Singapore Cancer Network (SCAN) Guidelines for the Initial Evaluation, Diagnosis and Management of Retroperitoneal Soft Tissue Sarcoma
The Singapore Cancer Network (SCAN) Sarcoma Workgroup

Abstract

Introduction: The SCAN sarcoma workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the initial evaluation, diagnosis and management of patients with retroperitoneal soft tissue sarcoma. Materials and Methods: The workgroup utilised a consensus approach to create high quality evidence-based clinical practice guidelines suited for our local setting. Results: Various international guidelines from the fields of radiology, pathology, surgical, medical and radiation oncology were reviewed. Recommendations on the role of radiological imaging, pathology, surgery, radiotherapy and systemic therapy in the management of retroperitoneal soft tissue sarcoma were developed. Conclusion: These guidelines form the SCAN Guidelines 2015 for the diagnosis, staging and optimal management of patients with retroperitoneal soft tissue sarcoma.

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Key words: Asian patients, Retroperitoneum, Sarcoma, STS, Treatment

Introduction

Soft tissue sarcoma (STS) is a rare and heterogeneous group of cancers representing <1% of all newly diagnosed malignancies. As an entity, it is made up of more than 50 pathologically and molecularly distinct subtypes of sarcomas. Originating at any site in the body, approximately 15% of STS originate from the retroperitoneal region. Based on the National Cancer Centre Singapore’s (NCCS) sarcoma database, the 3 most common STS histotypes include well differentiated/dedifferentiated liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma (UPS) (formerly termed malignant fibrous histiocytoma).

While several international guidelines for treatment of retroperitoneal STS exist, due to unique differences in patient population, healthcare structure and reimbursement issues, direct application of these international guidelines to the local context is oftentimes not possible. Hence, there exists a need to develop a set of local Singaporean guidelines to address this unique patient population and sarcoma practice within our healthcare context.

In this consensus statement, we aim to provide an evidence-based approach to the initial diagnosis, investigation and subsequent management of retroperitoneal STS.

The SCAN Guidelines for the Initial Evaluation, Diagnosis and Management of Patients with Retroperitoneal STS

The SCAN Guidelines are clinical practice guidelines for the initial evaluation, diagnosis and management of patients with retroperitoneal STS.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on the management of retroperitoneal STS. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of patients...
with retroperitoneal STS.

Guideline Recommendations/Development

The SCAN Sarcoma Workgroup comprises a panel of 14 members with special interests in the management of sarcoma. Members come from diverse specialities including orthopaedic surgery, pathology, diagnostic radiology and medical, radiation, surgical, paediatric and musculoskeletal oncology. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

A consensus approach was used to develop guidelines streamlined to the Singapore context. First, available resources were considered. High quality guidelines3-6 were selected for review and structured approaches developed for guideline evaluation. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. The SCAN guidelines were then written with consensus from workgroup members for each recommendation. Calibration of guidelines to the local context based on available Singapore data was encouraged. The final phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 4 main management issues which were selected for this topic:

1. Radiological imaging
2. Pathology
3. Histological diagnosis
4. Surgery
5. Radiotherapy
6. Systemic therapy

The following international guidelines were selected for review:

- “Soft Tissue Sarcoma” (version 2.2014) by von Mehren M et al3
- “Improving Outcomes for People with Sarcoma” by the National Collaborating Centre for Cancer4
- “Soft Tissue and Visceral Sarcomas: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Sarcoma Network Working Group, 20125
- “Guidelines for the Management of Bone Sarcomas” by Grimer RJ et al6

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of sarcoma, it will be reviewed earlier.

1. Radiological Imaging

Regardless of presentation and clinical history, cross-sectional imaging, in the form of computed tomography (CT) and/or magnetic resonance imaging (MRI) is essential in any approach to sarcoma.7 CT is recommended as the first-line investigation. High resolution, thin slices CT scan with coronal and sagittal multiplanar reconstruction (MPR) capability is desired, with both intravenous and oral contrast medium administration.9 Intravenous contrast-enhanced helical CT scan of the abdomen and pelvis is the minimum investigation to be performed. This allows for characterisation of the mass, local staging, delineation of the margins and differentiation from adjacent organs and vascular structures. Differentiation between retroperitoneal, intraperitoneal, and visceral origin is essential.4,5,7,8

A CT scan of the thorax to assess for any lung metastatic disease and other intrathoracic pathology can also be performed at the same time.3-5,7,9 In lieu of a CT thorax scan, a plain erect frontal chest radiograph may be obtained for screening.

