Surgery for retroperitoneal soft tissue sarcomas: aggressive re-resection of recurrent disease is possible

R Lochan, JJ French, DM Manas

Regional Sarcoma Centre, Hepatopancreatobiliary and Transplantation Surgery, Department of Surgery, Freeman Hospital, Newcastle upon Tyne, UK

ABSTRACT

INTRODUCTION Retroperitoneal soft tissue sarcomas represent a relatively rare and complex therapeutic problem where surgery forms the mainstay of treatment and is technically demanding. In this study, we review a single UK centre's experience with the surgical management of retro-peritoneal soft tissue sarcoma.

PATIENTS AND METHODS We present analysis of data on patients treated between 1997 and 2006, our first 75 patients. Data collected from the Access database, included patient demographics, staging modalities, peri-operative details, treatment, outcome, pathological diagnosis and subsequent complications.

RESULTS A total of 75 patients (M:F, 44:31) underwent 115 resectional procedures as part of the management of retroperitoneal soft-tissue sarcoma. There were 12 major complications for the 115 procedures (morbidity of 8.69%). The 30-day operative mortality was zero and the 90-day mortality rate was 1.33% (1/75). Follow-up ranged from 16–131 months. The median disease-free survival was 69 months (range, 59–78 months). Recurrences developed in 46 patients; median time to overall recurrence was 13 months (range, 3–71 months). Of these 46, 22 developed localised recurrence, which was amenable to further resection. In the cohort of patients with recurrent disease, median survival in those who underwent surgery was 53 months (range, 30–76 months) and median survival in those who did not undergo surgery was 30 months (range, 18–41 months) and this difference was statistically significant (log rank, $P = 0.01$).

CONCLUSIONS Extensive resectional surgery with minimal morbidity, devoid of mortality is feasible in the treatment of retroperitoneal sarcoma. Development of recurrent disease is a significant factor influencing survival; however, localised recurrences are amenable to surgery and this can lead to improved survival.

KEYWORDS

Retroperitoneal sarcoma – Local recurrence – Aggressive surgical resection – Survival

Accepted 19 July 2010; published online 8 September 2010

CORRESPONDENCE TO

DM Manas, Professor and Consultant Surgeon Hepato-Pancreato-Biliary, Abdominal Organ Transplant and Sarcoma Surgery, Department of Surgery, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK

T: +44 (0)191 244 8379; F: +44 (0)191 223 1152; E : derek.manas@nuth.nhs.uk

Retroperitoneal soft tissue sarcomas (RPSTS) are a complex group of tumours whose biological behaviour is poorly understood. For most retroperitoneal sarcomas, microscopically complete surgical excision is the best means of achieving long-term survival and this is technically challenging. This is because of their close proximity to viscera and neurovascular structures around the axial skeleton. In addition, they are a heterogeneous group of neoplasms and their outcome depends on tumour biology. Even in the commonest subtype (*i.e.* liposarcoma), the 5-year survival can vary from 41.9% for well-differentiated liposarcomas¹ to 7.8% for the poorly differentiated variety. Thus a multidisciplinary approach to their management with surgical resection playing a major role is increasingly adopted. However, chemotherapy and radiotherapy have a limited role in the

management of these tumours as a sole modality though there is a growing body of evidence that selected tumours benefit with a multimodality approach utilising chemotherapy and or radiotherapy in the adjuvant or neo-adjuvant setting with resectional surgery.

Our unit is affiliated to one of the supraregionally designated extremity sarcoma units in the UK. We evaluate patients with RPSTS mainly from the North of England and, frequently, from other areas of the UK. We have sought to evaluate the outcome of surgical management of our first 75 patients.

Patients and Methods

Data were retrospectively collected into an Access database,

on patients undergoing surgery for intra-abdominal soft tissue sarcoma between 1997 and 2003 and prospectively from 2004 to date. Overall, 110 non-extremity sarcomas were referred of which 81 were retroperitoneal. Data recorded included patient demographics, staging investigative modalities, peri-operative details, treatment, outcome, pathological diagnosis and subsequent complications.

All patients underwent a contrast enhanced computerised tomographic (CECT/CT) scan of the chest abdomen and pelvis to stage the disease. Additional imaging including contrast magnetic resonance (MR) scan; MR angiogram was performed selectively depending on the CT findings. Where radiology was equivocal as to the nature of the tumour, a further laparoscopy and diagnostic trucut biopsy was performed under a general anaesthetic using a protected port.

