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Original Paper

The Management of Retroperitoneal Soft Tissue Sarcomas

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Over a 5-year period, all retroperitoneal soft tissue sarcomas (119) referred to the Royal Marsden Hospital, London, U.K., were recorded prospectively on a database and managed with a consistent treatment policy. On multivariate analysis, the significant factors responsible for determining prognosis were grade and completeness of excision. Despite improvements in surgical clearance rates (nearly 50% completely excised in this series), the prognosis was poor with 2- and 5-year survival rates of 53 and 20%, respectively. Further improvements in survival rates will depend on better adjuvant treatment. Copyright © 1996 Published by Elsevier Science Ltd

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INTRODUCTION

SOFT TISSUE sarcomas (STS) are rare, accounting for 1% of all malignant tumours [1]. Ten per cent of such tumours occur in the retroperitoneum [2–6] and the prognosis of these is particularly poor with 5-year survival rates of 12–40% [7–11].

All previously described series [7–12] except one [13] have been retrospective and over extended periods in order to achieve numbers sufficient for meaningful analysis. There are many disadvantages to such an approach which may lead to bias; incomplete data collection (especially from early years), change of treatment protocols and improvement in operative and postoperative care, will all influence results in a series spanning decades.

All sarcomas referred to the Royal Marsden Hospital (RMH), London, U.K., have been managed by one consultant surgeon with a consistent treatment policy. Between 1990 and 1995, 119 patients were treated for retroperitoneal STS. This cohort of patients was studied and compared with 120 patients from the RMH database treated between 1970 and 1990 [14]. The purpose of this was to eradicate any bias associated with retrospective series and assess whether exposure of all patients to the same treatment protocols over a relatively short period had any influence on prognosis. This would also challenge, or confirm, our previous statement [14] that any future advancements in the treatment of retroperitoneal STS would involve systemic adjuvant therapy and not improved surgery.

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PATIENTS AND METHODS

All patients with a diagnosis of retroperitoneal STS that were referred to and treated at the RMH between 1990 and 1995 were included. Gynaecological and paediatric sarcomas were specifically excluded. Data were collected prospectively and stored in a database which was updated at regular intervals so that events such as local recurrence, development of metastases, or death were recorded in real time.

In patients who had begun their treatment at another hospital, diagnosis was made by review of pathological material and previous scans. Patients investigated at our unit were diagnosed by either computer tomography (CT) scan alone or a combination of CT scan and Tru-Cut biopsy (Travenol Laboratories, Thetford, U.K.). All patients were initially assessed by CT scanning [15, 16] and, following surgery, scanning was only repeated if local recurrence was suspected. Pulmonary CT scans were routinely used for staging. The decision to operate was based on an estimate of resectability, the stage, symptoms and performance status of the patient.

Pathological specimens were reported, and material from other hospitals reviewed, by one consultant histopathologist and assigned to one of three grades; high, intermediate or low [17, 18]. For the purposes of review, surgical clearance was defined as clear pathological margins. For intracapsular and debulking procedures, clearance was obviously incomplete.

Performance status was evaluated using the WHO guidelines [19] and was available for all patients at the time of presentation.

Survival was measured from the date of presentation to the RMH as this was the most reliably recorded time of diagnosis [20]. Life-tables were constructed using the Kaplan–Meier

method and were compared using the log-rank test and the log-rank test for trend [21]. Multivariate analysis was undertaken using Cox's Regression model (BMDP Statistical Software Inc. program 21).

Clinical

During the 5-year period specified, 119 patients with retroperitoneal STS were referred to the Surgical Unit at the RMH. The mean age was 51 years (range 14–81) and the sex distribution 66:53 male to female. The performance status revealed 17 in category 0, 77 in category 1 and 25 in categories 2–4.

Operative treatment

Of the 119 patients referred, 111 underwent surgery, 65 before presentation to the RMH and 69 after (which included 23 of the 65 undergoing a second operation following referral). Where a definitive operation was performed, 66 procedures were for primary sarcomas, and 42 for local recurrence. Of those undergoing surgery where accurate data were available, 47 were defined as completely excised and 49 as incompletely excised. 34 patients had a second, 7 a third and 1 a fourth laparotomy for symptomatic local recurrence.

Non-operative treatment

No surgery was undertaken in 8 patients. Chemotherapy was either given as primary treatment for patients presenting with metastatic or inoperable disease, or after the development of unresectable local recurrence. A total of 49 patients received chemotherapy at some time.

