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Original Research Article

The importance of the margin of resection and external radiation in non-lipomatous retroperitoneal sarcoma

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ABSTRACT

Background: Prior studies evaluating the impact of adjuvant or neoadjuvant radiation on clinical outcomes of patients with non-lipomatous retroperitoneal sarcoma have been underpowered.
Methods: We queried the National Cancer Database to identify patients undergoing surgical resection of retroperitoneal sarcoma with non-lipomatous histology from 2004 to 2016. Multivariable logistic regression and Cox proportional hazards modelling with patients stratified by tumor size were used to identify factors associated with overall survival.
Results: 3,394 patients met inclusion criteria. 592 had small (<5 cm), 1,186 had intermediate (5–10 cm), and 1,616 had large (>10 cm) tumors. Use of either neoadjuvant or adjuvant radiotherapy was associated with improved survival for patients with intermediate (neoadjuvant HR 0.67, CI [0.46, 0.98]; adjuvant HR 0.61, CI [0.50, 0.76]) and large (neoadjuvant HR 0.50, CI [0.37, 0.68]; adjuvant HR 0.56, CI [0.47, 0.69]) tumors, while adjuvant radiation therapy was associated with a survival benefit for small-sized tumors (HR 0.67, CI [0.46, 0.99]).
Conclusions: Radiation therapy is associated with an overall survival benefit in patients presenting undergoing resection of non-lipomatous retroperitoneal sarcoma.

Introduction

Retroperitoneal sarcomas frequently present late in the course of disease and commonly abut or involve vital organs and adjacent neurovascular structures. For such reasons, achieving a complete resection with negative histologic margins may be technically challenging and carry risk of significant morbidity.[1] External beam radiation has been an important adjunct to surgery. Given in the adjuvant, neoadjuvant, or intraoperative settings, radiotherapy has been used as a method to manage microscopic residual tumor and improve rates of tumor clearance.[2,3]

Most of the studies on the efficacy of radiotherapy in retroperitoneal sarcoma are underpowered retrospective evaluations of single-institutional series. These generally evaluate populations with heterogeneous histologic subtypes and grades. The majority of tumors included in these series are liposarcomas, many of which are low grade and carry limited potential for aggressive behavior. The results of the studies are mixed with some identifying an association between radiotherapy and survival and others finding no association between radiotherapy and survival or disease recurrence.[4–8]

In the current work, we attempt to better define the role of radiation in the treatment of retroperitoneal sarcoma. We used the National Cancer Database to compare survival profiles for patients with non-lipomatous sarcoma undergoing surgical resection with and without adjuvant or neoadjuvant radiation therapy.

Methods

Data source and patient selection

The National Cancer Database is a national clinical oncology database administered jointly by the American Cancer Society and the American College of Surgeons. The database currently captures

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an estimated 70% of cancers diagnosed annually in the United States from approximately 1,500 hospitals accredited by the Commission on Cancer.

We queried the National Cancer Database for records of patients undergoing surgical resection of primary retroperitoneal sarcoma between 2004 and 2016. Patients with non-lipomatous retroperitoneal sarcoma were identified by cross-referencing patients with retroperitoneal tumors as identified by International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topography codes for the retroperitoneumum with those having ICD-O-3 histology codes for non-lipomatous sarcomas (Table 1).

Patients that were less than 18 years of age, those with metastatic disease, those who received intra-operative radiation or both neoadjuvant and adjuvant radiation, underwent tumor debulking as opposed to complete resection or had a delayed presentation to the operating room after diagnosis (>30 weeks), as well as those with unknown values for variables included in our models were excluded from the study population.

Variable coding

Overall survival was defined as the time from diagnosis to death (due to any cause). The extent of tumor resection was coded as simple resection/enucleation, radical resection, or debulking surgery based on NCDB codes for surgery of the primary site. Simple resection and enucleation were grouped together as these represented operations not requiring resection of an adjacent organ, while radical resections involved *en bloc* removal of one or more adjacent organs. Debulking surgeries were excluded in an attempt to limit our study to the impact of radiotherapy on tumors for which complete surgical resection was possible. Patient age was categorized as < 50 years, 50–70 years, and >70 years. Tumor size was stratified into three categories for analysis: small (<5 cm), intermediate (5–10 cm), and large (>10 cm). Surgical volume was categorized by the total number of operations performed at that center in the study period and dividing all centers into quartiles by total number of cases.

