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Original Research Article

The importance of the margin of resection and radiotherapy in retroperitoneal liposarcoma

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ABSTRACT

Background: Prior studies evaluating the impact of adjuvant or neoadjuvant radiotherapy on clinical outcomes in retroperitoneal liposarcoma have been underpowered.
Methods: We queried the National Cancer Database for patients undergoing resection of retroperitoneal liposarcoma from 2004 to 2016. Cox proportional hazards modeling stratified by tumor size was used to identify factors associated with overall survival.
Results: 4018 patients met inclusion criteria. 251 had small (<5 cm), 574 intermediate (5–10 cm), and 3193 large (>10 cm) tumors. Positive surgical margins were correlated with risk of death across all tumor size categories (<5 cm HR 2.33, CI [1.20, 4.55]; 5–10 cm HR 1.49, CI [1.03, 2.14]; >10 cm HR 1.30, CI [1.12, 1.51]). Adjuvant radiotherapy was associated with improved survival for patients with large tumors only (HR 0.75, CI [0.64, 0.89]).
Conclusions: In retroperitoneal liposarcoma, adjuvant radiation is associated with improved survival only for patients with tumors larger than 10 cm. Radiation should be used sparingly in patients with smaller tumors.
Summary: The use of radiotherapy in the management of retroperitoneal sarcoma remains controversial. We isolated retroperitoneal liposarcomas only and identified a survival benefit from radiotherapy treatment only in tumors larger than 10 cm and only in the adjuvant setting.

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Introduction

Lipomatous retroperitoneal tumors typically present in a delayed fashion as large mass lesions found incidentally on imaging done to evaluate unrelated symptoms.[1] Although most of these tumors are benign lipomas, liposarcomas do occur with some regularity, representing more than 50% of all retroperitoneal sarcomas. Primary treatment involves surgical resection to negative margins.[2] Attaining negative surgical margins is frequently made difficult, however, by the size of the tumor and involvement of adjacent vital organs and neurovascular structures.

Radiotherapy has been used an adjunct to surgery to manage residual disease and facilitate tumor clearance. Decisions regarding the use of radiation therapy can be complicated, however, by the location of the tumors, the fact that it is difficult to reliably diagnose liposarcoma from benign lipomatous tumors on biopsy, and the fact that many liposarcomas are low-grade and have limited potential for aggressive behavior. Decisions regarding the use of radiotherapy are further complicated by potential of radiation to irreversibly injure adjacent organs that serve to provide vital functions to the patient. This risk increases with irradiation of larger tumors and in the postoperative setting, with irradiation of larger tumor beds that abut multiple vital structures.[3] Treating clinicians must carefully evaluate the potential risks and benefits of radiotherapy, particularly in cases where a larger tumor size would necessitate irradiating a large portion of the retroperitoneum. Prior studies evaluating the use of radiation in treating liposarcoma have generally been retrospective single institutional studies including

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multiple histologies. The results of these are mixed with some suggesting a benefit to radiation and others finding none.[4–6]

In the current study, we attempt to better define the role for radiation therapy in patients with liposarcoma. We use the National Cancer Database to compare survival profiles for patients undergoing surgical resection with and without radiation therapy.

Methods

Data source and study design

The National Cancer Database is a national clinical oncology database founded and administered jointly by the American Cancer Society and the American College of Surgeons. The database currently contains data on 34 million patients from over 1500 Commission on Cancer-accredited institutions, capturing an estimated 70% of cancers diagnosed annually in the United States.

We queried the National Cancer Database for patients undergoing surgical resection of primary liposarcoma between 2004 and 2016. Patients with primary liposarcoma were identified by cross-referencing those designated as having an International Classification of Diseases for Oncology, 3rd edition (ICD-*O*-3) topography code for retroperitoneal tumors with those having ICD-*O*-3 histology codes for liposarcomas with malignant potential (Supplemental Table I).

Patients that were less than 18 years of age, those with metastatic disease, those undergoing intra-operative radiotherapy, or receiving both neoadjuvant and adjuvant radiation, those undergoing tumor debulking as opposed to complete resection, those having an R2 (grossly positive) surgical margin, and those having a delayed presentation to the operating room after diagnosis (>30 weeks), as well as those with unknown values for variables included in our modeling, were excluded. Patients undergoing debulking procedures and those undergoing R2 resections were excluded in an attempt to limit our study to that of the impact of radiotherapy on tumors for which gross total resection was possible. We elected to do this as we felt that there would be essentially little room for debate of the merits of radiation in patients left with gross evidence of residual local disease following resection.

