Surgical outcome and patterns of recurrence for retroperitoneal sarcoma at a single centre

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ABSTRACT

INTRODUCTION Retroperitoneal sarcoma is a surgically managed condition that can recur locally following macroscopically complete resection. Owing to the low incidence of the condition, advances in treatment are reported infrequently but complete compartmental resection and adjuvant or neoadjuvant radiotherapy are areas under investigation. Given the practical difficulty of randomised trials, observational data can highlight advantages from progressive treatment approaches.

METHODS A retrospective database of consecutive retroperitoneal sarcoma resections performed at a single referral centre between March 1997 and March 2013 was interrogated. Histological, radiological and clinical data were collected. Univariate and multivariate analyses for disease free and overall survival were performed to establish independent predictors of disease recurrence and patient survival.

RESULTS A total of 79 patients underwent 90 resections (63 primary). The mean five-year overall and disease free survival rates were 55.3% and 24.8% respectively. Higher patient age, high tumour grade, presence of extraretroperitoneal disease and invasive tumour phenotype were found to significantly predict survival following multivariate analysis. Half (50%) of the tumours displayed invasive behaviour on histopathology and 42% of locoregional recurrence was intraperitoneal.

CONCLUSIONS Retroperitoneal sarcoma is commonly an infiltrative tumour and often recurs outside of the retroperitoneum. These features limit the therapeutic impact of interventions that focus on gaining local control such as complete compartmental resection and radiotherapy. It seems likely that future advances in the management of this cancer will involve new systemic agents to treat this frequently systemic disease.

KEYWORDS

Retroperitoneal sarcoma – Recurrence – Overall survival – Disease free survival – Soft tissue sarcoma – Invasion

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Retroperitoneal sarcoma (RPS) is a rare, histologically heterogeneous condition for which surgery in fit patients with resectable disease is the standard of care.¹ Prognosis is poorer than that of soft tissue sarcomas located outside the retroperitoneum; the five-year overall survival (OS) rate is approximately 50% and declines to 20–30% at ten years.² While variation is seen between histological subtypes, RPS has a predilection for local recurrence and has been previously thought of as a pushing tumour with little infiltration of surrounding tissues. Recent work, however, has suggested that although recurrence can be locoregional, it is often not in the original disease bed.^{3,4}

Predictors of OS reported throughout the literature are completeness of resection, tumour grade and histological subtype. As grade and histology are not modifiable factors at diagnosis, efforts to improve management have been focused on local control through adjuvant radiotherapy or

radical surgical techniques.^{5–9} Although radiotherapy has been adopted into routine management of extremity sarcomas, its application to RPS cases is limited by the radiosensitive viscera that border the retroperitoneum and its role is therefore less clear.¹

Observational series have suggested improvements to disease free survival (DFS) without an improvement in OS.⁸ This mirrors the findings from randomised controlled trials (RCTs) of radiotherapy in extremity sarcomas.¹⁰ The STRASS trial, underway at present, is a RCT aiming to define the prognostic impact of neoadjuvant radiotherapy in RPS.⁹ Case series reports of conventional surgery and complete compartmental resection (CCR) have demonstrated a similar picture of clear improvement of DFS, with a less convincing improvement of OS.^{6,7} As a RCT comparing CCR and conventional surgery is not feasible, the relative impact of these surgical approaches must be discerned

from meta-analysis of case series. The aim of this retrospective case series was to examine factors associated with patient outcome following surgery for RPS and to analyse the location of disease recurrence.

Methods

A database at The Freeman Hospital of RPS resections performed between March 1997 and March 2013 was interrogated. The inclusion criteria required a histological diagnosis of soft tissue sarcoma resected from the retroperitoneal or intraperitoneal space as a primary tumour or recurrence of such a primary. Tumours of gynaecological, skeletal or abdominal origin were excluded, as were gastrointestinal stromal tumours, rhabdomyosarcomas, small round blue cell sarcomas, osteosarcomas, chondrosarcomas, fibromatosis and sarcomatoid or metastatic carcinomas. All patients had given written consent allowing their clinical data to be used in research.

Tumour grade (using the Fédération Nationale des Centres de Lutte Contre le Cancer system), size, whether it was single site or multifocal and invasive phenotype were extracted from histopathology consultant reports. Resections with margins that appeared disease free microscopically or only on macroscopic examination (referred to as R0 and R1 respectively) were grouped together as complete microscopic examination of excisions was not feasible owing to the large surface area of the tumours. Resections leaving macroscopic residual disease are referred to as R2. All patients received serial cross-sectional imaging following surgery. This was reviewed by a specialist consultant to detect the presence of residual disease or disease recurrence with date and locus (Fig 1). Survival status and other clinical information was extracted from patient records.