Statistical analyses

Univariate comparisons of demographic and pre-treatment clinical characteristics were made using Chi-squared and student's t-tests where appropriate. Multivariable logistic regression was performed to identify factors associated with receipt of either neoadjuvant or adjuvant radiotherapy and with negative surgical margins. Cox proportional hazards analysis was then performed separately for each tumor size category to determine the effect of neoadjuvant or adjuvant radiotherapy on survival. 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 using a p value < 0.05. This project was approved by the Stritch School of Medicine Institutional Review Board.

Results

Univariate comparison of demographic and pathologic characteristics by tumor size

11,583 patients underwent surgical resection of primary retroperitoneal sarcoma between 2004 and 2016. After excluding patients with lipomatous histology and missing data, we were left with 3,394 patients meeting all inclusion criteria. 592 (17.4%) patients had small (<5 cm) tumors, 1,186 (34.9%) had intermediate (5–10 cm) tumors, and 1,616 (47.6%) had large (>10 cm) tumors. 284 (8.4%) underwent neoadjuvant radiotherapy, 923 (27.2%) received adjuvant radiotherapy, and 2,187 (64.4%) were not treated with any radiotherapy. Baseline demographic, histopathological, and treatment characteristics for our patient population are shown in Table 2. Those with small tumors were statistically more likely to have well-differentiated pathology than those with large tumors. Those with small tumors were also statistically more likely to reside in a zip code with a higher national income quartile. Patients with large tumors were more likely to undergo radical resection and have positive histologic margin on final pathology.

Table 1
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	8800	sarcoma, NOS
		8801	spindle cell sarcoma
		8803	giant cell sarcoma
		8804	epithelioid sarcoma
		8805	undifferentiated sarcoma
		8810	fibrosarcoma, NOS
		8811	fibromyxosarcoma
C494	connective, subcutaneous and other soft tissues of abdomen	8813	fascial fibrosarcoma
		8825	myofibroblastic sarcoma
		8840	myxosarcoma
		8890	leiomyosarcoma, NOS
		8891	epithelioid leiomyosarcoma
		8896	myxoid leiomyosarcoma
		8900	rhabdomyosarcoma, NOS
C496	connective, subcutaneous and other soft tissues of trunk, NOS	8901	pleomorphic rhabdomyosarcoma
		8902	mixed type rhabdomyosarcoma
		8910	embryonal rhabdomyosarcoma
		8912	spindle cell rhabdomyosarcoma
		8920	alveolar rhabdomyosarcoma
		9120	hemangiosarcoma
		9540	malignant peripheral nerve sheath tumor

Table 2
Baseline patient demographic and histopathologic characteristics.

