

EDUCATIONAL ARTICLES

Update on Sarcomas of Bone and Soft Tissue

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Introduction

Sarcomas are malignant tumours of connective tissue.¹ They may show a wide range of differentiation, for example towards bone (osteosarcoma), adipose tissue (liposarcoma) and blood vessel differentiation (angiosarcoma). Sarcomas occur in both soft tissue and bone, the former being significantly more common with respective incidences of 30 and 8 cases per million of population per annum. There are therefore approximately 150 new soft tissue sarcomas and 40 bone sarcomas annually in Scotland.

It is easy to think that sarcomas only affect the limbs and therefore tend to be the preserve of the orthopaedic surgeon, but all sites including the trunk, retroperitoneum, chest wall, head and neck and gynaecological tract can be affected and therefore clinicians in all areas should have some awareness of basic principles. Most cases, around 75% do, however, affect the limbs.

Causes of Sarcomas

Most sarcomas arise sporadically and the underlying cause is not apparent. There are, however, several well recognised predispositions both genetic and environmental. In the former group, neurofibromatosis Type 1, which is due to mutations of the NF1 gene on chromosome 17 (17q11), is associated with the development of malignant peripheral nerve sheath tumours. Other syndromes include familial retinoblastoma (mutation of the RB1 gene at 13q14), the Li Fraumeni syndrome (p53 gene at 17p13) and Rothmund Thompson syndrome (RECQL4 gene at 8q24) all of which predispose to osteosarcomas, and the first two to soft tissue sarcomas, as well as tumours of other lineages. Rhabdomyosarcoma in childhood may also arise in patients with Beckwith-Wiedemann syndrome, a congenital overgrowth syndrome with a complex and heterogeneous group characterised by gene imprinting which is associated with abnormalities of a series of genes on chromosome 11. Diaphyseal aclasis, an autosomal inherited condition characterised by multiple exostoses and failure to remodel the metaphysis of long bones is associated with an increased risk of peripheral chondrosarcoma. Three main genes are involved, for example the EXT1 gene on chromosome 8q24.

Non genetic predisposition to sarcoma development includes previous radiotherapy, for example for breast or cervical carcinoma or Hodgkin's disease, usually after an interval of at least 4 years or so. As has long been known, sarcomas of bone, both osteosarcoma and undifferentiated high grade sarcoma, complicate Paget's disease, but at least anecdotally the incidence of this appears to have fallen, perhaps due to the use of osteoclast modifying drugs principally bisphosphonates. Rarely sarcomas may complicate benign lesions including sporadic chondromas, fibrous dysplasia and benign nerve sheath tumours. Chronic lymphoedema, whether post radiotherapy or for other reasons, predisposes to development of angiosarcoma.

Classification and Clinical Features

Bone Sarcomas

There are only a few forms of primary sarcoma of bone, the three major ones being osteosarcoma, Ewing's tumour and chondrosarcoma. Less common still are non-bone forming sarcomas of primitive fibroblastic cells (fibrosarcoma/ malignant fibrous histiocytoma), together with rarities such as angiosarcoma, chordoma, a tumour of the neuroaxis arising from notochord remnants, and adamantinoma, a tumour showing mixed epithelial and fibroblastic differentiation which bizarrely almost uniquely affects the tibia.

Malignant primary bone tumours usually present with pain, then swelling and, usually later still, with pathological fracture. Unfortunately, because of their rarity and the consequent lack of awareness of the possibility, patients often present late and the diagnosis is often also delayed, resulting in a poorer prognosis than in comparable countries.²

Osteosarcoma is the classic bone sarcoma of adolescence, occurring in the metaphyses of long bones with around 50% around the knee. Patients present with persistent localised bone pain and, later, with swelling. The tumour metastasises early by blood, mainly to lung. Osteosarcoma, by definition, is a malignant tumour whose cells form bone, and while there are several subtypes most of these are important more because of difficulties in

diagnosis than in therapy or prognosis. An exception is parosteal osteosarcoma, a rare but radiologically and histologically distinctive low grade tumour which arises on the bone surface and can be mistaken for an unusual exostosis. Osteosarcoma does occur in the middle aged and elderly, but in this age group around half of patients have some predisposing cause such as Paget's disease or previous irradiation.

