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The importance of preoperative diagnosis for management of patients with suspected retroperitoneal sarcoma

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Abstract

Soft tissue sarcoma is an umbrella term which encompasses over 60 histological tumour types. Approximately 15% of soft tissue sarcomas arise in the retroperitoneum. This complex group of tumours pose unique management challenges due to their often large size, histological heterogeneity and complexity of anatomical relationships. This review discusses the management of retroperitoneal tumours including the need for preoperative diagnosis, the evidence for neoadjuvant radiotherapy, the role of multivisceral resection and the importance of a multidisciplinary team approach.

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Introduction

Soft tissue sarcoma (STS) describes a rare group of malignancies of mesenchymal origin. There are approximately 60 subtypes of soft tissue sarcoma[1] with wide variation in natural history and prognosis.

Approximately 15% of STS arise in the retroperitoneum, with an overall incidence of 0.5-1 per 100,000[2]. The most common subtypes of retroperitoneal sarcoma (RPS) are liposarcoma (63%) and leiomyosarcoma (19%)[3] and less common subtypes include synovial sarcoma, solitary fibrous tumour, malignant peripheral nerve sheath tumour and undifferentiated pleomorphic sarcoma[3, 4]. Liposarcoma is further subdivided into well differentiated, dedifferentiated, myxoid, round cell and pleomorphic subtypes. The anatomical complexity of the retroperitoneum and proximity of the tumour to vital structures limit the ability to achieve a wide margin as is performed for patients with STS in the extremity. The large size, complex anatomical relationships and tumour growth patterns account for a significant risk of intra-abdominal recurrence. The anatomical and pathological complexity of RPS requires individualized multidisciplinary management, which will be discussed below.

Diagnosis, Staging and workup

Patients with RPS usually present with an asymptomatic or incidental mass.

Tumours are often large with a median size at presentation of 20cms[3]. A full history and examination is important to exclude differential diagnoses particularly lymphoma, metastatic germ cell tumour, gastrointestinal stromal tumour, primary tumours of the kidney or adrenal, and extra-adrenal pheochromocytoma. Benign masses such as

hibernoma, chronic abscess, schwannoma and angiomyolipoma should also be considered.

Patients should undergo a full extent of disease workup including CT scan of the chest, abdomen and pelvis. If the imaging demonstrates an adipocytic mass, this may represent a renal or adrenal angiomyolipoma versus a retroperitoneal liposarcoma. If the entire mass is solid (with no adipocytic component), it is important to exclude a secretory mass, such as pheochromocytoma or germ cell tumour prior to biopsy. This can be done with tumour markers including serum β hCG as well as urinary catecholamines.

Further anatomical characterisation can be performed with MRI or angiography (CT or MR angiography) to optimally characterize the relationship of the tumour to the retroperitoneal musculature and vasculature. Functional imaging with PET scanning can provide useful additional information, highlighting sites of maximal metabolic activity. In Australia, there is not currently a rebate available for PET scans in patients without a confirmed diagnosis of sarcoma.

Patients should undergo a diagnostic core needle biopsy for histological diagnosis. Australian guidelines recommend that the biopsy be performed as part of the multidisciplinary work up, within a sarcoma centre to ensure that the tract does not traverse the peritoneal cavity and to facilitate the pathology review by a designated sarcoma pathologist[5-7]. This should be performed via a retroperitoneal approach (usually under CT guidance) and should target the most solid component of the

tumour. Diagnostic accuracy may be aided by targeting the most metabolically active component of the tumour (as defined by PET scan[8]).

By contrast with core needle biopsy, fine needle aspiration cytology has far lower rates of diagnostic accuracy (as low as 60.5%[9]) and lacks the tissue architecture and tissue volume required for full diagnostic testing including molecular and chromosomal analysis. As such, FNA should be avoided as a diagnostic test for patients with suspected RPS.

An expert sarcoma pathologist should evaluate the core biopsy[5].

Immunohistochemistry and molecular techniques can be performed on the core biopsy to aid diagnosis eg. MDM-2 expression by fluorescence in-situ hybridization (FISH) is confirmatory of liposarcoma, (this is particularly helpful in distinguishing between dedifferentiated liposarcoma and other high grade tumours)(Table 1).

Preoperative diagnosis is important for a number of reasons; firstly, to exclude other diagnoses; secondly, to determine pathological subtype which provides important prognostic information and helps plan optimal surgical resection and/or neoadjuvant therapy.

