Prognostic implications of histological organ involvement in retroperitoneal sarcoma

R. Tyler [ID] [1],*, M. Lee[1], V. Ierodiakonou[2], J. Hodson[2], P. Taniere[2], M. Almond[2], S. Ford[2] and A. Desai[2]

[1]College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, UK
[2]Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, UK

Correspondence to: Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham B15 2TH, UK
(e-mail: robert.tyler@nhs.net)

Abstract

Background: The prognostic significance of histological organ involvement by retroperitoneal sarcoma subtype is unknown. The present study aimed to describe organ involvement across the subtypes, and the implications for survival.

Methods: Patients undergoing surgery for primary retroperitoneal sarcoma at the Queen Elizabeth Hospital, Birmingham from April 2005 to September 2018 were identified retrospectively. Histological organ involvement was classed as pushing, infiltrative or neither. Univariable and multivariable Cox regression models were produced to analyse the association between histological organ involvement and both overall (OS) and recurrence-free (RFS) survival for the cohort as a whole, and by histological subtype.

Results: Data were available for a total of 197 patients, of whom 171 (86.8 per cent) had at least one organ resected. Infiltrative organ behaviour was seen in 37 patients (18.8 per cent), and pushing behaviour in 67 (34.0 per cent). For the cohort as a whole, infiltration (hazard ratio (HR) 4.32, 95 per cent c.i. 2.35 to 7.93; $P < 0.001$), but not pushing (HR 1.62, 0.90 to 2.92; $P = 0.106$), was associated with significantly shorter OS, in comparisons with a group with neither of these behaviours. However, this effect was found to differ significantly by histological subtype ($P = 0.009$). For patients with dedifferentiated liposarcoma, there was no significant association between tumour behaviour and either OS ($P = 0.508$) or RFS ($P = 0.313$). However, in leiomyosarcoma, infiltrative behaviour was associated with shorter OS ($P = 0.002$), and both infiltrative ($P < 0.001$) and pushing ($P = 0.010$) behaviours were associated with shorter RFS, compared with tumours with neither behaviour. Multivariable analyses of both OS and RFS returned similar results.

Conclusion: The prognostic implications of organ involvement in retroperitoneal sarcoma vary by histological subtype.

Introduction

Sarcomas are a heterogeneous group of tumours of mesenchymal origin. There are around 3300 cases of soft tissue sarcoma diagnosed each year in the UK, accounting for 1.3 per cent of cancer diagnoses[1]. Soft tissue sarcomas predominantly affect the extremities, followed by the retroperitoneum. Retroperitoneal sarcomas (RPS) account for around 15 per cent of all sarcomas. The majority of these are well differentiated (WDLPS) or dedifferentiated (DDLPS) liposarcomas (70 per cent) and leiomyosarcomas (LMS) (15 per cent); there are smaller numbers of other histological types, such as undifferentiated pleomorphic sarcomas, solitary fibrous tumours, and malignant nerve sheath tumours[2].

RPS generally respond poorly to neoadjuvant therapy, and the only potential curative option is resectional surgery, where the primary aim is to leave no macroscopic disease, if possible[3]. To achieve this, some centres advocate *en bloc* resection, whereby potentially uninvolved organs are also resected, in order to obtain a margin of healthy tissue. Despite radical surgery, local recurrence is common, especially in liposarcoma, and is the leading cause of death[4]. Opponents of extended surgery point to this fact

to advocate a more conservative approach, with organs only being resected when directly invaded.

Resected organs can show signs of histological organ involvement (HOI). Mussi and colleagues[5] described two such patterns. The first is 'pushing', where an organ is embedded in a tumour without being invaded; this has also been referred to as 'adherent' in the literature[6]. The second is 'infiltrative', where clear evidence is noted of direct tumour infiltration into an organ[5].

Rates of organ involvement have been described by several groups[7–9]. Toulmonde and colleagues[9] and Fairweather *et al.*[7] explored HOI as an adverse prognostic factor in RPS; the latter described HOI as independent risk factor for overall survival (OS), and called for external validation of their findings. However, both groups examined RPS as an entirety, rather than as heterogeneous subtypes.

Although the effect of HOI has been Toulmin studied previously, evidence is currently lacking regarding whether the type of HOI (pushing or infiltrative) is prognostically relevant and, if so, in which histological subtypes. As the surgical approach is influenced by histology, a greater understanding of organ involvement by subtype would be a useful addition to aid surgical planning,

and to inform the debate on the rationale for organ resection. The present study aimed to describe patterns of organ involvement, both pushing and infiltrative, across histological subtypes, and the implications of this for recurrence-free survival (RFS) and OS.

Methods

Patients undergoing surgery with curative intent for primary RPS from April 2005 to September 2018 were identified from the clinical databases of a soft tissue sarcoma referral centre, Queen Elizabeth Hospital, Birmingham. Patients with benign, metastatic or recurrent disease were excluded, as were those with gastrointestinal tumours and paragangliomas. All patients were discussed at a sarcoma multidisciplinary team meeting. The operative approach was informed by preoperative imaging and biopsy results, as well as intraoperative findings.