MRI scans should be reserved to answer specific problems. With its superior tissue contrast resolution, MRI can be used to assess vascular and neural invasion and to characterise the solid, cystic and necrotic areas of the mass.3,5,7,8 Scans with and without intravenous MRI contrast medium administration is recommended when this modality is employed.

Preoperative core needle biopsy, if required, should be under CT guidance, with the track and targeted region determined after discussion with the surgical team. The National Comprehensive Cancer Network (NCCN) guidelines state that pre-resection biopsy is necessary in patients receiving preoperative radiation therapy (RT) or chemotherapy; fine needle aspiration is generally insufficient to obtain material sufficient to make a diagnosis, given multiple sarcoma subtypes and a variety of histological and fluorescence in situ hybridisation markers that can be brought
to bear on diagnosis (see below on biopsy guidelines). The utility of whole body MRI and positron emission tomography (PET) CT imaging is still being evaluated for both staging and post-treatment follow-up, with research still ongoing.

2. Pathology

The differential diagnoses of a retroperitoneal sarcoma (RPS) are diverse. Before considering a diagnosis of sarcoma, meticulous clinico-pathological effort should be made to exclude the possibility of sarcomatoid carcinoma or mesothelioma, metastasis and benign pseudo-sarcomatous entities. Careful correlation with the clinician and radiologist may yield critical information about the tumour (e.g. history of familial syndromes, necrosis, relationship with adjacent organs) that will greatly aid in narrowing the differential diagnoses.

In adults, the most common groups of RPS are often high-grade, which includes liposarcomas, leiomyosarcomas and undifferentiated pleomorphic sarcoma. Liposarcomas can be broadly divided into 3 unique classes: well differentiated/dedifferentiated, myxoid/round cell, and pleomorphic subtypes. RPS in paediatric patients are uncommon and more likely to be rhabdomyosarcomas, extraosseous primitive neuroectodermal tumour (PNET), neuroblastomas, and Wilms tumours.

Biopsy Specimen

If biopsy specimens are required, preliminary investigation generally involves obtaining multiple core biopsies (at least 5 cores) using needles of at least 16 gauge to subtype the tumour and assess tissue viability for further ancillary testing. Malignancy grading may be underestimated in small biopsies; therefore, a final diagnosis can only be reliably obtained after definitive tumour resection. Frozen-section technique for immediate diagnosis should be avoided due to suboptimal histological interpretation and lack of immediate ancillary support.

Resection Specimen

As with sarcoma elsewhere, tumour site, size, depth, vascular invasion and margin status should be recorded. Detailed discussions of the tumour datasets and gross handling are comprehensively covered in various pathology colleges and organisations guidelines. For RPS where tumours are often large and voluminous, a few practical suggestions could be made. Firstly, coordination between the surgeon and pathologist is important to ensure that fresh tissue is available for molecular studies and tumour banking. Secondly, “intelligent” sampling of critical sites (e.g. interface region in a dedifferentiated tumour) rather than blind extensive sampling is more cost-effective in obtaining the correct diagnosis. Thirdly, tumours with heterogeneous appearance should be generously sampled to investigate heterologous or dedifferentiated elements.

3. Histological Diagnosis

Histological diagnosis should be made according to the latest (2013) World Health Organization (WHO) classification. Except in a few situations (e.g. preoperative chemotherapy, rarely metastasising tumours or newer entities not categorised in the current grading system), grading of the sarcoma should be provided following the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system (Table 1), which is based on tumour differentiation, mitotic count and necrosis. Histological assessment of these tumours involves careful morphological examination complemented by ancillary investigations. Morphological examination involves a systematic pattern-based approach analysing parameters that generally include: a) architecture, b) cytomorphological features, and c) stromal characteristics. Identifying specific types of cells (e.g. lipoblasts, rhabdomyoblasts) can be extremely helpful in subtyping the tumour. For pleomorphic sarcomas it is critically important to subtype these tumours accurately wherever possible because each sarcoma is biologically and prognostically distinct. For example, a pleomorphic liposarcoma has a considerably worse prognosis than a dedifferentiated liposarcoma. Furthermore, what is seen to be UPS under the microscope may actually be 1 aspect of a well differentiated/dedifferentiated liposarcoma.

