Diagnosis and management of soft tissue sarcoma

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Soft tissue sarcomas are a heterogeneous group of tumours of mesodermal origin. Although they are rare, accounting for less than 1% of all malignant tumours, half of patients diagnosed will die from the sarcoma.\(^1\)\(^-\)\(^7\) Lumps are commonly encountered in primary and specialist care, and differentiating benign from possibly malignant lesions can be difficult. The estimated benign:malignant ratio is 100:1. A family doctor will see about one case of soft tissue sarcoma for every 24 years of practice.\(^2\)\(^-\)\(^3\) However, prognosis is related to size at presentation, so early recognition, referral to a specialist (see National Institute for Health and Clinical Excellence (NICE) guidelines), and appropriate treatment improve outcomes.\(^2\)\(^-\)\(^3\) Evidence from cohort studies suggests that patients experience delays in referral,\(^8\)\(^-\)\(^9\) and in the United Kingdom referrals to specialist sarcoma centres often fall outside the recommended two week window for suspected cancer.\(^2\)\(^-\)\(^4\) We review evidence from national guidelines, randomised trials, and observational studies to provide the non-specialist with a guide to diagnosis, appropriate referral, and management of patients with suspected soft tissue sarcoma, focusing on a multidisciplinary approach. We limit our discussion of management to the treatment of soft tissue sarcoma of the extremities—the most common site.

Who gets soft tissue sarcomas?

International incidence rates vary from 1.8 to 5.0 cases per 100 000 per year.\(^5\)\(^-\)\(^7\) In the United States, about 10 600 new cases were diagnosed in 2009, with 3820 deaths.\(^8\)\(^-\)\(^9\) In the UK, 1500-2000 new cases are diagnosed annually.\(^1\) Soft tissue sarcomas can occur at any age, but incidence increases with age. Certain subtypes, such as rhabdomyosarcoma, are more common in children and young adults. These tumours, which account for 7-10% of paediatric cancers, are an important cause of death in those aged 14-29 years.\(^10\)\(^-\)\(^12\) A US registry based study of 17 364 patients showed an average age for diagnosis of 57.4 years.\(^3\) Large scale epidemiological studies and national cancer registries show that men and women are affected equally.\(^1\)\(^-\)\(^4\)

What are the main types of soft tissue sarcoma?

Soft tissue sarcomas are heterogeneous and usually differentiate towards one tissue type. The World Health Organization has defined more than 50 histological subtypes, although these subtypes cannot predict the clinical course.\(^1\)\(^-\)\(^2\) Table 1 summarises the main sarcomas by line of differentiation.

What causes soft tissue sarcoma?

Published epidemiological studies of soft tissue sarcoma are largely centre based rather than population based and suffer from selection bias. Most sarcomas seem to arise de novo, with no obvious cause. Several inherited genetic diseases have been associated with an increased risk of developing soft tissue sarcoma, including Li-Fraumeni syndrome,\(^11\)\(^-\)\(^13\) Gardner’s syndrome, inherited retinoblastoma,\(^11\)\(^-\)\(^13\) and neurofibromatosis. Radiation induced soft tissue sarcoma is rare but has been associated with radiotherapy for breast cancer and lymphoma, with an average time between exposure and diagnosis of more than 10 years.\(^11\)\(^-\)\(^13\)
UK DEPARTMENT OF HEALTH CRITERIA FOR URGENT (TWO WEEK) REFERRAL OF A SOFT TISSUE LESION

- Soft tissue mass >5 cm (golf ball size)
- Painful lump
- A soft tissue lump that is increasing in size
- A lump of any size that is deep to the muscle fascia
- Recurrence of a lump after previous excision

tumour presentation of about 10 years. A Finnish population based study of 295,712 subjects and 147 sarcomas found an increased incidence of sarcoma in younger patients (under 55) who had received radiotherapy (odds ratio 2.1, 95% confidence interval 1.6 to 2.6). Exposure to chemical carcinogens including vinyl chloride, dioxins, and phenoxyacetic herbicides has been associated with an increased incidence of soft tissue sarcoma. A retrospective cohort study of 21,863 workers exposed to phenoxyherbicides, chlorophenols, and dioxins in 12 countries found a standardised mortality ratio of 2.0 for exposure and development of soft tissue sarcoma compared with national mortality rates. Kaposi’s sarcoma is caused by human herpesvirus 8 and Epstein Barr virus may have a role in the development of soft tissue sarcoma in immunodeficiency.