Variable coding

Overall survival was defined as the time from diagnosis to death due to any cause. Surgery type was coded based on the extent of the surgery performed and was categorized as simple resection/enucleation or radical resection, as specified by the NCDB within the "surgery of the primary site" variable. This variable contains discrete codes for tumor destruction, local excision, tumor enucleation, radical resection, and debulking operations. Simple resections and enucleations were grouped together as these represented surgeries not requiring resection of an adjacent organ, while radical resections involved *en bloc* removal of one or more adjacent organs.

Patient age was categorized as < 50 years, 50–70 years, and >70 years. Tumor size was stratified into three categories: small (<5 cm), intermediate (5–10 cm), and large (>10 cm). Facilities were grouped into volume quartiles using the total number of cases performed at a center in the study period.

Statistical analyses

Univariate comparisons of demographic and pre-treatment clinical characteristics were made using Chi-squared and student's *t*-test where appropriate. Multivariable logistic regression was performed to identify factors associated with receipt of either neoadjuvant or adjuvant radiotherapy and with margin-negative resection. Cox proportional hazards analysis was then performed separately for each tumor size category to measure the association between neoadjuvant and adjuvant radiotherapy on survival. In this Cox analysis, patients with large tumors demonstrated an association between radiation and survival. To better understand the relation between radiation and survival within this size cohort, we subsequently developed Cox proportional hazards models for patients with large (>10 cm) tumors with the cohort further stratified by histologic grade. Variables included in our multivariable models were selected *a priori* as those thought most likely to be determinates of clinical outcome. All statistical analyses were performed in R v3.6.0 (The R Foundation for Statistical Computing). Confidence intervals (CI) are reported to a 95% significance level. All tests were two-sided, and a p value < 0.05 was considered significant. This project was reviewed and approved by the Stritch School of Medicine Institutional Review Board.

Results

Univariate comparison of demographic and pathologic characteristics by tumor size

8,531 patients underwent surgical resection of primary retroperitoneal liposarcoma between 2004 and 2016. 1,674 (19.6%) of these had some missing data and were excluded for this reason. Other reasons for exclusion included those mentioned in the methods section above. 4,018 patients met all inclusion criteria. 251 (6.2%) of these had small (<5 cm) tumors, 574 (14.2%) had intermediate (5–10 cm) tumors, and 3,193 (79.5%) had large (>10 cm) tumors. 279 (6.9%) underwent neoadjuvant radiotherapy, 699 (17.3%) received adjuvant radiotherapy, and 3,040 (75.7%) were not treated with any radiotherapy. Baseline demographic, histopathological, and treatment characteristics for our patient population are shown in Table 1. Approximately half of tumors across all size categories were well-differentiated. Patients presenting with large tumors were more likely to be treated in high volume centers, require radical resection, have positive histologic margins on final pathology, and be treated with radiation. On univariate comparison, use of radiation appeared evenly distributed across histologic grade categories with approximately half of patients receiving neoadjuvant radiotherapy having "high grade" (poorly differentiated or undifferentiated) histology (136/279 = 49%) and approximately half of patients receiving adjuvant radiotherapy (366/699 = 52%) having high grade histology. We had a relatively small number of patients in this series treated with neoadjuvant therapy. This was particularly true in the small size subgroups. 37 patients with small or moderate-sized tumors received radiation prior to resection. 242 patients with large tumors were treated with neoadjuvant therapy. Of those 242, 119, again approximately half (49.2%), had high grade histology.

Multivariable regression identifying factors associated with the use of radiotherapy

We performed stepwise multivariable logistic analyses attempting to identify factors associated with the use of either neoadjuvant or adjuvant radiotherapy. Our final models adjusted for age, sex, insurance status, Charlson-Deyo comorbidity index (CCI), patient income quartile, facility treatment volume, tumor grade and size, and surgical margins. Factors associated with the use of radiotherapy in the neoadjuvant setting were higher facility case volume (>75%ile OR 3.45, CI [2.01, 6.09]) and advanced histologic grade (undifferentiated OR 1.66, CI [1.17, 2.33]).

Table 1
Baseline patient demographic and histopathologic characteristics.