Ancillary Investigations

A panel of immunohistochemical stains is routinely ordered primarily to determine the tumour lineage. Some of the common stains used in approaching RPS would

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Table 1. Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) Histological Grading Criteria

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<tr>
<th>Tumour Differentiation</th>
<th>Necrosis</th>
<th>Mitotic Count</th>
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<tbody>
<tr>
<td>(1) Well</td>
<td>(0) No necrosis</td>
<td>(1) 0 – 9</td>
</tr>
<tr>
<td>(2) Moderate</td>
<td>(1) &lt;50% tumour necrosis</td>
<td>(2) 10 – 19</td>
</tr>
<tr>
<td>(3) Poor</td>
<td>(2) ≥50% tumour necrosis</td>
<td>(3) &gt;19</td>
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*Established on the basis of per 10 HPF: 1 HPF measures 0.1734 mm². Note: The individual score for each parameter (i.e. tumour differentiation, necrosis, and mitotic count) is in parenthesis. The sum of the scores of the 3 parameters determines the grade of malignancy. Grade 1: total score 2,3; Grade 2: 4,5; Grade 3: 6-8.
include: a) MDM2 and CDK4 for well differentiated or dedifferentiated liposarcoma; b) H-caldesmon and desmin for smooth muscle differentiation, c) membranous CD99 expression for PNET, d) S-100 for neural differentiation, which in some cases of dedifferentiated liposarcoma can be positive, and d) broad spectrum cytokeratin to exclude sarcomatoid carcinomas or mesotheliomas or more rarely other cytokeratin positive sarcoma (e.g. synovial sarcoma).

Molecular tests play a critical role in the diagnostic algorithm of problematic cases. These tests are often regarded as the “gold standard” in confirming diagnosis, especially in sarcomas with recurrent chromosomal translocations. In the context of RPS, molecular tests could be used to detect HDM2 and CDK4 amplification for well differentiated and dedifferentiated liposarcoma, translocation t(12;16)(q13;p11) for myxoid liposarcoma and EWS gene rearrangement for Ewing’s/PNET and desmoplastic small round cell tumour. As with other ancillary investigations, molecular tests are complementary but not a substitute for histological diagnosis.

In summary, due to its complexity, diagnosing RPS requires meticulous pathological examination with careful clinical and radiological correlation. With the availability of new ancillary diagnostic tools, every effort should be made to accurately subtype a high-grade sarcoma before signing it out as a “high-grade undifferentiated pleomorphic sarcoma”.

4. Surgery

Surgery is the mainstay of treatment for STS and the principles of management of RPS do not differ significantly from those of extremity sarcomas. All RPS are considered deep tumours (thus making the differentiation between superficial and deep tumours, a recognised prognostic factor for sarcoma outcomes, useless), located beneath the fascial plane, and their location often also results in a late diagnosis, with an average size of well over 10 cm at presentation. As such, the prognosis is considerably worse in view of these factors. A preoperative biopsy is usually not required if the radiological images are consistent with a retroperitoneal liposarcoma. However, it is useful for the exclusion of other non-sarcomatous tumours, and when preoperative treatment with radiation or chemotherapy is being considered. In a resectable lesion, surgery can be planned for and must achieve adequate margins. The emphasis is on obtaining wide or radical margin remains, though these margins are much harder to define. In the extremity, where a wide margin is attained by removing a rim of 1 cm to 2 cm of normal tissue and radical resection typically necessitates a compartmental resection, the retroperitoneum is less compartmentalised and structures within it are often in close proximity, if not adjacent to the sarcoma. A contrast-enhanced CT scan is critical to define the potentially involved organs, with the absence of a distinct fat plane in such cases. It is also noted that with the diagnosis of dedifferentiated liposarcoma, the normal appearing fat surrounding will oftentimes represent well differentiated liposarcoma and should be removed en bloc intraoperatively. Resection with a curative intent must take into account the need for functionality after the surgery. Multivisceral resections are not uncommon, and may encompass an en bloc resection of surrounding structures such as the large or small intestine, kidney, stomach, spleen and, occasionally, the vascular structures. Resection of a portion of the aorta will require reconstruction, most often with a prosthetic graft. In recurrent tumours, the planes for dissection become less distinct, and clear margins may necessitate the removal of adherent organs, as true invasion may be difficult to ascertain. It has been shown that patients with RPS are more likely to receive a complete resection of their tumour and have improved survival if they were treated at a specialist tertiary centre, and at a hospital with a high volume of sarcoma work.

