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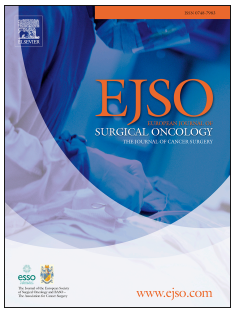

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Primary Retroperitoneal Soft Tissue Sarcoma: Imaging appearances, pitfalls and diagnostic algorithm

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Abstract

Although retroperitoneal sarcomas are rare tumors, they can be encountered by a wide variety of clinicians as they can be incidental findings on imaging or present with non specific symptoms and signs. Surgical resection can offer hope of cure and patient outcomes are improved when patients are managed in high volume specialist centers. Failure to recognize retroperitoneal sarcomas on imaging can lead to inappropriate management in inexperienced centers. Therefore it is critical that a diagnosis of retroperitoneal sarcoma should be considered in the differential diagnosis of a retroperitoneal mass with prompt referral to a soft tissue sarcoma unit. In particular, the most common retroperitoneal sarcoma subtypes, liposarcoma and leiomyosarcoma, have characteristic imaging appearances which are discussed. This review therefore aims to set the context and guide clinicians through a diagnostic pathway for retroperitoneal masses in adults which arise extrinsic to the solid abdominal viscera.

Keywords

Soft Tissue Sarcoma; Retroperitoneum; Diagnosis; MRI; CT

Introduction

Retroperitoneal soft tissue sarcomas (RPS) are rare tumours which account for approximately 12-15% of all soft tissue sarcomas with a mean incidence of 2.7 per million[1]. RPS are frequently incidental findings in the work-up for non-related symptoms or diseases and can grow to an extremely large size in the retroperitoneum before symptoms or signs of abdominal pain, back pain, bowel obstruction or a palpable abdominal mass develop[2,3]. Surgical resection is the only hope for cure and is therefore the treatment of choice for localized disease[1,4,5,6,7]. After tumor grade, the long- term survival following RPS resection is most dependent on the completeness of surgical resection. Other important factors are patient age, tumor subtype, tumor size, multifocality and

centralized multidisciplinary management in a specialist sarcoma center [7].

The most frequent sarcoma subtypes in the retroperitoneum in adults over 55 are well-differentiated liposarcoma (WDL) and dedifferentiated liposarcoma (DDL) (40%) and leiomyosarcoma (LMS) (27%). In younger age groups leiomyosarcoma becomes more common than liposarcoma[8]. Other less common subtypes occurring in the retroperitoneum include solitary fibrous tumor (SFT), undifferentiated pleomorphic sarcoma (UPS), malignant peripheral nerve sheath tumor, synovial sarcoma and extraosseous Ewing's sarcoma. However, because soft tissue sarcoma accounts for only a third of retroperitoneal tumors, other diagnoses must be considered[7].

In comparison to extremity soft tissue sarcomas, the prognosis of RPS is significantly worse[9,10,11]. This difference is largely due to the difficulties that surgeons face in achieving wide resection margins which relates to the location of tumour within the retroperitoneum which frequently results in a large tumour size and complex anatomical relationships with critical vasculature and viscera at presentation[12].

In view of the complexity of the retroperitoneal space and the multitude of organs involved, achieving optimal resection margins can be challenging. Hence, patients with RPS are best diagnosed and treated in experienced high-volume soft tissue sarcoma centres therefore maximizing the chance of obtaining wide surgical margins and improving overall survival. This recommendation is supported by studies which demonstrate improved prognosis for patients with RPS treated in high-volume sarcoma centres[1,4,5,13,14,15,16,17,18].

Failure to recognise retroperitoneal sarcomas on imaging can lead to inappropriate management in inexperienced centres. This can have catastrophic consequences due to incomplete resecrions or contamination of the patients peritoneal cavity with tumor which jeopardises the patients chance of a curative operation. Therefore referral in situations of indecision is advisable. In contrast to other cancer types and even extremity sarcoma, the cause of death for patients with RPS is often growth of an irresectable recurrent tumor instead of distant

metastases. This is especially the case for liposarcoma in the retroperitoneum. This makes adequate surgery by experts, guided by appropriate pre-operative imaging even more important.

This review therefore aims to set the context and guide clinicians through a diagnostic pathway for retroperitoneal masses in adults arising extrinsic to the solid abdominal viscera.