In all cases, imaging and histology were reviewed in a multidisciplinary team meeting. We follow a policy of treating chemo- and radiosensitive tumours with primary chemo- or radiotherapy as appropriate with salvage surgery for recurrent disease. Chemo-/radio-insensitive tumours (*i.e.* retroperitoneal sarcomas) were treated with radical surgery when operable. Our criteria for inoperability include: (i) a medically unfit patient; (ii) local inoperability; and (iii) extra-abdominal disseminated disease. In selected cases, a palliative debulking resection was performed where the patient had a good performance score and was symptomatic from the disease. After surgery, all patients were followed up for at least 5 years being assessed clinically at 3-monthly intervals for the first 2 years and 6-monthly thereafter. Surveillance was performed with imaging to identify recurrence. Chest, abdomen and pelvic CT scans were obtained at 6-monthly intervals for the first 2 years and when clinically indicated thereafter. These patients were treated purely based on the disease and the patient fitness and consent to undergo treatment. No attempt was made to select/randomise patients for primary/ recurrent resectional surgery.

Statistical analysis was performed using a SPSS v15 statistical package. Standard methods of descriptive analysis as well as univariate and multivariate analysis of the data were performed using ANOVA and multiple logistic regressions to assess factors influencing survival.

Results

Eighty-one patients with retroperitoneal sarcomas were referred during the study; of these, 75 patients (M:F, 44:31) underwent surgery as part of the management of retroperitoneal soft-tissue sarcoma. Seventy-two had primary disease, whilst three underwent resection of a recurrence from a primary intra-abdominal sarcoma resected elsewhere. A total of 115 resectional procedures was carried out (summarised in Fig. 1).

Figure 1 Summary of management of patients.

En bloc resection of retroperitoneal sarcoma with macroscopically clear margin was achieved in 106 out of 115 procedures, which necessitated various organ resections – 35 nephrectomies, 32 small bowel resections, 29 large bowel resections, 12 hepatectomies, eight urinary bladder resections, four gastric resections, two distal pancreatic resections) and nine major vascular resections (one aortic, four IVC and four external iliac artery resections). At least one organ was resected along with the neoplastic mass, as evidenced by the median 1.6 (range, 1–6) organs resected per operative procedure.

There were 12 major complications in 10 patients, giving a procedure related morbidity of 10% and patient specific morbidity of 16%. Specific complications included intra-abdominal sepsis ($n = 9$) necessitating percutaneous intervention in six and laparotomy in three patients, gastrointestinal ischaemia necessitating bowel resection ($n = 2$) and lower limb ischaemia needing vascular grafting ($n = 1$). There were no early deaths (nil 30-day mortality) and 1 in-hospital death (mortality rate 1.33%) at 73 days due to uncontrollable intra-abdominal sepsis.

The major histological type was liposarcoma ($n = 24$) followed by leiomyosarcoma ($n = 15$). Other histological types included sarcoma not other specified ($n = 12$), rhabdomyosarcoma ($n = 6$), malignant peripheral nerve sheath tumour ($n = 3$), fibrosarcoma ($n = 3$), endometrial stromal tumour ($n = 3$) and other rare miscellaneous tumours ($n = 9$), like angiosarcoma, lymphosarcoma.

Table 1 Factors predisposing to recurrent disease

Variable			Impact of variable on time to recurrence
Grade of tumour	G1 (<i>n</i> = 45)	^a G2 (<i>n</i> = 30)	^a <i>P</i> = 0.01
Histological type of tumour	Liposarcoma (<i>n</i> = 24)	^b Non-liposarcoma (<i>n</i> = 51)	^b <i>P</i> = 0.01
Size of tumour	< 10 cm (<i>n</i> = 19)	^c > 10 cm (<i>n</i> = 56)	^c <i>P</i> = 0.04
Resection status	R0 (<i>n</i> = 51)	^d R1 (<i>n</i> = 24)	^d <i>P</i> = 0.05

Of the initial 72 primary resections, all were macroscopically completely resected; however, pathological examination revealed that 51 were R0 and 21 were R1. Forty-three (59.7% of the 72 primary resections) have developed recurrence. The three other initial resections (primaries resected elsewhere) all resulted in R1 resections and all recurred.

