma (40%) and leiomyosarcoma (25%)—median survival ranges from approximately 3 to 12 years for high- and low-grade tumors, respectively.¹ After tumor grade, the most important factor impacting survival is extent of resection, as incomplete resection is associated with a 70% higher risk of death.² However, negative margins are often difficult to achieve, especially in large tumors that encroach on vital organs or other structures, and incomplete resection occurs in up to one-fifth of operations.^{2,3}

There are several hypothetical benefits for the use of neoadjuvant radiation therapy (RT) in patients with RPSs. As compared with adjuvant RT, administration of radiation in the preoperative period may allow the radiation oncologist to better define the target volume so that the RT can be focused on the tumor rather than the adjacent normal structures. If RT is delivered after surgery, the adjacent normal structures frequently fall into the postoperative tumor bed, which can limit the radiation dose to the target and increase the amount of radiation to normal structures. This may be a particular concern for bowel, which can become fixed as a consequence of fibrosis and adhesions, so that the same segment of bowel receives daily radiation during adjuvant RT.^{3,4} In addition, several studies have suggested that preoperative RT may improve short-term oncologic outcomes (eg, tumor resectability and achievement of negative margins) in retroperitoneal and other soft tissue sarcomas.⁵ Finally, there is some evidence that preoperative RT may decrease locoregional recurrence.^{5–8} Unlike extremity sarcoma, mortality among patients with RPSs is often secondary to local recurrence rather than distant metastasis.⁹ Thus, it is conceivable that improvements in local control may translate to increases in overall survival, although this remains widely debated.^{5–8}

Notably, a randomized controlled trial evaluating the efficacy of neoadjuvant RT in the treatment of RPS has never been completed. In 2006, the American College of Surgeons Oncology Group had to terminate its phase 3 trial Z9031 because of inadequate patient accrual. Eight years later, efforts are underway by the European Organisation for Research and Treatment of Cancer (EORTC) to recruit patients for a similar, multicenter trial (EORTC 62092-22092).¹⁰ However, even if accrual is successful, results are still years away.

The National Cancer Data Base (NCDB) is administered by the American College of Surgeons together with the American Cancer Society and at present contains data from more than 1500 cancer institutions including more than 30 million patients.¹¹ The Commission on Cancer estimates that the NCDB captures approximately 70% of all cancer diagnoses in the United States.¹¹ Thus, the NCDB is a particularly valuable tool for evaluating rare malignancies in which highly specialized treatment modalities are offered only at select

institutions. The purpose of this study was to utilize the NCDB to evaluate long-term oncologic outcomes associated with neoadjuvant RT for RPSs.

METHODS

The NCDB participant user file for 1998 through 2011 was utilized for this retrospective analysis. Patients were identified as having undergone resection of an RPS first by querying all patients treated at a NCDB participating institution for tumors in the retroperitoneal location with *International Classification of Diseases for Oncology, Third Edition (ICD-O-3)* topography codes C480 and C494-6. Relevant histologic subtypes were selected on the basis of *ICD-O-3* histology codes 8800, 8801, 8802, 8804, 8810, 8830, 8851, 8852, 8854, 8858, 8890, 9120, and 9540 (all of which represent soft-tissue sarcomas). Other inclusion criteria included malignant behavior, primary cancer diagnosis, no distant metastasis, and known status for preoperative RT.

Subjects were then classified by the use of neoadjuvant RT, defined by the NCDB as “radiation therapy given before surgery to the primary site.”¹² Baseline characteristics and outcomes between groups were compared using Pearson χ^2 test for categorical variables and analysis of variance for continuous variables. Multivariable logistic regression was used to predict factors that were associated with the administration of neoadjuvant RT. To control for confounding in the use of neoadjuvant RT, we developed propensity scores, which we defined as the conditional probability of being treated with RT before major resection. Patients were then matched on these propensity scores, using a 2:1 nearest neighbor algorithm. The following variables were used in our propensity match: patient age, sex, race, Charlson/Deyo comorbidity score, patient census tract education and income levels, tumor size, histologic subtype, histologic grade, treatment facility type (academic or community hospital), and extent of resection. Adjusted medians and proportions between the propensity-matched groups were then compared, and long-term survival among the groups was evaluated using the Kaplan-Meier method with comparisons based on the log-rank test.