Management of primary retroperitoneal sarcoma

Surgery remains the mainstay of treatment for retroperitoneal sarcomas. In the majority of cases, one or more organs need to be resected together with the tumor in order to achieve complete resection. Very often, the ipsilateral hemicolon and kidney are resected 'en block' with the tumor. Depending on the histological diagnosis a clear multidisciplinary discussion is warranted to determine if radical surgical strategy is possible and if so whether a neo-adjuvant approach is also recommended. In certain clinical scenarios where surgery may be technically challenging in attaining clear resection margins, radiotherapy and /or systemic therapy may be considered to improve local control rates. Therefore, adequate evaluation of the imaging is of vital importance of designing appropriate treatment strategies.

The role of radiotherapy (RT) in the management of RPSs continues to evolve but remains controversial. It has been difficult to determine the absolute benefit of pre-operative or adjuvant RT from retrospective case series as treatment outcomes have been influenced by patient selection, surgical expertise, resection margins, histological grade and subtype and size[19,7,20,21,22]. Improved radiotherapy treatment techniques such as image guided radiotherapy and intensity modulated radiotherapy offers better target volume definition and more highly conformal radiation therapy to the tumour whilst minimising acute and long term side effects which may result from toxicity to neighbouring structures such as bowel or kidney[23]. A Phase III multicenter randomized trial to compare surgery alone to preoperative RT and surgery has been developed to determine if the addition of preoperative RT can reduce the risk of local

recurrence. The EORTC 62092-22092 STRASS Trial is currently recruiting patients from both Europe and North America. As it nears accrual, the STRASS study will hopefully provide clarification on the role of RT in the primary setting.

Systemic therapy may play a role in the management of primary RPS. In certain histological subtypes, e.g. Ewings' sarcoma there is a clear role for neoadjuvant chemotherapy. Otherwise there is no clear role for neoadjuvant / adjuvant chemotherapy in the majority of cases[24]. Future developments require effective histologically driven systemic therapy options to improve surgical resection and consequently improve local control rates and overall survival. Gronchi et al has evaluated the role of high dose infusional ifosfamide and radiotherapy which has shown promising results in a Phase I/II study demonstrating the schedule is feasible and deliverable[25].

Imaging technique

Contrast-enhanced computed tomography (CT) is the most useful and widely available primary imaging investigation. Because soft tissue sarcoma accounts for only a third of retroperitoneal tumors arising extrinsic to the solid abdominal viscera, other diagnoses must be considered[26]. Percutaneous core needle biopsy usually confirms the diagnosis and is the gold standard for diagnosis, but rarely lesions are not amenable or high risk for biopsy and the differential diagnosis based on imaging becomes crucial. MRI is reserved for patients with allergy to iodinated contrast agents or problem solving where for example muscle, bone or foraminal involvement is equivocal on CT. MRI may also be useful for delineating disease in the pelvis. For patients where radiotherapy (RT) is considered, MRI can be useful for assessing local tumor extent and surrounding edema, which is optimally included in the treatment volume[27]. Due to the variability of tumor grade, FDG PET/CT has no routine role but again can be used for problem solving. It is utilized when pulmonary abnormalities are detected on CT, which may be suspicious but not diagnostic for metastasis or rarely to evaluate possible multifocal intra-abdominal disease.

Tissue diagnosis

The retroperitoneum can host a multitude of benign or malignant pathologies. Image-guided percutaneous coaxial core needle biopsy (14 or 16 gauge) is the most accurate diagnostic modality and the preferred method to establish a histological diagnosis[12]. Although occasionally a biopsy can be done free-hand if the tumor is large and palpable, image guidance is usually preferable to prevent inadvertent damage to neighbouring structures. Also, several RPS have necrotic or even cystic areas, and image guidance provides the opportunity to get tissue material from solid tumor areas. A histological diagnosis is essential to discriminate benign retroperitoneal tumours or other malignant processes from sarcomas, to identify chemosensitive pathology, diagnose tumours in which neoadjuvant therapy is indicated, and to diagnose metastatic disease presenting as a retroperitoneal mass[28]. Core needle biopsy of a retroperitoneal sarcoma (RPS) is safe, reliable and must be strongly recommended unless the imaging is pathognomonic of a dedifferentiated/well-differentiated liposarcoma and no preoperative neoadjuvant treatment is planned. Multiple needle cores (ideally 4-5) should be obtained to allow for histologic and molecular subtyping. The retroperitoneal route should be the preferred route and the transperitoneal approach only utilised when the tumour is inaccessible for biopsy by the retroperitoneal route. Risk of needle track seeding is minimal and core needle biopsy does not negatively influence the oncological outcome[29] The transperitoneal approach should be the last resort and only performed after specialist sarcoma multidisciplinary team discussion.