Ewing's Sarcoma is an extremely aggressive tumour which affects younger children with a peak incidence between 10 – 15 years. It seldom occurs under the age of 5, or over 30. Patients present with persistent pain and swelling and often there is fever or elevated white count which might suggest osteomyelitis. As well as long bones, flat bones such as those of the pelvic and shoulder girdle are affected and there is often a large soft tissue mass at presentation. Histologically this is a malignant round cell tumour: in recent years advances in cytogenetics and molecular genetics have established that this is a primitive neuroectodermal tumour characterised by a group of distinctive translocations, primarily $t(11;22)(q24, q12)$. An identical tumour arises in soft tissue.

Chondrosarcoma, unlike osteosarcoma and Ewing's tumour is mainly a tumour of middle aged and elderly and is rare under 20 years. The most common sites are the pelvis, femur and shoulder girdle, and tumours can arise within the medullary cavity or on the bone surface, usually from pre-existing exostoses. The clinical history is often long, with pain over some months or years, a mass being a late feature. Tumours of the acetabulum are especially prone to late presentation. Chondrosarcomas are usually of much lower grade than Ewing's or osteosarcoma, and their often central location and tendency to local extension and recurrence rather than metastasis accounts for much of the morbidity and mortality.

Soft Tissue Sarcomas are much more heterogeneous with over 50 different forms. The World Health Organisation has helpfully subclassified soft tissue tumours into 4 categories: benign, frankly malignant, and two groups of tumours of intermediate behaviour: those, like fibromatosis, which behave in a locally aggressive manner but do not seldom metastasise and those low grade sarcomas which metastasise uncommonly.

For clinical purposes, soft tissue sarcoma is usefully subdivided into three groups: low grade sarcomas, paediatric high grade sarcoma and adult high grade sarcomas.

Low grade sarcomas occur mainly in adults and include well differentiated liposarcoma, a tumour which often arises within the retroperitoneum and therefore may cause the death of the patient by repeated local recurrences and without metastasising; a significant proportion of these tumours transform into a sarcoma of higher grade, so-called dedifferentiation.

Paediatric high grade sarcomas include rhabdomyosarcoma, both embryonal and alveolar variants, the latter having a worse prognosis, Ewing's sarcoma and synovial sarcoma. In general, patients present with a swelling, which can affect a wide variety of sites. Embryonal rhabdomyosarcoma, for example may present as a polypoid mass protruding from the vagina, the nose or ear.

Adult high grade sarcomas occur predominantly in the deep soft tissue of the limbs and include leiomyosarcoma, round cell and pleomorphic variants of liposarcoma, synovial sarcoma and malignant peripheral nerve sheath tumours. At present the grade of the tumour is much more important than the histological subtype, but as new therapies are discovered determination of histological type may be of more than academic interest. The commonest diagnosis until recently was of malignant fibrous histiocytoma, which is now recognised by most authors to be an undifferentiated high grade sarcoma. Synovial sarcoma is a tumour of considerable interest; its name reflected its tendency to occur close to joints (although virtually never within them) and its supposed histological resemblance to reactive synovium. It is now clear that the tumour has nothing to do with synovium, but the name is useful and has been retained. The incidence has substantially increased as the histological spectrum has widened from the traditional biphasic tumour with both connective tissue and epithelium to monophasic and poorly differentiated tumours showing no epithelial differentiation. The key to this has been the discovery of a group of characteristic translocations between chromosomes X and 18.

Diagnosis: Imaging, Pathology, New Techniques

The correct approach to a suspected bone or soft tissue sarcoma is that the patient should be assessed clinically and the lesion imaged, preferably by MR scan, although ultrasound is of increasing value. In almost all cases (with the possible exception of an intra-abdominal tumour) a biopsy will be required to establish a tissue diagnosis, and in the UK this will usually take the form of a needle biopsy

under radiological control. In Scandinavia fine needle cytology has been widely practiced. Open biopsy remains an option, particularly when these less invasive techniques have proved unsuccessful. Two important clinical errors are worthy of mention. Firstly, "shelling out" or simple enucleation of a soft tissue sarcoma by an inexperienced surgeon who has not considered the possibility of malignancy is unfortunate as it leads to a high risk of local recurrence or further surgery more radical than would otherwise be required. Secondly, internal nailing of a pathological fracture through a sarcoma, either due to failure to recognise the fracture as pathological or more commonly on the assumption that the lesion is a metastatic carcinoma, disseminates tumour cells throughout the entire length of the affected bone.

