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Neoadjuvant radiotherapy followed by surgery compared with surgery alone in the treatment of retroperitoneal sarcoma: a population-based comparison

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ABSTRACT

Introduction Retroperitoneal sarcoma (RPS) encompasses a heterogeneous group of malignancies with a high recurrence rate after resection. Neoadjuvant radiotherapy (NRT) is often used in the hope of sterilizing margins and decreasing local recurrence after excision. We set out to compare local recurrence-free survival (LRFS) and overall survival (OS) in patients treated with or without NRT before resection.

Methods Patients diagnosed with RPS from February 1990 to October 2014 were identified in the Alberta Cancer Registry. Patients with complete gross resection of RPS and no distant disease were included. Patient, tumour, treatment, and outcomes data were abstracted in a primary chart review.

Baseline characteristics were compared using the Wilcoxon nonparametric test for continuous data and the Fisher exact test for dichotomous and categorical data. Survival was analyzed using Kaplan–Meier curves with log-rank test. Cox regression was performed to control for age, sex, tumour size, tumour grade, date of diagnosis, multivisceral resection, and intraoperative rupture.

Results Resection alone was performed in 62 patients, and resection after NRT, in 40. Use of NRT was associated with multivisceral resection and negative microscopic margins. On univariate analysis, NRT was associated with superior median LRFS (89.3 months vs. 28.4 months, $p = 0.04$) and OS (119.4 months vs. 75.9 months, $p = 0.04$). On multivariate analysis, NRT, younger age, and lower tumour grade predicted improved LRFS and OS; sex, tumour size, date of diagnosis, multivisceral resection, and tumour rupture did not.

Conclusions In this population-based study, NRT was associated with superior LRFS and OS on both univariate and multivariate analysis. When feasible, NRT should be considered until a randomized controlled trial is completed.

Key Words Sarcoma, radiotherapy

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INTRODUCTION

Retroperitoneal sarcoma (RPS) is a rare, but often lethal disease, affecting 2.7 individuals per 1,000,000 population annually[1]. The cornerstone of curative-intent treatment is *en bloc* resection of an intact tumour[2,3]. Local recurrence affects more than 60% of patients, who can experience such a recurrence up to 15 years after treatment[4]. The significance of microscopic margins is unclear, although there is some evidence for better outcomes with R0 than with R1 resection[3]. Chemotherapy is minimally effective in most settings[5,6], but it potentially has roles in downsizing borderline resectable lesions and in treating the small proportion of chemosensitive subtypes of RPS such as dedifferentiated liposarcoma, undifferentiated pleomorphic sarcoma, and leiomyosarcoma[7]. The addition of chemotherapy to preoperative radiation therapy (RT) regimens as a radiosensitizer is a topic of new interest, but is as yet poorly understood[8].

Neoadjuvant radiotherapy (NRT) has been adopted for RPS in some centres, because it is thought to sterilize

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resection margins to increase the likelihood of an R0 resection[3]. However, the utility of NRT has been difficult to establish clinically[9]. Several retrospective studies have suggested a lower rate of local recurrence with NRT[10–14]. Some studies have suggested an effect on overall survival (OS)[10,14], but more have not[3,11–13]. The Multi-institutional Collaborative RPS Working Group demonstrated a lower rate of local recurrence, but no OS benefit with perioperative (pre- or post-resection) RT[15].

The Alberta Cancer Registry is an ideal resource for investigating RPS. In the province (population 4,067,175)[16], most patients with RPS are treated at 2 tertiary referral centres, the Cross Cancer Institute in Edmonton and the Tom Baker Cancer Centre in Calgary, allowing for a detailed retrospective review over a long period of time.

We therefore set out to investigate the effect of age, tumour grade, tumour size, NRT, and intraoperative tumour rupture on local recurrence-free survival (LRFS) and OS.

METHODS

Patients

All patients more than 18 years of age with a pathology diagnosis of sarcoma and site code C48.0 ("retroperitoneum") within the Alberta Cancer Registry from February 1990 to October 2014 were identified. Patients undergoing complete gross resection of their RPS as determined by the operative surgeon were included. Exclusion criteria were treatment for a retroperitoneal sarcoma before the specified date range, metastatic disease at presentation, unavailability of the index operative details, receipt of postoperative adjuvant radiation, and a tumour thought to be of gastrointestinal or gynecologic origin.