The aim of surgery was removal of the entire macroscopic tumour burden in a single specimen. Contiguous non-vital organs were removed if invaded macroscopically, or it was felt that removing these organs increased the chances of microscopically negative margins. A standard *en bloc* approach to resection, involving compartectomy for all RPS, was refined by the authors, and tailored to fit the patient and tumour histology.

Patient surveillance imaging and follow-up was informed by European Society for Medical Oncology guidelines[10], and tailored to tumour grade and histological subtype. The majority of patients attended follow-up for 5 years at the soft tissue sarcoma referral centre; however, as the unit receives UK-wide referrals, some were followed up at local centres, and clinical progress tracked there.

Standard patient demographics were collected, alongside pathological variables, including: histological subtype, tumour size, grade, tumour necrosis, tumour rupture, neoadjuvant and adjuvant therapy, and the numbers and types of organ resected. Tumours were graded based on the Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) definitions[11]. As these were not applicable to all tumour types, such as chordoma and solitary fibrous tumour, patients with these tumours were excluded from analyses of tumour grade and considered as a 'not applicable' category for multivariable analysis. Margins were defined as macroscopically complete (R0/R1) or incomplete (R2). Postoperative morbidity was quantified by the highest Clavien–Dindo grade of complication occurring within 30 days of surgery[12].

Histopathological assessment

All histological specimens were evaluated by specialist sarcoma pathologists, according to international guidelines[13]. Pathological assessment was based on one formalin-fixed, paraffin-embedded tissue block per cm of tumour up to a maximum of 12. All subtype appearances were sampled, such as lipomatous, firm necrotic, and oedematous. Margins or areas of concern were highlighted by the surgeon either by means of comments on the request form, operative notes made available at the time of sampling, or by surgeons physically present in the department.

Tumour behaviour was initially quantified separately for each organ; organs were defined as any solid or hollow viscera, bony structure, nerve, blood vessel or muscle[7]. Evidence was gathered from surgical pathology reports and confirmed on re-review by a single expert pathologist. If ambiguity existed about which type

of tumour behaviour was present, slides were re-examined. For each resected organ, the tumour behaviour was classed as either 'infiltration', 'pushing' or 'neither' in accordance with the description by Mussi and colleagues[5]. As such, infiltration was deemed present where there was clear evidence, on microscopic assessment, of either focal or diffuse permeation/invasion by nests or single cells of tumour into normal organs, for example normal renal cortex or tunica muscularis of the bowel. Pushing tumours encompassed those that were in direct contact with organs, with no healthy tissue to separate them at this point but had no evidence of direct infiltration on microscopic assessment. 'Neither' described a setting where healthy tissue, such as retroperitoneal fat, lay between the tumour and nearby organs. Organs that were not resected were assigned to the neither group. For analysis, patients were classified by the highest level of HOI observed across all organs, based on the ordered scale of neither, pushing, and infiltration.

DDLPS was defined as liposarcoma with any evidence of dedifferentiation, even if the majority of the tumour was well differentiated; liposarcomas were otherwise classified as WDLPS. In line with previous studies, isolated ureteral involvement was recorded separately; however, when the kidney was involved in addition to the ureter, the two structures were combined and counted only once. Organ invasion was not recognized if a tumour originated from within that organ, such as LMS in the inferior vena cava, unless the tumour infiltrated through it and into surrounding tissues.

Survival outcomes

For survival outcomes, follow-up commenced at the time of surgery, with patients being censored at the time of final clinic attendance. Because the surveillance programme lasted for 5 years, follow-up was truncated at this point, with all patients being censored. Recurrence was initially divided into local recurrence (LR) and distant metastasis (DM), with both of these outcomes being death-censored. Six patients were followed up at external centres that did not share follow-up data; recurrence status was not therefore available for these patients, although dates of death were recorded, where applicable. As such, these patients were excluded from analyses of recurrence but included in the analysis of OS. Analysis of LR additionally excluded patient who had R2 resection. RFS was calculated based on a composite outcome of death, LR or DM.

Statistical analysis

Continuous variables are reported as mean(s.d.) where approximately normally distributed, and median (i.q.r.) otherwise. Comparisons of factors between tumour behaviour groups were performed using Kruskal–Wallis tests for ordinal or continuous variables, and Fisher's exact test for nominal variables. Survival outcomes were initially assessed using univariable Cox regression models to generate hazard ratios (HRs), 95 per cent confidence intervals, and *P* values. Kaplan–Meier curves were used to estimate survival rates and median survival times. Cox regression models were extended to include histology, and an interaction term between histology and tumour behaviour, to assess whether the effect of tumour behaviour differed by histology. Where this interaction term was significant, subgroup analyses were performed by histology, to visualize this effect.

Multivariable Cox regression models were produced to adjust for the effects of other potentially confounding factors. To account

for the potential interaction between tumour histology and behaviour, a composite variable was produced, which grouped patients based on the combination of these two factors. This variable was then entered into the model at the first step, with a backwards stepwise approach (removal at $P > 0.100$) used to select independent predictors of outcomes for inclusion in the model. The resulting model was evaluated using different reference categories for the composite tumour histology and behaviour variable, in order to calculate HRs comparing across the categories of tumour behaviour within each subgroup of tumour histology.

$P < 0.050$ was deemed indicative of statistical significance throughout. All analyses were performed using SPSS® version 22 (IBM, Armonk, NY, USA).