Histopathological examination is based on the interpretation of conventional haematoxylin and eosin stained sections, supplemented by immunohistochemistry, to identify the presence of proteins which indicate the form of differentiation shown, and increasingly by classic cytogenetic or molecular genetic analysis. Indeed, the apparently specific translocations which have now been recognised in a significant proportion of soft tissue sarcomas in particular constitute the gold standard when light microscopy is equivocal. In addition to the importance in diagnosis and classification, these techniques are likely to explain the underlying molecular mechanisms of oncogenesis and should allow the development of targeted therapies.

Histological grading of adult soft tissue sarcomas can be performed using a variety of systems,³ but that of the French Federation of Cancer Centres is widely used and is reproducible. It assesses three parameters, namely the degree of differentiation (similarity to normal tissues), mitotic activity and extent of tissue necrosis and allocates a tumour to one of three grades.

Staging

Once the diagnosis of sarcoma is reached, the patient requires staging: as indicated MR is usually the best imaging modality for the primary tumour. For metastasis, CT of chest is required, since blood borne metastasis to lung is the principal form of spread, although some tumours, principally Ewing's tumour, show a higher tendency to spread to marrow and other bones and therefore a bone marrow biopsy, usually from iliac crest, is indicated. If chemotherapy is planned, the appropriate tests of renal and cardiac function are required.

Treatment

Treatment of these tumours falls naturally into several groups

a) Tumours largely treated by surgical excision. This includes most adult soft tissue sarcomas of both low and high grade and those sarcomas of bone less sensitive to chemotherapy. Local control of these tumours depends on the adequacy of excision, this depending on the skill of the surgeon, the grade and the stage, i.e. extent of the primary tumour. Low grade soft tissue sarcomas can be treated by conservative local excision with a slender margin of normal tissue, while high grade sarcomas require wider margins, ideally, where anatomically possible by excision of a full anatomical compartment such as the adductor compartment of the thigh. When margins are compromised by the large size of the lesion or by proximity to critical structures, especially neurovascular bundles, a narrow margin may be supplemented by local radiotherapy. Less clear is the value of adjuvant chemotherapy in these tumours; although many studies suggest better local control and delayed time to relapse, overall survival is not improved. Inevitably, for some larger sarcomas local resection is impossible and amputation is still sometimes required. Although some sarcomas, for example epithelioid sarcoma, may involve lymph nodes, formal lymphadenectomy is seldom required. Chondrosarcoma of bone is usually treated by a radical excision of the affected bone, with any reconstruction required.

b) Tumours treated by neoadjuvant chemotherapy followed by local therapy. This group includes most childhood high grade soft tissue sarcomas and both Ewing's sarcoma and conventional osteosarcoma. The underlying principle is that since these tumours are significantly sensitive to chemotherapy, early drug treatment attempts to control both the disseminated micrometastases that are known to be present and to reduce the size of the primary tumour to allow less radical surgery. This has resulted in significant improvements in outcome over the past three decades.⁴ For bone sarcomas, amputation can often be avoided with limb sparing surgery in the form of wide excision with reconstruction by endoprosthetic replacement, massive allograft or other techniques. Again, for those tumours involving critical structures, and those continuing to grow while on chemotherapy, amputation is still sometimes required. The survival for osteosarcoma in Scotland, as in comparable countries, has improved dramatically over the years since the introduction of high dose chemotherapy.⁵ Patients treated with chemotherapy are at significantly