Radiotherapy was used very selectively in view of the serious side-effects encountered from visceral (especially small bowel) irradiation, which is an unavoidable hazard of radiotherapy in this area [22–24]. Only 22 patients received radiotherapy, 10 of whom were irradiated as adjuvant treatment following surgery. When postoperative radiotherapy was thought necessary and where possible, a tissue expander was inserted to minimise damage to surrounding viscera [25].

RESULTS

Survival

Overall survival was 53% (CI = 42–64%) at 2 years and 20% (CI = 7–37%) at 5 years from presentation to the RMH. A distinct survival advantage was seen for low-grade tumours and those which were completely excised. In patients with low-grade tumours who also underwent complete excision, 5-year survival was 80%. Multivariate analysis of factors influencing survival is shown in Table 1.

Life-tables according to grade and completeness of resection are seen in Figures 1–3. Figure 1 shows overall survival for all 119 patients according to grade. In Figure 2, 95 patients are included, as 16 patients had definitive surgery outside a 6-month window of their presentation and were therefore excluded from the life-tables. Figure 3 represents survival curves for 57 of the above 95 patients who underwent surgery for a primary sarcoma (i.e. those with local recurrence excluded).

Pathology

Resected specimens were all sub-typed using immunohistochemical methods and graded acccording to extent of necrosis, mitotic index, cellularity, pleomorphism and degree of differentiation [17, 18]. Sixty-four (54%) of the tumours were high-grade, 24 (20%) were intermediate- and 21 (26%) low-grade. The frequency of histological subtypes is seen in Table 2. The mean tumour size was 17.5 cm (range 2.5–60 cm).

Table 1. Multivariate analysis of the significant risk factors for overall survival

Covariate	Hazard ratio (95% CI)	*P* value
Significant factors		
Surgery		
Complete	1.00	$P = 0.002$
Incomplete	2.7 (1.39–5.26)*	
Grade		
Low	1.00	
Intermediate	2.54 (0.94–6.81)	$P = 0.04$
High	6.43 (2.39–17.3)	
Non-significant factors		
Size		$P = 0.33$
Performance status		$P = 0.21$
Previous LR		$P = 0.84$
Previous DR		$P = 0.55$

* At any particular follow-up time, patients with incomplete excisions were 2.7 times more likely to die compared with patients with complete excisions.
LR, local recurrence; DR, distant recurrence.

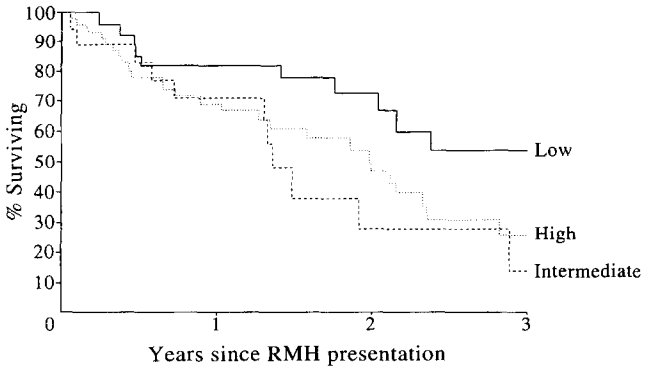
Complications and follow-up

There were no deaths within the 30-day postoperative period. The major complication rate was 11.6%, which is shown in Table 3. Follow-up data were available on all but 6 patients up to the time of death or their last clinic attendance. The 2-year local recurrence rate for patients who had surgery prior to referral to the RMH was 29 out of 59 compared with 16 out of 47 (not significant $P > 0.1$) for those who had definitive surgery at the RMH. 52 patients died with a median follow-up of 355 days.