	<5 cm	5–10 cm	>10 cm	p
n	251	574	3193	
Age (%)				0.835
<50 years old	31 (12.4)	86 (15.0)	445 (13.9)	
50–70 years old	146 (58.2)	314 (54.7)	1765 (55.3)	
>70 years old	74 (29.5)	174 (30.3)	983 (30.8)	
Sex = F (%)	86 (34.3)	219 (38.2)	1389 (43.5)	0.002
Race (%)				0.511
White	221 (88.0)	513 (89.4)	2804 (87.8)	
Black	12 (4.8)	36 (6.3)	200 (6.3)	
Other	15 (6.0)	18 (3.1)	156 (4.9)	
Unknown	3 (1.2)	7 (1.2)	33 (1.0)	
Insurance Status (%)				0.037
Private Insurance	112 (44.6)	289 (50.3)	1469 (46.0)	
No Insurance	6 (2.4)	9 (1.6)	75 (2.3)	
Medicaid	8 (3.2)	14 (2.4)	167 (5.2)	
Medicare	116 (46.2)	253 (44.1)	1395 (43.7)	
Other government	3 (1.2)	3 (0.5)	47 (1.5)	
Unknown	6 (2.4)	6 (1.0)	40 (1.3)	
Facility Type (%)				0.002
Community Program	16 (6.4)	35 (6.1)	126 (3.9)	
Comprehensive Community Program	74 (29.5)	171 (29.8)	812 (25.4)	
Academic/Research Program	136 (54.2)	294 (51.2)	1906 (59.7)	
Integrated Network Program	25 (10.0)	74 (12.9)	349 (10.9)	
Facility Location (%)				0.754
New England	16 (6.4)	35 (6.1)	155 (4.9)	
Middle Atlantic	44 (17.5)	95 (16.6)	636 (19.9)	
South Atlantic	45 (17.9)	107 (18.6)	606 (19.0)	
East North Central	48 (19.1)	97 (16.9)	531 (16.6)	
East South Central	16 (6.4)	37 (6.4)	171 (5.4)	
West North Central	17 (6.8)	50 (8.7)	281 (8.8)	
West South Central	14 (5.6)	30 (5.2)	193 (6.0)	
Mountain	17 (6.8)	32 (5.6)	165 (5.2)	
Pacific	34 (13.5)	91 (15.9)	455 (14.2)	
Income Quartile (%)				0.096
<25%	38 (15.1)	84 (14.6)	444 (13.9)	
25–50%	42 (16.7)	129 (22.5)	647 (20.3)	
50–75%	55 (21.9)	112 (19.5)	786 (24.6)	
>75%	116 (46.2)	249 (43.4)	1316 (41.2)	
Charlson-Deyo Comorbidity Index (%)				0.732
0	195 (77.7)	443 (77.2)	2383 (74.6)	
1	43 (17.1)	97 (16.9)	603 (18.9)	
2	8 (3.2)	23 (4.0)	150 (4.7)	
3+	5 (2.0)	11 (1.9)	57 (1.8)	
Hospital Volume (%)				0.004
<25% (≤ 21 cases)	63 (25.1)	158 (27.5)	662 (20.7)	
25–50% (22–43 cases)	55 (21.9)	136 (23.7)	717 (22.5)	
50–75% (44–103 cases)	67 (26.7)	137 (23.9)	837 (26.2)	
>75% (>103 cases)	66 (26.3)	143 (24.9)	977 (30.6)	
Surgery Type = Radical Resection (%)	31 (12.4)	67 (11.7)	927 (29.0)	<0.001
Surgical Margins (%)				<0.001
R0	167 (66.5)	355 (61.8)	1691 (53.0)	
Positive, NOS	25 (10.0)	67 (11.7)	439 (13.7)	
R1	43 (17.1)	135 (23.5)	877 (27.5)	
Unable to evaluate	16 (6.4)	17 (3.0)	186 (5.8)	
Grade (%)				0.555
Well-differentiated	133 (53.0)	297 (51.7)	1614 (50.5)	
Moderately differentiated	30 (12.0)	55 (9.6)	317 (9.9)	
Poorly differentiated	59 (23.5)	134 (23.3)	825 (25.8)	
Undifferentiated/anaplastic	29 (11.6)	88 (15.3)	437 (13.7)	
Clinical Stage (%)				<0.001
1	160 (63.7)	311 (54.2)	1587 (49.7)	
2	65 (25.9)	74 (12.9)	439 (13.7)	
3	26 (10.4)	189 (32.9)	1167 (36.5)	
Radiotherapy Sequence (%)				<0.001
No RT	195 (77.7)	388 (67.6)	2457 (76.9)	
Pre-op RT	10 (4.0)	27 (4.7)	242 (7.6)	
Post-op RT	46 (18.3)	159 (27.7)	494 (15.5)	

