Extremity soft tissue sarcomas: what's hot and what's not

This paper aims to provide evidence-based guidance for the general orthopaedic surgeon faced with the presentation of a potential soft tissue sarcoma in an extremity.

Soft tissue sarcomas (STSs) are a group of malignant tumours that derive from cells of mesenchymal origin. The group is characteristically diverse, with over 50 different histopathological subtypes recorded. Soft tissue sarcomas most commonly present as a lump and usually affect the limbs. As a result, orthopaedic surgeons are usually the first clinicians that this patient group sees for a clinical review in secondary care.

Currently, the average size of an STS at the time of diagnosis in the United Kingdom is 10 cm.[1] Recognising that tumour size directly correlates with outcome, it is important that all orthopaedic surgeons place special emphasis on how to reduce the risk of missing this challenging diagnosis. We present current hot topics in STS management, highlighting a range of key 'do's and don'ts', as well as discussing some areas of controversy.

HOT! INCREASING INCIDENCE

STSs are rare, and comprise approximately 1% of all adult cancers.[2,3] In 2010, 3272 new cases of STS were diagnosed in the UK. This equates to an annual incidence of between 51 and 54 per million population for males and females respectively, around one per orthopaedic consultant in the UK per year.[4]

The recorded incidence of STSs has increased by 26% over the last two decades.[5] It is not known if this is a genuine increase in disease incidence, or a representation of improvements in the ability to diagnose STSs.

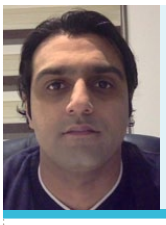
STSs may occur at any age, but are most commonly diagnosed in middle-age and the older adult, with more than 65% of cases occurring in those aged 50 or over.[5]

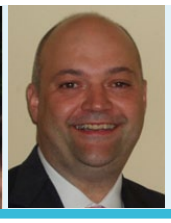
HOT! EARLY DIAGNOSIS

Overall, benign soft tissue tumours are one hundred times more common than STSs. This huge disparity means the diagnosis of an STS is commonly overlooked.[6] A suspicion of malignancy is the first step to diagnosis. Failure to recognise an STS, or instigate appropriate first line management can result in lost opportunities for limb salvage, and increased mortality.[7-10] The presence of metastatic disease when an STS is diagnosed is a poor prognostic factor,[11] and usually proves incurable with a reported three-year survival of just 25%.[12] This combined with the linear relationship between STS size and the development of metastases further highlights the importance of early, appropriate investigations and obtaining a histopathological diagnosis.[1] It should also be noted that even in the absence of metastatic disease, prognosis steadily worsens as STS size increases at the time of diagnosis.[1]

HOT! MULTIDISCIPLINARY DISCUSSION

All patients diagnosed with or suspected of having an STS should be discussed at a sarcoma multi-disciplinary team (MDT) meeting prior to treatment. Ideally, a clinician responsible for the care of each patient should be present, although the regional nature of sarcoma management in the UK can make this difficult (with many sarcoma services and MDTs being held remotely from referring hospitals or trusts.) At a minimum, all patients should be referred with a detailed history and clinical assessment, and all imaging modalities that have been undertaken at the referring hospital should be made available to the Sarcoma MDT service. This will allow access to expert management and key worker (specialist nurse) support for the patient, as required by the NICE Quality Standard (QS78).





M.S. Patel, *MBChB (Hons) MRCS, ST6 Trauma and Orthopaedics Leicester Orthopaedics, UK*
N.C. Eastley, *MBChB, BMedSci, MRCS, Clinical Research Fellow in Soft Tissue Sarcoma, East Midlands Sarcoma Service & Leicester Orthopaedics, UK*
R.U. Ashford, *(Shef) FRCS (Tr & Orth) Consultant Orthopaedic & Musculoskeletal Tumour Surgeon, East Midlands Sarcoma Service & Leicester Orthopaedics, UK*
Email: robert.ashford@sky.com