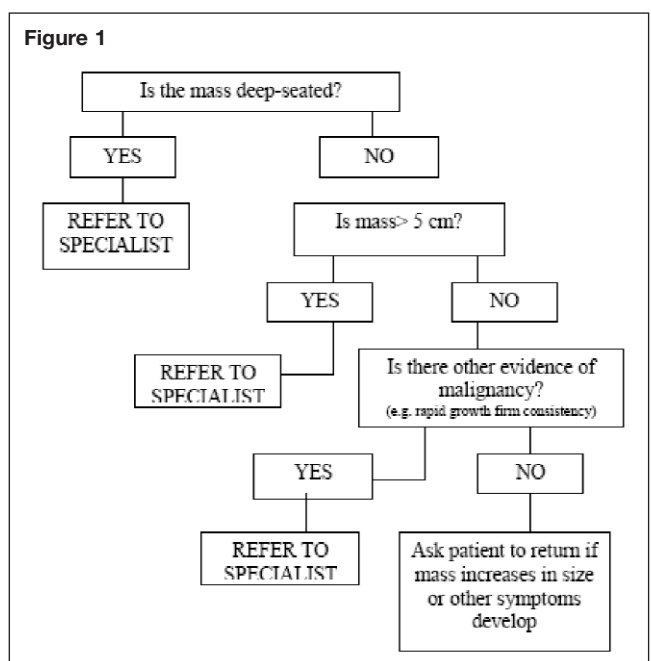
increased risk of developing second tumours.⁶

c) New targeted treatments. There has been much recent interest in gastrointestinal stromal tumours (GISTs) a group of sarcoma-like lesions of the gut wall. Most of these contain activating mutations of the c-kit gene and overexpress its product the cell surface protein CD117, a molecule with tyrosine kinase activity which activates a signalling cascade promoting cell proliferation. Imatinib (Glivec) is a tyrosine kinase inhibitor which inhibits this molecule and has considerable anti-tumour activity⁷ in a tumour previously regarded as resistant to traditional chemotherapy.

Referral guidelines

Revised guidelines for referral of patients with possible bone and soft tissue sarcomas have recently been published (Scottish Referral Guidelines for Suspected Cancer 2007) and are the subject of a Health Department Letter (NHS HDL (2007) 09).⁸

The key points for soft tissue sarcoma are that most soft tissue tumours are benign with only 1 in 200 malignant. Features of a soft tissue mass suggestive of malignancy include size greater than 5 cms, pain, growth and recurrence after previous excision. Deep seated masses, regardless of size are suspect. Reassuringly, lumps which are superficial *and* painless *and* less than 5 cms *and* static in size are extremely unlikely to be malignant. The algorithm in Figure 1 is offered as a diagnostic guide.



Guidelines for bone sarcoma suggest that patients with unexplained bone pain of increasing severity or persistent

bone pain or tenderness and those with non-mechanical bone pain particularly disturbing rest or sleep should be considered to have bone cancer until proven otherwise and should be immediately referred for an x-ray. Even with a normal x-ray persistent symptoms demand reassessment and repeat x-rays. Patients presenting with a suspected spontaneous fracture or one occurring with minor trauma should be considered to have an underlying bone cancer and should be referred urgently for x-ray and further investigation.

The Scottish Managed Clinical Network for Sarcoma⁹

This, the first Scottish National Cancer Managed Clinical Network, was established in 2004 with financial support from National Services Division. Its work includes two multidisciplinary teams, one serving Edinburgh, Borders and Fife and the other serving the West of Scotland, Dundee, Aberdeen and Inverness, these meeting weekly by teleconference. In both, the radiology and pathology are reviewed and an agreed treatment plan formed. In addition, the Network holds an annual educational meeting, conducts audits and research and aims to establish national standards of care.

Key messages

1. Patients in Scotland often present late to their general practitioner, and referral to specialists is often also delayed. Any soft tissue mass greater than 5 cms, increasing in size or deep seated should be regarded as malignant until proven otherwise. Unexplained bone pain in an adolescent or mature adult is worthy of careful assessment including radiology.
2. Any biopsy must be sited in such a way that it does not compromise the success of any subsequent resection, and ideally should be carried out by or with the knowledge of the surgeon likely to carry out definitive treatment. Radiological guided needle biopsies are usually the first modality to be employed.
3. No soft tissue tumour with the features described should be shelled out, no matter how apparently well encapsulated.
4. Intramedullary nailing of any pathological fracture should not be carried out without an initial biopsy unless there is clear evidence that this is due to myeloma or carcinoma and not a primary sarcoma.
5. All patients with a diagnosis of sarcoma should be discussed at a multidisciplinary team meeting and a treatment plan agreed.

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