Data were then abstracted by chart review. Patient demographics included sex and date of birth. Tumour characteristics included date of diagnosis, tumour maximum dimension, tumour grade and histologic type, and presence of distant metastases at diagnosis.

Treatment

The timing and dose of NRT were recorded. Resections were classified as multivisceral (including involved adjacent organs), tumour-only, or debulking (gross residual disease). Tumour rupture, including intraoperative biopsy and inadvertent capsule breach, was noted. Microscopic margin status was classified as positive, negative, or not reported, based on the original pathology report.

Outcomes

Patients were considered to have experienced a recurrence when they converted from no evidence of disease to evidence of disease based on biopsy or convincing radiographic findings. Recurrence was classified as local (retroperitoneal), distant (extra-abdominal or sarcomatosis), or both.

Statistical Analysis

Baseline characteristics of the groups receiving and not receiving NRT were compared using the Wilcoxon nonparametric test for continuous variables and the Fisher exact test for categorical variables.

Descriptive statistics are used to characterize the sites of recurrence in the NRT and resection-only groups. The proportions of patients experiencing local recurrence (with or without distant recurrence) and distant recurrence only were compared by Fisher exact test.

The LRFS and OS in the NRT and resection-only groups were compared using Kaplan–Meier analysis and the log-rank test, with an *a priori p* value for significance of 0.05.

Patient age and sex, date of diagnosis, multivisceral resection, tumour maximum diameter, tumour grade, rupture, and NRT were included in a Cox regression analysis for LRFS and OS.

RESULTS

Screening criteria identified 173 patients in the Registry. Patients were excluded for non-target pathology [$n = 2$ (1 with gastrointestinal stromal tumour, 1 with uterine leiomyosarcoma)], diagnosis at autopsy ($n = 1$), unavailability of index resection details ($n = 5$), postoperative adjuvant RT ($n = 2$), metastatic disease at presentation ($n = 23$), and primary not resected or gross residual disease ($n = 38$). Of the 102 remaining patients, 62 underwent resection alone, and 40 received NRT followed by resection.

The median dose of NRT was 49 Gy in 25 fractions. Surgery was generally performed 4–6 weeks after completion of NRT. Receipt of NRT was associated with multivisceral resection (87.5% vs. 66.1%, $p = 0.02$), negative margins (72.5% vs. 30.6%, $p < 0.001$), and later date of diagnosis (80.0% in 2003–2014 vs. 43.5% before 2003, $p < 0.001$). No statistically significant associations with age, sex, histology (well-differentiated liposarcoma vs. other), tumour grade, tumour size, or rupture were observed (Table I). No patient received neoadjuvant chemotherapy. Two patients received adjuvant chemotherapy, both of them in the resection-only group. Median follow-up was 90 months.

Recurrence was documented in 17 patients in the NRT group (43%). Of those 17 patients, 6 experienced local recurrence only; 4, distant recurrence only; and 7, both. In the resection-only group, recurrence was documented in 39 patients (63%): 24 local, 4 distant, and 11 both. As a proportion of all patients with recurrence, those with local recurrence, whether associated with distant recurrence or not, therefore constituted 76% of the NRT group and 90% of the resection-only group ($p = 0.23$).

On univariate analysis, NRT was associated with superior median LRFS (89.3 months vs. 28.4 months, $p = 0.04$) and OS (119.4 months vs. 75.9 months, $p = 0.04$). On multivariate analysis, age, grade, and receipt of NRT were statistically significant predictors of LRFS and OS; sex, tumour size, histologic type, extent of surgery, rupture, and date of diagnosis were not (Tables II and III).

Kaplan–Meier survival analysis with log-rank test demonstrated a statistically significant improvement in both LRFS and OS associated with NRT ($p = 0.04$ in both cases, Figure 1).