For patients where a definitive resection is planned which may incorporate nephrectomy, split renal function assessment (eg using MAG-3 scan) should be considered to ensure adequate function of the contralateral kidney

Patients should be discussed at a multidisciplinary meeting prior to commencing treatment. Radiological opinion is useful in determining the total extent of the tumour and to ensure concordance between the imaging characteristics and the pathology findings. The best chance to achieve a curative resection is at the first operation therefore careful planning is required. In a large multicenter series from France, patients who were not discussed preoperatively at a MDM had almost twice the rate of intra-abdominal recurrence compared to those where multidisciplinary planning was performed (56% versus 32%; $P=0.0001$)[10].

AJCC Staging system and predicting outcome

The current staging system (AJCC 7th edition) for sarcoma provides little prognostic stratification for patients with RPS[11, 12]. T stage is based on size and depth. Most RPS are greater than 5cms in size (T2) and all are deep (as compared to superficial) by definition (T2B). Nodal involvement is extremely rare (N0). In the absence of metastatic disease, the only predictor of outcome in the current AJCC Staging System is tumour grade. Large retrospective series have identified histological subtype, multifocality, invasion of surrounding structures, increasing age and an incomplete resection as being predictive of poor outcome[10, 12, 13].

The most common site of recurrence for RPS is intraabdominal with up to 60% of patients recurring by 10 years[3, 4, 14]. Patterns of recurrence can be predicted based on histological subtype. Liposarcoma has a high rate of local recurrence, with

a relatively low rate of distant metastasis, particularly well differentiated liposarcoma where distant metastases are extremely rare. By contrast leiomyosarcoma has a relatively low rate of local recurrence of <25% but a high rate of distant metastasis particularly for high grade tumours. Histotype is an independent predictor of outcome[4] and is expected to form part of the 8th edition of the AJCC staging system.

Role of radiotherapy

For patients with extremity sarcoma, the role of radiotherapy (RT) (either in the neoadjuvant or adjuvant setting) in improving rates of limb preservation is well established[15]. High level data supporting a role for RT in RPS is lacking. If RT is to be administered, a pre-operative regimen is generally preferable to postoperative as toxicity (particularly small bowel toxicity) is significantly reduced due to the mass effect of the tumour displacing the small bowel away from the radiation field allowing a smaller field to be treated. Limited data regarding the use of 3D conformal postoperative RT suggests tolerability[16]. When delivered in a neoadjuvant setting, RT often does not reduce tumour size and the practice of the authors is to plan surgery between five and eight weeks following the completion of RT.

The ACOSOG Z9031 study comparing neoadjuvant RT with surgery alone closed early due to lack of accrual[17]. The currently accruing STRASS trial (EORTC 62092-22092) is an international phase III randomized controlled trial with a similar trial

design and is due to complete accrual soon and will hopefully provide a definitive answer to this question.

In the absence of high level data, there is extensive retrospective data supporting the role of neoadjuvant RT. A recently published propensity scored matched analysis using the National Cancer Database compared 563 patients who received preoperative RT with 6290 patients who underwent surgery alone. The median overall survival was 110 months in the RT group compared with 66 months in the surgery alone group (HR = 0.67; $P < 0.001$)[18]. Smaller retrospective series also demonstrate superior outcome for preoperative XRT [10, 19-21].

Role of chemotherapy

The current Australian guidelines' evidence based recommendation reads "use of post-operative chemotherapy in adult type soft tissue sarcomas is not the current standard of care." This is based on a large meta-analysis[22] as well as a subsequent RCT (EORTC 62931)[23]. Patients with RP sarcoma are under-represented in these studies and particularly for patients with high grade tumours and chemosensitive histologic subtypes (synovial sarcoma, myxoid liposarcoma), chemotherapy may be considered. In rare cases of paediatric-like histology (extraskelatal Ewing's sarcoma, small blue round cell tumour), chemotherapy is a key part of the multidisciplinary management.

Extent of surgery

Surgery for RPS often requires resection of adjacent/involved organs to achieve complete clearance. Primary RPS is rarely unresectable, but occasionally multifocality, encasement of the coeliac artery, superior mesenteric vessels or portal vein or bilateral renal vascular involvement would be contraindications to surgery.

Knowledge of the histological subtype is vital in planning the type and extent of surgery. Figure 1 highlights the difficulty of imaging alone in diagnosing and planning management. The patient in Figure 1A had a leiomyosarcoma (arising in the right gonadal vein) and required a complete resection of the tumour, which was possible without adjacent organ resection. By contrast, the patient in Figure 1B with liposarcoma required resection of the solid component of the tumour en bloc with all of the fat in the ipsilateral retroperitoneum including all perinephric fat which was likely to be infiltrated with well differentiated liposarcoma.