Characteristic	<5 cm	5–10 cm	>10 cm	p
n (%)	592 (17.4%)	1186 (34.9%)	1616 (47.6%)	
Age (%)				0.02
<50 years old	119 (20.1)	223 (18.8)	265 (16.4)	
50–70 years old	308 (52.0)	576 (48.6)	875 (54.1)	
>70 years old	165 (27.9)	387 (32.6)	476 (29.5)	
Sex = F (%)	332 (56.1)	749 (63.2)	931 (57.6)	0.003
Race (%)				0.08
White	510 (86.1)	986 (83.1)	1308 (80.9)	
Black	55 (9.3)	142 (12.0)	227 (14.0)	
Other	20 (3.4)	49 (4.1)	63 (3.9)	
Unknown	7 (1.2)	9 (0.8)	18 (1.1)	
Insurance Status (%)				0.66
Private Insurance	294 (49.7)	547 (46.1)	752 (46.5)	
No Insurance	19 (3.2)	38 (3.2)	48 (3.0)	
Medicaid	18 (3.0)	61 (5.1)	89 (5.5)	
Medicare	245 (41.4)	509 (42.9)	690 (42.7)	
Other government	7 (1.2)	15 (1.3)	19 (1.2)	
Unknown	9 (1.5)	16 (1.3)	18 (1.1)	
Facility Type (%)				0.037
Community Program	27 (4.6)	66 (5.6)	75 (4.6)	
Comprehensive Community Program	193 (32.6)	367 (30.9)	430 (26.6)	
Academic/Research Program	297 (50.2)	615 (51.9)	911 (56.4)	
Integrated Network Program	75 (12.7)	138 (11.6)	200 (12.4)	
Facility Location (%)				0.147
New England	27 (4.6)	43 (3.6)	67 (4.1)	
Middle Atlantic	84 (14.2)	221 (18.6)	244 (15.1)	
South Atlantic	130 (22.0)	251 (21.2)	380 (23.5)	
East North Central	114 (19.3)	213 (18.0)	273 (16.9)	
East South Central	43 (7.3)	86 (7.3)	102 (6.3)	
West North Central	63 (10.6)	108 (9.1)	153 (9.5)	
West South Central	25 (4.2)	72 (6.1)	111 (6.9)	
Mountain	25 (4.2)	62 (5.2)	85 (5.3)	
Pacific	81 (13.7)	130 (11.0)	201 (12.4)	
Income Quartile (%)				0.04
<25%	76 (13.0)	212 (18.2)	292 (18.4)	
25–50%	132 (22.6)	240 (20.5)	338 (21.3)	
50–75%	141 (24.1)	270 (23.1)	399 (25.2)	
>75%	236 (40.3)	446 (38.2)	556 (35.1)	
Charlson-Deyo Comorbidity Index (%)				0.82
0	459 (77.5)	912 (76.9)	1231 (76.2)	
1	104 (17.6)	209 (17.6)	279 (17.3)	
2	20 (3.4)	46 (3.9)	72 (4.5)	
3+	9 (1.5)	19 (1.6)	34 (2.1)	
Hospital Volume (%)				0.008
<25% ($\leq$ 21 cases)	168 (28.4)	303 (25.5)	365 (22.6)	
25–50% (22–43 cases)	155 (26.2)	282 (23.8)	415 (25.7)	
50–75% (44–103 cases)	113 (19.1)	290 (24.5)	426 (26.4)	
>75% (>103 cases)	156 (26.4)	311 (26.2)	410 (25.4)	
Histology (%)				<0.001
Leiomyosarcoma	334 (56.4)	749 (63.2)	977 (60.5)	
Sarcoma, NOS	96 (16.2)	228 (19.2)	361 (22.3)	
Fibrosarcoma	88 (14.9)	122 (10.3)	145 (9.0)	
Rhabdomyosarcoma	6 (1.0)	17 (1.4)	23 (1.4)	
Peripheral Nerve Sheath	11 (1.9)	27 (2.3)	37 (2.3)	
Other	57 (9.6)	43 (3.6)	73 (4.5)	
Surgery Type = Radical Resection (%)	13 (2.2)	137 (11.6)	272 (16.8)	<0.001
Surgical Margins (%)				<0.001
R0	465 (78.5)	871 (73.4)	1094 (67.7)	
Positive, NOS	35 (5.9)	96 (8.1)	153 (9.5)	
R1	67 (11.3)	165 (13.9)	242 (15.0)	
R2	8 (1.4)	16 (1.3)	52 (3.2)	
Unable to evaluate	17 (2.9)	38 (3.2)	75 (4.6)	
Grade (%)				<0.001
Well-differentiated	147 (24.8)	145 (12.2)	167 (10.3)	
Moderately differentiated	169 (28.5)	315 (26.6)	398 (24.6)	
Poorly differentiated	183 (30.9)	485 (40.9)	677 (41.9)	
Undifferentiated/anaplastic	93 (15.7)	241 (20.3)	374 (23.1)	
Clinical Stage (%)				<0.001
1	290 (49.0)	294 (24.8)	357 (22.1)	
2	286 (48.3)	330 (27.8)	430 (26.6)	
3	16 (2.7)	562 (47.4)	829 (51.3)	
Radiotherapy Sequence (%)				<0.001
No RT	423 (71.5)	702 (59.2)	1062 (65.7)	