How does soft tissue sarcoma present?

Soft tissue swellings are common and most are benign. Patients typically present with a painless mass that has been growing slowly for months or years. Tumours often do not limit function or affect general health so may be discovered incidentally. This history and presentation, alongside the rarity of these sarcomas, commonly leads to malignant tumours being considered benign when initially examined. So what points to possible malignancy? A national multicentre cohort study of 4508 adults showed the anatomical distribution of soft tissue sarcomas to be thigh, buttock, and groin (46%); torso (18%); upper extremity (13%); retroperitoneum (13%); and head and neck (9%). The UK Department of Health guidelines highlight the clinical features that should prompt urgent referral to a specialist in soft tissue sarcoma (box). A prospective study of 365 patients with soft tissue sarcoma aimed to see which referral criteria were most useful. It found that depth of tumour seemed to be a sensitive marker of malignancy.

The initial consultation should look for the presence of suspicious features (box). Examine the lump to ascertain its size, anatomical site, and whether it is painful. Note whether on direct palpation the lump is fixed to the skin or situated directly beneath the skin where the margins are relatively easily defined. Restricted movement, accentuated by muscle contraction, implies fixation of the lump to the underlying deep fascia. This information should be contained in any letter of referral.

Guidelines for referral to specialist care

The US National Comprehensive Cancer Network, European Society of Medical Oncology, and recent UK consensus guidelines based on 2006 NICE guidance recommend that general practitioners and non-specialist centres rapidly refer all patients with a suspicious soft tissue mass to a specialist referral centre that provides a protocol driven multidisciplinary approach to diagnosis and treatment.

Cohort studies have shown that these guidelines are often not adhered to. A prospective study of 216 patients in a UK centre found that 20% of patients experienced a median delay of 14 months before seeing a sarcoma specialist. An important reported consequence of delayed referral is an increase in tumour size, which affects prognosis.

Two recent studies from different UK sarcoma centres showed that 74-94% of their referrals fell outside the recommended two week window. There is little current evidence that the two week rule is resulting in earlier diagnosis of soft tissue sarcoma. This suggests a lack of awareness of optimal referral pathways by general practitioners and poor public awareness regarding soft tissue lumps.

Referral to specialist sarcoma centres also helps to prevent “whoops procedures,” where an unsuspected soft tissue lump is excised, usually by a non-specialist, and subsequent histological diagnosis shows soft tissue sarcoma with inadequate excision margins. A retrospective case note review of 104 patients in the US showed that half of patients who had undergone such procedures had done so in a non-specialist centre. A retrospective study of 203 patients showed that 69% of patients with high grade sarcomas who had “whoops procedures” had microscopic residual disease and increased rates of local recurrence.

A comparative study of 260 patients treated at specialist sarcoma centres or district general hospitals found that local recurrence occurred in 19% vs 39%, respectively. However, five year survival rates did not differ significantly. Although the benefit of treatment in specialist centres is difficult to quantify, it is recommended as best practice.

How is suspected soft tissue sarcoma investigated?

NICE guidelines recommend that patients with suspected soft tissue sarcoma are urgently referred for rapid assessment at a one stop diagnostic clinic where triple assessment with clinical history and examination, ultrasound imaging, tissue biopsy, and specific imaging can be undertaken. Each English cancer network has stated the location of these diagnostic clinics, enabling a more rapid diagnostic pathway from primary care. The recommended first line investigation is not clearly stipulated in the guidelines and depends on local expertise and radiology facilities.