There is controversy within the surgical literature about the role of resection of uninvolved organs which abut the tumour, such as the colon and kidney, in order to achieve a wider margin[24]. Early data suggests that this aggressive surgical approach, considered as akin to compartment resection performed for extremity sarcoma leads to reduced rates of intraabdominal recurrence[25]. This more aggressive approach is associated with higher rates of morbidity. A multivisceral surgical approach to the patient in figure 1B would involve right hemicolectomy and right nephrectomy. The patient in Figure 2A had a large left-sided retroperitoneal liposarcoma and underwent preoperative radiotherapy followed by a multivisceral resection of the left retroperitoneum including left nephrectomy, left hemicolectomy

and stripping of the psoas fascia with skeletonisation of the aorta and left iliac vessels.

Given the difficulty of demonstrating superior outcomes for multivisceral resection in a randomised controlled trial, an international collaborative network (the Trans-Atlantic Retroperitoneal Sarcoma Working Group) has established a multi-institutional prospective registry to collect surgical and outcome data for patients undergoing treatment for primary RPS in high volume centres. The Sarcoma Service at the Peter MacCallum Cancer Centre is participating in this collaborative effort.

Centralisation of care

As is the case for other complex surgical procedures, evidence is emerging of the superior outcomes for patients treated in centralized specialist sarcoma centres. Lower rates of tumour rupture have been shown[26], and the NICE (National Institute for Clinical Excellence) guidelines from the UK have recently recommend centralised care for patients with STS (<https://www.nice.org.uk/guidance/qs78>).

A large multicenter series from France demonstrated lowest rates of abdominal recurrence in high volume centres and centres where patients were discussed in a multidisciplinary meeting[10].

Conclusion

Retroperitoneal sarcoma is a rare cancer with complex management algorithms and high rates of intra-abdominal recurrence. Preoperative diagnosis is a critical step in identifying the histological subtype to allow optimal treatment planning. The best chance to minimize recurrence risk is at the time of initial diagnosis. Patients should be referred to a specialist sarcoma centre, discussed in a preoperative multidisciplinary meeting and an individualized treatment plan formulated.

Table 1: Diagnostic features on core biopsy for common retroperitoneal sarcoma histologic subtypes

Figure 1: A – retroperitoneal leiomyosarcoma in a 34 year old woman, B – retroperitoneal liposarcoma in a 42 year old man. The perinephric fat in figure A (indicated by arrow) is normal, however the perinephric fat in figure B (arrows) is malignant and should be incorporated in the resection.

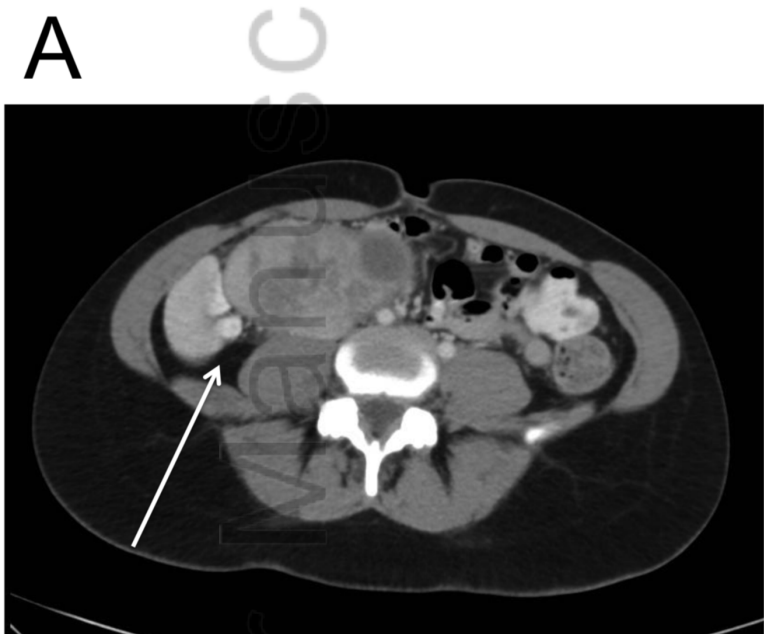
Figure 2: A – well differentiated liposarcoma displaying solid (a) and adipocytic (b) elements. B – Following left retroperitoneal compartment resection with enbloc resection of psoas fascia, left kidney and left colon. All tissue to the left of the aorta and left common iliac artery and superficial to psoas is incorporated in the specimen.