Results are reported as median (interquartile range), proportions (%), and odds ratios (95% confidence interval) as applicable. *P* values less than 0.05 indicate statistical significance, and we controlled for type I error at the level of the comparison. All statistical analyses were performed using R (The R Foundation for Statistical Computing, version 3.0.2, Vienna, Austria).

RESULTS

A total of 11,324 patients were identified who had undergone resection of an RPS. Subjects were grouped by neoadjuvant RT (696 patients, 6.1%) versus no neoadjuvant RT (10,628 patients, 93.9%). During the study period, there was an increase in the use of neoadjuvant RT from approximately 4% of patients in 1998 to nearly 15% in 2011. The most pronounced increase in neoadjuvant RT occurred between 2005 and 2010 (Fig. 1).

Baseline characteristics are shown in Table 1. Patients who underwent neoadjuvant RT were slightly younger (58 vs 59; *P* = 0.005) and more likely to be male sex (55.9% vs 48.8%; *P* < 0.001). In addition, they were more likely to have been treated at an academic/ research

hospital (71.4% vs 46.5%; $P < 0.001$) than at a community or comprehensive community program and thus lived further from their treatment centers (26 vs 11 miles; $P < 0.001$). There were no differences between groups with regard to preoperative comorbidities, income, or education.

Focusing on tumor characteristics, patients who underwent neoadjuvant RT were more likely to have larger tumors and higher-grade tumors (Table 1). With regard to histologic subtype, neoadjuvant RT was more common among giant cell sarcomas (11.4% vs 3.8%), malignant fibrous histiocytomas (12.9% vs 11.5%), myxoid liposarcomas (8.5% vs 6.6%), pleomorphic liposarcomas (3.9% vs 2.5%), spindle cell sarcomas (7.8% vs 4.2%), and sarcomas not otherwise specified (12.5% vs 8.5%). Neoadjuvant RT was less common among dedifferentiated liposarcomas (5.7% vs 10.0%), leiomyosarcomas (23.3% vs 29.9%), and well-differentiated liposarcomas (6.8% vs. 14.3%). Patients who underwent neoadjuvant RT were also more likely to have received neoadjuvant chemotherapy (25.3% vs. 2.4%; $P < 0.001$). Using logistic regression, independent predictors of neoadjuvant RT use included male sex, tumor size larger than 5 cm, treatment at an academic/research program, and tumor grade higher than well-differentiated (Table 2).

After propensity adjustment, all variables except for neoadjuvant chemotherapy were highly similar (Table 3). Propensity-adjusted postoperative treatment specifics and outcomes are shown in Table 4. As expected, neoadjuvant RT was associated with a delay to surgery (median 114 vs 10 days; $P < 0.001$). Patients who underwent neoadjuvant RT were less likely to go on to receive both adjuvant RT (6.3% vs 32.9%; $P < 0.001$) and adjuvant chemotherapy (6.1% vs 14.3%; $P < 0.001$). Neoadjuvant RT was associated with a higher rate of negative margins (77.5% vs 73.0%; $P = 0.014$). There was no difference in 30-day mortality or readmission. Hospital length of stay was 1 day longer (6 vs 5 days; $P = 0.027$) in the group receiving neoadjuvant RT.