(*continued on next page*)

Table 2 (*continued*)

Characteristic	<5 cm	5–10 cm	>10 cm	p
Pre-op RT	14 (2.4)	100 (8.4)	170 (10.5)	
Post-op RT	155 (26.2)	384 (32.4)	384 (23.8)	
Chemotherapy Treatment (%)				<0.001
No	523 (89.4)	980 (83.9)	1263 (79.7)	
Yes	44 (7.5)	158 (13.5)	263 (16.6)	
Unknown	18 (3.1)	30 (2.6)	59 (3.7)	

Multivariable regression identifying factors associated with the use of radiotherapy

We performed a stepwise multivariable logistic analysis to identify factors associated with the use of neoadjuvant and adjuvant radiation. Our final models adjusted for age, sex, race, insurance status, Charlson-Deyo comorbidity index (CCI), patient income quartile, facility treatment volume, surgical margins, tumor grade, size, and histology. Factors associated with the use of radiation in the neoadjuvant setting included facility case volume (>75%ile OR 3.43, CI [2.07, 5.78]), larger tumor size (>10 cm OR 5.28, CI [3.06, 9.93]), and having fibrosarcoma as the primary histology (OR 0.34, CI [0.17, 0.62]).

Factors associated with utilization of adjuvant radiation included age (>70 years old OR 0.72, CI [0.54, 0.97]), high facility case volume (>75%ile OR 0.51, CI [0.37, 0.69]), larger tumor size (>10 cm OR 0.78, CI [0.62, 0.99]), positive surgical margin (R1 OR 2.09, CI [1.68, 2.59]), advanced histologic grade (undifferentiated OR 2.63, CI [1.92, 3.64]), and having a fibrosarcomatous histology (OR 2.05, CI [1.58, 2.65]).

Multivariable regression identifying factors associated with margin negative resection

Multivariable logistic analysis stratified by size was used to identify factors associated with achieving a margin-negative

Table 3
Multivariable logistic regression predicting odds of margin-negative surgical resection.