Results

Demographics

Data were available for a total of 197 patients, with a mean(s.d.) age at surgery of 61.8(13.4) years. The most common histology was liposarcoma (35.0 per cent DDLPS, 25.9 per cent WDLPS). The majority of tumours were of FNCLCC grade 3 (45.8 per cent). Neoadjuvant and adjuvant therapies were used in 7.7 and 9.9 per cent of patients respectively. Further details of the cohort are reported in Table 1.

Patient outcomes

R status was recorded for 183 patients, of whom seven (3.8 per cent) underwent R2 resections. The 30-day Clavien–Dindo grade III–V complication rate was 15.6 per cent, with four postoperative deaths (2.2 per cent). Long-term follow-up was truncated at 5 years after surgery; median follow-up for the cohort was 29 (i.q.r. 15–57) months. The recurrence status was not recorded in six patients, so analysis of DM was based on 191 patients. Analysis of LR additionally excluded those who had R2 resections, leaving 184 patients for analysis.

During follow-up, there were 70 deaths. Kaplan–Meier estimated survival rates were 86.8, 60.0, and 50.6 per cent at 1, 3, and 5 years respectively. A total of 70 patients developed LR and 45 DM, of whom 26 developed both. Kaplan–Meier estimated death-censored recurrence rates at 5 years were 43.2 and 33.2 per cent for LR and DM respectively. Treating LR or DM as a composite outcome gave overall death-censored recurrence rates of 23.7, 49.1, and 62.9 per cent at 1, 3, and 5 years respectively (median 37 months). Estimated RFS rates were 74.0, 46.3, and 31.3 per cent at 1, 3, and 5 years respectively (median 33 months).

Resection rates and tumour behaviour by organ

Resection of at least one organ was performed in 171 patients (86.8 per cent); the most commonly resected organs were kidney (56.3 per cent) and colon (54.3 per cent). In total, 506 organs were resected, a median of 2 (mean 2.6, range 0–8) per patient. The highest level of HOI was infiltration in 37 patients (18.8 per cent) and pushing in 67 (34.0 per cent); the remainder exhibited neither behaviour (93, 47.2 per cent). Further details of tumour behaviour and resection rates for each organ are reported in Table S1.

Associations with tumour behaviour

Tumour behaviour varied by year of surgery, there being fewer pushing and infiltrating tumours resected more recently ($P = 0.014$). Patient demographics did not differ significantly between the three tumour behaviour groups (Table 2). However, a significant difference in tumour histology was observed ($P = 0.002$); 56.8 per cent of tumours in the infiltration group were

Table 1 Patient demographics and tumour details

	n	No. of patients*
Age at surgery (years)†	197	61.8(13.4)
BMI (kg/m²)†	187	27.1(5.7)
White ethnicity	197	181 (91.9)
Men	197	109 (55.3)
Year of surgery	197	
2005–2009		37 (18.8)
2010–2014		80 (40.6)
2015–2018		80 (40.6)
Histology	197	
WDLPS		51 (25.9)
DDLPS		69 (35.0)
LMS		39 (19.8)
Other		38 (19.3)
Tumour size (cm)‡	192	21 (14–30)
FNCLCC grade§	166	
1		52 (31.3)
2		38 (22.9)
3		76 (45.8)
Tumour necrosis	187	77 (41.2)
Tumour rupture	196	7 (3.6)
Neoadjuvant therapy	195	
None		180 (92.3)
Radiotherapy		9 (4.6)
Chemotherapy		5 (2.6)
Chemoradiotherapy		1 (0.5)
Adjuvant therapy	191	
None		172 (90.1)
Radiotherapy		14 (7.3)
Chemotherapy		5 (2.6)
No. of organs resected¶	197	
0		26 (13.2)
1		35 (17.8)
2		38 (19.3)
3		43 (21.8)
4		24 (12.2)
5		20 (10.2)
> 5		11 (5.6)
R2 resection	183	7 (3.8)
Clavien–Dindo complication grade (within 30 days)	180	
No complication		100 (55.6)
I–II		52 (28.9)
III–IV		24 (13.3)
V (death)		4 (2.2)

*With percentages in parentheses unless indicated otherwise; values are †mean(s.d.) and ‡median (i.q.r.). §Excludes 21 patients with underlying pathology for whom Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) grading was not applicable. ¶The ureter is not counted when resected alongside the kidney. n, Total number of patients, after excluding those with missing data for the stated factor. WDLPS, well differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; LMS, leiomyosarcoma.

DDLPS, compared with 35.8 and 25.8 per cent in the pushing and neither groups respectively. Tumour infiltration was also associated with a significantly higher risk of tumour rupture ($P = 0.043$). Tumours in the infiltration and pushing groups had significantly higher FNCLCC grades ($P = 0.005$), were larger in size ($P = 0.006$), and associated with resection of a larger number of organs ($P < 0.001$) than the group showing neither behaviour. However, rates of R2 resection were similar in the three groups ($P = 0.416$), as was the complication rate ($P = 0.690$).