SPSS® version 21 (IBM, New York, US) was used for statistical analysis. Kaplan-Meier survival analysis was performed for each univariate variable, with significance for DFS and OS being determined by a Mantel-Cox test. Cox regression analysis was performed for each multivariate variable collected to produce two-tailed *p*-values. Further multivariate analysis was performed with all variables that demonstrated individual prognostic significance to

determine which variables were statistically significant independent predictors of OS and DFS. A *p*-value of <0.05 was considered statistically significant.

Regarding nomenclature in this manuscript, recurrence that occurred in the retroperitoneum or peritoneal sac has been termed locoregional. Recurrence outside of these two spaces is referred to as metastatic. The division of locoregional recurrence into retroperitoneal and intraperitoneal recurrence is also key to our data. An invasive phenotype

Table 1 Clinical features of retroperitoneal sarcoma cohort

		<i>n</i>
Sex	Male	45 (50.0%)
	Female	45 (50.0%)
Disease resected	Primary	63 (70.0%)
	Recurrent	27 (30.0%)
Resection clearance	R0/R1	80 (88.9%)
	R2	10 (11.1%)
	Piecemeal	23 (25.6%)
FNCLCC grade	1	135 (38.9%)
	2	17 (18.9%)
	3	38 (42.2%)
Histology	Well differentiated liposarcoma	34 (37.8%)
	Dedifferentiated liposarcoma	26 (28.9%)
	Leiomyosarcoma	12 (13.3%)
	Sarcoma not otherwise specified	8 (8.9%)
	Other	7 (7.8%)
Recurrence locus	None	32 (35.6%)
	Retroperitoneal	21 (23.3%)
	Intraperitoneal	16 (17.8%)
	Distant	11 (12.2%)
	R2 – N/A	10 (11.1%)
Locality	Unifocal	55 (61.1%)
	Multifocal	35 (38.9%)
Invasive	No	45 (50.0%)
	Yes	45 (50.0%)
Chemotherapy	No	72 (80.0%)
	Neoadjuvant	15 (16.7%)
	Neoadjuvant and adjuvant	3 (3.3%)
Radiotherapy	No	81 (90.0%)
	Neoadjuvant	1 (1.1%)
	Adjuvant	8 (8.9%)
FNCLCC = Fédération Nationale des Centres de Lutte Contre le Cancer

Figure 1 Computed tomography including radiotherapy planning for a primary retroperitoneal sarcoma (left) and the subsequent retroperitoneal recurrence (right) in the same patient

Figure 2 Hazard ratios with 95% confidence intervals of the variables found to be independent predictors of overall survival on multivariate analysis

Table 2 Site of disease recurrence following macroscopically complete resection broken down by tumour grade (using the Fédération Nationale des Centres de Lutte Contre le Cancer system) and observed invasiveness

	Location of recurrence			No recurrence
	Retroperitoneal	Intraperitoneal	Distant	
Grade 1 (<i>n</i> =33)	30%	12%minutes	6%	52%
Grade 2 (<i>n</i> =17)	41%	12%	12%	35%
Grade 3 (<i>n</i> =30)	17%	33%	23%	27%
Invasive (<i>n</i> =37)	24%	27%	14%	35%
Non-invasive (<i>n</i> =43)	30%	14%	14%	42%

was attributed on histological grounds to tumours that showed microscopic invasion into neighbouring viscera.

Results

A total of 79 patients had 90 resections of RPS and the mean age at resection was 60 years (range: 27–87 years). Prior to surgery, disease was intra-abdominal or metastatic in eight cases (9.1%). The mean follow-up duration was

61 months (range: 0–178 months) and the median survival was 67 months (range: 44.5–89.5 months). The overall five-year DFS and OS rates were 24.8% (95% confidence interval [CI]: 19.2–30.4%) and 55.3% (95% CI: 49.9–60.7%) respectively. For primary resections (*n*=63), the five-year DFS and OS rates were 30.8% (95% CI: 23.6–38.0%) and 58.7% (95% CI: 52.3–65.1%) respectively. There were three perioperative deaths, from intraoperative haemorrhage, postoperative cardiac arrest and multiorgan failure