DISCUSSION

In our cohort, NRT was associated with superior LRFS and OS in both univariate and multivariate analysis. Overall,

TABLE I Clinicopathologic characteristics of 102 patients receiving neoadjuvant radiation therapy (RT) before resection or resection only for retroperitoneal sarcoma

Variable	Neoadjuvant RT		*p* Value
	No	Yes	
Patients *(n)*	62	40	
Mean age (years)	60.0	56.7	0.16[a]
Sex [*n* (%)]			
Men	24 (38.7)	17 (42.5)	0.84[b]
Women	38 (61.3)	23 (57.5)	
Tumour grade [*n* (%)]			
1	23 (39.7)	14 (40.0)	0.24[b]
2	6 (10.3)	8 (22.9)	
3	29 (50.0)	13 (37.1)	
Histology [*n* (%)]			
WDLS	17 (27.4)	13 (32.5)	0.66[b]
Other	45 (72.6)	27 (67.5)	
Maximum diameter			
Median (cm)	184.0	136.5	
<20 cm [*n* (%)]	33 (53)	27 (67.5.0)	0.22[b]
>20 cm [*n* (%)]	29 (47)	13 (32.5)	
Resection type [*n* (%)]			
Multivisceral	41 (66.1)	35 (87.5)	0.02[b]
Tumour-only	21 (33.7)	5 (12.5)	
Tumour rupture or spillage [*n* (%)]			
No	42 (70.0)	32 (80.0)	0.35[b]
Yes	18 (30.0)	8 (20.0)	
Margins [*n* (%)]			
Positive	29 (46.8)	9 (22.5)	<0.001[b]
Negative	19 (30.6)	29 (72.5)	
Not stated	14 (22.6)	2 (5.0)	
Diagnosis year [*n* (%)]			
1990–2002	35 (56.5)	8 (20.0)	<0.001[b]
2003–2014	27 (43.5)	32 (80.0)	

[a] By the Wilcoxon nonparametric test.
[b] By the Fisher exact test.
WDLS = well-differentiated liposarcoma.

TABLE II Multivariate associations between clinico-demographic factors and local recurrence-free survival

Factor	HR	95% CI	*p* Value
nRT	0.43	0.24 to 0.79	0.01
Age	1.03	1.01 to 1.05	0.01
Sex			
Women		1	
Men	1.22	0.69 to 2.12	0.49
Tumour size			
<20 cm		1	
≥20 cm	0.58	0.31 to 1.07	0.08
Grade			
1		1	
2	5.46	1.97 to 15.14	0.001
3	4.44	1.66 to 11.89	0.003
Histology			
Other		1	
WDLS	1.24	0.44 to 3.50	0.68
Rupture			
No		1	
Yes	1.39	0.75 to 2.58	0.30
Resection type			
Multivisceral		1	
Tumour-only	0.82	0.42 to 1.60	0.57
Diagnosis year			
1990–2002		1	
2003–2014	0.77	0.42 to 1.39	0.38

HR = hazard ratio; CI = confidence interval; nRT = neoadjuvant radiation therapy; WDLS = well-differentiated liposarcoma.

on multivariate analysis, age, tumour grade, and nRT were found to be statistically significant predictors of LRFS and OS. A trend toward less local recurrence as a fraction of all recurrences was evident in the nRT group, but was not statistically significant.

Comparing our results with those reported in the literature, the data appear to be mixed. That inconsistency was well demonstrated by Nussbaum *et al.*[17] in their recent publication of a U.S. National Cancer Database study of RT for RPS. Those authors suggested that the lack of clearly demonstrable treatment effect in the literature to date is partly attributable to the inherent biases of small sample size.

Currently, other than the ongoing randomized phase III STRASS trial (European Organisation for Research and Treatment of Cancer 62092, NCT01344018 at https://ClinicalTrials.gov/), no published randomized study has compared nRT with resection alone for RPS.

In two prospective trials of nRT for high-risk lesions involving a total of 72 patients, median survival was not reached after a follow-up of more than 60 months. The 5-year LRFS was 60% compared with 20%–50% in historical controls[18].