Outcomes by tumour behaviour

In univariable analysis, OS differed significantly between the three groups of tumour behaviour, with 5-year survival rates of 16.4 per cent in those with infiltration, 52.2 per cent in those with pushing, and 64.9 per cent for patients with tumours with neither behaviour ($P < 0.001$) (Fig. 1a). Comparisons with the neither

Table 2 Associations with tumour behaviour

	n	Tumour behaviour			P¶
		Neither	Pushing	Infiltration	
Age at surgery (years)*	197	60.5(14.6)	62.8(12.9)	63.1(10.9)	0.743#
BMI (kg/m²)*	187	27.6(6.2)	26.4(5.0)	27.0(5.9)	0.429#
White ethnicity	197	83 (89.2)	63 (94.0)	35 (94.6)	0.540
Men	197	51 (54.8)	35 (52.2)	23 (62.2)	0.617
Year of surgery	197				0.014#
2005–2009		16 (17.2)	12 (17.9)	9 (24.3)	
2010–2014		28 (30.1)	40 (59.7)	12 (32.4)	
2015–2018		49 (52.7)	15 (22.4)	16 (43.2)	
Histology	197				0.002
WDLPS		31 (33.3)	18 (26.9)	2 (5.4)	
DDLPS		24 (25.8)	24 (35.8)	21 (56.8)	
LMS		19 (20.4)	10 (14.9)	10 (27.0)	
Other		19 (20.4)	15 (22.4)	4 (10.8)	
Tumour size (cm)†	192	18 (11–26)	25 (17–30)	21 (15–38)	0.006#
FNCLCC grade‡	166				0.005#
1		31 (41.3)	16 (29.1)	5 (13.9)	
2		19 (25.3)	10 (18.2)	9 (25.0)	
3		25 (33.3)	29 (52.7)	22 (61.1)	
Tumour necrosis	187	36 (41.4)	23 (35.4)	18 (51.4)	0.294
Tumour rupture	196	2 (2.2)	1 (1.5)	4 (10.8)	0.043
Neoadjuvant therapy	195	6 (6.6)	5 (7.5)	4 (10.8)	0.725
Adjuvant therapy	191	10 (11.2)	5 (7.5)	4 (11.4)	0.731
No. of organs resected§	197				<0.001#
0		26 (28.0)	0 (0.0)	0 (0.0)	
1–2		36 (38.7)	25 (37.3)	12 (32.4)	
3–4		21 (22.6)	32 (47.8)	14 (37.8)	
≥ 5		10 (10.8)	10 (14.9)	11 (29.7)	
R2 resection	183	5 (6.0)	1 (1.5)	1 (2.9)	0.416
Clavien–Dindo complication grade	180				0.690#
No complication		46 (56.1)	36 (57.1)	18 (51.4)	
I–II		26 (31.7)	17 (27.0)	9 (25.7)	
III–V		10 (12.2)	10 (15.9)	8 (22.9)	

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r.). ‡Excludes 21 patients with underlying pathology for whom Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) grading was not applicable. §The ureter is not counted when resected alongside the kidney. n, Total number of patients, after excluding those with missing data for the stated factor. WDLPS, well differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; LMS, leiomyosarcoma. ¶Fisher's exact test, except #Kruskal–Wallis test.
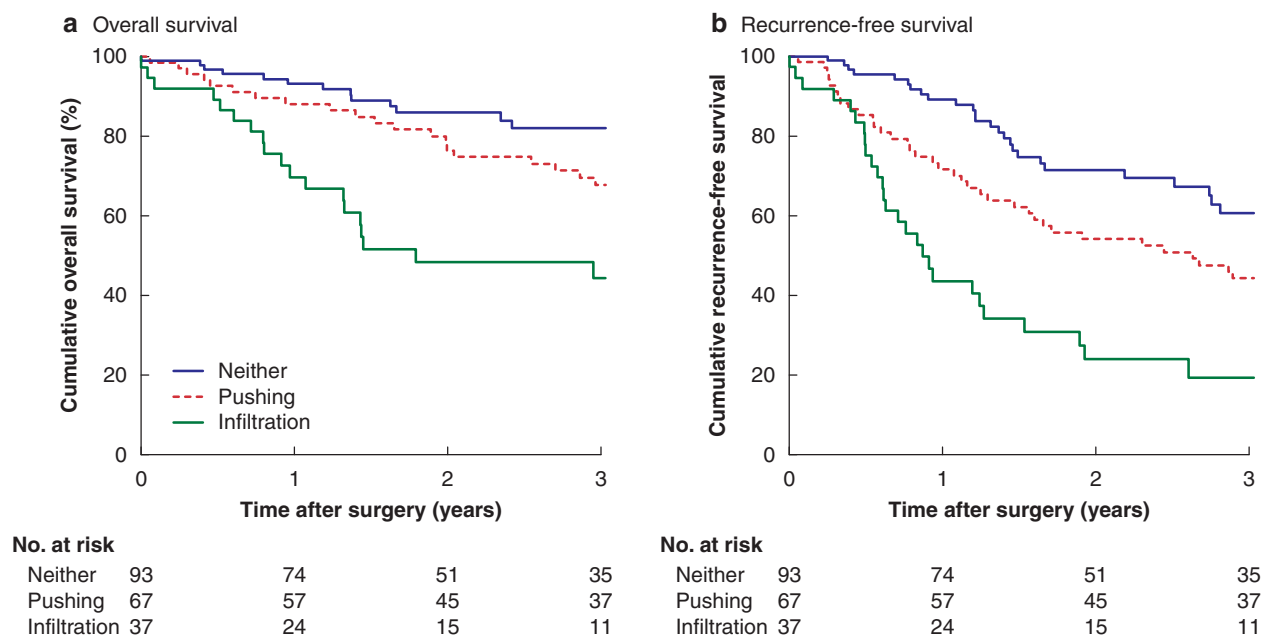