	Small (<5 cm), n = 592				Intermediate (5–10 cm), n = 1,186				Large (>10 cm), n = 1,616			
	HR	Lower	Higher	p	HR	Lower	Higher	p	HR	Lower	Higher	p
Age (ref = < 50 years old)												
50–70 years old	1.34	0.75	2.35	0.31	1.05	0.71	1.53	0.82	1.14	0.83	1.56	0.42
>70 years old	2.00	0.94	4.29	0.07	0.72	0.44	1.18	0.20	0.94	0.62	1.42	0.76
Sex (ref = male)	0.77	0.49	1.20	0.25	1.01	0.75	1.35	0.95	1.01	0.80	1.26	0.96
Race (ref = White)												
Black	0.63	0.31	1.31	0.20	0.87	0.57	1.35	0.54	0.89	0.64	1.23	0.47
Other	1.92	0.58	8.80	0.33	0.57	0.31	1.10	0.09	0.74	0.43	1.29	0.28
Unknown	0.35	0.07	2.00	0.20	1.07	0.25	7.40	0.93	0.55	0.21	1.48	0.22
Insurance status (ref = private)												
No insurance	1.42	0.43	6.50	0.60	1.05	0.50	2.40	0.89	0.66	0.35	1.25	0.20
Medicaid	1.02	0.31	4.04	0.98	0.84	0.47	1.57	0.58	0.70	0.44	1.13	0.14
Medicare	0.72	0.41	1.25	0.24	1.13	0.78	1.64	0.51	1.09	0.81	1.46	0.58
Other government	0.58	0.11	4.48	0.55	1.89	0.48	12.58	0.42	0.45	0.17	1.23	0.11
Unknown	1.06	0.22	7.84	0.94	5.60	1.04	104.26	0.10	1.81	0.62	6.60	0.31
Charslon Deyo Comorbidity Score (ref = 0)												
1	0.84	0.49	1.47	0.53	1.07	0.75	1.55	0.71	0.98	0.73	1.31	0.88
2	0.36	0.13	1.01	0.04	0.57	0.30	1.11	0.09	0.71	0.43	1.19	0.18
3+	2.71	0.43	53.11	0.37	0.39	0.14	1.05	0.06	0.71	0.34	1.53	0.36
Hospital Volume (ref = < 25%ile)												
25–50% (22–43 cases)	0.98	0.54	1.78	0.94	1.32	0.90	1.95	0.16	1.26	0.90	1.75	0.18
50–75% (44–103 cases)	1.65	0.80	3.46	0.18	1.48	0.95	2.29	0.08	1.12	0.77	1.61	0.55
>75% (>103 cases)	2.77	1.24	6.19	0.01	2.77	1.64	4.72	0.00	1.47	0.97	2.23	0.07
Income Quartile (ref = < 25%)												
25–50%	1.15	0.54	2.43	0.71	1.16	0.75	1.81	0.50	1.11	0.79	1.58	0.55
50–75%	0.96	0.45	2.01	0.91	1.18	0.77	1.82	0.45	1.14	0.82	1.60	0.43
>75%	0.85	0.41	1.67	0.64	1.14	0.76	1.69	0.53	1.08	0.78	1.48	0.64
Facility Type (ref = community cancer)												
Comprehensive community cancer	2.32	0.82	6.25	0.10	1.12	0.61	2.03	0.70	0.59	0.33	1.03	0.07
Academic/research	1.02	0.33	3.02	0.97	1.00	0.51	1.95	0.99	0.87	0.47	1.59	0.65
Integrated network cancer program	1.28	0.42	3.77	0.66	1.09	0.54	2.16	0.82	0.87	0.46	1.63	0.68
Grade (ref = Well differentiated)												
Moderately differentiated	0.64	0.34	1.18	0.16	1.16	0.73	1.85	0.52	0.72	0.47	1.10	0.14
Poorly differentiated	0.43	0.23	0.78	0.01	0.93	0.60	1.43	0.74	0.68	0.45	1.00	0.06
Undifferentiated	0.37	0.17	0.76	0.01	0.87	0.53	1.41	0.57	0.58	0.38	0.89	0.01
Surgery Type (ref = simple resection/enucleation)	7.81	1.23	160.51	0.07	0.85	0.56	1.32	0.46	0.87	0.65	1.18	0.37
Histology (ref = Leiomyosarcoma)												
Sarcoma, NOS	2.06	1.10	4.09	0.03	1.18	0.82	1.71	0.37	0.76	0.58	1.01	0.06
Fibrosarcoma	1.43	0.79	2.71	0.26	1.48	0.91	2.47	0.12	0.98	0.66	1.48	0.93
Rhabdomyosarcoma	2.46	0.36	49.40	0.43	0.68	0.24	2.06	0.46	0.91	0.36	2.49	0.84
Peripheral Nerve Sheath	1.61	0.36	11.51	0.58	1.58	0.61	4.91	0.38	0.58	0.29	1.18	0.13
Other	2.12	0.97	5.07	0.07	1.83	0.85	4.43	0.14	1.12	0.66	1.97	0.69
Neoadjuvant Radiotherapy Treatment (ref = no RT)	3.00	0.52	57.28	0.31	0.87	0.53	1.48	0.60	1.66	1.13	2.49	0.01

Table 4
Risk-adjusted odds of death from any cause from Cox proportional hazards model predicting overall survival (OS). Lower and Higher represent the lower and upper bounds of the 95% confidence interval, respectively.