Several recent studies using the U.S. Surveillance, Epidemiology, and End Results Program and the U.S. National Comprehensive Cancer Network databases have investigated the effect of RT on OS in RPS, with conflicting results (Table IV). Four studies demonstrated no effect on

TABLE III Multivariate associations between clinico-demographic factors and overall survival

Factor	HR	95% CI	*p* Value
nRT	0.42	0.19 to 0.90	0.03
Age	1.03	1.00 to 1.05	0.02
Sex			
Women	1		
Men	1.00	0.52 to 1.95	0.99
Size			
<20 cm	1		
≥20 cm	0.96	0.48 to 1.93	0.91
Grade			
1	1		
2	4.00	1.21 to 13.17	0.02
3	3.30	1.09 to 9.96	0.03
Histology			
Other	1		
WDLS	0.81	0.24 to 2.70	0.73
Rupture			
No	1		
Yes	1.02	0.49 to 2.10	0.96
Resection type			
Multivisceral	1		
Tumour-only	1.01	0.47 to 2.16	0.99
Diagnosis year			
1990–2002	1		
2003–2014	0.88	0.42 to 1.83	0.73

HR = hazard ratio; CI = confidence interval; nRT = neoadjuvant radiation therapy; WDLS = well-differentiated liposarcoma.

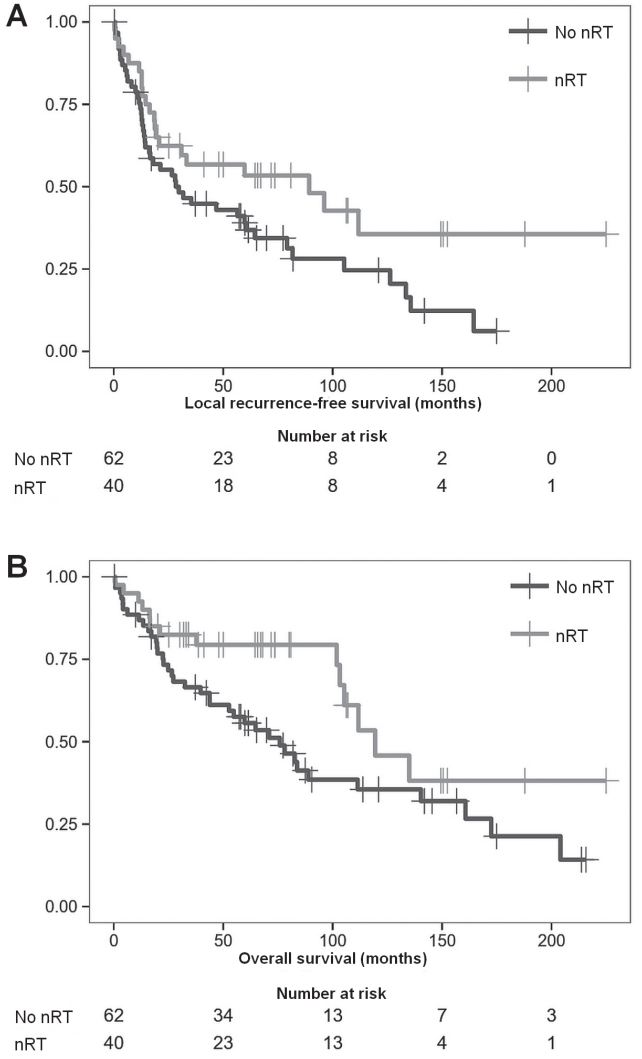

FIGURE 1 Kaplan–Meier plots of (A) local recurrence-free survival and (B) overall survival with or without the use of neoadjuvant radiation therapy (nRT).

os[13,19,21,22], and four demonstrated a benefit[17,20,23,24]. The relevant datasets were limited in that they lacked specific recurrence data for an evaluation of LRFS or disease-free survival. Only two of the studies[17,23] compared resection alone with nRT; the rest included other radiation modalities in one of the arms. In studies comparing any RT with no RT, most patients receiving RT did so postoperatively.

Some of the more robust literature is derived from multi-institutional cooperative groups. The Multi-institutional Collaborative RPS Working Group, an effort of 9 high-volume centres, demonstrated improved LRFS with perioperative RT [hazard ratio (HR): 0.58; $p = 0.001$], but no effect on OS (HR: 0.98; $p = 0.864$)[15]. In a report of the Trans-Atlantic Retroperitoneal Sarcoma Working Group, restricted to liposarcoma (stratified into 3 cohorts according to grade), perioperative RT was, on univariate analysis, associated with improved local control in all cohorts; that association disappeared after control for confounders was introduced. No effect of RT on distant metastasis or OS was observed[25].