Ultrasound

A prospective cohort study of 358 patients with soft tissue masses showed that ultrasound can rapidly triage benign and more suspicious lesions. If clinical suspicion of malignancy exists but referral criteria are not met, an urgent ultrasound can help decide how fast to refer. But for lesions with a high degree of clinical suspicion, do not delay immediate referral to a specialist centre by imaging requests. Ultrasound guided biopsy of the lesion within a specialist centre helps avoid specific anatomical structures and ensures biopsy of viable rather than necrotic tumour tissue.
Plain radiography

For lumps that arise in extremities plain radiography can rule out a mass that arises from bone. Certain soft tissue sarcomas, and synovial sarcoma, may show characteristic calcification.

Computed tomography and magnetic resonance imaging

Magnetic resonance imaging is the preferred method of initial imaging for soft tissue sarcoma of the extremities, trunk, and head and neck in most specialist centres. Computed tomography is the gold standard for preoperative staging and is commonly used to assess intra-abdominal masses. Debate about which of the two modalities is superior continues. A multicentre trial, which included 133 evaluable soft tissue sarcomas and correlated radiological findings with histological and intraoperative findings found no statistically significant difference between the two modalities for efficacy of local staging of soft tissue sarcomas of the extremities. Small comparative studies have suggested that magnetic resonance imaging may be slightly better than computed tomography because it provides multiplanar images with better spatial orientation. UK consensus guidelines state that high resolution computed tomography has a role in the identification of bony involvement and preoperative assessment to exclude pulmonary metastases. The role of routine positron emission computed tomography scanning for diagnosis and monitoring of soft tissue sarcoma is currently unknown.

Biopsy

A histological diagnosis is needed to guide treatment planning. Core needle biopsy is the standard approach to diagnosing suspicious lesions, and open incision biopsy, with its high complication rate (12-17%) and association with a more radical resection, is no longer recommended. Several cores are needed to improve diagnostic accuracy. Single centre prospective and retrospective studies have shown that core needle biopsy has a diagnostic sensitivity of 90-95%; it is quicker than open biopsy, cheaper, and morbidity is lower. A single centre study of 530 patients found a sensitivity of 96.3% in differentiating soft tissue sarcomas from benign tumours, with a complication rate of 0.4%. Ultrasound and computed tomography guided biopsies are used when the tumour is difficult to palpate or necrotic. In the rare instance that open biopsy is needed it should be undertaken in a specialist centre.

Fine needle aspiration is not recommended in the initial diagnostic evaluation of a suspicious mass. A review of five studies found that this technique had a lower diagnostic accuracy than core biopsy. It may have a role in confirming disease recurrence.

NICE guidelines recommend that biopsy results should be interpreted by a specialist sarcoma pathologist in close conjunction with a surgeon and radiologist. Although histological diagnosis is the gold standard, newer methods such as cytogenetics and immunocytochemistry can aid diagnosis by identifying tumour lineage.

What affects the prognosis of soft tissue sarcoma?

Stage and grade of tumour

Information on tumour stage can help estimate prognosis and survival and plan management. Several systems are used to stage soft tissue sarcoma. The most widely accepted are those from the American Joint Committee on Cancer (AJCC) (table 2) and International Union against Cancer (IUCC) (table 3), which include information on both tumour grade and stage. The Musculoskeletal Tumour Society staging system (table 4) also takes into account whether the tumour is intracompartmental or extracompartmental and presence of regional and distant metastases.

Tumour grade is related to prognosis. High grade tumours are poorly differentiated or undifferentiated; they carry a high likelihood of metastasis and poor patient survival. A study of 1240 patients from a national database found that tumour grade was the most important prognostic factor in metastatic recurrence.

A recent systematic review found an overall five year survival for patients with soft tissue sarcoma of 60-80%. A study of 2136 prospectively followed patients estimated sarcoma specific death to be 36% after 12 years. In the largest population based study assessing survival in patients with soft tissue sarcoma of the extremities, advanced age, large tumour size, and high grade all contributed to adverse prognosis and increased 10 year sarcoma specific mortality. This agrees with other population based studies and a large single centre study, both of which found metastatic disease at presentation and tumour depth to be adverse prognostic indicators.