Fine-needle aspiration (FNA) cytology rarely yields diagnostic information. An open or laparoscopic surgical incision biopsy of a retroperitoneal mass must be strongly discouraged as it requires an unnecessary operation, exposes the peritoneal cavity to contamination by sarcoma, distorts subsequent planes of dissection, may put vital neurovascular structures at risk and may not provide representative diagnostic tissue due to lack of three-dimensional image guidance[30].

Differential diagnosis and Diagnostic algorithm

Particularly where large masses distort anatomy, distinction between peritoneal and retroperitineal masses can be challenging however displacement of retroperitoneal organs is a useful indicator that a tumour is retroperitoneal in origin[31,32]. Although retroperitoneal sarcomas are rare, the majority (70%) are liposarcomas and therefore interrogating imaging of an indeterminate retroperitoneal mass should begin with a purposeful search for the presence of abnormal macroscopic fat. This forms the first decision in the proposed diagnostic algorithm (Figure 1) in which imaging features can be used to guide diagnosis. Careful interrogation will sometimes reveal that the fat containing mass originates from the kidney or adrenal leading to a diagnosis of renal angiomyolipoma (AML) or adrenal myelolipoma (ML) respectively (Figure 2). The presence of renal cortical defects and prominent vessels strengthens diagnosis of the former[33] and adrenal ML tend to be more well defined than RP liposarcoma, with a frosted glass aspect which is related to the bone marrow inside the fat. If the fat containing mass is not clearly arising from the solid abdominal viscera the diagnosis of retroperitoneal liposarcoma should be considered and referral to a soft tissue sarcoma unit made where percutaneous biopsy will be performed. Expansile macroscopic fat external to the solid abdominal viscera is highly suspicious for well differentiated liposarcoma and the presence of septations or solid enhancing elements suggests dedifferentiation (Figure 3). Calcifications can be present and are reported to indicate dedifferentiation and poor prognosis or may represent sclerosing or inflammatory variants of WDL[34,35]. Although rare in the retroperitoneum benign fat-containing extragonadal dermoids, hibernomas and lipomas can also mimic RP liposarcomas (Figure 2). If there are known risk factors, extramedullary haematopoiesis can also present as a fat containing mass although fat is not always present in this condition.

Occasionally the presence of fat is not immediately obvious and a careful and focused assessment for its presence is essential (Figure 4). Failure to recognize

the presence of abnormal fat is the commonest reason for misdiagnosis and mismanagement. If the well differentiated component is not recognized incomplete resection may result which deprives the patient of curative surgery. Furthermore several foci of dedifferentiation can be misinterpreted as multifocal disease contraindicating surgery or leading to piecemeal resection, however in reality this is usually separate foci of dedifferentiation within a single contiguous liposarcoma with well differentiated elements between the solid masses. This is still classified and should be treated as unifocal disease. The risk for surgery by surgeons unfamiliar with the pattern of presentation is to classify the disease as multifocal or to focus on and resect only the higher density component of tumor at surgery while the low-grade liposarcoma remains[30].

It is important to be mindful of the fact that absence of macroscopic fat in a retroperitoneal mass does not exclude a diagnosis of RP liposarcoma. This may represent disease that has dedifferentiated throughout (Figure 3) or a sclerosing subtype.

A previous history of malignancy or positive serum markers may suggest a diagnosis of metastatic adenocarcinoma, melanoma or germ cell tumour. Testicular ultrasound can also be considered in younger male patients with indeterminate retroperitoneal mass lesions. Clinical history or urinary catecholamine measurements may point to a diagnosis of extra-adrenal phaeochromocytoma. Although rare, retroperitoneal fibrosis may also be considered especially where there is symmetrical ureteric involvement. With the rare exception of epitheliod sarcomas, rhabdomyosarcomas and clear cell sarcomas, sarcomas almost never spread to lymph nodes. Therefore the presence of lymph nodes should raise the possibility of an alternative diagnosis such as metastatic disease or lymphoma. Retroperitoneal lymphoma has classic imaging appearances of a homogeneous mass which encases rather than effaces vessels (Figure 2).

The presence of a large, heterogeneously enhancing, necrotic retroperitoneal mass contiguous with a vessel is highly suggestive of a venous LMS which is the second most common sarcoma encountered in the RP. These usually arise from

the IVC below the level of the hepatic veins but they do also arise from smaller vessels such as the renal veins or less commonly the gonadal veins[36] (Figure 5). They commonly have an exophytic component, which can make differentiation from extrinsic compression challenging.