In retrospective studies, results have been conflicting. Some studies have found no benefit from perioperative RT[26,27]; several have demonstrated improved LRFS[11,28–31]; and several have demonstrated benefits in both LRFS and OS[10,14,32,33] (Table V).

There are several possible reasons for the conflicting results. Sample size is a concern, given that all the retrospective studies include a relatively small number of patients. Treatment regimens are not always uniform within study groups; many studies include patients with either preoperative or postoperative RT in a single treatment arm. Finally, there are arguments (discussed shortly) for the superiority of preoperative compared with postoperative RT, and the preoperative approach has been relatively poorly represented in retrospective studies. With the exception of Kelly *et al.*[11] and Snow *et al.*[31], studies delivered RT to patients postoperatively.

There are good theoretical reasons to propose the superiority of nRT over postoperative RT. In the treatment of RPS,

TABLE IV Studies in administrative databases of neoadjuvant radiation therapy (nRT) in retroperitoneal sarcoma

Reference	Database	Comparison	OS[a]	*p* Value
Nathan *et al.*, 2009[19]	SEER	RT[b] vs. none	HR: 0.95	0.6
Zhou *et al.*, 2010[20]	SEER	RT[c] vs. none	HR: 0.78	0.01
Tseng *et al.*, 2011[21]	SEER	RT[d] vs. none	82 vs. 87 months	0.11
Choi *et al.*, 2012[22]	SEER	RT[e] vs. none	Kaplan–Meier curve only	0.10
Nussbaum *et al.*, 2015[13]	NCDB	nRT vs. no nRT[f]	5-Year: 53.2% vs. 54.2%	0.695
Ecker *et al.*, 2016[23]	NCDB	nRT vs. no RT	129.2 vs. 84.3 months	0.046
Nussbaum *et al.*, 2016[17]	NCDB	nRT vs. no RT	HR: 0.70	<0.0001
		Postoperative RT vs. no RT	HR: 0.78	<0.0001
Bates *et al.*, 2018[24]	SEER	Postoperative RT vs. no RT	HR: 0.8	0.029

[a] Treatment compared with control.
[b] Postoperative in 83.1%.
[c] Preoperative and postoperative proportions not specified.
[d] Postoperative in 80.4%.
[e] Postoperative in 80.2% of patients after propensity score matching.
[f] Of the no-nRT group, 32.9% received postoperative RT.
OS = overall survival; SEER = U.S. Surveillance, Epidemiology, and End Results program; HR = hazard ratio; NCDB = U.S. National Cancer Database;

TABLE V Summary of retrospective studies of perioperative radiation therapy in retroperitoneal sarcoma

Reference	Patients		OS[e]	*p* Value	RFS[e]	*p* Value
	(N)	(*n* w/nRT)				
Stoeckle *et al.*, 2001[30]	165	3	—	—	RR: 0.31[b]	<0.001
Hassan *et al.*, 2004[27]	97	16	—	—	41% vs. 45%[c]	0.76
Bonvalot *et al.*, 2009[26]	249	36	—	—	HR: 0.52[b]	0.116
Gronchi *et al.*, 2009[32]	288	—[d]	HR: 0.55	0.008	HR: 0.65[b]	0.057
Sampath *et al.*, 2010[29]	261	6	—	—	HR: 0.42[b]	<0.05
Gronchi *et al.*, 2012[33]	331	—[d]	HR: 0.64	0.05	HR: 0.57[b]	0.02
Trovik *et al.*, 2014[14]	97	5	71% vs. 52%[e]	0.019	77% vs. 39%[e]	<0.001
Kelly *et al.*, 2015[11]	204	30	—	—	HR: 0.26[b]	0.03
Lane *et al.*, 2015[10]	74	9	HR: 0.30	0.02	HR: 0.34[c]	<0.01
Snow *et al.*, 2018[31,f]	88	57	HR: 1.0	0.93	HR: 0.33[b]	0.014