	Small (<5 cm), n = 592				Intermediate (5–10 cm), n = 1,186				Large (>10 cm), n = 1,616			
	HR	Lower	Higher	p	HR	Lower	Higher	p	HR	Lower	Higher	p
Age (ref = < 50 years old)												
50–70 years old	1.56	0.89	2.76	0.12	1.41	1.04	1.91	0.03	1.18	0.92	1.50	0.19
>70 years old	1.96	1.01	3.78	0.05	2.39	1.65	3.47	0.00	1.51	1.11	2.05	0.01
Sex (ref = male)	0.90	0.63	1.28	0.54	0.75	0.61	0.93	0.01	0.79	0.67	0.92	0.00
Race (ref = White)												
Black	0.90	0.45	1.80	0.77	1.06	0.76	1.49	0.73	0.72	0.56	0.92	0.01
Other	1.08	0.41	2.81	0.88	0.49	0.28	0.86	0.01	0.84	0.52	1.35	0.47
Unknown	1.45	0.34	6.11	0.62	0.21	0.03	1.53	0.12	0.91	0.44	1.86	0.79
Insurance Status (ref = private)												
No insurance	0.67	0.20	2.22	0.51	1.19	0.65	2.17	0.58	1.00	0.62	1.61	0.99
Medicaid	1.65	0.61	4.49	0.33	1.17	0.69	1.98	0.56	1.02	0.71	1.47	0.90
Medicare	1.87	1.21	2.88	0.00	0.95	0.72	1.25	0.72	1.33	1.08	1.64	0.01
Other government	1.88	0.54	6.56	0.32	2.47	1.19	5.14	0.02	1.66	0.76	3.62	0.20
Unknown	4.64	1.35	16.00	0.01	0.62	0.22	1.73	0.36	1.00	0.51	1.96	0.99
Charslon-Deyo Comorbidity Index (ref = 0)												
1	1.83	1.24	2.70	0.00	1.15	0.90	1.48	0.26	1.35	1.11	1.65	0.00
2	4.02	2.03	7.96	0.00	1.50	0.96	2.32	0.07	1.29	0.91	1.82	0.15
3+	5.39	2.38	12.19	0.00	2.79	1.52	5.12	0.00	1.93	1.08	3.44	0.03
Hospital Volume (ref = < 25%ile)												
25–50% (22–43 cases)	0.79	0.51	1.24	0.30	0.71	0.54	0.93	0.01	0.91	0.72	1.16	0.45
50–75% (44–103 cases)	0.94	0.51	1.72	0.83	0.57	0.41	0.79	0.00	0.71	0.54	0.93	0.01
>75% (>103 cases)	0.62	0.32	1.18	0.15	0.55	0.37	0.80	0.00	0.72	0.53	0.98	0.04
Income Quartile (ref = < 25%)												
25–50%	1.01	0.60	1.70	0.98	0.95	0.70	1.28	0.71	1.36	1.06	1.74	0.02
50–75%	0.92	0.53	1.59	0.76	0.75	0.55	1.01	0.06	0.98	0.76	1.25	0.85
>75%	0.78	0.46	1.32	0.36	0.73	0.55	0.96	0.03	0.96	0.76	1.22	0.77
Facility Type (ref = community cancer)												
Comprehensive community cancer	1.32	0.63	2.73	0.46	1.22	0.79	1.88	0.38	1.11	0.74	1.67	0.60
Academic/research	1.11	0.48	2.56	0.81	1.09	0.66	1.80	0.73	1.40	0.91	2.17	0.13
Integrated network cancer program	1.50	0.65	3.46	0.34	1.31	0.79	2.16	0.29	1.23	0.79	1.93	0.35
Histology (ref = Leiomyosarcoma)												
Sarcoma, NOS	1.00	0.63	1.59	0.99	1.40	1.09	1.79	0.01	1.21	1.00	1.47	0.05
Fibrosarcoma	0.50	0.28	0.89	0.02	0.72	0.49	1.06	0.10	1.09	0.78	1.51	0.62
Rhabdomyosarcoma	0.00	0.00	Inf	0.99	1.40	0.68	2.86	0.36	1.78	0.87	3.64	0.12
Peripheral Nerve Sheath	0.61	0.12	3.10	0.55	1.86	1.03	3.39	0.04	1.91	1.17	3.12	0.01
Other	1.31	0.79	2.19	0.29	1.72	1.07	2.78	0.02	1.63	1.13	2.37	0.01
Surgical Margins (ref = R0)												
Margins positive, but unspecified	1.68	0.93	3.05	0.09	1.91	1.40	2.59	0.00	1.44	1.11	1.86	0.01
R1	1.54	0.94	2.52	0.08	1.39	1.06	1.84	0.02	1.42	1.15	1.76	0.00
R2	3.10	1.10	8.69	0.03	3.42	1.77	6.61	0.00	2.16	1.50	3.10	0.00
Unable to evaluate	0.84	0.30	2.37	0.74	1.64	1.02	2.65	0.04	1.97	1.42	2.75	0.00
Grade (ref = Well differentiated)												
Moderately differentiated	1.32	0.76	2.29	0.33	1.10	0.73	1.65	0.65	1.66	1.13	2.43	0.01
Poorly differentiated	2.87	1.74	4.74	0.00	2.30	1.59	3.32	0.00	3.33	2.33	4.75	0.00
Undifferentiated	2.27	1.26	4.07	0.01	2.40	1.61	3.57	0.00	3.17	2.19	4.59	0.00
Radiotherapy Sequence (ref = no RT)												
Pre-op RT	1.01	0.30	3.34	0.99	0.67	0.46	0.98	0.04	0.50	0.37	0.68	0.00
Post-op RT	0.67	0.46	0.99	0.04	0.61	0.50	0.76	0.00	0.56	0.46	0.68	0.00
Surgery Type (ref = simple resection/enucleation)												
Radical Resection	1.18	0.45	3.07	0.73	1.42	1.06	1.90	0.02	1.26	1.03	1.54	0.02
Chemotherapy Treatment (ref = No)												
Yes	1.50	0.82	2.76	0.19	1.05	0.79	1.39	0.759	0.97	0.79	1.20	0.80
Unknown	0.74	0.22	2.53	0.63	1.14	0.65	1.99	0.647	0.81	0.55	1.21	0.31