The finding of a large, well circimscribed solid, vascular tumor, particularly with prominent feeding vessels should alert the radiologist to the possible diagnosis of solitary fibrous tumor (Figure 5). Lipomatous hemangiopericytoma is a subtype of SFT that contains fat[37].

Benign nerve or nerve sheath tumours are also encountered in the retroperitoneum. These are usually rounded and well defined but malignant peripheral nerve sheath tumour is an important differential diagnosis due to its aggressive biology and poor prognosis. Frequently MPNSTs arise from neurofibromas and 50% occur in the setting of neurofibromatosis type I [38]. Clinically, pain is a classic presenting symptom in patients with MPNST. Radiologically, MPNSTs and neurofibromas may appear indistinguishable as both neurofibromas and MPNSTs may contain areas of low attenuation however only MPNSTs show invasion of local structures, rapid growth and onset of pain[39] (Figure 5). The characteristic dumbbell lesion that expands the intervertebral foramina is more easily diagnosed as a neurofibroma.

Some sarcoma subtypes such as synovial sarcoma typically have cystic looking elements and can be mistaken for either abscess or even haematoma. Careful interrogation for solid enhancing elements in combination with correlation with clinical history is paramount but in cases of uncertainty biopsy is essential.

Imaging to guide operability

Once the diagnosis of RPS is established and the patient is fit enough to undergo major surgery, the next stage is to evaluate for surgical operability. Patient selection for curative surgery should include an assessment of technical resectability, taking into account tumor biology and behaviour, response to treatment and the likelihood of obtaining local tumor control weighed against morbidity of radical resections[40]. Full staging CT including CT thorax is required

to assess for the presence of metastatic disease. This is particularly important for patients with leiomyosarcoma where up to 50% have pulmonary metastases at presentation [36].

The aim of surgical resection should be to achieve a macroscopic complete R0/R1 resection and one important aspect of this endpoint is better patient selection through critical analysis of preoperative imaging. Inadequate preoperative evaluation and planning may lead to inadequate incisions, tumor rupture, incomplete resections and underestimation or organs, critical nerves and blood vessels resulting in excessive bleeding or unplanned organ or nerve damage[12].

The tumor size, location and relationship (i.e. adjacent, encasement or invasion) to adjacent viscera, parietal wall, bone and neurovascular structures must be defined to plan for possible adjacent visceral resection. Resection of the ipsilateral kidney and adjacent hemicolon is often required and any abnormality of the contralateral kidney or involvement of the contralateral renal vein should be reported[28]. Multifocality is a poor prognostic sign and should be noted but should not be confused with large tumors consisting of areas of different grade, necrosis and differentiation[40].

Common causes for nonresectability or contraindications to resectability are metastases, encasement of the celiac axis, porta hepatis and superior mesenteric vessels or extensive involvement of bone or spinal cord [30]. For IVC leiomyosarcomas specifically, the extent of inferior vena cava involvement and relationship to the renal and retrohepatic veins and any intraluminal component must also be described. Lumbar vessels and collateral veins in the retroperitoneum can be a source of significant intra-operative blood loss and should be identified on the preoperative CT scan (Figure 4). Compressive venous effects increase the risk for venous thromboembolism and the pulmonary artery tree should also be assessed for pulmonary embolism[28].

Possible extension of tumors outside the abdominal cavity through the diaphragmatic hiatus, inguinal canal, sciatic notch or obturator foramen should be described in order for surgical planning to encompass the extension into an en bloc resection[30] (Figure 4).

Follow up imaging

Following resection, surveillance with contrast-enhanced CT of the chest, abdomen and pelvis is useful for detection of local recurrence or metastatic disease because recurrence on imaging may predate symptomatic recurrence by years. The interval for follow up is generally agreed as every 3-6 months for the first 5 years followed by annual imaging thereafter. However this strategy is based on general consensus as there is no specific data on the effectiveness of routine follow up. As risk of recurrence does not plateau, follow up should be at least 10 years or even indefinite[12]. Particularly for younger patients where the radiation risks from multiple CT examinations might cause some concern the follow up can be performed with MRI of the abdomen and pelvis supplemented with CT thorax[41]. Recurrences can be difficult to detect particularly if they are of small volume fat attenuation or associated with loops of bowel and for liposarcomas any new fat densities or changes in fat attenuation should be regarded with suspicion[42]. All relevant imaging studies performed prior to resection of the primary RPS should be obtained and reviewed, as should all subsequent imaging studies, in particular the initial postoperative baseline imaging to determine whether prior resection was in fact grossly incomplete. At recurrence both the extent and rate of progression are essential to inform management decisions[43].