Factors associated with use of adjuvant radiotherapy were advanced patient age (>70 years old OR 0.71, CI [0.51, 1.00]), higher facility case volume (>75%ile OR 0.34, CI [0.24, 0.48]), positive resection margins (R1 OR 1.94, CI [1.58, 2.37]), advanced histologic grade (undifferentiated OR 2.31, CI [1.76, 3.01]), and larger tumor size (5–10 cm OR 1.68, CI [1.14, 2.51]).

Multivariable regression identifying factors associated with margin negative resection

Multivariable logistic regression was used to identify factors associated with achieving a margin-negative resection (Table 2). Our final model adjusted for age, sex, insurance status, CCI, surgery type, facility treatment volume, tumor size, grade, and receipt of neoadjuvant radiotherapy. In our final model, factors associated with lower adjusted odds of achieving a margin negative resection included older age, comorbid disease, advanced histologic grade, and larger tumor size. Treatment with neoadjuvant radiation was not associated with margin status.

Cox modeling predicting factors associated with overall survival

Cox proportional hazard modeling was performed on subgroups stratified by tumor size to identify factors associated with overall survival (Table 3). In general, patient age, comorbid disease state, and insurance type were associated with overall survival across tumor size categories. Margin negative resection was likewise associated with improved survival across tumor size categories, and increasing histologic grade associated with increased risk of death across tumor size categories. In the analyses stratified by size, radiotherapy treatment was associated with improved survival when given in the adjuvant setting to patients presenting with large (>10 cm) tumors only. This association was independent of histologic grade and resection margin status. There was no association of adjuvant radiation with overall survival in patients presenting with small or intermediate sized tumors. Neoadjuvant radiotherapy was not associated with survival. Insurance status was associated with overall survival in select subgroups, with patients with intermediate-sized tumors with “other government” insurance (e.g. Indian Health, VA patients at a non-VA facility) and patients with large tumors with Medicaid having increased risk-adjusted odds of death.

To better understand the potential for radiation to impact survival in the large-sized tumors, we also performed Cox proportional hazards modeling on patients with large tumors stratified by grade (Table 4). In this analysis, adjuvant radiotherapy was associated with survival only for patients with poorly differentiated or undifferentiated tumor grade. Neoadjuvant radiotherapy was not associated with overall survival in this analysis.

Discussion

In this study, we used the National Cancer Database to better define the role of radiation in the treatment of retroperitoneal

Table 2
Multivariable logistic regression predicting odds of margin-negative surgical resection.

	OR	Lower	Higher	p
Age (ref = < 50 years old)				
50–70 years old	0.85	0.70	1.04	0.11
>70 years old	0.79	0.62	1.00	0.05
Sex (ref = male)	1.01	0.89	1.15	0.86
Race (ref = White)				
Black	1.06	0.81	1.38	0.67
Other	1.04	0.78	1.41	0.77
Unknown	1.08	0.59	2.00	0.80
Insurance status (ref = private)				
No insurance	0.93	0.60	1.43	0.72
Medicaid	0.81	0.60	1.10	0.17
Medicare	0.89	0.76	1.04	0.15
Other government	0.84	0.48	1.46	0.54
Unknown	1.15	0.66	2.05	0.62
Charslon Deyo Comorbidity Score (ref = 0)				
1	0.92	0.78	1.08	0.32
2	0.71	0.52	0.96	0.03
3+	0.89	0.56	1.41	0.62
Hospital Volume (ref = < 25%ile)				
25–50% (22–43 cases)	0.98	0.80	1.19	0.82
50–75% (44–103 cases)	0.99	0.80	1.24	0.95
>75% (>103 cases)	1.16	0.91	1.47	0.25
Income Quartile (ref = < 25%)				
25–50%	1.19	0.96	1.49	0.11
50–75%	1.04	0.84	1.29	0.70
>75%	1.06	0.87	1.29	0.53
Facility Type (ref = community cancer)				
Comprehensive community cancer	1.06	0.76	1.49	0.71
Academic/research	1.14	0.79	1.64	0.47
Integrated network cancer program	0.85	0.59	1.23	0.38
Grade (ref = Well differentiated)				
Moderately differentiated	0.80	0.65	1.00	0.05
Poorly differentiated	0.81	0.70	0.94	0.01
Undifferentiated	0.82	0.68	0.99	0.04
Tumor Size (ref = < 5 cm)				
5–10 cm	0.83	0.60	1.12	0.22
>10 cm	0.56	0.43	0.73	0.00
Surgery Type (ref = simple resection/enucleation)	0.96	0.83	1.12	0.64
Neoadjuvant Radiotherapy Treatment (ref = no RT)	1.17	0.91	1.50	0.23

