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RESEARCH ARTICLE

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Factors associated with disease-free and abdominal recurrence-free survival in abdominopelvic and retroperitoneal sarcomas

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Abstract

Background and Objectives: Retroperitoneal and abdominopelvic sarcomas are rare heterogeneous malignancies. The only therapy proven to improve disease-free survival (DFS) is RO/R1 surgical resection. We sought to analyze whether additional factors such as radiation and systemic therapy were associated with DFS and abdominal recurrence-free survival (RFS).

Methods: Retrospective review of adults (≥18) with resectable abdominopelvic and retroperitoneal sarcomas who underwent intent-to-cure surgery at a high-volume tertiary referral center between 1998 and 2015. The main outcome measures were DFS and abdominal RFS.

Results: Overall, 159 patients met the criteria for inclusion. Median follow-up was 4.8 years (range 0.1–18.9 years). The most common histology was liposarcoma (49%). Systemic therapy was administered to 48% of patients and was not associated with improved outcomes. The neoadjuvant radiotherapy group (11%) had improved adjusted DFS (5.46 years, 95% CI [3.68, 7.24] vs. 3.1 years, 95% CI [2.48, 3.73]) and abdominal RFS (6.14 years, 95% CI [4.38, 7.89] vs. 3.22 years, 95% CI [2.61, 3.84]). The adjuvant radiotherapy group (19%) had no improvement.

Conclusions: In a cohort of patients undergoing resection for retroperitoneal or abdominopelvic sarcoma, neoadjuvant radiation improved DFS and abdominal RFS. A follow-up of over three years was needed to appreciate a difference in outcomes.

KEYWORDS

abdominal RFS, disease-free survival, liposarcoma, radiation, retroperitoneal sarcoma

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1 | INTRODUCTION

Retroperitoneal and abdominopelvic sarcomas represent a histologically heterogeneous group of tumors that carry a poor prognosis compared to the more prevalent extremity sarcomas.^{1–5} To date, surgical excision with RO or R1 margins remains the best chance for cure, reinforcing the importance of abdominal recurrence-free survival (RFS).^{6–9} Recurrence after treatment is common even after resection with negative margins and is associated with decreased survival.¹⁰ Pathologic margin status is difficult to determine conclusively on large tumors and it is possible that even "marginnegative" resections may leave microscopic tumor behind. Therapies that treat residual disease may, therefore, improve outcomes in recurrence and mortality.

Unfortunately, systemic chemotherapy and radiation therapy have not been shown to conclusively improve abdominal RFS, disease-free survival (DFS), or overall survival in retroperitoneal or abdominopelvic sarcomas; though radiotherapy has shown benefit in extremity sarcoma.^{11,12} Additional information about the therapeutic value of radiotherapy in non-extremity sarcoma would be beneficial given the significant associated toxicities, especially in the postoperative setting. Large observational studies show radiotherapy is administered to 25%-45% of retroperitoneal sarcoma patients, with a trend towards increased use of neoadiuvant radiotherapy in recent years.¹³⁻¹⁷ While results were mixed, some of these studies found modest improvements in overall survival.^{13-15,17} Another observational study of the National Cancer Database (NCDB) that focused exclusively on neoadjuvant radiotherapy found an improved negative margin rate but no effect on overall survival as compared to surgical treatment alone.¹⁸ Prospective and randomized controlled trials have been more limited, with the first trial studying neoadjuvant radiation therapy (ACOSOG Z9031) closing prematurely due to low participation. More recently, STRASS (EORTC 62092), an international randomized, controlled trial comparing neoadjuvant radiotherapy and surgery compared to surgery alone, was successfully completed and while the trial failed to demonstrate a survival or RFS benefit with a median follow up of 43.1 months, a subgroup analysis suggests that there may be a benefit in RFS for those with liposarcoma.¹⁹ Data on systemic therapies are even more limited.²⁰

With the ambiguity of the current data, we sought to assess the use of neoadjuvant and adjuvant therapy for abdominopelvic and retroperitoneal sarcoma at a high-volume sarcoma center and regional referral hospital. Our aims were to investigate the association between tumor characteristics, neoadjuvant and adjuvant systemic and radiation therapies, with the two outcomes of DFS and local recurrence.