Fig. 1 Kaplan–Meier curves for survival outcomes by tumour behaviour

a Overall and **b** recurrence-free survival. Analysis of recurrence-free survival excludes six patients for whom the recurrence status was not recorded as they were followed up externally. Univariable Cox regression: **a** P < 0.001, **b** P < 0.001

Table 3 Associations between tumour behaviour and survival outcomes

	Overall P*	Pushing		Infiltration	
		Hazard ratio	P	Hazard ratio	P
Overall survival					
Whole cohort	<0.001	1.62 (0.90, 2.92)	0.106	4.32 (2.35, 7.93)	<0.001
WDLPS	_*	_*		_*	
DDLPS	0.508	1.44 (0.60, 3.46)	0.409	1.70 (0.69, 4.22)	0.248
LMS	0.004	1.39 (0.37, 5.18)	0.625	6.52 (1.99, 21.30)	0.002
Other histology	<0.001	1.32 (0.45, 3.83)	0.610	14.50 (3.55, 59.10)	<0.001
Recurrence-free survival					
Whole cohort	<0.001	1.68 (1.07, 2.65)	0.025	3.73 (2.24, 6.21)	<0.001
WDLPS	_*	_*		_*	
DDLPS	0.313	1.24 (0.60, 2.56)	0.556	1.76 (0.83, 3.72)	0.137
LMS	0.002	3.54 (1.35, 9.27)	0.010	7.44 (2.31, 24.00)	<0.001
Other histology	<0.001	1.37 (0.54, 3.45)	0.510	15.60 (3.75, 64.50)	<0.001

Values in parentheses are 95 per cent confidence intervals. WDLPS, well differentiated liposarcoma; DDLPS, dedifferentiated liposarcoma; LMS, leiomyosarcoma. Results are from univariable Cox regression models: overall P refers to comparison between three tumour behaviour groups (neither *versus* pushing *versus* infiltration); hazard ratios and associated P values represent pairwise comparisons between stated *versus* neither group. *Not calculable, as there were no events in one of the tumour behaviour groups.

group found infiltration (HR 4.32, 95 per cent c.i. 2.35 to 7.93; $P < 0.001$), but not pushing (HR 1.62, 0.90 to 2.92; $P = 0.106$), to be associated with significantly shorter OS (*Table 3*).

A progressive reduction in RFS was observed across the three groups ($P < 0.001$) (*Fig. 1b*). Median RFS was 48 months for the neither group, compared with 32 months (HR 1.68, 1.07 to 2.65; $P = 0.025$) in those with pushing and 10 months (HR 3.73, 2.24 to 6.21; $P < 0.001$) in those with infiltration (*Table 3*). Death-censored analyses of the types of recurrence showed significantly increased rates of LR ($P < 0.001$), but not DM ($P = 0.064$) in those with infiltration; neither of these outcomes was significantly increased in those with pushing behaviour ($P = 0.417$ and $P = 0.223$ respectively).

Subgroup analysis by histology

Patients with WDLPS tumours were excluded from the subgroup analysis owing to the small number of outcomes; 5-year OS and RFS rates were 98.0 and 71.4 per cent respectively. For the remaining patients, Cox regression models were produced, with tumour behaviour, histology, and an interaction term as co-variables. These found the interaction terms to be significant for analyses of both OS and RFS ($P = 0.009$ and $P = 0.002$ respectively), implying that the association between tumour behaviour and survival outcomes varied based on the tumour histology.

This effect is shown in *Table 3* and visualized in *Figs 2* and *3*. For patients with DDLPS, neither OS nor RFS differed by tumour behaviour ($P = 0.508$ and $P = 0.313$ respectively). However, both outcomes differed significantly for the subgroup of LMS ($P = 0.004$ and $P = 0.002$ respectively). In keeping with the results for the cohort as a whole, in patients with LMS, tumour infiltration was found to be associated with significantly shorter OS ($P = 0.002$), whereas both pushing ($P = 0.010$) and infiltration ($P < 0.001$) were associated with significantly shorter RFS. For the subgroup of other tumour types, tumour infiltration, but not pushing, was associated with both significantly shorter OS and RFS ($P < 0.001$).

Multivariable analysis

Multivariable models were produced for the outcomes OS and RFS, which considered all factors from *Table 2* for inclusion, except Clavien–Dindo grade. The resulting models found OS to be significantly shorter in patients receiving neoadjuvant therapy

($P = 0.010$) and in those with lower BMI ($P = 0.026$), whereas FNCLCC grade 3 tumours were associated with significantly shorter RFS ($P = 0.046$) (*Table 4*). After accounting for these factors, the effects of tumour behaviour within the histological subgroups were consistent with those of the univariable analyses.