To ensure completeness of survival data, the NCDB reports only vital status for patients after 5 years have elapsed since the time of diagnosis. Thus, long-term survival from the time of diagnosis was evaluated for all patients who were diagnosed between 1998 and 2006. First, survival was estimated among all patients who underwent surgery during this period ($n = 7759$; Fig. 2). Among all comers, there was no statistically significant difference in 5-year survival among groups treated with or without neoadjuvant RT (53.2% vs 57.8%; $P = 0.254$). Next, propensity-matched groups were compared to adjust for confounding variables ($n = 1172$; Fig. 3). Using the Kaplan-Meier method, again there was no observable difference in 5-year survival (53.2% vs 54.2%; $P = 0.695$) for patients treated with or without neoadjuvant RT (Fig. 3). Because the classification of sarcoma subtype can be a diagnostic challenge, we evaluated survival for leiomyosarcomas alone ($n = 285$), as these tumors can be stained for specific smooth muscle markers and thus may have greater diagnostic uniformity. Again, there was no difference in survival, and these curves closely mirrored our overall survival plots (Fig. 4). Finally, in an exploratory analysis investigating the effect of neoadjuvant RT among only higher-grade tumors (moderately, poorly, and undifferentiated/anaplastic histology; $n = 823$), we detected a small but statistically significant 5-year survival advantage (49.1% vs 46.2%; $P = 0.022$) for patients treated with neoadjuvant RT (Fig. 5).

DISCUSSION

In 2007, Caudle and colleagues³ published one of the largest series documenting survival data for patients treated with neoadjuvant RT for RPSs. The size of their study sample was 14 subjects, revealing the paucity of information regarding this patient population. In their retrospective review, the authors found that grossly negative surgical margins were achieved in 13 patients, and among this group, only one-third had a local recurrence within a year, with 1-year survival approaching 90%.³ Other larger series out of Case Western Reserve University (n = 19),¹³ Tom Baker Cancer Center in Canada (n = 25),¹⁴ and MD Anderson Cancer Center/University of Toronto (n = 57),⁷ however, have reported less favorable long-term outcomes, describing 5-year survival of approximately 40%, 74%, and 50%, respectively (n values reflect number of patients undergoing neoadjuvant RT, followed by surgical resection). These equivocal outcomes data—and more importantly—the complete lack of clinical trials or even large retrospective data, make it increasingly difficult to establish whether preoperative RT improves survival, and if so, which patients are likely to derive a benefit (Table 5). This uncertainty is especially important given the potential for rare—albeit clinically meaningful—radiation toxicities, such as gastrointestinal upset/dehydration, intestinal obstruction, ureteral stricturing, leukopenia, and anemia/bleeding.^{3,15,16}

Following the early termination of the American College of Surgeons Oncology Group-Z9031 trial in 2006, 6 years elapsed before the EORTC began recruiting patients for their phase 3 randomized trial of neoadjuvant RT (EORTC 62092-22092).¹⁰ In the interim, little survival data have surfaced regarding preoperative RT for RPSs. Published reports in that time have included several additional single-institution reviews,^{8,13,15,17,18} 2 prospective studies evaluating survival only among patients treated with radiation,^{16,19} and 2 preliminary trials evaluating the safety and efficacy of concomitant chemoradiation therapy^{20,21} (Table 5). Here, we utilize the NCDB to help better define the impact of neoadjuvant RT for this malignancy and to provide more meaningful survival data for patients treated with preoperative RT. By using a large, nationwide clinical cancer database, we are able to identify more than 11,000 patients who underwent surgery for RPSs, among whom 696 underwent preoperative RT. Thus, this analysis represents by far the largest study to date examining long-term outcomes associated with preoperative RT, followed by surgical resection.

Of note, we first observed that the use of preoperative RT had increased over 3-fold throughout our study period, which is in concordance with our group's previous research in this area.²² Although only 4% of patients received neoadjuvant RT in 1998, by 2011 the rate was close to 15%. Although during that time there were several studies suggesting that preoperative RT could improve resectability and possibly decrease locoregional recurrence,^{5–8} there certainly existed no level 1 evidence concluding that neoadjuvant RT improved survival. In this study, we found that preoperative RT was associated with higher rates of negative margins (77.5% vs 73.0%). Notably, this improvement in margin status seemed to be the result of decreased macroscopic (9.3% vs 14.2% positivity rate) rather than microscopic (13.2% vs 12.9% positivity rate) margins. Therefore, it is conceivable that neoadjuvant RT shifted a similar percentage of patients from resections with a grossly

positive margins (R2) to resections with positive microscopic margins (R1) as it did R1 resections to complete resections with negative margins (R0). It is less likely that neoadjuvant RT converts an R2 resection into an R0 resection. The NCDB does not provide data on concomitant resection of adjacent organs, which could act as an additional marker for larger resections; however, extent of resection, as measured via the criteria in the NCDB, was similar between groups, as was tumor size.