Conclusion

Delayed diagnosis or misdiagnosis of patients with RPS may result in increased tumor size or metastases or even inadequate first line treatment at the time of referral to a sarcoma centre which in turn is associated with a worse prognosis. Imaging is crucial in this pathway and systematic appraisal of contrast enhanced CT images facilitates early diagnosis and treatment planning. Although RPS are

rare, the most common subtypes LPS (70%) and LMS (15%) have characteristic imaging appearances. Therefore, recognition of abnormal fat in the retroperitoneum is most helpful for the diagnosis of the most common RPS which is liposarcoma, and masses originating from vessels may indicate the second most common subtype leiomyosarcoma. It is essential that patients with suspected RPS are referred immediatley to a high-volume sarcoma centre where they can be diagnosed and treated using a multidisciplinary team approach which includes a specialist team of sarcoma surgeons, medical oncologists, clinical oncologists/radiation oncologists, radiologists, pathologists and nursing staff.

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Figure 1: **Proposed diagnostic algorithm.** The differentials offered are not exhaustive but the flow chart offers guidance on key decision making based on cross sectional imaging appearances.(STS - soft tissue sarcoma).

Figure 2. **Retroperitoneal sarcoma mimics**. A: Renal angiomyolipoma – the fat density mass medial to the right kidney is associated with a renal cortical defect (arrow) and prominent vessels (dashed arrow); B: Hibernoma – the bland fat density retroperitoneal mass was thought to represent well differentiated liposarcoma however biopsy confirmed a benign hibernoma; C: Extragonadal dermoid (arrow) contains soft tissue, fat and calcified elements; D: Lymphoma – the homogeneous retroperitoneal mass encases vessels (arrow) and infiltrates the sacral foramina (dashed arrow); E: Schwannoma– well defined retroperitoneal displaces rather than invades local structures and contains foci of cystic degeneration arrow).

Figure 3. **Varying contrast enhanced CT appearances of retroperitoneal liposarcomas.** A: Well differentiated liposarcoma –The bland fat density retroperitoneal mass has typical imaging appearances of well differentiated liposarcoma; B: Well and dedifferentiated liposarcoma – This retroperitoneal mass has bland well differentiated components (arrow) surrounding the kidney but the solid enhancing component (dotted arrow) suggests dedifferentiation; C: Dedifferentiated liposarcoma – There is no macroscopic fat within this retroperitoneal liposarcoma which has completely dedifferentiated.

Figure 4. **Surgical planning.** Contrast enhanced CT in the same patient (A and B) demonstrates a soft tissue mass in the left retroperitoneum (A, arrow) which represents dedifferentiated disease but inferior slices show the well differentiated component posterior to the left kidney (B, arrow). Identification of the well differentiated component is crucial for diagnosis but also surgical planning as the whole tumour must be removed. Contrast enhanced CT in a second patient (C and D) shows a partly calcified mass anterior to the external iliac vessels (C, arrow) representing dedifferentiated liposarcoma however an inferior slice confirms that a well differentiated component (D, arrow) has passed below the inguinal ligament along the spermatic cord (D, arrow). Sagittal CT reconstruction of a patient with leiomyosarcoma shows tumor within the IVC (E, black dashed arrow). It is critical to forwarn the surgeon of the large lumbar vein which drains into the posterior IVC at the cranial aspect of the tumor where a surgical clamp could inadvertently tear the vein (E, white arrow). Axial contract enhanced CT in a patient with liposarcoma (F) shows 2 foci of differentiation (arrows) however this is not multifocal disease – this is multiple foci of dedifferentiation embedded in well differentiated tumor (dashed arrow).

Figure 5. **Contrast enhanced CT appearances of further retroperitoneal sarcoma subtypes.** Retroperitoneal leiomyosarcomas are classically well defined, enhancing masses which originate from the IVC (A) but they may also arise from other vessels such as the renal vein (arrow, B). Solitary fibrous tumours are typically large masses which display avid enhancement with

prominent feeding vessels (arrow, C). MPNTs can be mistaken for benign nerve sheath tumours but local invasion of the adjacent psoas (arrow, D) indicates the aggressive nature of this mass which was a histologically proven MPNST.