DISCUSSION

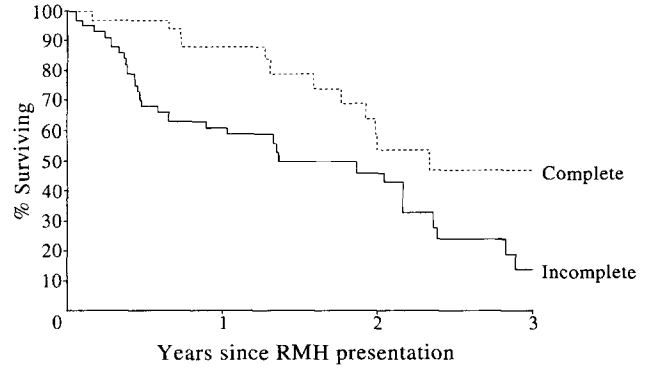
Soft tissue sarcomas within the retroperitoneum have a worse prognosis compared with extremity sarcomas of the same grade [24, 26]. They present later and are therefore larger at presentation. Furthermore, because of the multiplicity of the surrounding structures within the retroperitoneal area, involvement of adjacent organs is common [7, 10, 14, 27]. This makes surgery technically more demanding and means that less than 50% of primary retroperitoneal STS are rendered disease-free compared with 89% of limb and limb-girdle STS [24]. This difference is explained only by site; the grade and biology of the tumours being similar. Moreover, there is still no effective adjuvant treatment available [7, 13, 28]. Radiotherapy is limited by the tolerance of surrounding tissues [28] and many trials using single agent [29], or combination chemotherapy [30], have been unable to show an overall survival benefit.

Owing to the rarity of STS in the retroperitoneum, most reported series [7–10, 12] date back over periods of up to 20 years with all the inherent disadvantage of retrospective analysis over such a period. As our last series [14] showed, it is difficult to obtain complete data retrospectively, and drawing conclusions from survival data over a period which has wit-



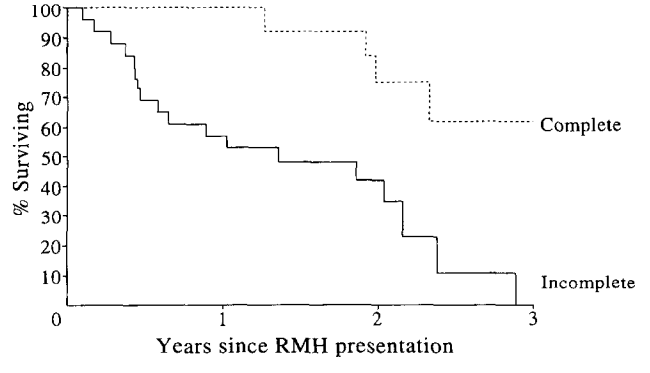
Numbers at risk				
Low	31	21	13	7
Intermediate	24	10	3	1
High	64	28	13	5

Figure 1. Survival according to tumour grade. Chi-square = 7.18, $P < 0.05$.



Numbers at risk				
Complete	46	23	12	5
Incomplete	49	25	13	3

Figure 2. Survival according to completeness of excision for all patients operated on within 6 months of presentation. Chi-square = 7.00, $P < 0.01$.



Numbers at risk				
Complete	30	15	8	3
Incomplete	27	14	6	0

Figure 3. Survival according to completeness of excision for patients with primary sarcomas (operations for local recurrence excluded). Chi-square = 12.93, $P < 0.005$.

nessed advances in pre-operative assessment (modern methods of cross-sectional imaging) and postoperative care is obviously difficult.

This series reviewed 119 patients diagnosed and treated within a period of 5 years using the same management protocols. When operated on at the RMH, the surgery was performed by the same consultant surgeon. As surgery has previously been shown to be the main influence on survival [7, 8, 10, 12–14], we endeavoured to resect all tumours with clear pathological margins which involved resection of adjacent

Table 2. Histological subtypes

Histology	Frequency (%)
Leiomyosarcoma	49 (41)
Liposarcoma	30 (25)
Sarcoma (not otherwise specified)	15 (13)
Malignant nerve sheath tumour	10 (8)
MFH	5 (4)
Haemangiopericytoma	2 (2)
Chondrosarcoma	2 (2)
Rhabdomyosarcoma	2 (2)
Fibrosarcoma	1 (1)
Angiosarcoma	1 (1)
Synovial sarcoma	1 (1)
Ewing's sarcoma	1 (1)
Total	119

MFH, malignant fibrohistiocytoma.

Table 3. Postoperative complications following RMH surgery

Complication	Frequency (%)
None	61 (88)
Infection (major)	2 (3)
Lymphoedema severe	2 (3)
Major wound dehiscence	1 (1)
Deep vein thrombosis	1 (1)
Multiple complications	2 (3)
Total	69

organs where necessary. Where patients had already undergone surgery prior to referral, if this was thought to be inadequate (from the pathology report and/or operation note), they were re-explored to resect the bed of the tumour where possible.