Discussion

This is the first study in RPS to explore the rates and prognostic significance of HOI by tumour histology. RPS are heterogeneous in terms of tumour biology and patterns of failure, and require separation, where patient numbers allow, into distinct histological subtypes. The results show that, although organ involvement is independently predictive of poor OS and RFS in RPS as an entity, when examined by histological subtype, key differences exist. Organ involvement appears to carry more prognostic significance in LMS than in DDLPS. Of interest, by dividing tumour behaviour into pushing and infiltrating subtypes, it becomes evident that pushing tumours, although not directly invading, still carry poorer long-term outcomes .

Patient demographics did not vary across the groups of tumour behaviour. Tumour behaviour differed by histology, with DDLPS having the highest rates of infiltration (30.4 per cent). This is interesting, as liposarcomas are generally considered to be pushing tumours, although pushing was observed in 34.8 per cent of DDLPS. Tumour behaviour varied significantly across the years of surgery ($P = 0.014$). As tumour histology was significantly associated with tumour behaviour, this change over time was driven by an evolving case mix, and larger referral network for the sarcoma unit.

Infiltrating tumours were significantly larger in size, of higher grade, and had higher rates of rupture than non-infiltrating tumours. Notably, the R2 resection rate and 30-day complication rates did not differ significantly between tumour behaviours. This suggests that larger, higher-grade tumours that infiltrate and push may be resectable with no additional morbidity or compromise of margin status. This is especially important, considering a major argument against liberal multivisceral resection in RPS is morbidity outweighing the survival benefit.

LMS accounted for 39 tumours (19.8 per cent), of which 10 were infiltrating and 10 pushing. In this subgroup, infiltration
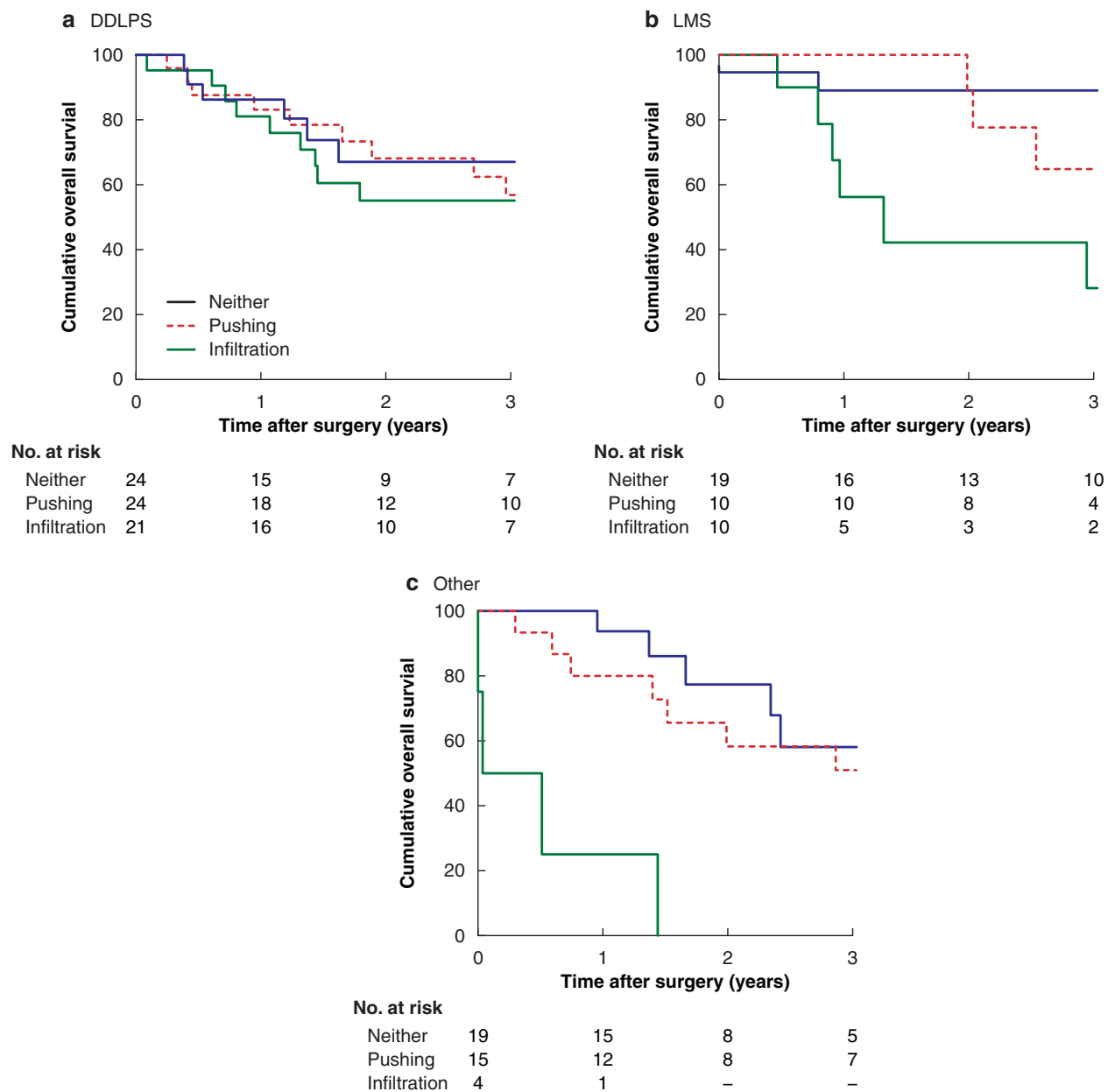
Fig. 2 Kaplan–Meier curves for overall survival by tumour behaviour within histology subgroups

a Dedifferentiated liposarcoma (DDLPS), **b** leiomyosarcoma (LMS), and **c** other histology. Patients with well differentiated liposarcoma were excluded, because of the low event rate in this subgroup. **a** $P = 0.508$, **b** $P = 0.004$, **c** $P < 0.001$ (univariable Cox regression).