Table 3
Risk-adjusted odds of death from any cause from Cox proportional hazards model predicting overall survival (OS) on the patient cohort stratified by size. Lower and Higher represent the lower and upper bounds of the 95% confidence interval, respectively.

	Small (<5 cm), n = 265				Intermediate (5–10 cm), n = 594				Large (>10 cm), n = 3341			
	HR	Lower	Higher	p	HR	Lower	Higher	p	HR	Lower	Higher	p
Age (ref = < 50 years old)												
50–70 years old	3.18	0.95	10.62	0.06	1.64	0.87	3.08	0.13	1.38	1.09	1.75	0.01
>70 years old	7.19	1.95	26.46	0.00	3.56	1.78	7.10	0.00	2.70	2.07	3.54	0.00
Sex (ref = male)	0.94	0.54	1.65	0.83	0.77	0.56	1.07	0.12	0.85	0.75	0.97	0.01
Race (ref = White)												
Black	0.62	0.12	3.18	0.57	0.44	0.20	0.97	0.04	1.09	0.86	1.39	0.48
Other	0.29	0.04	2.27	0.24	0.57	0.20	1.67	0.31	0.95	0.70	1.30	0.75
Unknown	10.22	1.59	65.82	0.01	0.78	0.10	6.09	0.82	1.80	1.07	3.05	0.03
Insurance status (ref = private)												
No insurance	1.03	0.14	7.52	0.98	2.74	0.92	8.20	0.07	1.47	0.96	2.24	0.07
Medicaid	0.64	0.08	5.41	0.68	1.69	0.63	4.57	0.30	1.50	1.12	2.01	0.01
Medicare	0.89	0.48	1.65	0.71	1.30	0.87	1.94	0.20	1.16	0.98	1.36	0.08
Other government	0.80	0.08	7.98	0.85	8.51	1.04	69.50	0.05	1.46	0.89	2.40	0.13
Unknown	0.81	0.09	7.04	0.85	0.66	0.16	2.80	0.57	1.58	0.96	2.60	0.07
Charslon Deyo Comorbidity Score (ref = 0)												
1	0.91	0.45	1.84	0.79	1.05	0.70	1.58	0.81	1.18	1.01	1.37	0.03
2	4.58	1.44	14.57	0.01	1.51	0.79	2.89	0.21	1.46	1.12	1.88	0.00
3+	22.90	6.67	78.55	0.00	3.01	1.33	6.84	0.01	1.96	1.30	2.97	0.00
Hospital Volume (ref = < 25%ile)												
25–50% (22–43 cases)	0.56	0.24	1.31	0.18	0.60	0.38	0.95	0.03	0.85	0.70	1.02	0.08
50–75% (44–103 cases)	0.62	0.26	1.48	0.28	0.66	0.37	1.15	0.14	0.90	0.73	1.11	0.33
>75% (>103 cases)	0.72	0.28	1.87	0.50	0.37	0.20	0.71	0.00	0.80	0.63	1.01	0.06
Income Quartile (ref = < 25%)												
25–50%	0.58	0.22	1.54	0.27	0.95	0.59	1.54	0.83	0.86	0.71	1.05	0.15
50–75%	0.64	0.26	1.57	0.33	0.76	0.46	1.26	0.29	0.78	0.64	0.95	0.01
>75%	0.82	0.36	1.85	0.63	0.66	0.43	1.01	0.05	0.76	0.63	0.92	0.00
Facility Type (ref = community cancer)												
Comprehensive community cancer	0.52	0.17	1.54	0.23	1.26	0.69	2.28	0.46	1.16	0.84	1.60	0.35
Academic/research	0.85	0.26	2.78	0.78	1.79	0.83	3.86	0.14	1.13	0.80	1.60	0.48
Integrated network cancer program	0.74	0.20	2.76	0.65	0.74	0.36	1.50	0.40	0.98	0.68	1.40	0.90
Surgical Margins (ref = R0)												
Margins positive, but unspecified	2.03	0.89	4.65	0.09	1.59	0.99	2.54	0.06	1.58	1.32	1.88	0.00
R1	2.29	1.17	4.47	0.02	1.53	1.06	2.20	0.02	1.29	1.12	1.50	0.00
R2	5.65	1.34	23.74	0.02	0.75	0.22	2.51	0.64	2.64	1.96	3.55	0.00
Unable to evaluate	1.30	0.45	3.76	0.63	1.50	0.65	3.45	0.34	1.38	1.08	1.76	0.01
Grade (ref = Well differentiated)												
Moderately differentiated	3.70	1.62	8.44	0.00	1.12	0.61	2.08	0.71	1.58	1.25	1.98	0.00
Poorly differentiated	3.84	1.99	7.39	0.00	2.76	1.89	4.03	0.00	3.06	2.64	3.55	0.00
Undifferentiated	1.59	0.64	3.96	0.32	2.40	1.58	3.66	0.00	2.75	2.32	3.26	0.00
Radiotherapy Sequence (ref = no RT)												
Pre-op RT	1.63	0.56	4.79	0.37	1.08	0.51	2.32	0.84	0.94	0.73	1.20	0.61
Post-op RT	0.53	0.25	1.12	0.10	1.11	0.78	1.58	0.55	0.76	0.64	0.90	0.00
Surgery Type (ref = simple resection/enucleation)												
Radical Resection	1.96	0.89	4.30	0.10	1.66	1.04	2.65	0.04	1.12	0.98	1.28	0.11