2 | MATERIALS AND METHODS

This is a retrospective cohort of all adults (diagnosed over 18 years old) with resectable abdominopelvic and retroperitoneal sarcomas who underwent surgery with intent-to-cure at a high-volume institution from January 1, 1998 to January 1, 2015. Patients were identified in the institutional cancer registry who had a diagnosis of any sarcoma subtype originating within the abdomen, retroperitoneum, and/or pelvis. Chart review of these patients confirmed the diagnoses. Patients were excluded if there was medical record evidence of unresectability based on tumor board or surgeon note, or metastatic disease at diagnosis. If medical record evidence suggested that sarcoma was resectable before the operation, but it was later found to be unresectable peri-operatively, it was included in the analysis (intent-to-cure). Gastrointestinal stromal tumors, visceral sarcomas, and abdominal wall sarcomas were excluded from this study. This study was approved by the institutional IRB (#HUM00068553).

2.1 | Tumor characteristics

Histologic subtype was based on the first surgical resection pathology specimen determined by a soft tissue sarcoma specialized pathologist. If FNCLCC number grading was not available, grade was coded according to the pathologic description as shown in Table 1. Some patients underwent care, including their first resection, at an outside institution before presenting to our hospital. The study team reviewed all available information and any information not available was determined to be "unknown."

2.2 | Treatment characteristics

Treatment predictor variables included in the analysis were neoadjuvant radiation, adjuvant radiation, neoadjuvant systemic therapy, and adjuvant systemic therapy. Classification as neoadjuvant therapy was based on the presence of measurable disease at initiation of treatment and adjuvant was after resection of all gross disease. Palliative therapies were recorded but not included in analysis. Nonpalliative (therapeutic) modalities used to treat a recurrence were also excluded from the analysis.

2.3 | Outcome measures

To determine overall DFS and local RFS, we calculated the time from surgical resection to recurrence, irrespective of radiation or systemic therapy timing. Abdominal RFS was defined as number of years without recurrence in the retroperitoneum or abdomen. Recurrence in the parenchyma of the liver was considered distant recurrence.

2.4 | Statistical analysis

All data were analyzed using Stata version 16. For univariate analysis, comparisons of continuous variables were performed using non-parametric *t*-tests. Comparisons of categorical variables were

TABLE 1 Patient and tumor characteristics

Characteristics	Total patients = 159
Sex-n (%)	
Female	77 (48%)
Age	
Mean (range)	58 (19-87)
Alive—n (%)	63 (40%)
Race-n (%)	
White	136 (86%)
Black, Hispanic, or Asian	14 (8.8%)
Unknown	9 (6%)
Histology—n (%)	
Liposarcoma	78 (49%)
Leiomyosarcoma	47 (30%)
Pleomorphic sarcoma	8 (5%)
Fibrosarcoma	4 (2.5%)
Other	22 (14%)
Tumor location—n (%)	
Retroperitoneal	132 (83%)
Abdominal	26 (16%)
Pelvic	1 (<1%)
Tumor grade—n (%)	
FNCLCC 1 or low	36 (23%)
FNCLCC 2 or intermediate	5 (3%)
FNCLCC 3 or high	103 (65%)
Not provided	15 (9%)
Tumor size ^a , cm—mean (SD)	19 (12)
^a Unknown for eight patients.	

^aUnknown for eight patients.

performed using Pearson X^2 or Fisher's exact test if a category had five or fewer events. Multiple regression with predictive margins and 95% confidence intervals was used to calculate values for adjusted DFS and abdominal RFS. For neoadjuvant radiation therapy, we calculated time-to-event endpoints using Kaplan–Meier curves for the treatment groups. A p < 0.05 was considered significant.

3 | RESULTS

3.1 | Study population

One hundred fifty-nine patients met the criteria for inclusion. A summary of patient and tumor characteristics is available in Table 1 and a more detailed description of tumor histology by primary site and therapy type is available in Table A1 and A2, respectively. In this cohort, 77 (48%) were female and the mean \pm SD age at diagnosis was 58 \pm 14 years; median

TABLE 2 Treatments and outcomes

Characteristics	Total patients = 159
Margin status—n (%)	
RO	77 (48%)
R1	61 (38%)
R2	13 (8.2%)
Unresectable	4 (2.5%)
Unknown	4 (2.5%)
Recurrence–n (%)	97 (61%)
Local	79 (50%)
Distant	32 (20%)
Total follow up, years-mean (SD)	5.3 (4)
Disease-free survival, years-mean (SD)	3.3 (3.7)
Radiation therapy $-n$ (%)	47 (30%)
Adjuvant	31 (19%)
Neoadjuvant	17 (11%)
Systemic therapy—n (%)	76 (48%)
Adjuvant	44 (28%)
Neoadjuvant	33 (21%)
Combination therapy $-n$ (%)	37 (23%)
Adjuvant systemic + adjuvant RT	17 (11%)
Adjuvant systemic + neoadjuvant RT	4 (2.5%)
Neoadjuvant systemic + adjuvant RT	9 (5.7%)
Neoadjuvant systemic + neoadjuvant RT	10 (6.3%)
Palliative therapy $-n$ (%)	62 (39%)
Resections per patient-n (%)	
1	118 (74%)
2	25 (16%)
3	8 (5%)
4 or more	8 (5%)