In survival analysis, we first assessed unadjusted survival (ie, among all 7759 patients with survival data) and found no difference in 5-year survival for patients treated with and without pre-operative RT (53.2% vs 57.8%; $P = 0.254$). Next, we compared propensity-matched groups to attempt to control for bias in tumor and patients characteristics that may have affected the decision to administer RT. Among this cohort, again we found no difference in overall survival (54.1% vs 54.4% 5-year survival). Finally, we compared survival among patients with higher-grade sarcomas. Here, we identified a small but statistically significant survival advantage for patients treated with neoadjuvant RT (49.1% vs 46.2%; $P = 0.022$). Although these results are encouraging, they must be interpreted with caution. Patients who underwent preoperative RT had a relative delay to surgery of 104 days compared with patients who did not undergo RT. During this period, it is likely that the majority of patients were restaged radiographically. Patients who were identified as having developed metastatic disease at this time may not have proceeded to surgery, thereby enriching the group that did not receive neoadjuvant RT group for patients at a higher risk for early recurrence. In addition, in this retrospective review, it is possible that other kinds of selection bias may have influenced the decision of the treating physicians to use preoperative RT. Therefore, it is not clear whether preoperative RT does indeed provide a survival advantage for patients with higher-grade sarcomas.

However, our findings do not exclude a potential benefit for RT in the treatment of RPSs. First, it is possible that adjuvant RT can be used in select cases (eg, among higher-grade sarcomas, after local vs more aggressive resection, and after margin-positive resection) to improve outcomes.^{23–25} The fact that 27.1% (vs 6.3%) of patients who did not receive neoadjuvant RT went on to receive postoperative RT may mask the magnitude of the benefit of preoperative RT. In addition, although we adjust for tumor size and histologic grade, it is impossible to account for more subjective radiographic findings, such as the preoperative assessments of “resectability” or “likelihood of achieving negative margins” that are used by surgeons to select patients for neoadjuvant treatment modalities. Thus, although our data suggest that patients with higher grade sarcomas may be a subgroup that benefits from preoperative RT, it is possible that we have yet to identify a more select subset of patients who derive an even greater survival advantage from RT. Finally, there is some evidence that combined neoadjuvant chemotherapy and RT may be needed to achieve an optimal effect,^{20,21} and only 25% of patients in our study received both treatment modalities.

Moreover, although the NCDB is the largest clinical cancer database using national standardized coding definitions and data transmission specifications, there are nonetheless other limitations that must be acknowledged. First, because this is a large retrospective analysis, there exists the inherent possibility for selection bias regarding patients chosen to receive neoadjuvant RT and bias at the level of the observer with regard to data collection.

Second, our analysis is limited by the variables and outcomes captured through the NCDB. As such, our ability to describe the extent of resection is limited by reporting of margin status and 4 grades of surgery type ranging from “excision” to “radical resection.” Correspondingly, although we can categorize patients by the administration of neoadjuvant RT, we do not have data describing the dose or type of radiation used specifically within the neoadjuvant period. This lack of granularity may be particularly important given the increasing interest in “aggressive” resections^{24,25} and in delivering escalating doses of neoadjuvant radiotherapy to the area of anticipated close or positive margin.^{8,15,18,19} Moreover, advances in radiation technology, such as intensity-modulated RT, have improved the ability to focus the high-dose radiation region to the target to minimize treatment toxicity.^{16,18} Third, the pathologic diagnosis of sarcomas—including histologic subtyping and grading—may not be uniform across centers. However, our subgroup analysis of leiomyosarcomas—a tumor that can specifically be distinguished by its expression of smooth muscle markers—corresponded well with our overall analysis, increasing our confidence that differences in pathologic evaluation were not a major limitation. Finally, we are unable to comment on short-term postoperative outcomes such as surgical site infection, wound complications, other major morbidity, and hospital cost, although many of these data have previously been reported by our group and others.^{3,22,26,27}