was associated with significantly shorter OS, whereas both pushing and infiltration were associated with poorer RFS; these findings were consistent in both univariable and multivariable analyses. Poor RFS in LMS tends to be driven by distant metastatic disease, although Smith and co-workers[15] reported an abdominal local recurrence rate of 20 per cent at 3 years. Based on these data, it could be considered that infiltrative tumour behaviour reflects a more aggressive tumour biology in LMS, leading to both local and distant recurrence, and eventually death. Therefore, it could be argued that, in the presence of overt macroscopic invasion by a LMS, noted at the time of surgery, a less aggressive surgical policy should employed because of expected poor long-term survival rates.

The most commonly resected histology in this study was DDLPS. As a subtype, 30.4 per cent of such tumours infiltrated at least one organ, the most common being the colon in seven patients followed by the iliopsoas in six. In patients with DDLPS, neither OS or RFS differed by tumour behaviour in either univariable or multivariable analysis. Nevertheless, even without a significant effect on local and overall recurrence, the high rates of infiltration by this subtype warn against a more conservative surgical approach.

A total of 51 WDLPS were resected. Crucially, the potential for these tumours to be locally invasive was shown in two patients, in whom the iliopsoas and diaphragm were invaded. This has been described by previous groups, challenging the view that these lesions are low-grade benign entities, and reinforcing the
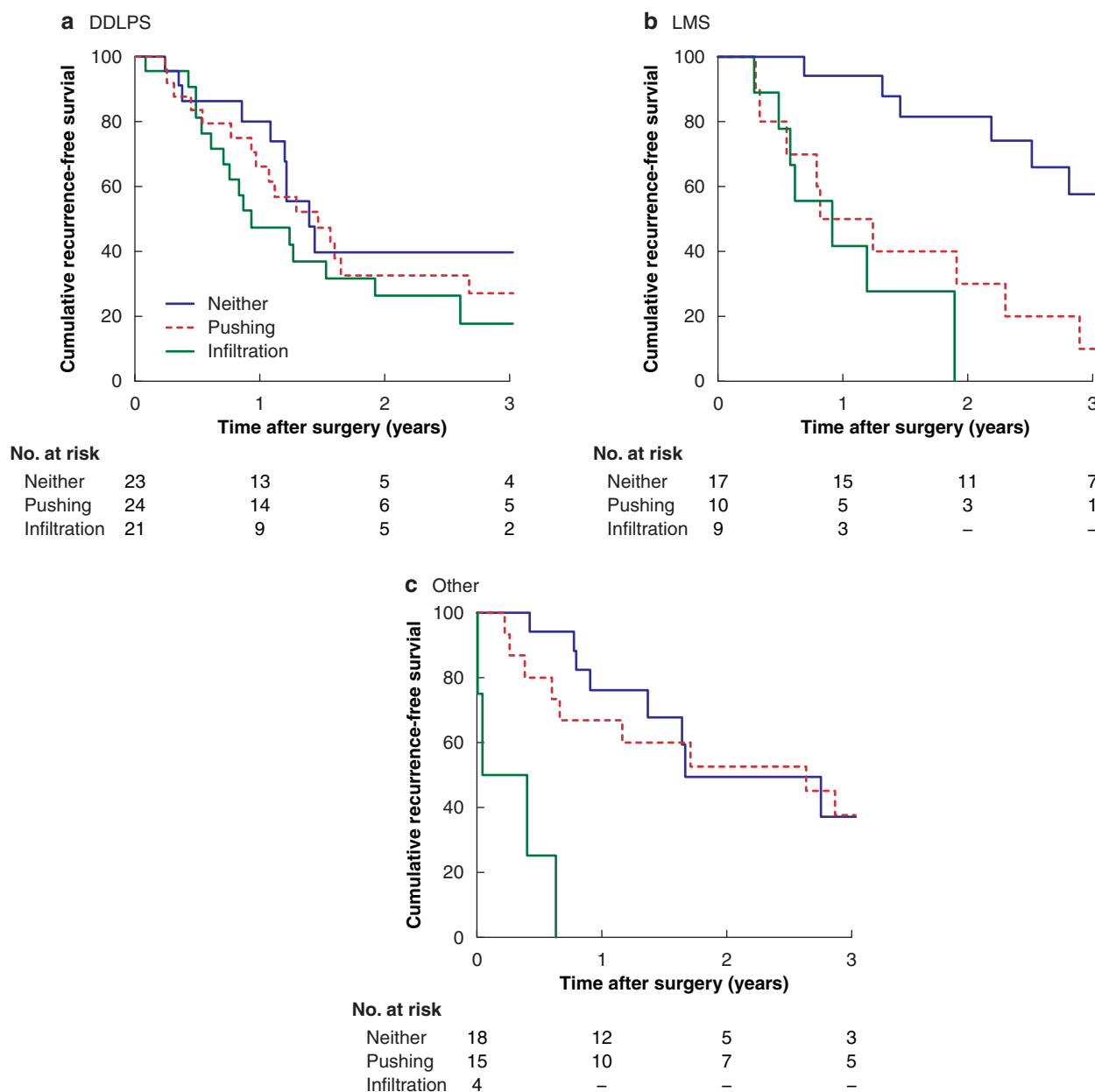
Fig. 3 Kaplan–Meier curves for recurrence-free survival by tumour behaviour within histology subgroups