[a] Intervention compared with control.
[b] For local recurrence.
[c] For local or metastatic recurrence.
[d] Not stratified by preoperative compared with postoperative delivery.
[e] 5-Year results.
[f] Only study specific for nRT.
w/nRT = with neoadjuvant radiation therapy; OS = overall survival; RFS = recurrence-free survival; RR = relative risk; HR = hazard ratio.

nRT is justified in part by extrapolation from the success of RT in sarcoma of the extremities. When a limb-sparing approach is selected, local control is significantly improved with adjunctive RT[34–36]. However, microscopically negative margins are more difficult to obtain in RPS than in sarcoma of the extremities, because of the typically greater size and more prohibitive anatomic barriers to wide resection[37]. Indeed, some authors argue that nearly all RPS resections have at least a focally positive microscopic margin, which can be missed on pathologic section because of the difficulty of assessing a large lesion[38,39]. Radiation therapy might therefore be expected to have a greater oncologic benefit in the preoperative setting, by sterilizing the margins of the eventual resection and reducing the opportunity for viable tumour to be left in the operative bed. Those effects ought, in turn, to improve OS, given that repeat resection is usually difficult or impossible, and options for systemic therapy are limited. Further, delivering RT with tumour *in situ* allows for more precise targeting of the lesion and limits the exposure of adjacent organs, possibly preventing treatment interruption for toxicity. Those considerations appear to be supported by a comparison of preoperative

compared with postoperative RT in the U.S. National Cancer Database, which demonstrated improved OS (HR: 0.72; $p < 0.01$) and cancer-specific mortality (HR: 0.64; $p < 0.01$) in the preoperative group[40]. Finally, postoperative RT is, in many cases, simply not feasible because of the large field sizes and higher doses required when RT is delivered postoperatively—especially with the small bowel or other dose-limiting structures potentially within the field.

Our study demonstrated, on univariate and multivariate analysis alike, improved LRFS and OS with NRT, which accords with some published retrospective series and contrasts with others. It seems plausible that, in some prior negative studies, the benefits of RT were blunted by the inclusion of patients who received RT postoperatively. Without directly addressing that question, our study adds to the evidence that NRT might be superior to resection alone.

We believe that our study design provides certain advantages over some of the studies discussed earlier. Although our study was population-based, the concentration of cases in 2 centres allowed for the collection of data about local recurrence, which has not been possible in administrative databases. At the same time, the study population was larger than that in many single-centre series and likely more representative of the population at large. To our knowledge, ours is only the second study (Snow *et al.*[31] being the first) with institution-level data in which the intervention arm was limited to NRT rather than to perioperative RT. It is the first such study to apply multivariate analysis. Snow *et al.* did not include a multivariate analysis, and the authors note that NRT was strongly associated with treatment at a high-volume centre and was therefore likely confounded by greater extent of surgery, use of core biopsy, and greater experience of the treating team.

The retrospective nature of our study imposes certain limitations. Most importantly, the NRT and resection-only groups differed with respect to extent of surgery, margin positivity, and date of diagnosis. It is therefore possible that some of the apparent treatment effect is a result of changing practice patterns such as multidisciplinary referral and oncologically superior biopsy and resection techniques. The rationale for NRT compared with resection alone, discussion at a multidisciplinary tumour board, and resection at a high-volume centre were not available as data points. That lack is somewhat mitigated by our inclusion of multivisceral resection in the multivariate analysis, because that technique would be expected to be more prevalent at high-volume centres. Treatment at a high-volume centre would also be expected to have become more universal in recent years, and our multivariate therefore controlled for date of diagnosis.

The number of tumours with unreported margins (15 of 102) prevented inclusion of margin status in the multivariate analysis. That lack is somewhat mitigated by the inclusion of tumour rupture, which would be associated with positive margins.