CONCLUSIONS

In this study, we demonstrate that long-term survival is similar between patients treated with and without neoadjuvant RT. However, there may be a small (~3%) survival benefit for patients with higher-grade sarcomas, but this remains unclear, and this observation should be tested in a prospective clinical trial. Therefore, our retrospective results provide further clinical equipoise for the ongoing EORTC trial and can be used to encourage centers to endorse participation in this important study. Of note, we found that patients who underwent neoadjuvant RT were more likely to have been treated at an academic/research hospital than at a community or comprehensive community program. One reason for this difference may be that patients at an academic/research hospital may be more likely to be evaluated by a multidisciplinary team that includes a radiation oncologist before surgical resection. It is also possible that radiation oncologists at academic centers may have more experience treating relatively uncommon tumors such as RPSs with radiotherapy. Therefore, they may be more comfortable with delivering RT to a large volume of the abdomen. Regardless, this finding suggests that clinical trials for RPS that include neoadjuvant RT should target academic/research hospitals to increase the likelihood of patient accrual. Continued investigation of the role of RT is certainly needed to better define which patients with RPSs may benefit from neoadjuvant RT.

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FIGURE 1.
Use of neoadjuvant radiation for retroperitoneal sarcomas by year.

FIGURE 2.

Kaplan-Meier survival for neoadjuvant RT versus no neoadjuvant RT in RPS among all patients.

FIGURE 3.

Kaplan-Meier survival for neoadjuvant RT versus no neoadjuvant RT in RPS among propensity matched groups.

FIGURE 4.

Kaplan-Meier survival for neoadjuvant RT versus no neoadjuvant RT in leiomyosarcomas among all patients.

FIGURE 5.

Neoadjuvant RT versus no neoadjuvant RT for non-well-differentiated RPS.

TABLE 1

Baseline Patient Characteristics

Variable	Overall (n = 11,324)	Preoperative RT (n = 696)	No preoperative RT (n = 10,628)	P
<i>Patient characteristics</i>				
Age, yr (IQR)	59 (48–71)	58 (47–68)	59 (48–71)	0.005
Female	5747 (50.8%)	307 (44.1%)	5440 (51.2%)	<0.001
Race				0.219
White	9526 (85.4%)	598 (87.7%)	8928 (85.3%)	
Black	1201 (10.8%)	63 (9.2%)	1138 (10.9%)	
Other	425 (3.8%)	21 (3.1%)	404 (3.9%)	
Charlson Comorbidity Score				0.476
0	5939 (81.3%)	436 (83.2%)	5,503 (81.2%)	
1	1108 (15.2%)	73 (13.9%)	1035 (15.3%)	
2	256 (3.5%)	15 (2.9%)	241 (3.6%)	
Education above median	6461 (60.3%)	401 (61.9%)	6060 (60.2%)	0.426
Income above median	7397 (69.1%)	435 (67.1%)	6962 (69.2%)	0.292
Distance to cancer center (IQR)	11.6 (4.7–34.4)	26 (8–84)	11 (5–32)	<0.001
Treatment facility				<0.001
Community Cancer Program	827 (7.5%)	14 (2%)	813 (7.9%)	
Comprehensive Community Cancer Program	4908 (44.5%)	183 (26.6%)	4725 (45.7%)	
Academic/Research Program	5302 (48%)	491 (71.4%)	4811 (46.5%)	
Insurance				< 0.001
Private	5877 (54.3%)	357 (55.5%)	5520 (54.2%)	
Medicare	3850 (35.5%)	208 (32.3%)	3642 (35.8%)	
Medicaid	610 (5.6%)	33 (5.1%)	577 (5.7%)	
Government	95 (0.9%)	15 (2.3%)	80 (0.8%)	
Uninsured	398 (3.7%)	30 (4.7%)	368 (3.6%)	
<i>Tumor characteristics</i>				
Tumor size (mm)	105 (60–175)	115 (78–170)	105 (60–180)	0.856
Tumor size				<0.001
<5 cm	1757 (17.6%)	50 (8.1%)	1707 (18.2%)	
5–9.9 cm	2799 (28.1%)	182 (29.4%)	2617 (28%)	
10.0–19.9 cm	3385 (33.9%)	292 (47.1%)	3093 (33.1%)	
>20.0 cm	2033 (20.4%)	96 (15.5%)	1937 (20.7%)	
Grade				<0.001
Well differentiated	2681 (29.2%)	90 (15.3%)	2591 (30.2%)	
Moderately differentiated	1421 (15.5%)	83 (14.1%)	1338 (15.6%)	
Poorly differentiated	2954 (32.2%)	229 (39%)	2,725 (31.8%)	
Undifferentiated/anaplastic	2111 (23%)	185 (31.5%)	1926 (22.4%)	
Histology				<0.001
Dedifferentiated liposarcoma	1104 (9.7%)	40 (5.7%)	1064 (10%)	
Epithelioid sarcoma	182 (1.6%)	11 (1.6%)	171 (1.6%)	