Follow-up ranged from 16–151 months. At present, 26 patients have died of progressive disease, 29 are alive with no evidence of disease and 18 are alive with residual disease (6, progressive disease; 8, stable disease; Fig. 2). Median disease-free survival for all histological types was 69 months (range, 59–78 months) and that for liposarcoma was 76 months (range, 69–78 months).

On univariate regression analysis, significant factors influencing recurrence (*n* = 46) were high grade of tumour (*n* = 30; *P* = 0.001), non-liposarcoma histology (*n* = 51; *P* = 0.01), large (> 10 cm) size of primary tumour (*n* = 56; *P* = 0.04) and R1 resection (*n* = 24; *P* = 0.05; Table 1). High-grade of tumour significantly worsened overall survival (Fig. 3), while larger size (> 20 cm) did not influence this (*P* = 0.550). Logistic regression revealed that the most important factor influencing survival was the presence of recurrent disease (*P* = 0.03).

Of the initial 75 resections, 46 have recurred. Twenty-two of which were localised disease within the abdomen while 24 developed distant and/or abdominal carcinomatosis. In the localised recurrence group (*n* = 22), further aggressive surgery

(*n* = 40 resections) was performed (1 patient, 8 re-resections; 2 patients, 4 re-resections; 3 patients, 3 re-resections; 7 patients, 2 re-resections; and 11 patients, single re-resection each). Amongst patients with recurrent disease, median survival with disease was 53 months (range, 30–76 months) in those who underwent repeat surgery and survival in those with recurrence who did not undergo surgery was 30 months (range, 18–41 months) and this difference was statistically significant (log rank, *P* = 0.01; Fig. 4). Currently, of the 47 patients alive (29 disease free and 18 with disease), 15 have undergone at least one repeat resection of disease.

Median time to local intra-abdominal recurrence was 16 months (range, 2–98 months), whilst time to overall recurrence was 13 months (range, 3–71 months). We found that the median time to local recurrence was dependent on margin of excision (*P* = 0.05; R0 = 17 months; R1 = 11 months) whilst median time to overall recurrence was not dependent on completeness of excision (*P* = 0.26; R0 = 14 months; R1 = 13 months). Amongst the patients who developed recurrent/metastatic disease (*n* = 46; 22 locally recurrent and 24 metastatic), 31 were high-grade neoplasms.

Discussion

Soft tissue sarcomas are a heterogeneous group of neoplasms which vary widely not only in the tissues of their origin but also in their biological behaviour as reflected by their histological picture and treatment outcomes.² Their unifying feature is the mesodermal origin of the tissues from which they arise. They can develop at nearly all anatomical sites within the body and the retroperitoneum is an especially common site of occurrence. Retroperitoneal soft-tissue sarcomas (RPSTS) are challenging neoplasms, first in view of their inherent chemo- and radio-resistant nature and second their location which is best characterised as being in the 'silent zone', which results in their asymptomatic growth to result in involvement of numerous vital structures.

In the UK, there were 385 cases of RPSTS registered in the year 2004. Thus, it is apparent that they are rare tumours (<http://www.statistics.gov.uk/downloads/theme_health/MB1_35/Table7_web.xls>). Every year, about 10–12 patients are referred to our unit which covers a population of about 3.2 million in the North of England. Most of these patients are considered for surgery. It has been suggested⁵ that inadequate specialisation in the UK in the management of these difficult and challenging tumours may explain the lower resection rate and 5-year survival rates (local recurrence rate of 45%, 5-year survival of 44% and median survival for primary disease of 36 months) as compared to large reports from North American centres (median survival of 72 months for patients with primary disease).⁴

The aim of this study was to analyze factors contributing to outcomes in a large, well-characterised cohort of prospectively

followed patients with RPSTS managed at a single institution in the UK. In particular, we analyzed the effect of a policy of aggressive surgical treatment on subsequent local recurrence, metastasis, and disease-specific survival rates. We were also interested in ascertaining whether our philosophy of aggressively re-resecting localised recurrences resulted in an improved outcome.