### Table 2 | American Joint Committee on Cancer grading system

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristic</th>
</tr>
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<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Primary tumour &lt;5 cm (T1a: superficial; T1b: deep)</td>
</tr>
<tr>
<td>T2</td>
<td>Primary tumour ≥5 cm (T2a: superficial; T2b: deep)</td>
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</tbody>
</table>

### Table 3 | International Union against Cancer staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Low grade, small, superficial or deep (T1 a-b, N0, M0)</td>
</tr>
<tr>
<td>IB</td>
<td>Low grade, large, superficial (T2a, N0, M0)</td>
</tr>
<tr>
<td>IIA</td>
<td>Low grade, large, deep (T2b, N0, M0)</td>
</tr>
<tr>
<td>IIB</td>
<td>High grade, small, superficial or deep (T1a-b, N0, M0)</td>
</tr>
<tr>
<td>IIC</td>
<td>High grade, large, superficial (T3a, N0, M0)</td>
</tr>
<tr>
<td>III</td>
<td>High grade, large, deep (T2b, N0, M0)</td>
</tr>
<tr>
<td>IV</td>
<td>Any metastasis (any T, N1, or M1)</td>
</tr>
</tbody>
</table>

### Table 4 | Musculoskeletal Tumour Society staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Low</td>
<td>Intra-compartmental</td>
</tr>
<tr>
<td>IB</td>
<td>Low</td>
<td>Extracompartmental</td>
</tr>
<tr>
<td>IIA</td>
<td>High</td>
<td>Intra-compartmental</td>
</tr>
<tr>
<td>IIB</td>
<td>High</td>
<td>Extracompartmental</td>
</tr>
<tr>
<td>III</td>
<td>Any</td>
<td>Regional or distant metastases (or both)</td>
</tr>
</tbody>
</table>
Table 5: Classification of surgical margins in soft tissue sarcoma

<table>
<thead>
<tr>
<th>Type</th>
<th>Surgical dissection</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralesional</td>
<td>Margin runs through the tumour</td>
<td>Microscopic disease remains</td>
</tr>
<tr>
<td>Marginal</td>
<td>Surgical margin runs through pseudocapsule or reactive zone</td>
<td>Tumour satellites remain in the reactive tissue—high local recurrence rate</td>
</tr>
<tr>
<td>Wide</td>
<td>En bloc resection within the same compartment as the tumour with a cuff of normal tissue</td>
<td>May leave skip lesions—low recurrence rate</td>
</tr>
<tr>
<td>Radical</td>
<td>En bloc resection of the entire compartment</td>
<td>No residual—minimal risk of local recurrence</td>
</tr>
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Histological subtype

Several single centre studies have shown that histological subtype may help predict prognosis.12,18-24 A recent retrospective analysis of 17 364 patients from a population based study showed that within a tumour grade, survival differed according to histological type, but small numbers in some histological groups limited interpretation of the findings.16-18 Advances in genetic diagnosis and in the ability to predict the behaviour of certain histological subtypes of tumour may affect treatment planning and staging in the future.

How are soft tissue sarcomas managed?

Management of soft tissue sarcomas requires a multidisciplinary approach, as stated by national guidelines and protocols.2,10-12 Treatment aims to ensure long term survival, avoid local recurrence, and maximise patient function while minimising morbidity. This is achieved by various combinations of surgery, radiotherapy, and chemotherapy. Treatment decisions are best made by a specialist multidisciplinary team of surgeons, pathologists, radiologists, medical oncologists, and clinical oncologists. The team will take into account the tumour’s site and stage plus the patient’s comorbidities and treatment preferences.

Surgery

Surgery is the mainstay of treatment in patients with localised disease. It aims to excise the soft tissue sarcoma completely, along with a biological barrier of normal tissue. Table 5 summarises the four categories of surgical margin that have been described histologically.16-24 No international consensus exists on what constitutes an acceptable resection margin. Limb salvage surgery, which aims to retain a functional limb (to maintain a good postoperative quality of life) while providing an acceptable resection margin (to ensure a low risk of recurrence), is the standard of care for most patients with soft tissue sarcoma of the extremities. UK consensus guidelines state that 1 cm of normal soft tissue or equivalent (for example, fascia) is an acceptable margin.12 A tumour’s proximity to important anatomical structures such as nerves and blood vessels can make it difficult to achieve an acceptable tumour-free margin.