Variable	Overall (n = 11,324)	Preoperative RT (n = 696)	No preoperative RT (n = 10,628)	P
Fibrosarcoma NOS	340 (3%)	14 (2%)	326 (3.1%)	
Giant cell sarcoma	487 (4.3%)	79 (11.4%)	408 (3.8%)	
Hemangiosarcoma	163 (1.4%)	5 (0.7%)	158 (1.5%)	
Leiomyosarcoma	3342 (29.5%)	162 (23.3%)	3180 (29.9%)	
Liposarcoma (well differentiated)	1568 (13.8%)	47 (6.8%)	1521 (14.3%)	
Malignant fibrous histiocytoma	1309 (11.6%)	90 (12.9%)	1219 (11.5%)	
MPNST	290 (2.6%)	21 (3%)	269 (2.5%)	
Myxoid liposarcoma	761 (6.7%)	59 (8.5%)	702 (6.6%)	
Pleomorphic liposarcoma	294 (2.6%)	27 (3.9%)	267 (2.5%)	
Sarcoma NOS	987 (8.7%)	87 (12.5%)	900 (8.5%)	
Spindle cell sarcoma	497 (4.4%)	54 (7.8%)	443 (4.2%)	
<i>Treatment specifics</i>				
Neoadjuvant RT	696 (6.1%)	696 (100%)	0 (0%)	<0.001
Neoadjuvant chemo	191 (4.3%)	95 (25.3%)	96 (2.4%)	<0.001
Surgery type				0.001
1: Excision	8714 (77%)	536 (77%)	8178 (76.9%)	
2: Complete resection	1011 (8.9%)	38 (5.5%)	973 (9.2%)	
3: Resection with debulking	410 (3.6%)	28 (4%)	382 (3.6%)	
4: Radical resection	1189 (10.5%)	94 (13.5%)	1095 (10.3%)	

IQR indicates interquartile range; MPNST, malignant peripheral nerve sheath tumors; NOS, not otherwise specified.

TABLE 2**Predictors of RT Use Before Resection**

Predictor	Odds Ratio	Upper 95%	Lower 95%	P
Age (per year)	0.99	0.99	1.00	0.118
Female sex	0.74	0.60	0.93	0.008
Race (ref = white)				
Black	0.91	0.63	1.32	0.628
Other	0.78	0.43	1.39	0.349
Charlson/Deyo	0.85	0.68	1.07	0.165
Education above median	1.28	0.98	1.68	0.070
Income above median	0.77	0.59	1.02	0.066
Tumor size (ref: <5 cm)				
5–9.9 cm	2.32	1.51	3.55	<0.001
10.0–19.9 cm	3.02	2.00	4.55	<0.001
>20.0 cm	1.36	0.85	2.18	0.201
Facility type (ref = community)				
Academic/research program	2.73	2.15	3.46	<0.001
Tumor grade (ref = well differentiated)				
Moderately differentiated	1.67	1.12	2.48	0.012
Poorly differentiated	2.03	1.48	2.80	<0.001
Undifferentiated/anaplastic	2.29	1.65	3.18	<0.001