follow-up was 4.8 years (interquartile range 1.8–7.6 years, range 0.1–18.9 years). The most common histologic types were liposarcoma (n = 78, 49%) and leiomyosarcoma (n = 47, 30%). Liposarcomas were more likely to be low grade compared with leiomyosarcomas (43% vs. 4%, p < 0.001). The majority (87%) of tumors were retroperitoneal. Because our analysis was based on patients undergoing an intent-to-treat surgical resection, four (2.5%) patients were included who underwent curative-intent surgery but were found on inspection of the abdomen to be unresectable. With regard to treatment, more patients underwent systemic therapy (48%) compared to radiation therapy (30%) (Table 2).

Of the 47 patients who had radiation therapy, 36% had neoadjuvant radiation. Radiation dose information was available for all patients, with median 50.4 Gy administered using standard fractionation (range 45–66 Gy). Radiation was performed at an outside institution in 14 patients, or 30% of the radiation cohort. While most patients who received radiation did well, radiation toxicity was severe in four patients (8.5%). Two patients from the neoadjuvant radiotherapy group experienced significant nausea, vomiting, and weight loss, with one of the patients halting therapy early due to these adverse effects. While unlikely to be directly related to radiation, two (one neoadjuvant, one adjuvant) patients suffered a pulmonary embolism and completed therapy on anticoagulation. However, all three neoadjuvant patients who experienced toxicity were able to undergo planned surgical resection.

3.2 | Disease factors affecting overall DFS and abdominal RFS

Mean abdominal RFS was 3.59 years, 95% CI (2.78, 4.41) for liposarcomas and 3.82 years, 95% CI (2.76, 4.89) for leiomyosarcomas. On

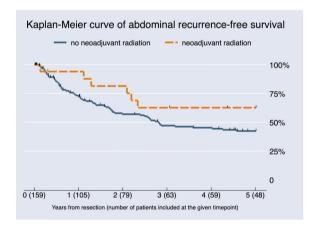


FIGURE 1 Kaplan–Meier curve comparing time to abdominal recurrence in patients undergoing neoadjuvant radiation with patients who underwent adjuvant or no radiation therapy up to 5 years follow-up. Hash marks overlying each curve represent censored patients

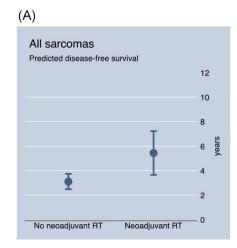
univariate analysis, there was no association between histologic subtype (leiomyosarcoma or liposarcoma) and improved DFS or abdominal RFS. Within the liposarcoma subgroup, well-differentiated liposarcomas were associated with improved DFS (5.00 years, 95% CI [3.34, 6.65] vs. 2.81 years, 95% CI [1.94, 3.67], p = 0.011) and abdominal RFS (5.00 years, 95% CI [3.34, 6.64] vs. 2.81 years, 95% CI [1.97, 3.65], p = 0.010) compared to dedifferentiated and pleomorphic subtypes. Grade 1 tumors compared to Grade 2 or 3 tumors across all histologic types were associated with improved DFS (4.51 years, 95% CI [3.16, 5.88] vs. 2.93 years, 95% CI [2.26, 3.61], p = 0.027) but not abdominal RFS (4.49 years, 95% CI [3.14, 5.84] vs. 3.18 years, 95% CI [2.49, 3.87], p = 0.069). Neither tumor location nor tumor size was associated with DFS or abdominal RFS.