Table 3 Statistical description of the variables found to significantly predict OS in months when considered individually					
Variable	Category	n	Mean OS	SE	p-value
Age	≥60 years	54	110.4 months	13.0 months	0.012
	<60 years	36	71.3 months	11.1 months	
Extraretroperitoneal disease	No	82	94.2 months	9.3 months	0.013
	Yes	8	41.8 months	16.0 months	
Organs removed	<3	79	95.7 months	9.4 months	0.004
	≥3	11	36.6 months	16.1 months	
Invasive	Yes	45	119.8 months	12.1 months	<0.001
	No	45	55.5 months	10.1 months	
Recurrence	None	32	152.5 months	13.9 months	0.001
	Retroperitoneal	21	93.8 months	14.3 months	0.037
	Intraperitoneal	16	39.8 months	8.5 months	<0.001
	Distant	11	82.5 months	22.5 months	0.042
	Residual	10	51.0 months	21.8 months	0.001
FNCLCC grade	1 or 2	52	127.4 months	10.9 months	<0.001
	3	38	33.2 months	6.8 months	
Resection margin	R0/R1	80	94.8 months	9.2 months	0.002
	R2	10	29.7 months	11.4 months	
Histology	WDLS	34	119.0 months	13.2 months	0.010
	DDLS	26	81.1 months	16.2 months	0.038
	Leiomyosarcoma	12	40.3 months	11.4 months	0.678
	Other	18	70.0 months	19.2 months	0.194

OS = overall survival; SE = standard error; FNCLCC = Fédération Nationale des Centres de Lutte Contre le Cancer; WDLS = well differentiated liposarcoma; DDLS = dedifferentiated liposarcoma

secondary to pneumonia. The mean maximal tumour diameter was 205mm (range: 50–560mm) and 62 resections (70.0%) included 1 or more organs, most commonly large bowel (40.0%). Further description of the clinical features can be found in Table 1.

Of the 90 resections, 80 (88.9%) were R0/R1. Among this subgroup, 31 patients (38.8%) remained disease free throughout radiological surveillance. Of the remaining 49 R0/R1 resections, 22 (44.9%) recurred in the retroperitoneum (Fig 1), 16 (32.7%) in the peritoneum and 11 (22.4%) at a distant site. Grade 3 tumours were significantly more likely to recur in the peritoneum than in the retroperitoneum ($p=0.009$). Metastases were also more common in higher grade tumours (Table 2). Tumours displaying an invasive phenotype recurred in the peritoneum more frequently than in the retroperitoneum but this trend did not reach significance when analysing this subset of 38 resections ($p=0.2$).

Following multivariate analysis of the eight variables that were significant individual predictors of OS (Table 3), four of the variables were statistically significant independent predictors of OS (Fig 2). These were invasive phenotype observed on histopathology ($p=0.003$), patient age ($p=0.001$),

presence of distant disease at time of resection ($p=0.014$) and grade ($p=0.015$). Delivery of chemotherapy or radiotherapy, invasive phenotype, piecemeal status and histological subtype demonstrated significance as predictors of DFS following univariate analysis but only tumour grade remained statistically significant following multivariate analysis ($p<0.0001$) (Fig 3).

Discussion

In this single centre study of primary and secondary RPS resections, the five-year OS rate of 55.3% is consistent with that in other referral centres while the five-year DFS rate of 24.8% is lower than in other reports.¹ This is probably a reflection of surgical approach as morbidity has been shown to increase with the number of organs resected in CCR and DFS has been shown to be greater with CCR. It follows, therefore, that DFS is likely to be greater relative to OS in centres practising CCR, as has been described,^{6,7} and that DFS is likely to be lesser relative to OS in centres performing non-CCR resection (and thus removing fewer organs). Our centre does not approach each case with CCR. However, if adjacent organ invasion is evidenced by

preoperative imaging or intraoperative appearance, then that organ is resected, bearing in mind the risk of morbidity and mortality.

Our data are consistent with the wide spread of disease recurrence rates between centres, and the varied relationship between five-year DFS and OS within centres.^{4,6} It is noteworthy that although CCR has been shown to improve DFS universally for RPS, OS has only been shown to benefit from CCR in low grade RPS.⁷ This observation could in some part be explained by our finding that high grade RPS is significantly more likely to recur outside of the original disease bed and so local control would be less relevant to preventing disease recurrence.

If there is an improvement to be made in the management of these high grade sarcomas, it will come from a systemic therapy. While traditional chemotherapy agents have only a palliative role in RPS, novel targeted inhibitors such as MDM2-p53 binding antagonists are in phase 1 clinical trials and showing promise.¹¹ Despite the heterogeneity of RPS, the genetic configuration of *MDM2* amplification with TP53 wild type status exists in the majority of these tumours and is thought to confer susceptibility to these targeted agents.^{12,15}

Recent publications have described the invasive behaviour of RPS, helping to explain the propensity to local recurrence. Previously, only high grade RPS was thought to be invasive but Mussi *et al* and Toulmonde *et al* found invasive behaviour in 25% and 33% respectively of the well differentiated liposarcoma (WDLs) cases they reported.^{3,4} Half (50%) of the tumours resected in our series demonstrated invasive behaviour on histopathological examination but the proportion was reduced (35%) when considering WDLs patients only. The difficulty of microscopically examining the surface of a 20cm tumour completely is noted. In their extensively histologically sampled prospective series, Mussi *et al* describe infiltration of at least one organ in 80% of their patients.⁵ As one of the four independent predictors of OS in our study, this invasive phenotype is a key aspect of RPS biology and offers an explanation as to how CCR has no proven survival benefit at present.