liposarcoma. Patients were stratified by tumor size in order to further differentiate which patients might most benefit from radiation treatment. We identified a significant survival benefit for margin-negative resection across all tumor sizes. We also found a survival benefit with radiotherapy in patients with large tumors (>10 cm) only when given in the adjuvant setting. This association was independent of histologic grade and margin. Additional modeling stratified by histologic grade within the large-tumor subgroup indicated that patients with large tumors of poorly differentiated or undifferentiated histology are more likely to benefit from adjuvant radiation. We found no association between neoadjuvant radiotherapy and survival for any tumor size. We did also find an association between insurance type and survival for some subgroups. Although this association was not consistent across groups, we believe this reflects the better access to care and social support among privately insured patients.

These findings have important implications for the peri-operative management of patients presenting with lipomatous masses in the retroperitoneum suggesting that radiation should play a limited role in the treatment of patients with tumors less than 10 cm in size. The findings also suggest that use of radiation in the neoadjuvant setting may not be associated with any improvement in survival and use of this therapy should be considered carefully given recognized toxicities associated with radiation therapy.

Although two recent single-institution studies have identified an association between use of radiation and recurrence free survival,[7,8] prior retrospective analyses have, in general, failed to reach a consensus regarding the use of radiotherapy with individual studies presenting conflicting results regarding the benefits in either local control or overall survival. One study of 425 patients from the United States Sarcoma Collaborative identified no association between radiotherapy and either recurrence rates or survival.[9] A slightly larger analysis of 607 patients from the Transatlantic Retroperitoneal Sarcoma Working Group found an improvement to local control from radiotherapy on univariate analysis, but the association was not significant after adjusting for margin status and tumor size and grade.[10] While these studies do adjust for histology in their multivariable models, the analyses are not stratified by size, and the inclusion of multiple histologic subtypes limits the applicability of the results and also limits the ability to measure the value of radiation in liposarcoma specifically. One

Table 4
Risk-adjusted odds of death from any cause from Cox proportional hazards model predicting overall survival (OS) on patients with large (>10 cm) stratified by grade. Lower and Higher represent the lower and upper bounds of the 95% confidence interval, respectively.