TABLE 3

Adjusted Baseline Characteristics After Propensity Matching

Variable	Preoperative (n = 696)	No preoperative RT (n = 1392)	P
<i>Patient characteristics</i>			
Age, yr (IQR)	58 (47–68)	59 (47–68)	0.394
Female	307 (44.1%)	609 (43.8%)	0.913
Race			0.464
White	598 (87.7%)	1,171 (86%)	
Black	63 (9.2%)	150 (11%)	
Other	21 (3.1%)	41 (3%)	
Charlson Comorbidity score			0.407
0	436 (83.2%)	880 (84.2%)	
1	73 (13.9%)	146 (14%)	
2	15 (2.9%)	19 (1.8%)	
Education above median	401 (61.9%)	788 (61.2%)	0.818
Income above median	435 (67.1%)	851 (66.1%)	0.695
Distance to cancer center (IQR)	26 (8–84)	17 (6–50)	0.294
Treatment facility			0.534
Community Cancer Program	14 (2%)	22 (1.6%)	
Comprehensive Community Cancer Program	183 (26.6%)	392 (28.5%)	
Academic/Research Program	491 (71.4%)	960 (69.9%)	
Insurance			0.418
Private	357 (55.5%)	725 (54.7%)	
Medicare	208 (32.3%)	439 (33.1%)	
Medicaid	33 (5.1%)	89 (6.7%)	
Government	15 (2.3%)	21 (1.6%)	
Uninsured	30 (4.7%)	51 (3.8%)	
<i>Tumor characteristics</i>			
Tumor size (mm)	115 (78–170)	110 (70–160)	0.721
Tumor size			0.549
<5 cm	50 (8.1%)	88 (7.1%)	
5–9.9 cm	182 (29.4%)	399 (32.1%)	
10.0–19.9 cm	292 (47.1%)	581 (46.7%)	
>20.0 cm	96 (15.5%)	175 (14.1%)	
Grade			0.996
Well differentiated	90 (15.3%)	184 (15.7%)	
Moderately differentiated	83 (14.1%)	164 (14%)	
Poorly differentiated	229 (39%)	453 (38.6%)	
Undifferentiated/anaplastic	185 (31.5%)	373 (31.8%)	
Histology			0.955
Dedifferentiated liposarcoma	40 (5.7%)	74 (5.3%)	
Epithelioid sarcoma	11 (1.6%)	19 (1.4%)	

Variable	Preoperative (n = 696)	No preoperative RT (n = 1392)	P
Fibrosarcoma NOS	14 (2%)	43 (3.1%)	
Giant cell sarcoma	79 (11.4%)	151 (10.8%)	
Hemangiosarcoma	5 (0.7%)	9 (0.6%)	
Leiomyosarcoma	162 (23.3%)	305 (21.9%)	
Liposarcoma (well differentiated)	47 (6.8%)	91 (6.5%)	
Malignant fibrous histiocytoma	90 (12.9%)	211 (15.2%)	
MPNST	21 (3%)	45 (3.2%)	
Myxoid liposarcoma	59 (8.5%)	122 (8.8%)	
Pleomorphic liposarcoma	27 (3.9%)	58 (4.2%)	
Sarcoma NOS	87 (12.5%)	166 (11.9%)	
Spindle cell sarcoma	54 (7.8%)	98 (7%)	
<i>Treatment specifics</i>			
Neoadjuvant RT	696 (100%)	0 (0%)	<0.001
Neoadjuvant chemo	95 (25.3%)	24 (3.9%)	<0.001
Surgery type			0.991
1: Excision	536 (77%)	1080 (77.6%)	
2: Complete resection	38 (5.5%)	73 (5.2%)	
3: Resection with debulking	28 (4%)	56 (4%)	
4: Radical resection	94 (13.5%)	183 (13.1%)	

IQR indicates interquartile range; MPNST, malignant peripheral nerve sheath tumors; NOS, not otherwise specified.