HOT! BIOPSY AT A SARCOMA CENTRE

If imaging is non-diagnostic, all lesions with suspicious features on clinical assessment should undergo a biopsy prior to surgical intervention. The aim of a biopsy is to gain a histological diagnosis with minimal morbidity without compromising on subsequent definitive management. Although the majority of biopsy procedures are technically relatively simple, poorly performed attempts can result in a reduction in diagnostic accuracy, limb salvage opportunities and overall survival. Major biopsy error rates of 18% and unnecessary amputation rates of 4.5% have been reported in cases of musculoskeletal tumours.[13] Biopsy errors occur far more commonly when biopsies are performed outside an STS treatment centre. Recognising this, biopsies should not be performed unless planned in conjunction with a sarcoma multi-disciplinary team. Ideally, musculoskeletal radiologists (under the guidance of a specialist sarcoma surgeon) should undertake the majority of biopsies of potential STSs. Open biopsies are sometimes indicated, and these should be performed by a sarcoma specialist or at least under their guidance.

Biopsies should also only be performed after the completion of local staging (i.e. after the lump has undergone optimal local imaging as determined by a specialist sarcoma MDT). This is essential as it is only after local staging that a clinician can select the biopsy tract/site that is most likely to facilitate subsequent limb salvage treatment. Secondly, a biopsy can cause oedema and other tissue changes that can interfere with the interpretation of subsequent imaging.

A biopsy can be performed either by percutaneous core or open techniques. A core needle biopsy's low morbidity and high diagnostic accuracy usually make it the technique of choice.[14] Specimens should be sent for microbiological analysis as well as histopathology.

The principles of biopsy for a suspected STS are as follows:

1. The biopsy technique and approach should be determined by a surgeon experienced in the management of STSs
2. The biopsy approach should be along the planned incision of the definitive surgical resection
3. The biopsy tract should take the shortest route to the lesion and:
   a. Should not violate more than one anatomical compartment
   b. Must avoid any nearby neurovascular bundles
4. The periphery of the lesion (and junction with normal tissue) should be biopsied rather than the central necrotic area which improves diagnostic yield.

HOT! INDUCTION RADIOTHERAPY

It has been demonstrated that radiotherapy has an association with a lower rate of STS local recurrence, although a significant effect on overall survival has not been established.[15-17] Radiotherapy is indicated for high grade, large or previously incompletely excised STSs.[15,17] Small, low grade tumours excised with adequate margins can be treated by surgery alone, avoiding the morbidity of radiotherapy.[17]

Radiotherapy may be administered pre- or post-operatively. The advantages of pre-operative (induction) radiotherapy include a smaller radiation field and lower radiation dose. The main disadvantage of radiotherapy before surgery is an increased risk of subsequent wound complications. In contrast, post-operative radiotherapy is not associated with any increase in wound problems, although requires a higher dose of radiation, increasing the risk of late complications including tissue fibrosis and lymphoedema.

Despite the increased rate of wound complications seen, there has been a seed change in the UK over the past few years, with a steady move towards induction radiotherapy. This approach allows all local anti-cancer treatment to be delivered in the event of a wound infection or breakdown, when post-operative radiotherapy would otherwise have to be delayed.

HOT – NEW TECHNIQUES IN RADIOTHERAPY

Intensity modulated radiotherapy (IMRT) is a technique that allows radiotherapy to be delivered to complex-shaped targets whilst minimising exposure to surrounding normal tissues. IMRT facilitates the delivery of radiation to STSs, which wrap around organs at risk such as in the pelvis, spine and head and neck regions. Without IMRT techniques it may be impossible to get the required dose to the tumour without causing unacceptable toxicity.

Proton beam therapy (PBT) uses high-energy proton beams instead of conventional radiographs to treat cancer. The main benefit of this type of radiotherapy is from the beam characteristic known as the Bragg peak. This allows the radiotherapy to stop at a precise dose, with no dose beyond this point. As a result, far less normal tissue is irradiated and leads to a reduction in late side effects. The overall dose delivered to the tumour is the same as conventional radiotherapy; it is just more precisely delivered.