	Well differentiated, n = 1614				Moderately differentiated, n = 317				Poorly or undifferentiated, n = 1262			
	HR	Lower	Higher	p	HR	Lower	Higher	p	HR	Lower	Higher	p
Age (ref = < 50 years old)												
50–70 years old	2.28	1.40	3.70	0.00	1.41	0.68	2.93	0.35	1.08	0.79	1.47	0.65
>70 years old	5.11	3.01	8.68	0.00	3.43	1.34	8.75	0.01	1.92	1.34	2.76	0.00
Sex (ref = male)	0.90	0.72	1.11	0.33	0.80	0.48	1.32	0.38	0.91	0.77	1.08	0.27
Race (ref = White)												
Black	0.94	0.62	1.43	0.78	0.62	0.24	1.59	0.32	1.33	0.75	2.38	0.33
Other	1.25	0.77	2.02	0.36	0.62	0.13	2.86	0.54	0.81	0.51	1.28	0.37
Unknown	1.46	0.69	3.06	0.32	0.00	0.00	Inf	1.00	3.53	1.41	8.81	0.01
Insurance status (ref = private)												
No insurance	1.20	0.49	2.96	0.69	2.47	0.82	7.43	0.11	1.33	0.75	2.38	0.33
Medicaid	1.17	0.64	2.13	0.61	1.17	0.47	2.91	0.74	1.56	1.04	2.33	0.03
Medicare	1.22	0.92	1.62	0.16	1.30	0.70	2.41	0.40	1.17	0.93	1.46	0.19
Other government	0.75	0.23	2.38	0.62	0.39	0.04	3.47	0.401	2.30	1.29	4.12	0.00
Unknown	3.46	1.80	6.68	0.00	0.00	0.00	Inf	1.00	1.10	0.48	2.54	0.83
Charslon Deyo Comorbidity Score (ref = 0)												
1	1.25	0.96	1.63	0.10	1.21	0.69	2.11	0.51	1.16	0.95	1.42	0.15
2	1.89	1.26	2.84	0.00	2.49	0.80	7.70	0.11	1.15	0.78	1.69	0.49
3+	2.70	1.48	4.95	0.00	2.80	0.22	34.90	0.42	1.52	0.78	2.96	0.22
Hospital Volume (ref = < 25%ile)												
25–50% (22–43 cases)	0.88	0.63	1.22	0.43	0.65	0.29	1.48	0.30	0.85	0.66	1.11	0.23
50–75% (44–103 cases)	0.92	0.64	1.31	0.63	1.37	0.56	3.34	0.49	0.85	0.64	1.15	0.29
>75% (>103 cases)	0.75	0.50	1.12	0.16	0.58	0.19	1.71	0.32	0.83	0.59	1.15	0.25
Income Quartile (ref = < 25%)												
25–50%	0.84	0.60	1.18	0.31	0.54	0.26	1.13	0.10	0.99	0.74	1.33	0.97
50–75%	0.62	0.44	0.88	0.01	0.34	0.16	0.72	0.00	0.99	0.75	1.32	0.96
>75%	0.70	0.51	0.96	0.03	0.42	0.22	0.81	0.01	0.90	0.69	1.17	0.43
Facility Type (ref = community cancer)												
Comprehensive community cancer	1.24	0.74	2.09	0.42	0.89	0.32	2.49	0.83	1.31	0.80	2.15	0.29
Academic/research	1.19	0.67	2.10	0.56	0.94	0.29	3.04	0.91	1.33	0.78	2.27	0.30
Integrated network cancer program	0.88	0.48	1.60	0.67	0.21	0.06	0.79	0.02	1.32	0.76	2.28	0.32
Surgical Margins (ref = R0)												
Margins positive, but unspecified	1.93	1.43	2.62	0.00	2.93	1.54	5.55	0.00	1.40	1.10	1.77	0.01
R1	1.41	1.10	1.82	0.01	1.27	0.72	2.26	0.41	1.26	1.04	1.53	0.02
Unable to evaluate	1.42	0.95	2.12	0.09	4.09	1.62	10.35	0.00	1.24	0.89	1.72	0.21
Radiotherapy Sequence (ref = no RT)												
Pre-op RT	1.09	0.70	1.68	0.71	0.86	0.31	2.37	0.77	0.76	0.54	1.07	0.11
Post-op RT	0.87	0.62	1.20	0.39	1.16	0.63	2.16	0.63	0.73	0.59	0.90	0.00
Surgery Type (ref = simple resection/enucleation)												
Radical Resection	1.36	1.06	1.74	0.02	1.38	0.82	2.32	0.22	1.01	0.84	1.20	0.95

randomized trial has recently published its results on the use of radiotherapy in retroperitoneal sarcoma.[6] This is an international study of 266 patients randomized to neoadjuvant radiotherapy vs resection alone. In this study, 198 patients (75%) had liposarcoma. For these patients, neoadjuvant radiotherapy was associated with improvements to abdominal recurrence-free survival but not metastasis-free survival. There have been two prior studies on retroperitoneal sarcoma using the National Cancer Database.[4,5] Both prior studies include various tumor histologies in their analysis. The largest study to date by Nussbaum et al. identified an overall survival benefit from either adjuvant or neoadjuvant radiotherapy,[4] while a smaller, more recent analysis by Leiting et al. identified a survival benefit only for the subsets of tumors that were high grade, leiomyosarcomas, or smaller than 15 cm.[5]