Improved adjuvant radiotherapy and reconstructive surgery have enabled more limited surgery to be performed and function to be preserved. The surgical objective of maintaining a functional limb may require a planned microscopic positive margin and adjuvant radiotherapy. A seminal prospective study showed that less radical surgery had no detrimental effect on overall survival but was associated with a higher rate of local recurrence compared with amputation.25 When considering more limited surgery make patients aware of the risks of tumour recurrence and the possibility of further surgery, including potential amputation.

Advances in reconstructive techniques have enabled limb preservation in complex cases in the form of pedicled and free tissue transfers (figure).

Early complications of surgery may include haemorrhage, wound infection, and deep venous thrombosis. Although, microvascular free flap reconstructions have a success rate of greater than 95%, they can fail or experience wound breakdown, which can delay subsequent planned adjuvant treatment. The patient must be told about the risks of these complications before surgery.

European Society of Medical Oncology guidance states that treatment by wide excision surgery is sufficient for low grade tumours that are superficial or deep and less than 5 cm, in addition to high grade superficial tumours.11

In advanced disease, surgery may be an appropriate palliative procedure. A single centre study found amputation rates of 9-14% in patients with recurrent soft tissue sarcoma of the extremities and less than 5% in those with primary disease.10-12,23 Amputation may be recommended when limb salvage surgery is not possible, after careful discussion with the patient regarding surgical morbidity compared with the pros and cons of other palliative treatment options. Typically such patients have high grade, large, recurrent tumours that often affect anatomically important sites. They are likely to have poor long term survival, and the need to relieve local symptoms such as pain or fungation may outweigh negative factors associated with amputation.

A surgical and reconstructive procedure can take up to 12 hours. A small single centre study assessing the cost effectiveness of limb reconstruction found that the mean length of stay was eight days and 6.6 days for procedures.
AREAS OF ONGOING RESEARCH

- New chemotherapeutic agents: for example, exatecan, a synthetic analogue of topoisomerase I inhibitor (EOTRC study)
- Proton beam therapy: reduces treated volume, enabling a higher radiation dose to be delivered to the tumour and reducing toxicity
- Targeted molecular therapies: drugs that target tumour growth factor pathways and induce apoptosis in tumour cells (for example, Apo2 ligand/TRAIL in osteosarcoma)
- Immunomodulant drugs: looking for tumour antigens to use as vaccines against soft tissue sarcomas

ADDITIONAL EDUCATIONAL RESOURCES FOR HEALTHCARE PROFESSIONALS


involving upper and lower extremities, respectively. The duration of postoperative rehabilitation will vary from patient to patient and according to the type of surgery. This will require intensive specialist nursing, physiotherapy, and occupational therapy.

A single centre prospective study found that the preoperative expectations of patients influenced functional outcome—uncertain expectations were associated with worse functional outcomes. This finding stresses the importance of clear preoperative communication with patients regarding the often long and difficult rehabilitative process and functional limitations that they may experience.

Radiotherapy

Prospective and retrospective studies have shown that radiotherapy improves local control in surgically resectable disease. Most intermediate or high grade soft tissue sarcomas, large deep low grade sarcomas, and incompletely resected tumours that are close to important structures (such as nerves and blood vessels) are candidates for radiotherapy. The optimum timing of radiotherapy for soft tissue sarcoma of the extremities is unclear. In the UK and other countries, postoperative radiotherapy is the standard approach. Preoperative radiotherapy can reduce the size of some radiosensitive tumours, such as myxoid liposarcoma. A recent systematic review and meta-analysis of five studies that compared preoperative and postoperative radiotherapy in localised resectable soft tissue sarcoma found a lower risk of recurrence in the preoperative radiotherapy group (odds ratio 0.61, 0.42 to 0.89). However, no overall survival benefit was seen. A multicentre, prospective randomised study of 190 patients found an increased incidence of wound complications in those receiving preoperative radiotherapy (35% v 17%), but this risk was negated when reconstruction involved imported vascularised tissue. A randomised phase III trial showed that the timing of radiotherapy had little effect on postoperative function. Further prospective randomised controlled trials are needed to evaluate the role of preoperative radiotherapy.