Currently, NHS England commissions two centres in the USA to provide a proton beam radiotherapy service to treat a highly-specific group of paediatric and adult cancers including chordomas and chondrosarcomas of the base of skull and spine and paraspinal soft tissue sarcomas. The indications are soon to become wider especially in the teenage and young adult sarcoma population. Two centres in the UK, The Christie and UCLH, are currently being built, with the intention that they will treat their first patients in 2018.

Stereotactic ablative radiotherapy (SABR) is precisely-targeted radiotherapy being delivered at much higher doses than standard radiotherapy. The dose per fraction is much higher than traditionally used, but the overall course of treatment much shorter. In 2015, the NHS commissioned a service to treat oligometastatic disease in patients with three or less distant metastases. This includes sarcoma patients.

HOT! LIMB SALVAGE SURGERY

The aim of STS management is to improve long-term survival and avoid local recurrence whilst maximising function and minimising morbidity. The two competing strategies are those of limb salvage (wide curative resection with excision of the disease and contaminated tissue followed by reconstruction), or amputation. Limb preserving (salvage) surgery is now the norm for surgical treatment of STSs. This is despite the fact that limb salvage surgery is associated with a higher

risk of local recurrence than amputation, and no improvement in tumour-related mortality.[2,18]

In superficial or fungating STSs, an *en-bloc* resection including the overlying skin and the tumour is recommended. Primary wound closure can be achieved in the majority of cases, although up to 38% of patients may require some form of soft tissue reconstruction, with 13% requiring microvascular flap reconstruction.[20]

Absolute indications for amputation are now very few. Relative indications include:

- Tumours bridging several anatomical compartments
- Tumours extensively involving neurovascular structures thereby preventing adequate surgical margins
- Tumours that require a surgical resection that would result in a limb with a poorer function than a below the knee prosthesis
- Tumours so large that the dose and field of radiation would carry an unacceptable risk of major complications
- Large tumours involving the foot and ankle
- Large fungating lesions

Despite the relative contraindications above, it should be noted that limb salvage surgery has been successfully used in STSs related to the foot. In such cases, marginal excisions can be accepted with post-operative radiation therapy to obtain local control, and large soft tissue transfers to obtain wound coverage.[21,22] Similarly, satisfactory function has also been demonstrated despite the sacrifice of the sciatic, tibial or peroneal nerves following STS resection of the lower limbs.[23]

HOT! AGGRESSIVE RECONSTRUCTIVE TECHNIQUES

Wound complications following surgery for STS in patients who have undergone induction radiotherapy can be as high as 50%.[24] Primary closure by vascularised tissue flaps as opposed to closure by skin approximation reduces this figure.[25,26] One study demonstrated that the involvement of plastic and reconstructive surgeons to assist with wound closure resulted in a lower trend for wound-related complications.[27]

We, like many other sarcoma units, would undertake complex STS resections after discussion with or performed in conjunction with a plastic and reconstructive surgeon, particularly in patients who have undergone pre-operative radiotherapy where the risk of wound breakdown is high.

NOT! INADVERTENT EXCISION

The ideal is that every STS surgical procedure is planned. If there is any concern regarding the nature of a lump, the patient should have adequate investigations and be referred to a sarcoma service prior to intervention. 'Whoops' procedures (excisions of a presumed benign soft tissue lump that subsequently on histological assessment is found to be malignant) should be avoided. The incidence of STS 'whoops' excision varies and has been demonstrated to be between 12% and 53% of new referrals to a specialist sarcoma unit.[28,29,30] The standard care for an inadvertent STS resection when seen in a sarcoma unit is to re-resect the 'tumour bed' to achieve wide margins. Although survival after a wide re-excision following a 'whoops' procedure is similar to that for a direct wide local excision for a primary STS, the morbidity is higher. This is because at least one additional operative procedure is required, a greater volume of tissue needs to be re-resected, soft tissue coverage procedures are more frequent, and up to 95% of such patients require adjuvant treatment.[31,32] The key to avoiding a 'whoops' procedure is a high index of suspicion and appropriate early investigation. Small and superficial lesions can be appropriately investigated with an ultrasound scan (ideally performed by a musculoskeletal radiologist). Large or deep lesions are best assessed by an MRI ultrasound scan again interpreted by a musculoskeletal radiologist. Finally, biopsies should be performed prior to resection as outlined above. As a principle, proceeding to surgery without a diagnosis is inappropriate for large (> 4.3 cm)[8] or deep lumps.