3.3 | Treatment factors affecting overall DFS and abdominal RFS

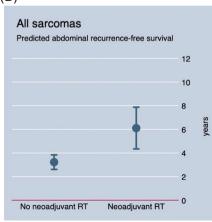
On univariate analysis, neoadjuvant radiation compared to no neoadjuvant radiation was associated with improved abdominal RFS (5.31 years, 95% CI [2.90, 7.15] vs. 3.23 years, 95% CI [2.65, 3.82], p = 0.029) but not DFS (4.66 years, 95% CI [2.20, 7.11] vs. 3.12 years, 95% CI [2.53, 3.72], p = 0.110) (Figure 1). After adjusting for tumor grade and resection margin, neoadjuvant radiation improved both DFS (5.46 years, 95% CI [3.68, 7.24] vs. 3.1 years, 95% CI [2.48, 3.73], p = 0.015) and abdominal RFS (6.14 years, 95% CI [4.38, 7.89] vs. 3.22 years, 95% CI [2.61, 3.84], p = 0.002) (Figure 2). Adjuvant radiation therapy was not associated with DFS or abdominal RFS. To determine if neoadiuvant radiation conferred differential treatment effects by histology, the liposarcoma and leiomyosarcoma subgroups were analyzed separately (Figures 3 and 4). In the liposarcoma subgroup, neoadiuvant radiation improved both adjusted DFS (8.86 years, 95% CI [6.45, 11.28] vs. 3.11 years, 95% CI [2.35, 3.89], p < 0.001) and abdominal RFS (8.86 years, 95% CI [6.45, 11.25] vs. 3.11 years, 95% CI [2.34, 3.88], p < 0.001). In the leiomyosarcoma subgroup, neoadjuvant radiation did not improve DFS (p = 0.715) or abdominal RFS (p = 0.575).

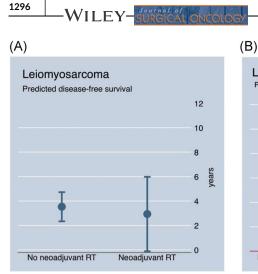
Systemic therapy was not associated with improved DFS or abdominal RFS, including adjuvant and neoadjuvant subgroups and

FIGURE 2 Predicted (A) disease-free survival and (B) abdominal recurrence-free survival with 95% confidence intervals, adjusting for grade and margin status, in the entire cohort (n = 141)









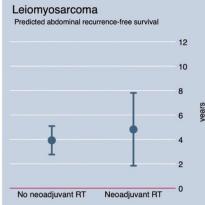
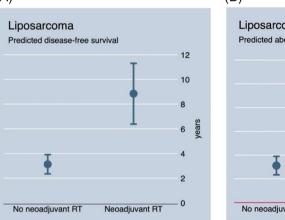
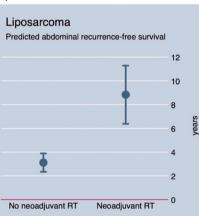


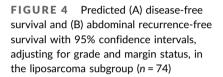
FIGURE 3 Predicted (A) disease-free survival and (B) abdominal recurrence-free survival with 95% confidence intervals, adjusting for grade and margin status, in the leiomyosarcoma subgroup (n = 44)











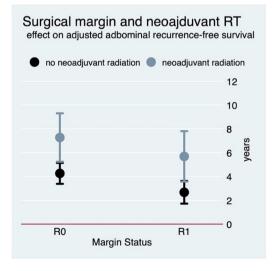


FIGURE 5 Predicted overall disease-free survival with 95% confidence intervals, adjusting for grade, based on surgical margin and receipt of neoadjuvant radiation therapy in the entire cohort

after adjusting for grade and resection margin. Systemic therapy was used more commonly in high-grade tumors (64% of Grade 2 and 3 tumors vs. 0% of Grade 1 tumors, p < 0.001). Systemic therapy was used more commonly in younger patients (regression coefficient -0.048, p < 0.001) so that the predicted probability of receiving systemic therapy was 48% at the mean age of 58 compared with 69% at age 40% and 29% at age 75. Liposarcomas were less likely to be treated with systemic therapy than other subtypes (35% vs. 61%, p = 0.001). There was no difference in systemic therapy utilization based on tumor size or location.

Margin status was a significant factor for both DFS and abdominal RFS. DFS for an RO margin was 4.19 years, 95% CI (3.39, 5.00), for an R1 margin was 2.90 years, 95% CI (2.02, 3.79), and for an R2 margin was 0.40 years, 95% CI (-1.61, 2.41). Abdominal RFS was also best for R0, followed by R1 and R2 (4.47 years, 95% CI (3.67, 5.26) for R0, 2.96 years, 95% CI (2.08, 3.83) for R1, and 0.41 years, 95% CI (-1.58, 2.40) for R2. A comparison of adjusted abdominal RFS based on neoadjuvant radiation and surgical margin is presented in Figure 5.