Preoperative radiation therapy is administered by some centres in an attempt to “sterilise the margins”, with its proponents citing the need for a lower dosage of required radiation to the well vascularised field and the still-present tumour obviating a need for a spacer to prevent radiation to other uninvolved organs. However, preoperative radiation would necessitate a preoperative core biopsy, and the issues of contamination and subsequent excision of the biopsy pathway should be considered. Postoperative radiation, in the absence of preoperative radiation therapy, is offered to those with an involved margin and in selected patients with high-grade and large tumours (extrapolated from data from extremity sarcomas), but definitive evidence has yet to be established for pre or postoperative radiation of RPS, in particular since radiation postoperatively will by definition lead to a greater degree of radiation to normal tissue, which is pushed out of the way in preoperative radiation treatment of a retroperitoneal STS (see below). In the event of an unresectable RPS, downstaging can be considered with chemotherapy or radiation.

In summary, surgery is the mainstay of treatment for RPS. Clear margins, including an intact pseudocapsule are necessary to decrease the local recurrence rates. This may necessitate en bloc multivisceral resection of organs that are adherent to the RPS.
5. Radiotherapy

Local relapse rates remain around 50% even with macroscopic complete resection, hence the interest in adjuvant therapies such as radiotherapy to improve local control. As with limb sarcomas, radiotherapy can be delivered either preoperatively or postoperatively. There are potential advantages to the preoperative approach:

- the primary tumour in situ represents a well defined target volume;
- the tumour itself acts as a spacer, displacing the small bowel from high dose treatment volume, thus reducing acute and late toxicity;
- radiotherapy may be more effective in the preoperative setting because of better oxygenation;
- preoperative radiotherapy may thicken the pseudo-capsule of the tumour, thus aiding surgical resection and reducing intraperitoneal spillage;
- it may render an unresectable tumour resectable.

Two prospective trials\(^1\) of preoperative radiotherapy have shown favourable local control rates of 60% following macroscopically complete resection. The dose for preoperative radiotherapy is 50 Gy. The use of advanced radiotherapy delivery techniques such as intensity modulated radiation therapy (IMRT) or tomotherapy allows selective dose escalation beyond 55 Gy to the margin at risk and may be considered.\(^2\) A randomised trial to compare surgery alone versus preoperative radiotherapy and surgery was attempted in North America, but closed due to poor accrual. A similar trial in Europe has been ongoing since 2012, but results are not expected until some years later.\(^3\) Intraoperative radiotherapy has been shown in retrospective series to improve local control rates and should be considered where available, usually in combination with pre- or postoperative external beam radiotherapy.\(^4\)

A non-randomised retrospective series\(^5\) has documented improved local control without overall survival benefit with postoperative radiotherapy. However, the presence of radiation dose-limiting structures in the postoperative target volume presents a significant challenge and often limits the dose to 50 Gy to 55 Gy to well defined areas at risk.\(^6\) If it is to be considered, the use of omentum or other tissue spacers to displace bowel from the tumour bed is recommended to reduce the risk of radiation induced bowel toxicity.\(^7\)

In summary, while a number of retrospective studies showing favourable local control with both pre- and postoperative radiotherapy exist, there is a distinct lack of level 1 randomised trial evidence for radiotherapy in RPS. Therefore, while the general indications for radiating any soft tissue sarcomas are still valid (large, intermediate-high grade, incompletely resected),\(^8\) the unique difficulties posed by the proximity of radiosensitive organs at risk mandate multidisciplinary discussion to determine feasibility and sequencing of radiation therapy.

6. Systemic Therapy

Knowledge of the histologic spectrum of RPS, in addition to appreciation of their significantly disparate biologies, is critical to optimal management. Well differentiated liposarcomas have the most favourable prognosis, and are disposed almost exclusively to local recurrence, with negligible incidence of distant metastasis. They are also of low histological grade with no known responses to cytotoxic chemotherapy. These factors thus suggest no rationale for adjuvant systemic therapy with cytotoxic agents in primary or recurrent well differentiated liposarcoma. Both dedifferentiated liposarcoma and leiomyosarcoma are high-grade tumours with equally poor prognosis relative to well differentiated liposarcoma. Crucially, this similar eventual survival is mediated by diametrically disparate patterns of recurrence—while dedifferentiated liposarcoma, akin to well differentiated liposarcoma, is chiefly prone to local recurrence, leiomyosarcoma manifests primarily distant relapses.\(^9\) This disparity in the pattern of treatment failure necessitates a tailored, histology-specific approach in thinking about primary and adjuvant therapy. For instance, of these diagnoses, it may be argued that leiomyosarcomas could benefit most from effective adjuvant systemic therapy.