CONCLUSIONS

In a population-based study, NRT was associated with improved LRFS and OS on both univariate and multivariate analysis. Where tumour and patient factors permit, NRT should be considered for RPS until a randomized controlled trial is completed.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES

1. Porter GA, Baxter NN, Pisters PW. Retroperitoneal sarcoma: a population-based analysis of epidemiology, surgery, and radiotherapy. *Cancer* 2006;106:1610–16.
2. El-Bared N, Taussky D, Mehiri S, Patocskai E, Roberge D, Donath D. Preoperative intensity modulated radiation therapy for retroperitoneal sarcoma. *Technol Cancer Res Treat* 2014;13:211–16.
3. Stahl JM, Corso CD, Park HS, *et al.* The effect of microscopic margin status on survival in adult retroperitoneal soft tissue sarcomas. *Eur J Surg Oncol* 2017;43:168–74.
4. Brennan MF, Antonescu CR, Moraco N, Singer S. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. *Ann Surg* 2014;260:416–21.
5. Strauss DC, Hayes AJ, Thomas JM. Retroperitoneal tumours: review of management. *Ann R Coll Surg Engl* 2011;93:275–80.
6. Miura JT, Charlson J, Gamblin TC, *et al.* Impact of chemotherapy on survival in surgically resected retroperitoneal sarcoma. *Eur J Surg Oncol* 2015;41:1386–92.
7. Almond LM, Gronchi A, Strauss D, Jafri M, Ford S, Desai A. Neoadjuvant and adjuvant strategies in retroperitoneal sarcoma. *Eur J Surg Oncol* 2018;44:571–9.
8. Dumitra S, Gronchi A. The diagnosis and management of retroperitoneal sarcoma. *Oncology (Williston Park)* 2018;32:464–9.
9. Cheng H, Miura JT, Lalehzari M, *et al.* Neoadjuvant radiotherapy for retroperitoneal sarcoma: a systematic review. *J Surg Oncol* 2016;113:628–34.
10. Lane WO, Cramer CK, Nussbaum DP, *et al.* Analysis of perioperative radiation therapy in the surgical treatment of primary and recurrent retroperitoneal sarcoma. *J Surg Oncol* 2015;112:352–8.
11. Kelly KJ, Yoon SS, Kuk D, *et al.* Comparison of perioperative radiation therapy and surgery versus surgery alone in 204 patients with primary retroperitoneal sarcoma: a retrospective 2-institution study. *Ann Surg* 2015;262:156–62.
12. De Wever I, Laenen A, Van Limbergen E. Pre-operative irradiation for retroperitoneal liposarcoma: results of a pilot study. *Acta Chir Belg* 2013;113:315–21.
13. Nussbaum DP, Speicher PJ, Gulack BC, *et al.* Long-term oncologic outcomes after neoadjuvant radiation therapy for retroperitoneal sarcomas. *Ann Surg* 2015;262:163–70.
14. Trovik LH, Ovrebo K, Almquist M, *et al.* Adjuvant radiotherapy in retroperitoneal sarcomas. A Scandinavian Sarcoma Group study of 97 patients. *Acta Oncol* 2014;53:1165–72.
15. Gronchi A, Strauss DC, Miceli R, *et al.* Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): a report on 1007 patients from the Multi-institutional Collaborative RPS Working Group. *Ann Surg* 2016;263:1002–9.