Patients in the systemic therapy subgroup were more likely to undergo neoadjuvant radiation than patients who received no systemic therapy (17% vs. 5%, p = 0.019). There was no difference in rates of neoadjuvant radiation between the RO/R1 margin group and the group of R2 or unresectable tumors; 82% of neoadjuvant radiation recipients had a R0 or R1 resection compared with 91% of those who did not receive neoadjuvant radiation, p = 0.39, even after controlling for tumor grade. There was also no difference in R0 rates (p = 0.41).

4 | DISCUSSION

This analysis of a single-institution cohort of abdominopelvic and retroperitoneal sarcoma provides a large sample of patients with substantial length of follow-up and demonstrated improved patient outcomes after administration of neoadjuvant radiation therapy. To date, no studies have demonstrated definitively that there is a benefit in neoadjuvant radiation for this population. The recently reported multi-center randomized controlled STRASS (EORTC 62092) trial revealed no benefit to the addition of radiation (HR 1.01, p = 0.95); however, results were reported after 3.6 years median follow-up, which is shorter than our median followup of 4.8 years.¹⁹ In addition, the trial did appear to identify some absolute treatment benefit in liposarcomas that was not statistically significant. In our study, the marginal benefit of neoadjuvant radiation was not detectable until after three years of follow-up and was primarily observed in the liposarcoma group. Our study therefore corroborates findings in STRASS (EORTC 62092) suggesting a differential treatment effect by histology, with liposarcomas receiving more therapeutic benefit after neoadjuvant radiation. Unlike STRASS (EORTC 62092) whose preoperative radiotherapy group included 35% well-differentiated liposarcomas, we were not able to perform any comparison by grade because no pure well-differentiated liposarcomas underwent neoadjuvant radiation in our study cohort. Additionally, some concerns with the STRASS trial include a high rate of protocol deviations as well as a very high neoadjuvant radiation toxicity rate, with >75% of patients having a grade \geq 3 toxicity, which is in contrast to the low toxicity rate (3/17, 18%) in our study as well as other reported studies.^{21,22}

In addition to our findings on neoadjuvant radiation, our analysis demonstrated findings similar to prior studies in that improved DFS is notable in histologically favorable sarcomas.^{5,10} In our cohort, low grade (Grade 1) tumors were associated with increased DFS and abdominal RFS compared to high-grade tumors. Regarding margin status, while prior studies comparing R0 and R1 tumors have shown similar DFS and abdominal RFS,²³ we did find a difference in DFS and abdominal RFS between R0 and R1 resections.

With regard to trends in treatment utilization, the majority of patients with RP sarcoma at our institution did not receive radiation therapy. However, of the 30% of patients who did receive it, adjuvant radiation was more commonly used than neoadjuvant radiation. Potential reasons for these observations include patient/surgeon preference, symptoms requiring immediate surgery, fear of becoming unresectable during radiation therapy, and lack of supporting data. Contrary to our hypothesis that adjuvant therapy would be used more often in patients with a positive margin, we did not find any association between margin status and receipt of adjuvant radiation. Adjuvant radiation decision-making may instead take into account a "close margin," as defined by the operative surgeon but not found in the pathology report. Also, at our institution adjuvant radiation would be considered for a positive margin after resection of a high grade tumor, but less so if low grade. Nonetheless, the patients who did receive radiation showed high rates of radiotherapy completion in both adjuvant and neoadjuvant groups, despite concerns that radiation therapy may not be completed, particularly within the postoperative period.

Of the patients who received therapeutic systemic therapy, 43% had a neoadjuvant approach. These patients had high grade sarcomas with aggressive histologic features, and therefore, as previously shown, systemic therapy did not improve DFS. Interestingly, it was still administered much more commonly than radiation likely due to the desire of the treatment team to assess the benefit of systemic therapy with tumor in place, or if the planned resection would include nephrectomy, to be able to administer chemotherapy safely. Most importantly, our observations once again emphasize the unmet need for better systemic treatments for liposarcoma and leiomyosarcoma.

While the STRASS trial suggests that neoadjuvant radiation does not portent benefit for retroperitoneal sarcoma, our data as well as others, suggest that some subtypes may benefit. We must be cautious in interpreting RFS benefit in low grade, well-differentiated liposarcoma, since many recurrences happen later, up to 10 years, and may not be picked up with short follow-up studies. This may be elucidated when longer follow-up is reported from the STRASS trial. Currently, STRASS 2, an international multi-center randomized trial which only includes patients with high grade dedifferentiated liposarcoma and leiomyosarcoma is designed to assess whether three cycles of neoadjuvant chemotherapy followed by surgery, versus surgery alone, will increase DFS. By limiting histological subtypes to those with the greatest metastatic risk, the trial has the potential to answer whether this approach is beneficial.