NOT! PRECONCEPTIONS

A long history does not exclude an STS. Similarly the preconception that a superficial lump is not a STS is also untrue. The average size of an STS at presentation in the UK is 10 cm.[1] However this figure ranges greatly from 0.2 cm to 45 cm,[1] meaning that as a result small lesions may also represent STSs.[1]

NOT! SURVIVAL

The crude mortality for STSs is a rate of 11 per million per year – a figure that has remained relatively static for the last 30 years.[6] Overall the five-year survival for STS patients is 50%.[33] Patients with STSs larger than 25 cm have an 8.5 times greater risk of dying than those with tumours smaller than 5 cm.

CONTROVERSIAL! NEW NICE GUIDELINES

NICE guidance NG12 was published in 2015.[34] Whereas previous guidance was based around the presence or absence of 'red flag' signs, the new guidance for STSs is predominantly based on ultrasound scan findings. Red flag signs are not considered in the document.

NICE recommends that an urgent USS is obtained, and should suspicious features be present, a two-week wait sarcoma referral be made. This creates a problem, as there is no emphasis or explanation made to clinicians of what signs or symptoms should increase suspicion of a STS. Instead, emphasis is placed on USS findings that in many cases may not be performed by musculoskeletal (MSK) radiologists. Conclusions such as 'a soft tissue sarcoma cannot be excluded', which are already common, are therefore likely to arise more frequently, which will ultimately increase the burden to the NHS, and possibly over-run sarcoma units with needless referrals, reducing the quality of care for others.

The clinical features that increase the probability of a soft tissue lesion being malignant formed the basis of the previous NICE guidelines.[41] These *red flag signs* include:

- a lump of increasing size
- a lump greater than 5 cm
- a painful lump
- a lump located deep to the deep fascia.

The presence of all four of these features yields a positive predictive value of 86% for a malignant soft tissue lesion, with a negative predictive value of 100% when all four are absent.[34]

Of the red flags, size is the best predictor of malignancy, whilst pain is the worst.[35] Recent recommendations suggest that the red flag size cut-off should be reduced to 4 cm.[12]

CONTROVERSIAL! CHEMOTHERAPY IN NON-METASTATIC STS

The role of adjuvant chemotherapy in the treatment of STS remains unproven, and it is not currently regarded as standard treatment in the UK. It may however be considered for individual cases where local relapse would be untreatable, or where adequate radiotherapy cannot be administered owing to the sensitivity of surrounding structures, for example, the spine. Induction chemotherapy may also be considered in selected cases to try to achieve cytoreduction in order to facilitate limb salvage surgery.

CONTROVERSIAL! FOLLOW-UP

The five-year cumulative incidence of STS local recurrence is between 17% and 39%.[36] Previous

local recurrence, positive surgical margins, metastatic disease, a high histopathological grade or stage, increasing age and a male gender are all poor prognostic factors.

There is no published data on specific follow-up protocols. High-risk patients often relapse within two to three years, although low-risk patients may relapse some ten years post-treatment. In some studies, relapse most commonly manifests itself as metastatic disease in the lungs.[7,35]

In our unit, all surgically treated sarcomas are followed up by clinical examination and chest radiography. For the first 2 years this is three-monthly, for years 3 to 5 six-monthly and annually thereafter until ten years. MRIs are undertaken at 3 months post-treatment as a baseline, and then if there is a suspicion of recurrence.

CONCLUSIONS

Extremity soft tissue lumps are extremely common. STSs are fortunately rare. Despite advances in management STSs still have a poor outcome with a 50% survival at five years.

STS size at the time of diagnosis directly impacts on survival, with large tumours having a worse prognosis. Delays in referral to a sarcoma centre also have a negative impact on prognosis. For this reason it is vital that all clinicians presented with a lump in the extremity or any soft tissues are extra-vigilant. It is better to over investigate a benign lump than to miss a STS.

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