16. Statistics Canada. Census Profile, 2016 Census: Alberta [Province] and Canada [Country] [Web page]. Ottawa, ON: Statistics Canada; 2019. [Available at https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/prof/details/page.cfm?Lang=E&Geo1=PR&Code1=48&Geo2=PR&Code2=01&Data=Count&SearchText=Canada&SearchType=Begins&SearchPR=01&B1=All; cited 30 November 2019]
17. Nussbaum DP, Rushing CN, Lane WO, *et al.* Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case–control, propensity score–matched analysis of a nationwide clinical oncology database. *Lancet Oncol* 2016;17:966–75.
18. Pawlik TM, Pisters PW, Mikula L, *et al.* Long-term results of two prospective trials of preoperative external beam radiotherapy for localized intermediate- or high-grade retroperitoneal soft tissue sarcoma. *Ann Surg Oncol* 2006;13:508–17.
19. Nathan H, Raut CP, Thornton K, *et al.* Predictors of survival after resection of retroperitoneal sarcoma: a population-based analysis and critical appraisal of the AJCC staging system. *Ann Surg* 2009;250:970–6.
20. Zhou Z, McDade TP, Simons JP, *et al.* Surgery and radiotherapy for retroperitoneal and abdominal sarcoma: both necessary and sufficient. *Arch Surg* 2010;145:426–31.
21. Tseng WH, Martinez SR, Do L, Tamurian RM, Borys D, Canter RJ. Lack of survival benefit following adjuvant radiation in patients with retroperitoneal sarcoma: a SEER analysis. *J Surg Res* 2011;168:e173–80.
22. Choi AH, Barnholtz-Sloan JS, Kim JA. Effect of radiation therapy on survival in surgically resected retroperitoneal sarcoma: a propensity score-adjusted SEER analysis. *Ann Oncol* 2012;23:2449–57.
23. Ecker BL, Peters MG, McMillan MT, *et al.* Preoperative radiotherapy in the management of retroperitoneal liposarcoma. *Br J Surg* 2016;103:1839–46.
24. Bates JE, Dhakal S, Mazloom A, Constine LS. The benefit of adjuvant radiotherapy in high-grade nonmetastatic retroperitoneal soft tissue sarcoma: a SEER analysis. *Am J Clin Oncol* 2018;41:274–9.
25. Haas RLM, Bonvalot S, Miceli R, *et al.* Radiotherapy for retroperitoneal liposarcoma: a report from the Transatlantic Retroperitoneal Sarcoma Working Group. *Cancer* 2019;125:1290–300.
26. Bonvalot S, Rivoire M, Castaing M, *et al.* Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control. *J Clin Oncol* 2009;27:31–7.
27. Hassan I, Park SZ, Donohue JH, *et al.* Operative management of primary retroperitoneal sarcomas: a reappraisal of an institutional experience. *Ann Surg* 2004;239:244–50.
28. Heslin MJ, Lewis JJ, Nadler E, *et al.* Prognostic factors associated with long-term survival for retroperitoneal sarcoma: implications for management. *J Clin Oncol* 1997;15:2832–9.
29. Sampath S, Hitchcock YJ, Shrieve DC, Randall RL, Schultheiss TE, Wong JY. Radiotherapy and extent of surgical resection in retroperitoneal soft-tissue sarcoma: multi-institutional analysis of 261 patients. *J Surg Oncol* 2010;101:345–50.
30. Stoeckle E, Coindre JM, Bonvalot S, *et al.* Prognostic factors in retroperitoneal sarcoma: a multivariate analysis of a series of 165 patients of the French Cancer Center Federation Sarcoma Group. *Cancer* 2001;92:359–68.
31. Snow HA, Hitchen TX, Head J, *et al.* Treatment of patients with primary retroperitoneal sarcoma: predictors of outcome from an Australian specialist sarcoma centre. *ANZ J Surg* 2018;88:1151–7.
32. Gronchi A, Lo Vullo S, Fiore M, *et al.* Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. *J Clin Oncol* 2009;27:24–30.
33. Gronchi A, Miceli R, Colombo C, *et al.* Frontline extended surgery is associated with improved survival in retroperitoneal low- to intermediate-grade soft tissue sarcomas. *Ann Oncol* 2012;23:1067–73.
34. Yang JC, Chang AE, Baker AR, *et al.* Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol* 1998;16:197–203.
35. Beane JD, Yang JC, White D, Steinberg SM, Rosenberg SA, Rudloff U. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. *Ann Surg Oncol* 2014;21:2484–9.
36. O'Sullivan B, Davis AM, Turcotte R, *et al.* Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002;359:2235–41.
37. Stojadinovic A, Leung DH, Hoos A, Jaques DP, Lewis JJ, Brennan MF. Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. *Ann Surg* 2002;235:424–34.
38. Anaya DA, Lev DC, Pollock RE. The role of surgical margin status in retroperitoneal sarcoma. *J Surg Oncol* 2008;98:607–10.
39. Larrier NA, Czito BG, Kirsch DG. Radiation therapy for soft tissue sarcoma: indications and controversies for neoadjuvant therapy, adjuvant therapy, intraoperative radiation therapy, and brachytherapy. *Surg Oncol Clin N Am* 2016;25:841–60.
40. Sampath S, Schultheiss TE, Hitchcock YJ, Randall RL, Shrieve DC, Wong JY. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma: multi-institutional analysis of 821 patients. *Int J Radiat Oncol Biol Phys* 2011;81:498–505.