Chemotherapy

The role of adjuvant chemotherapy in the management of soft tissue sarcoma of the extremities is controversial because the evidence for its use is conflicting. Different histological subtypes vary greatly in chemosensitivity—for example, myxoid liposarcomas are more chemosensitive than some other types. UK consensus guidelines do not advocate chemotherapy as standard management. The use of adjuvant chemotherapy may be considered in specific cases of advanced disease with palliative intent.

Several single centre studies and a multicentre phase II trial have suggested that neoadjuvant chemotherapy may be appropriate for patients who have large and high grade tumours (typically synovial sarcoma and liposarcoma) to shrink the tumour before palliative surgery.

Isolated limb perfusion

Isolated limb perfusion is used to treat melanoma. It is widely used in Europe to treat soft tissue sarcoma of the extremities, but it is available in only a few centres in the UK. High concentrations of tumour necrosis factor and melphalan (a chemotherapeutic agent) are delivered under hyperthermic conditions via arterial and venous cannula to a limb isolated by tourniquet compression. This treatment can be used to reduce tumour size to enable limb salvage procedures, or for palliative treatment. Single and multicentre studies of this technique have shown limb salvage rates of 74-87% in selected patients with intermediate or high grade disease.

How can metastatic disease be treated?

A large population based study found that 40-50% of patients with soft tissue sarcoma develop metastatic disease. Common sites of metastases include lung, local soft tissues, and local and distant lymph nodes. A single centre study of 716 patients found that about 20% of patients with soft tissue sarcoma of the extremities have isolated pulmonary metastases. The outlook for patients with metastatic disease is poor—estimated five year survival was 8% with pulmonary metastases and 59% with lymph node metastases in a recent small retrospective study. Metastases in isolated areas or a single organ may be managed with surgery with or without adjuvant treatment. Once metastases are discovered, restaging
the tumour will help to determine the risk to benefit ratio of any proposed treatment for the individual patient.

Follow-up for patients with soft tissue sarcoma of the extremities

Follow-up protocols for patients with treated soft tissue sarcoma are based on the rationale that early recognition and treatment of local or distant recurrence can prolong survival. A single centre study of 2123 patients found that two thirds of recurrences developed within two years of initial surgery. This reinforces the need for close surveillance, including regular history and clinical examination to look for local recurrence, with ultrasound or magnetic resonance imaging as needed. Furthermore, 9% of recurrences occurred after a disease-free interval of five years. There is little evidence to favour one follow-up regimen over another, and this area needs further research.

Chest radiography is the recommended technique for detecting pulmonary metastases and suspicious lesions are further investigated with computed tomography of the chest. Table 6 summarises the follow-up guidelines from the European Society for Medical Oncology.

Table 6 | Summary of European Society for Medical Oncology guidelines for follow-up in soft tissue sarcoma

<table>
<thead>
<tr>
<th>Year since diagnosis</th>
<th>Frequency of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>3-6 months</td>
</tr>
<tr>
<td>4-5</td>
<td>6 months</td>
</tr>
<tr>
<td>More than 5</td>
<td>Annually</td>
</tr>
<tr>
<td>Low grade tumours</td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>4-6 months</td>
</tr>
<tr>
<td>More than 5</td>
<td>Annually</td>
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</tbody>
</table>

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Patient consent obtained.

3 Taylor WSJ, Grimer RJ, Carter SR, Tillman RM, Abudu A, Jeyes L. “Two-week waits”—are they leading to earlier diagnosis of soft tissue sarcomas? Sarcoma 2010; online 26 September.

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