Characteristics, diagnosis and treatment of bone and soft tissue sarcomas

Bone and soft tissue sarcomas are rare, representing around 1% of all adult cancers. They mostly affect the musculoskeletal system but can metastasize, often to the lungs. Treatment involves the concerted application of surgery, radiotherapy and chemotherapy in an integrated manner to maximize survival and quality of life.

In the past three decades significant progress has occurred in the management of patients with musculoskeletal cancer, which has improved both survival and the quality of life of affected patients. The most significant change has been the improvement in surgical technique for resection of musculoskeletal cancer. Amputation, once the mainstay of treatment for patients with bony and soft tissue extremity sarcomas, has now largely been replaced by limb-sparing surgery using innovative approaches to restore function after tumour resection.

A second change in the management of these patients has been the introduction of combined-modality treatment using the concerted application of surgery, radiation therapy and chemotherapy in an integrated fashion to maximize survival and quality of life. The third change improving the survival of patients with musculoskeletal cancer has been the aggressive resection of metastatic deposits.

The development of limb-sparing surgery in conjunction with the dynamic advance in imaging and chemotherapy created the specialty of musculoskeletal oncology. Approximately 90–95% of all bone and soft tissue sarcomas can be treated by limb-sparing surgery, without compromising the patient's survival.

Soft tissue and bone sarcomas are a rare and heterogeneous group of tumours. Although bone and soft tissues comprise 75% of a person's average body weight, bone and soft tissue sarcomas represent less than 1% of all adult and 15% of paediatric malignancies.

Types of sarcoma

Sarcomas originate primarily from elements of the embryonic mesodermal layer. Soft tissue sarcomas are classified according to the adult tissue that they resemble. Bone sarcomas are usually classified according to the type of matrix production: osteoid-producing tumours are classified as osteosarcoma, and chondroid-producing sarcomas are classified as chondrosarcoma.

The three most common bone sarcomas are:

- Osteosarcoma
- Ewing's sarcoma
- Chondrosarcoma.

The most common soft tissue sarcomas are:

- Malignant fibrous histiocytoma
- Liposarcoma
- Leiomyosarcoma.

Although soft tissue sarcomas can arise anywhere in the body, the lower extremities are the most common site. Their incidence is 46% in the lower extremities, 19% in the trunk, 13% in the upper extremities, 12% in the retroperitoneum, 9% in the head and neck and 1% in other locations (Fletcher et al, 2002).

Biological behaviour

Tumours arising in bone and soft tissues have a characteristic pattern of biological behaviour because of their common mesenchymal origin. These unique patterns form the basis of staging systems and current treatment strategies.

Histologically sarcomas are graded as low, intermediate or high grade (Trojani et al, 1984). The grade is based on the tumour morphology, the extent of pleomorphism and atypia, mitoses and necrosis. The grade represents the tumour's biological aggressiveness and correlates with the likelihood of metastases.

In contradistinction to the true capsule that surrounds benign lesions, sarcomas are generally enclosed by a reactive zone, or pseudocapsule. This consists of compressed tumour cells and a fibrovascular zone of reactive tissue with variable inflammatory components. The thickness of the reactive zone varies with the histogenic type and grade of malignancy. High-grade sarcomas have a poorly defined reactive zone that may be locally invaded by the tumour.

Sarcomas respect anatomical borders; local anatomy influences the tumour growth by setting natural barriers to extension. In general, sarcomas initially grow within the anatomical compartment in which they arise. As the tumour progresses, the walls of that compartment are violated (either the cortex of bone or the aponeurosis of a muscle) and the tumour breaks into the surrounding compartment. Most bone sarcomas are bi-compartmental at the time of diagnosis; they destroy the overlying cortex and extend directly into the adjacent soft tissues (Malawer and Sugarbaker, 2001).