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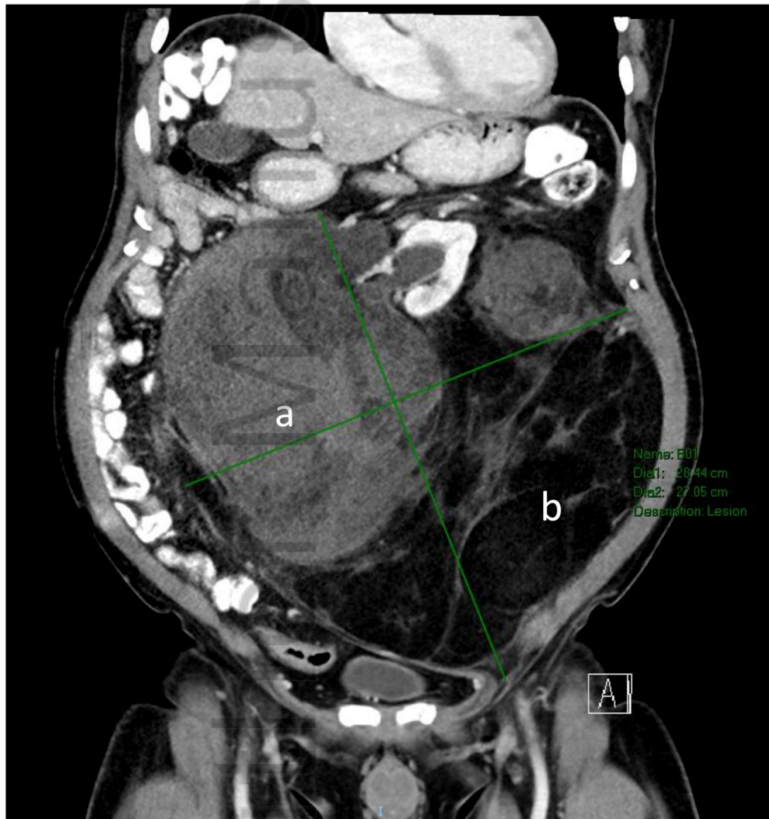
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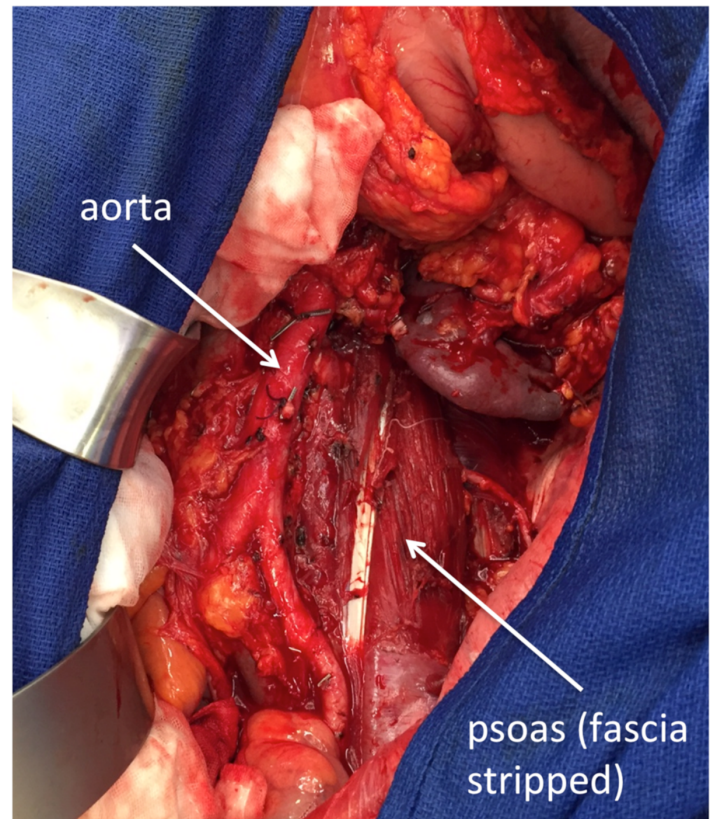


ANZJS sarc fig 1.tif

A



B



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Subtype	Immunohistochemistry	Molecular pathology
Liposarcoma		MDM2 amplification
Leiomyosarcoma	Smooth muscle actin, desmin	
Solitary fibrous tumour	STAT6	
Malignant peripheral nerve sheath tumour	S100, SOX10	
Ewing's sarcoma	CD99+	EWSR-1

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