Limitations to our study include the retrospective nature of analysis and study population limited to a single institution. Strengths of the study include granular patient data such as radiation dose, histology, and pathology reports, as well as robust longitudinal follow-up. Additionally, apart from an increase in the utilization of neoadjuvant radiation, treatments for retroperitoneal and abdominopelvic sarcoma have not changed substantially over the past 15 years, thereby rendering our reported long-term outcomes from surgery and radiation applicable to treatments imparted today.

5 | CONCLUSIONS

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At a single high-volume center, most patients experienced a recurrence after resection of their retroperitoneal or abdominal sarcoma. However, several factors influenced length of DFS, including tumor grade, margin status, and treatment with neoadjuvant radiation.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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See the Table 3 Table 4.

TABLE A1Primary site by histology

Histology	Histologic subtype	Total	Primary site Retroperitoneal	Abdominal	Pelvic
Liposarcoma	-	78	68	10	0
	Well differentiated	28	26	2	0
	Dedifferentiated	43	37	6	0
	Pleomorphic	7	5	2	0
Leiomyosarcoma	-	47	39	8	0
	Leiomyosarcoma	45	38	7	0
	Myxoid leiomyosarcoma	1	1	0	0
	Pleomorphic leiomyosarcoma	1	0	1	0
Pleomorphic sarcoma	-	8	5	3	0
Fibrosarcoma	-	4	3	1	0
Sarcoma	-	4	3	1	0
Alveolar soft part sarcoma	-	3	3	0	0
Solitary fibrous tumor	-	3	3	0	0
Fibromyxosarcoma	-	2	2	0	0
Spindle cell sarcoma	-	2	1	1	0
Angiosarcoma	-	1	1	0	0
Desmoplastic small round cell tumor	-	1	0	1	0
Pleomorphic rhabdomyosarcoma	-	1	1	0	0
Clear cell sarcoma	-	1	0	0	1
Myofibroblastic sarcoma	-	1	0	1	0
Synovial sarcoma	-	1	1	0	0
Pleomorphic osteosarcoma	-	1	1	0	0
Sclerosing epithelioid fibrosarcoma	-	1	1	0	0
	Total	159	132	26	1

TABLE A2 Therapy type by histology

			Radiation therapy ^a			Systemic therapy ^a			
Histology	Histologic subtype	Total	Neoadjuvant	Adjuvant	Any radiation	Neoadjuvant	Adjuvant	Any systemic	Surgery only
Liposarcoma	-	78	8	8	16	18	9	27	48
Liposarcoma	Well differentiated	28	1	0	10	0	0	0	27
	Dedifferentiated	43	6	6	12	17	7	24	17
	Pleomorphic	43	1	1	2	1	2	3	4
	Fleomorphic	47	6	12	18	6	18	24	17
Leiomyosarcoma	-								
	Leiomyosarcoma	45	6	11	17	6	18	24	16
	Myxoid leiomyosarcoma	1	0	1	1	0	0	0	0
	Pleomorphic leiomyosarcoma	1	0	0	0	0	0	0	1
Pleomorphic sarcoma	-	8	2	3	5	2	5	7	1
Fibrosarcoma	-	4	1	2	2	1	3	3	1
Sarcoma	-	4	0	1	1	1	2	3	1
Alveolar soft part sarcoma	-	3	0	2	2	0	1	1	1
Solitary fibrous tumor	-	3	0	0	0	0	0	0	3
Fibromyxosarcoma	-	2	0	2	2	0	2	2	0
Spindle cell sarcoma	-	2	0	0	0	0	2	2	0
Angiosarcoma	-	1	0	1	1	1	0	1	0
Desmoplastic small round cell tumor	-	1	0	0	0	1	0	1	0
Pleomorphic rhabdomyosarcoma	-	1	0	1	1	1	0	1	0
Clear cell sarcoma	-	1	0	0	0	1	0	1	0
Myofibroblastic sarcoma	-	1	0	0	0	0	1	1	0
Synovial sarcoma	-	1	0	0	0	0	1	1	0
Pleomorphic osteosarcoma	-	1	0	0	0	1	0	1	0
Sclerosing epithelioid fibrosarcoma	-	1	0	0	0	0	0	0	1
	Total	159	17	31	47	33	44	76	72

^aDoes not include palliative therapy.