Over a period of 9 years, we have treated 81 patients with RPSTS. In accordance with the values of multidisciplinary team management of complex patients in the UK, we discuss individual patient's imaging and other clinical details at our team meeting which includes radiologists, oncologists, pathologists, surgeons and nurses, all with a specialist interest in sarcoma surgery. Following a policy of aggressive surgery, the majority of these (75/81; 93%) have undergone surgical resection. As expected from a large volume centre,⁵ our patients have experienced acceptable complications and minimal mortality.

A total of 115 resections were carried out in 75 patients, 104 of which were with curative intent. After a median follow-up of 38 months (range, 16–131 months), we have 46 recurrences (46/75; 61%). This is in spite of a R0 resection rate of 68% (51/75) which is the current accepted standard in large series of patients.² A median of 1.6 adjacent organs (range, 1–6) were resected *en bloc* with the sarcoma. The majority of resections (51/72; 71%) of the primary tumour achieved pathologically negative margins; however, recurrence resections resulted in R0 for a fewer proportion of patients (19/43; 44%). Therefore, macroscopic clearance does not always mean complete removal of tumour. As has been described in previous reports, an R1 resection was a significant risk factor for recurrence. Other factors predisposing to recurrence were high grade of tumour, non-liposarcoma histology and large (> 10 cm) size of primary tumour (Table 1). These were also the same factors which have influenced survival in our patients, especially grade of tumour (Fig. 3). High-grade of tumours resulted in increased recurrences as seen in 31 of 46 patients with recurrent disease were of high-grade differentiation. Thus, tumour biology not only influences overall survival, but also local recurrence.

Resections of recurrences were more likely to result in a R1 pathological report – 29.16% (21/72) of primary tumours versus 55.81% (24/43) of recurrence resections. This reflects the fact that recurrences are more technically demanding. Given that the primary is aggressively resected with a curative intent leading subsequently to the surrounding viscera moving into the tumour bed, the recurrence tends to involve adjacent and other vital mainly vascular structures more frequently; achieving oncological clearance in this situation tends to be more difficult. This high rate of recurrence is a function not only of the complex anatomy of these neoplasms, but also of their infiltrative margins⁶ and higher grade (*vide supra*). Identification of these recurrences in the retroperitoneum is dependent to a great extent on regular clinical and radiological surveillance following initial surgery (*vide supra*), which is an important part of our postoperative manage-

Figure 4 Surgery for recurrent disease is associated with longer survival ($P = 0.01$).

ment of these patients and that could be one explanation for the high recurrence rate in spite of an initial R0 resection.

In general, these tumours are associated with a high local recurrence rate, 61% in our series. In an effort to improve local control, adjuvant radiotherapy has been suggested as an adjuvant treatment and there have been numerous retrospective case series and a few prospective non-randomized studies utilising radiotherapy pre-operatively, intra-operatively and postoperatively as adjuvant therapy especially in the R1 scenario and for high-grade tumours, describing better local control with this mode of adjuvant treatment.⁷ However, effective delivery of radiation to the retroperitoneum is limited by various factors most importantly the presence of radiosensitive organs in close proximity to the tumour bed – bowel, liver, pancreas, kidney and neural structures. In extremity sarcomas, this is not a limiting factor; indeed radiation has played a significant role in improving local control and bettering outcome. We do accept that pre-operative external beam radiotherapy (EBRT) is beneficial in selected patients.⁸ Recently, EBRT and intra-operative radiotherapy have been utilised in sequential fashion; however, toxicity continues to be a problem. In the absence of completed randomised trials,⁹ we have not offered radiotherapy in our group of patients. Our policy has been to achieve complete resection of the primary whenever possible and to aggressively re-resect recurrences. This is reflected in our high R0 rates and acceptable morbidity and minimal mortality figures. Adriamycin- or Ifosfamide-based chemotherapy has been utilised in the occasional patient in our series in the context of a clinical trial and this therapy is not standard in our practice.