Perhaps because of the predominance of well differentiated/ dedifferentiated liposarcoma in the retroperitoneum and its relative chemotherapy resistance, scant prospective data are available regarding the use of adjuvant chemotherapy specifically in resected localised primary RPS. Fewer than 10% of major adjuvant chemotherapy trials in sarcoma conducted thus far comprised patients with retroperitoneal disease.\(^10\) A retrospective analysis of neoadjuvant therapy in high-grade RPS revealed no improvement in survival relative to that predicted by the appropriate nomogram, although histopathologic response to neoadjuvant therapy predicted for improved outcomes compared with non-responders.\(^11\) There is no prospective data assessing the value of perioperative systemic therapy in the setting of locally recurrent disease. At this time, we do not recommend adjuvant chemotherapy as a routine standard of care in resected retroperitoneal STS except in rare chemotherapy sensitive subtypes more common in children, e.g. Ewing sarcoma.

While the objective of chemotherapy in the setting of unresectable or metastatic disease is palliative, a consideration especially relevant to RPS is the significant morbidity of bulky abdomino-peritoneal disease, thus amplifying the value of achieving substantive...
clinicoradiologic responses with systemic therapy. A large French study evaluating almost 600 patients with locally advanced or metastatic RPS demonstrated an objective response rate of 16% and a progression-free survival of nearly 6 months with palliative chemotherapy. 

Although histological subtype did not feature as a significant prognostic factor for chemotherapy response or overall outcome in this particular study, it remains the most important factor in choosing systemic agents for treatment. Well differentiated and dedifferentiated liposarcomas respond poorly to cytotoxic chemotherapy, associated with objective response rates of 10% to 12% with anthracycline-based treatment. 

A defining molecular pathway—amplification of the anti-apoptotic proteins HDM2, which inhibits the tumour suppressor p53, and CDK4, which suppresses the tumour suppressor retinoblastoma protein—is present in over 90% of well and dedifferentiated liposarcomas.

These aberrations have become molecular signatures used for definitive diagnosis of liposarcoma, and present unique therapeutic opportunities through pharmacological antagonism of HDM2 and CDK4 in tumours with functional p53 and Rb protein, respectively. Early phase clinical studies of both HDM2 and CDK4 inhibitors have revealed modest activity so far. In the case of leiomyosarcomas, there is moderate sensitivity, above and beyond anthracycline-based chemotherapy, to one of several agents given either singly or in combination, including gemcitabine in combination with docetaxel, single agent trabectedin (approved outside of US), dacarbazine or temozolomide, and gemcitabine in combination with dacarbazine. Other histologies that make up a small proportion of retroperitoneal disease include undifferentiated pleomorphic sarcoma, malignant peripheral nerve sheath tumours and solitary fibrous tumour. While the former 2 diagnoses are high-grade tumours often treated with anthracycline-based combination chemotherapy, solitary fibrous tumour has a more varied biology, and a less predictable response to cytotoxic agents. It has, however, been shown to derive benefit from therapy directed against vascular endothelial growth factor, either singly or in combination with chemotherapy. Pazopanib, a multitargeted tyrosine kinase inhibitor directed against vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor receptor and KIT, remains an option for any non-liposarcoma soft tissue sarcoma failing other chemotherapy in the recurrent or metastatic setting, having demonstrated significant benefit in progression-free survival in a landmark randomised phase 3 trial.

**Conclusion**

Due to its complexity, heterogeneity and rarity, retroperitoneal STS is a challenging disease to diagnose and treat and best managed in a high volume centre experienced in the management of these diseases. Guidelines contextualised to the local patient and unique healthcare setup in Singapore will hopefully streamline care and improve clinical outcomes for our sarcoma patients.

**Conflicts of Interest**

The workgroup members have nothing to disclose.

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