As in other series [7, 8, 10, 12–14] multivariate analysis showed resectability to be a statistically significant variable influencing survival and in this series nearly 50% (compared with 30% in the 1970–1990 series [14]) were surgically cleared. However, despite the above, there was surprisingly no survival advantage in this series with 53% alive at 2 years and only 20% at 5 years. These results are similar to the previous series [14], but appear slightly worse than many reported in the literature [7, 8, 10, 12, 26–28]. There are a number of reasons for this, but the most important is that most authors report survival rates only for those patients who have undergone complete resection, rather than the survival of all patients referred. The other important observation is that, in this cohort of patients, survival was measured from the time of referral to the RMH as this was the most reliable data of diagnosis. As the majority of RMH patients are tertiary referrals and half of the 119 patients had already undergone surgery elsewhere our survival figures are probably an underestimate of true survival.

Nevertheless, the prognosis of retroperitoneal STS remains worse than their extremity counterpart. Inability to obtain as wide surgical clearance and difficulty with post-operative radiotherapy have already been cited as possible explanations. In addition, a high percentage tend to be high-grade (50% in this series) and, because of their occult presentation, are larger than extremity tumours. Although we were unable to demonstrate size as an independent risk factor for survival in this cohort of retroperitoneal tumours, the fact that the mean tumour diameter was 17.5 cm cannot be ignored in comparisons with other sites. Unlike extremity sarcomas, even after complete surgical resection with histologically proven clear margins, local recurrence is the norm, with overall rates of between 60 and 90% in most reported series [7, 10, 14, 27]. Shiloni and associates [27] showed no survival benefit in patients undergoing total, compared with subtotal, resection of high-grade retroperitoneal STS. They dispute the concept of complete surgical clearance within the abdomen and maintain that there is a likelihood of microscopic residual disease in the majority of cases. From our knowledge of the spread of limb and limb-girdle sarcomas along tissue planes and hence the need for radical or wide resection to achieve local control, it is not surprising that the majority of retroperitoneal STS recur. When compared in this way, it emphasises the fallacy of true clearance within the abdominal cavity and explains why improvements in clearance rates do not translate into improved survival.

Multivariate analysis showed that both grade and resectability were significant risk factors for survival. Despite the poor prognosis for the majority of patients, in those with low-grade tumours which are completely resected the outlook is good; with a 5-year survival rate of 80% which is similar to those reported in the literature [23, 31].

Surgery, despite the constraints of obtaining wide clearance within the abdomen, still remains the only treatment capable of influencing survival. Surgery is also the only effective means of palliation, but an aggressive approach is needed if this is to be successful. Shiloni and colleagues [27] have shown that there was no difference in the outcome of patients undergoing palliative surgery compared with those who underwent exploration but no resection.

Few patients in this series received external beam radiotherapy (EBRT) and intra-operation radiotherapy (IORT) was not used. Despite improved field techniques and the use of spacers, complication rates remain high, and a clear survival benefit has yet to be shown [22, 32]. Kinsella and associates [22] in a comparative study of EBRT and IORT, albeit with small numbers, report complication rates of over 60% in each group. Although, as expected, the IORT group experienced significantly less gastrointestinal complications, more patients were left with severe sciatic or femoral neuropathies.

The situation regarding adjuvant chemotherapy remains unclear at present. Published individual trial results are contradictory, although most show no advantage for adjuvant chemotherapy with respect to improved survival. However, a recent meta-analysis by Tierney and associates [33], reviewing 15 trials (comparing adjuvant chemotherapy with no chemotherapy for STS at all sites), suggests a slight improvement in 2- and 5-year survival in favour of the chemotherapy groups. However, as the authors themselves point out, the only reliable way of confirming this is to evaluate the individual patient data in a time-to-event analysis. The results of this are awaited.

42 patients required more than one operation, and for local recurrence in the absence of metastatic disease, surgery was considered to be the optimum treatment. The grade of tumour, disease-free interval and the number of organs involved were all important factors in the decision to re-operate. However, knowing that the vast majority of patients

with multi-focal local recurrence were incurable, symptoms and performance status were the primary factors which influenced the timing of surgery. The detection of recurrence *per se* was not an automatic indication for further surgery.

In conclusion, surgery is currently the only effective treatment for the majority of retroperitoneal STS and the case for an aggressive resection policy is clear. However, even when surgical management is optimised, most patients still die from local recurrence or transperitoneal metastases. This emphasises the need for effective adjuvant therapy if the current survival rates in patients with retroperitoneal STS are to be improved.

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