Disease-free survival in our series is comparable to most other previous experiences.^{4,10} Our patients have a median disease-free survival of 69 months (range, 59–78 months). The most important factor influencing survival was the presence of recurrent disease ($P = 0.03$) and this has been described earlier.^{5,11} We noted that the time to local recurrence was dependent on the R status, *i.e.* patients who have undergone a R1 resection appeared to develop localised recurrence earlier as compared to those with a R0 resection and this is understandable. However, systemic (*i.e.* metastatic disease) was not dependent on the R status of the primary neoplasm. This seems to suggest that localised recurrence is a different ‘disease’ versus metastatic recurrence. This leads on to the possibility that local control can be aggressively undertaken to try and achieve long-term survival. Following this policy, we have offered repeat resections to patients who have developed localised intra-abdominal recurrence. The factors which preclude repeat resections of the recurrences are the same as those when surgery for the primary is contemplated, *i.e.* patients factors (fitness, choice) and tumour factors (extreme locations like retrohepatic/retrocaval situation especially when the lesion involves the confluence of the hepatic veins with the cava or extensive involvement of the SMA).

In patients with localised recurrences who undergo repeat resection median survival was much better, 53 months (range,

30–76 months) as compared to 40 months (range, 18–49 months) in those who did not undergo surgery and this difference was statistically significant (log rank, $P = 0.01$; Fig. 4). The benefit of survival appears to be secondary to achieving a degree of local control of these tumours. This is in spite of the majority of recurrence operations turning out to be R1 resections.

The 11 palliative debulking procedures achieved significant reduction in disabling symptoms, mainly pain, in the respective patients. However, intestinal obstruction ($n = 3$) was poorly palliated, as demonstrated previously.¹²

Conclusions

Extensive resectional surgery with acceptable morbidity and minimal mortality is feasible in the treatment of retroperitoneal sarcoma. Microscopically positive margins following apparently complete gross resection are common after both primary and recurrence resections. Development of recurrent disease is a significant factor influencing survival. In the absence of disseminated disease, aggressive resection of localised recurrences can improve outcome in selected patients. Palliative debulking procedures can provide relief of symptoms except in cases of multi-level intestinal obstruction.

References

1. Lahat G, Anaya DA, Wang X, Tuvin D, Lev D, Pollock RE. Resectable well-differentiated versus dedifferentiated liposarcomas: two different diseases possibly requiring different treatment approaches. *Ann Surg Oncol* 2008; **15**: 1585–93.
2. Perez EA, Gutierrez JC, Moffat Jr FL, Franceschi D, Livingstone AS, Spector SA *et al.* Retroperitoneal and truncal sarcomas: prognosis depends upon type not location. *Ann Surg Oncol* 2007; **14**: 1114–22.
3. Pirayesh A, Chee Y, Helliwell TR, Hershman MJ, Leinster SJ, Fordham MV *et al.* The management of retroperitoneal soft tissue sarcoma: a single institution experience with a review of the literature. *Eur J Surg Oncol* 2001; **27**: 491–7.
4. Lewis JJ, Leung D, Woodruff JM, Brennan MF. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. *Ann Surg* 1998; **228**: 355–65.
5. Gutierrez JC, Perez EA, Moffat FL, Livingstone AS, Franceschi D, Koniaris LG. Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients. *Ann Surg* 2007; **245**: 952–8.
6. Brennan MF. Local recurrence in soft tissue sarcoma: more about the tumor, less about the surgeon. *Ann Surg Oncol* 2007; **14**: 1528–9.
7. Kaushal A, Citrin D. The role of radiation therapy in the management of sarcomas. *Surg Clin North Am* 2008; **88**: 629–46, viii.
8. Pawlik TM, Pisters PW, Mikula L, Feig BW, Hunt KK, Cormier JN *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.
9. Hueman MT, Thornton K, Herman JM, Ahuja N. Management of extremity soft tissue sarcomas. *Surg Clin North Am* 2008; **88**: 539–57, vi.
10. Jaques DP, Coit DG, Hajdu SI, Brennan MF. Management of primary and recurrent soft-tissue sarcoma of the retroperitoneum. *Ann Surg* 1990; **212**: 51–9.
11. Gronchi A, Casali PG, Fiore M, Mariani L, Lo Vullo S, Bertulli R *et al.* Retroperitoneal soft tissue sarcomas: patterns of recurrence in 167 patients treated at a single institution. *Cancer* 2004; **100**: 2448–55.
12. Yeh JJ, Singer S, Brennan MF, Jaques DP. Effectiveness of palliative procedures for intra-abdominal sarcomas. *Ann Surg Oncol* 2005; **12**: 1084–9.