resection (Table 3). Our final model adjusted for age, sex, insurance status, CCI, surgery type, facility treatment volume, tumor grade, and receipt of neoadjuvant radiotherapy vs resection alone. Higher facility case volume was associated with increased risk-adjusted odds of achieving margin negative resection while advanced histologic grade was associated with lower odds across all size categories. Use of neoadjuvant radiation was associated with increased risk-adjusted odds of achieving margin negative resection in only the largest (>10 cm) size category.

Cox modelling predicting factors associated with overall survival

Cox proportional hazard modelling was performed on patient populations stratified by tumor size to determine factors associated with overall survival and their effect sizes (Table 4). Margin negative resection was associated with improved survival and increasing histologic grade was associated with increased risk of death across tumor size categories. Radiation treatment in given in either neoadjuvant or adjuvant settings was independently associated with improved survival for tumors > 5 cm. Radiation therapy given in the adjuvant setting was associated with survival for patients with small (< 5 cm) tumors. Radiation therapy given in the neoadjuvant setting, however, was not associated with survival in patients with small tumors. Advanced age and comorbid disease were also independently associated with increased risk of death for patients with tumors of all sizes. Female sex and treatment at a

high-volume center were independently associated with lower adjusted of risk of death in patients with tumors larger than 5 cm.

Discussion

In this study, we use the National Cancer Database to better define the role of radiation in the treatment of non-lipomatous retroperitoneal sarcoma. Patients were first stratified by tumor size in an effort to identify tumor categories that might be used to avoid unnecessary treatment. We identified a significant survival benefit for margin-negative resection across all tumor sizes. We also demonstrate a survival benefit with radiotherapy applied in either the adjuvant or neoadjuvant setting for tumors larger than 5 cm and in the adjuvant setting in tumors < 5 cm, independent of histologic grade or margin status.