a Dedifferentiated liposarcoma (DDLPS), **b** leiomyosarcoma (LMS), and **c** other histology. Patients with well differentiated liposarcoma were excluded because of the low event rate in this subgroup, as were those for whom the recurrence status was not recorded as they were followed up externally. **a** $P = 0.313$, **b** $P = 0.002$, **c** $P < 0.001$ (univariable Cox regression).

need for a wide margin of resection where safe and appropriate[5,9].

In multivariable analysis, OS was significantly shorter in patients who received neoadjuvant therapy (HR 3.05, 95 per cent c.i. 1.31 to 7.10; $P = 0.010$). As neoadjuvant therapy is rarely given at the study institution for liposarcoma or LMS, this identifies the more aggressive tumours in the subgroup with other histology. Rather surprisingly, patients with a lower BMI were found to have poorer OS. The protective effect of obesity has been described in several cancers, including colorectal, breast and prostate, but this may also reflect a preoperative cachectic state[21].

The study had some important limitations. A standardized approach to processing the pathological specimen was not predefined, and, owing to the size of these tumours, it is not guaranteed that all margins to major organs were assessed. In addition, a patient selection bias exists regarding organ resection, influenced by preoperative radiological imaging, age, comorbidities, and intraoperative dissection planes. Finally, as with all studies of this nature, it cannot be known that unresected organs were not pushed or invaded by the tumour, and remained *in situ*. Nevertheless, if pushing and infiltration in the neither group had been missed, the effect sizes would have been underestimated rather than overestimated.

This study has demonstrated that the prognostic implications of organ invasion vary according to histological subtype. This is important at a time when RPS surgery and management is becoming increasingly tailored to reflect tumour histology.

Table 4 Multivariable analysis of survival outcomes

	Overall survival		Recurrence-free survival	
	Hazard ratio	P	Hazard ratio	P
Histology/behaviour		0.009		0.019
DDLPS				
Neither	1.00 (reference)		1.00 (reference)	
Pushing	1.02 (0.36, 2.86)	0.977	0.94 (0.42, 2.11)	0.879
Infiltration	1.46 (0.52, 4.09)	0.473	1.90 (0.86, 4.22)	0.115
LMS				
Neither	1.00 (reference)		1.00 (reference)	
Pushing	4.20 (0.45, 39.1)	0.207	3.46 (1.09, 11.0)	0.036
Infiltration	13.6 (1.49, 124.3)	0.021	3.98 (1.08, 14.7)	0.038
Other histology				
Neither	1.00 (reference)		1.00 (reference)	
Pushing	1.66 (0.52, 5.24)	0.390	0.89 (0.32, 2.52)	0.829
Infiltration	26.8 (4.15, 173.6)	0.001	10.81 (1.79, 65.2)	0.009
BMI (per 5 kg/m^2)	0.66 (0.45, 0.95)	0.026		−†
Year of surgery		0.100		−†
2005–2009	1.00 (reference)			
2010–2014	1.57 (0.65, 3.81)	0.317		
2015–2018	0.65 (0.21, 2.02)	0.455		
FNCLCC grade		−†		0.052
1			1.00 (reference)	
2			1.30 (0.46, 3.70)	0.626
3			2.84 (1.02, 7.88)	0.046
Not applicable*			1.45 (0.35, 6.07)	0.607
Tumour necrosis		−†	0.60 (0.34, 1.04)	0.071
Neoadjuvant therapy	3.05 (1.31, 7.10)	0.010	2.14 (0.93, 4.93)	0.073

Values in parentheses are 95 per cent confidence intervals. *Patients with histologies for which Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) grading was not applicable were grouped into a separate category, to prevent their exclusion from the analysis. DDLPS, dedifferentiated liposarcoma; LMS, leiomyosarcoma. Multivariable Cox regression models were produced, with a variable consisting of all combinations of tumour histology and behaviour (9 groups) entered at the first step. Patients with well differentiated liposarcoma (WDLPS) were excluded from analysis owing to small number of outcomes. All factors in *Table 2*, except Clavien–Dindo grade, were considered for inclusion in the models, with a backwards stepwise approach used to produce parsimonious models. These models were then evaluated to produce hazard ratios comparing across tumour behaviours for each histology separately. After excluding patients with WDLPS and those with missing data on any of the factors considered, the final models were based on 115 patients, with 51 and 76 events for overall and recurrence-free survival respectively. Only factors selected for inclusion for the models of at least one of the two outcomes are shown in the table. †Not selected for inclusion by the stepwise procedure.

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Supplementary material

Supplementary material is available at *BJS Open* online.

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