TABLE 4

Propensity-Adjusted Treatment Specifics and Outcomes

Variable	Preoperative RT (n = 696)	No preoperative RT (n = 1392)	P
<i>Treatment characteristics</i>			
Days to definitive surgery (IQR)	114 (93–145)	10 (0–36)	<0.001
Adjuvant RT	44 (6.3%)	458 (32.9%)	<0.001
Adjuvant chemo	23 (6.1%)	88 (14.3%)	<0.001
<i>Surgical endpoints</i>			
Surgical margins			0.014
Negative	458 (77.5%)	855 (73%)	
Positive margin-microscopic	78 (13.2%)	151 (12.9%)	
Positive margin-macroscopic	55 (9.3%)	166 (14.2%)	
<i>Short-term outcomes</i>			
30-d mortality	6 (0.9%)	24 (1.9%)	0.163
30-d readmission	23 (4.6%)	35 (3.5%)	0.343
Hospital LOS (IQR)	6 (3–9)	5 (1–8)	0.027

IQR indicates interquartile range.

TABLE 5

Key Studies to Date Evaluating Neoadjuvant RT for Retroperitoneal Sarcomas

Authors (Year)	Institution	Study Design	Sample Size*	Key Results
Caudle et al (2007) ³	The University of North Carolina at Chapel Hill	Single-institution review	14	Low rates of treatment toxicity; 13/14 with gross negative margins, 7/14 with microscopic negative margins; median OS 21 mo
Zagar et al (2008) ¹³	Case Western Reserve University	Single-institution review	19	~40% 5-yr survival for patients treated with preoperative RT
White et al (2007) ¹⁴	Tom Baker Cancer Center (Calgary, AB)	Single-institution review	25	For primary tumors, actuarial 5-yr survival is 90%, DFS is 80%; for recurrent tumors, median disease-free interval is 91 mo
Pawlik et al (2006) ⁷	MD Anderson Cancer Center, University of Toronto (Ontario, Canada)	Review of 2 prospective trials	57	54/57 with gross negative margins; 5-yr survival for all patients 50%; 5-yr survival for patients with R0/R1 resection is 61%
McBride et al (2013) ⁸	Brigham and Women's Hospital	Single-institution review	33	Three-year locoregional recurrence of 37%; OS 64%; multifocal disease a predictor of local recurrence
Alford et al (2013) ¹⁷	Peter MacCallum Cancer Centre (Victoria, Australia)	Single-institution review	18	100% with gross negative margins; 5-yr local recurrence rate of 22%
El-Bared et al (2013) ¹⁸	Montreal University Health Centre (Quebec, Canada)	Single-institution review	21	Five-year survival is 51%; improved survival associated with lower grade; improved local control associated with R0 resection, smaller tumors, liposarcoma, and primary diagnosis
Smith et al (2014) ¹⁹	Princess Margaret Hospital, Mount Sinai Hospital (Ontario, Canada)	Multi-institutional phase II prospective trial	40	Five-year survival is 70%, 10-yr survival is 64%
Roeder et al (2012) ¹⁶	University of Heidelberg (Heidelberg, Germany)	Single-institution phase I/II prospective trial	20	Preoperative toxicity >grade 2 [†] in 2 patients; severe postoperative complications in 2/13 patients [‡]

* Evaluating preoperative RT, followed by surgical resection (if study included other treatment modalities/patient populations or no surgery).

[†] Based on Common Terminology Criteria for Adverse Events version 3.0.

[‡] Defined by the need for reintervention or intensive care treatment.

DFS indicates disease free survival; OS, overall survival.