These findings should help guide clinical decision-making regarding the treatment of patients presenting with non-lipomatous sarcomas in the retroperitoneum. Our analyses confirm the importance of achieving negative resection margins for patients with tumors of all sizes. Additionally, our analysis would indicate that there is an association between use of radiation and survival in patients with small (<5 cm) tumors when the radiation is given in the adjuvant setting. This finding is independent of histologic grade and margin status. We did not identify a survival benefit for radiation treatment when therapy is given in the neo-adjuvant setting for patients with small tumors. We were likely under-powered to detect a potential benefit due to a small number of patients treated with neoadjuvant therapy in this size cohort ($n = 14$). For larger tumors, we find a survival advantage for radiation therapy in either the adjuvant or neoadjuvant setting, regardless of histologic grade and margin status. Collectively, these findings suggest that anyone undergoing resection for a non-lipomatous retroperitoneal sarcoma should receive radiation therapy. For patients presenting with larger tumors, we tend to favor using radiation therapy in these patients prior to surgical resection given the potential to more easily target the site of disease and to use appropriate stereotactic (stereotactic external beam, intensity modulated or 3D conformal radiotherapy) methods more effectively when the tumor is *in situ* and thus visible on targeting imaging.

Prior retrospective analyses have failed to reach a consensus regarding the potential benefit of radiotherapy in either local control or overall survival. There have been two prior evaluations of this topic using the National Cancer Database. The first included 9,068 patients and found a survival benefit with both adjuvant and neoadjuvant radiation.[4] A smaller, more recent analysis showed a survival benefit with radiation for tumors of advanced grade, size <15 cm, and leiomyosarcomatous histology. The second did not distinguish between radiotherapy in the adjuvant vs neoadjuvant setting.[5] These prior studies using the National Cancer Database studies do adjust for tumor histology in their multivariable analyses but include such a large percentage of liposarcomas that it is difficult to draw useful conclusions regarding non-lipomatous sarcoma from them. There have been several retrospective single institution case studies. These include relatively small numbers of patients and have generally concluded that radiation treatment and resection margin are insignificant in determining overall survival and that tumor biology is the primary driver of recurrence and mortality.[6,7] All of these prior studies included patients with varying tumor histologies, with the vast majority of their patients having liposarcomas. There has been one randomized trial on the use of radiation in retroperitoneal sarcoma.[8] This is an international study of 266 patients randomized to neoadjuvant radiotherapy vs resection alone. In this study, 198 (75%) had liposarcoma. The results demonstrated a survival benefit for the subset of patients with liposarcoma but not for the subset with non-lipomatous histologies.

In contrast to these prior studies, our analysis focuses on non-lipomatous tumors with the intent to guide future clinical decision-making in these cases. These tumors are thought to have more consistent potential than liposarcomas to act aggressively, can be reliably distinguished from liposarcoma on pre-operative imaging and are thus more appropriate targets for neoadjuvant radiation. Our analysis is stratified by tumor size in an effort to further improve the applicability of our results. We identify an association between radiation given prior to or after resection and overall survival for tumors > 5 cm, independent of histologic grade, and following resection for tumors < 5 cm.

Our analysis had several limitations. It is a retrospective study and is thus subject to selection and omitted variable bias. Many relevant aspects of treatment are not formally captured and are impossible to include in our risk models. Resection margin is only coded as negative (R0), microscopically positive (R1), and macroscopically positive (R2). There is no information available on the specific distance from tumor to the margin. There is also no information given on the type or duration of systemic therapy. Such limitations may bias our models and conclusions in ways that are difficult to predict. The National Cancer Database does not track disease recurrence, and we were consequently unable to evaluate disease-specific survival. We would hypothesize that the survival benefit from radiotherapy found here is likely due to improvement in the local control and a reduction in risk of local recurrence, but we are unable to answer such questions here.

Conclusion

Despite identified limitations, our analysis demonstrates a survival benefit for radiotherapy in patients with non-lipomatous retroperitoneal sarcomas. A survival benefit was also observed in patients receiving margin-negative resection across all tumor sizes. These findings support the use of neoadjuvant radiation in patients undergoing resection of non-lipomatous sarcomas larger than 5 cm in size and suggest that radiation be used in the adjuvant setting in patients undergoing resection for smaller tumors.

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