In contrast to these prior studies, our analysis focuses on retroperitoneal liposarcoma. These tumors are generally easily distinguished from non-lipomatous histologies on pre-treatment imaging. Liposarcomas are more often low grade than non-lipomatous sarcoma and may have a more limited potential to benefit from radiation. Our analysis is initially stratified by tumor size and then further stratified by tumor grade in an effort to further improve the applicability of our results. We identify an association between radiotherapy given after resection and overall survival for tumors >10 cm. We find no benefit below that size threshold. The association between adjuvant radiation and survival appeared to be independent of histologic grade and resection margin status in our multivariable analysis. When the large cohort of tumors was further stratified by grade, however, only those that had poorly differentiated or undifferentiated histology seemed to benefit from adjuvant radiation therapy.

We were surprised by the lack of association between neoadjuvant therapy and survival in the large tumors. We also recognize an apparent discrepancy between the findings of our initial Cox model and the subsequent modeling of survival in the large tumors stratified by size: one model identifies an association between adjuvant radiation and survival in large tumors independent of grade, and one identifies an advantage only in high grade large tumors. We suspect the lack of association between neoadjuvant therapy and survival and the discrepancy in the Cox models is related to limitations in the power provided by the sample size. Our study included 119 patients with large, high-grade tumors treated with neoadjuvant radiation. We would expect that to be a large enough sample to detect an existent benefit to radiation, but it simply may not be. We had more significant limitations in sample sizes for small tumors treated with neoadjuvant radiation. Such limitations likely affect our ability to detect a benefit to neoadjuvant therapy when studied in the subgroup analyses. In our current practice we are definite proponents of neoadjuvant radiation and use it uniformly in patients that have large, high grade retroperitoneal liposarcomas and in moderately sized tumors for which we anticipate difficulty clearing surgical margins. We believe that this approach facilitates disease targeting, as it is easier to use stereotactic methods (stereotactic external beam, intensity modulated, or 3D conformal radiotherapy) to direct radiation when the tumor is *in situ* and can be visualized on imaging.

Our analysis has several additional limitations. It is a retrospective review of a large dataset and is thus subject to selection bias and omitted variable bias. Many relevant aspects of treatment, such as type of radiation, nature and severity of surgical complication, and measures of quality of life/functional health, are not captured in a standard fashion and are thus difficult if not impossible to include in our risk models. These limitations may bias our models in ways that are difficult to predict, potentially calling into question the reliability of our results. The National Cancer Database does not track disease recurrence, and we were consequently unable to make inferences on the impact of radiation on disease-specific survival. This limitation makes assessing the true value of radiation therapy in these patients difficult. We expect that the association between adjuvant radiation and survival we observe in large, high grade tumors reflects the fact that the radiation is sterilizing the tumor bed, preventing recurrence and ultimately metastasis from that recurrent disease. There is no way to investigate this hypothesis with the current dataset given the lack of information or disease recurrence.

Conclusion

Despite stated limitations, our analyses demonstrate a survival benefit from treatment with adjuvant radiotherapy for patients with retroperitoneal liposarcomas larger than 10 cm, particularly of poorly differentiated or undifferentiated grade. A survival benefit was also shown for patients receiving margin-negative resection across all tumor sizes. These findings suggest that adjuvant radiation should be used in the setting of large retroperitoneal liposarcoma >10 cm of poorly differentiated grade, but that radiation should be used sparingly in patients undergoing treatment for smaller, more well-differentiated tumors.

Supplemental Table I
International Classification of Diseases for Oncology, 3rd edition (ICD-*O*-3) codes for topography (A) and histology (B) that were used to identify the study population. NOS = not otherwise specified.

A		B	
Code	**Location**	**Code**	**Histology**
C480	retroperitoneum	8850	liposarcoma, NOS
		8851	liposarcoma, well differentiated
C494	connective, subcutaneous and other soft tissues of abdomen	8852	myxoid liposarcoma
		8853	round cell liposarcoma
		8854	pleomorphic liposarcoma
C496	connective, subcutaneous and other soft tissues of trunk, NOS	8855	mixed type liposarcoma
		8857	fibroblastic liposarcoma
		8858	dedifferentiated liposarcoma

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