Our data also show that 42% of locoregional recurrence is intraperitoneal rather than retroperitoneal, emphasising the tumour's ability to invade surrounding tissues and mirroring the multifocal patterns of recurrence described in 2014 by Tseng *et al*.¹⁴ This has implications for radiotherapy as there is a high risk of radiation enteritis from delivering treatment doses to intraperitoneal tissue. Consequently, radiotherapy cannot offer local control to a tumour that has seeded into the peritoneum. However, should the hypothesis that preoperative radiotherapy minimises the intraoperative dissemination of disease be correct, it could still improve disease control with or without systemic therapy. If a means of stratifying propensity for intraperitoneal seeding can be found from tumour behaviour or biology, then any therapeutic value from radiotherapy could be realised more fully by appropriate biomarker guided selective use.

Conclusions

RPS often demonstrates microscopic invasion of neighbouring tissues. Local recurrence is common following macroscopically complete resection and is located at the disease bed or in the peritoneum with comparable frequency, with local recurrence in high grade tumours more likely to be intraperitoneal. Invasive behaviour is more common than has been thought previously, even in low grade RPS. We propose that these features of invasiveness and recurrence outside of the disease bed explain the lack of a demonstrable survival benefit from interventions aiming to increase local control in RPS. In the absence of highly effective systemic agents, however, surgery will remain the mainstay of primary treatment.

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References

- Swallow CJ, Catton CN. Improving outcomes for retroperitoneal sarcomas: a work in progress. *Surg Oncol Clin N Am* 2012; **21**: 317–331.
- Toulmonde M, Le Cesne A, Mendiboure J *et al*. Long-term recurrence of soft tissue sarcomas. *Cancer* 2014; **120**: 3,003–3,006.
- Mussi C, Colombo P, Bertuzzi A *et al*. Retroperitoneal sarcoma: is it time to change the surgical policy? *Ann Surg Oncol* 2011; **18**: 2,136–2,142.
- Toulmonde M, Bonvalot S, Mèus P *et al*. Retroperitoneal sarcomas: patterns of care at diagnosis, prognostic factors and focus on main histological subtypes: a multicenter analysis of the French Sarcoma Group. *Ann Oncol* 2014; **25**: 735–742.
- Pasquali S, Vohra R, Tsimopoulou I *et al*. Outcomes following extended surgery for retroperitoneal sarcomas: results from a UK referral centre. *Ann Surg Oncol* 2015; **22**: 3,550–3,556.
- Bonvalot S, Miceli R, Berselli M *et al*. Aggressive surgery in retroperitoneal soft tissue sarcoma carried out at high-volume centers is safe and is associated with improved local control. *Ann Surg Oncol* 2010; **17**: 1,507–1,514.
- 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**: 1,067–1,073.
- Stucky CC, Wasif N, Ashman JB *et al*. Excellent local control with preoperative radiation therapy, surgical resection, and intra-operative electron radiation therapy for retroperitoneal sarcoma. *J Surg Oncol* 2014; **109**: 798–803.

9. Surgery With or Without Radiation Therapy in Treating Patients With Previously Untreated Nonmetastatic Retroperitoneal Soft Tissue Sarcoma (STRASS). ClinicalTrials.gov. <http://clinicaltrials.gov/ct2/show/NCT01344018> (cited December 2015).
10. 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.
11. Ray-Coquard I, Blay JY, Italiano A *et al*. Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with MDM2-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study. *Lancet Oncol* 2012; **13**: 1,133–1,140.
12. Ohnstad HO, Castro R, Sun J *et al*. Correlation of TP53 and MDM2 genotypes with response to therapy in sarcoma. *Cancer* 2013; **119**: 1,013–1,022.
13. Thway K, Flora R, Shah C *et al*. Diagnostic utility of p16, CDK4, and MDM2 as an immunohistochemical panel in distinguishing well-differentiated and dedifferentiated liposarcomas from other adipocytic tumors. *Am J Surg Pathol* 2012; **36**: 462–469.
14. Tseng WW, Madewell JE, Wei W *et al*. Locoregional disease patterns in well-differentiated and dedifferentiated retroperitoneal liposarcoma: implications for the extent of resection? *Ann Surg Oncol* 2014; **21**: 2,136–2,143.