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Metastatic pattern

Unlike carcinomas, bone and soft tissue sarcomas disseminate almost exclusively through the blood, with the lung the most common site of metastases. Approximately 10% of sarcomas will have overt lung metastases at the time of diagnosis, and in these patients the prognosis is poor. Abdominal and pelvic soft tissue sarcomas on the other hand typically metastasize to the liver and lungs.

Low-grade soft tissue sarcomas have a low rate (<15%) of subsequent metastasis, while high-grade soft tissue sarcomas have a significantly higher risk (>40%). Most patients with high-grade bone primary sarcoma have distant micrometastases at presentation, unlike those with soft tissue sarcomas; an estimated 80% of patients with osteosarcomas have micrometastatic lung disease at the time of diagnosis. Thus in most cases cure of high-grade primary bone sarcoma can be achieved only with systemic chemotherapy and surgery.

Soft tissue sarcomas have a smaller metastatic potential; because of this the role of chemotherapy in the treatment of soft tissue sarcoma and its impact on survival is still a matter of controversy.

Diagnosis

As bone and soft tissue sarcomas are rare, delays in their diagnosis are common. The median size for both bone and soft tissue sarcomas at the time of presentation is 10 cm. The typical feature of a bone tumour is a non-mechanical pain in the affected part that gradually progresses to wake the patient at night. Swelling is usually a late feature, after the tumour has extended out of the bone into soft tissues. A plain X-ray will usually diagnose the tumour, showing one or more of the following 'worrying' features:

- Bone destruction
- New bone formation
- Soft tissue swelling
- Periosteal elevation.

The presence of any of these should cause concern and lead to further investigation and biopsy if necessary.

Soft tissue 'lumps and bumps' are common, and less than 1% will be malignant. The features suggestive of potential malignancy include:

- Any lump >5 cm
- Any lump that is increasing in size
- Any lump deep to the fascia
- Any lump that is painful.

The more of these features that are present, the greater the risk of malignancy. Any patient presenting with any of these features should be referred for investigation and diagnosis; this will usually require magnetic resonance imaging (MRI) and biopsy.

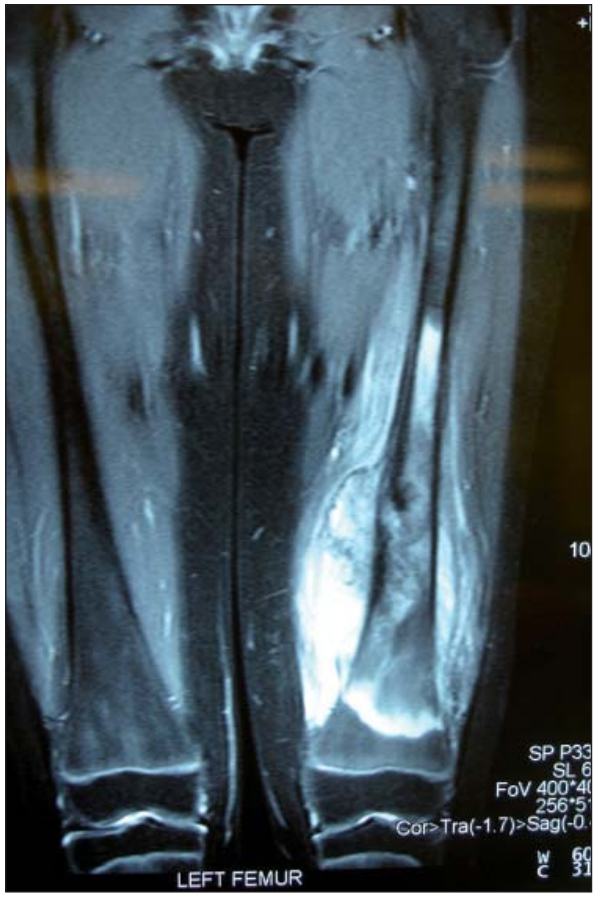
Imaging and staging

Staging of a musculoskeletal tumour is based on the findings of physical examination and the results of imaging studies. Biopsy and histopathological evaluation are essential final steps.

- Plain radiography remains the key imaging modality in the evaluation of bone tumours. Based on medical history, physical examination and plain X-rays, accurate diagnosis of bone tumours can be made in more than 80% of cases.
- Computed tomography (CT) is the imaging modality of choice to evaluate the extent of bone destruction, but is mainly used to evaluate the lungs for metastatic disease.
- MRI is superior to CT in the evaluation of the intramedullary and extraosseous extent of the bone tumour (*Figure 1*). MRI is the imaging method of choice to evaluate soft tissue tumours. The signal intensity of the tumour is assessed by comparing it with the adjacent soft tissues. Contrast-enhanced MRI is useful in evaluating the relationship of the tumour to blood vessels and nerves.
- Bone scan is currently used to determine the presence of metastatic disease or skip lesions, and is only worthwhile for potential bone sarcomas.

The staging systems that are most commonly used for the staging of soft tissue and bone sarcomas is the tumour, node and metastasis (TNM) system of the American Joint Committee on Cancer (Green et al, 2002) and the Enneking (1977) staging for bone and soft tissue

Figure 1. Magnetic resonance image showing a large intraosseous tumour with a significant soft tissue mass extending down subperiosteally to the growth plate. This is an osteosarcoma.



tumours, which is based on the histological grade (G), site (T) and the presence or absence of metastases (M) (*Tables 1–3*).

Biopsy

The biopsy is a key part of the management of potential bone and soft tissue sarcomas. It must be performed in a centre with close links to an experienced musculoskeletal pathologist. Needle biopsies are usually adequate and involve little violation of normal tissue. They may be carried out under CT, X-ray or ultrasound control. The role of frozen section remains controversial, and fine-needle aspiration cytology is only used in certain centres.

Treatment

Soft tissue sarcoma

Although surgery remains the principal therapeutic modality in soft tissue sarcoma, the extent of surgery required along with the optimum combination of radiotherapy and/or chemotherapy remains controversial. In general, the scope of the excision is dictated by the size of the tumour, its anatomical relation to normal structures such as neurovascular bundles and the degree of function that will be lost after operation. The aim is to achieve 'wide' or clear margins. If severe loss of function is likely, the key question is whether this can be minimized by the use of adjuvant/neoadjuvant radiotherapy or chemotherapy.

Surgery alone should be considered for subcutaneous or intramuscular high-grade sarcoma <5 cm, or any size of low-grade sarcoma if a wide excision with a good 1–2 cm cuff of surrounding fat and muscle can be achieved. If the excision margin is close, or if there is extramuscular involvement, adjuvant radiotherapy should be added to the surgical resection to reduce the probability of local recurrence (Rydholm et al, 1991; Baldini et al, 1999) (*Figure 2*).

For high-grade sarcomas >5 cm, local control requires a combination of surgery and radiotherapy. These patients are at significant risk of developing metastatic disease, but there remains uncertainty as to the value of chemotherapy in trying to prevent this.

Chemotherapy is usually indicated as neoadjuvant therapy in the treatment of soft tissue Ewing's sarcoma and rhabdomyosarcoma because of the chemosensitivity of these specific tumour types. For all other soft tissue sarcomas the effect of chemotherapy is unpredictable. Most randomized chemotherapy trials have shown no significant impact on overall survival; however, studies have found that chemotherapy does improve disease-free survival, with improved local control (Alvegard et al, 1989; Antman et al, 1990; Bramwell et al, 1994; Anon, 1997). Prognostic factors for soft tissue sarcomas are grade, size, depth, site and age of the patient.

Retroperitoneal and visceral sarcomas represent a particularly complex challenge because of their large size, their tendency to invade adjacent organs and the difficulty of achieving surgical resection. The survival rate of these tumours is 20–40% of that for extremity soft tissue sarcomas, and the most important prognostic factor for survival of this tumour is achieving good margins at surgery (Singer et al, 1995; Lewis et al, 1998).

Table 1. Tumour, node and metastasis (TNM) classification of soft tissue sarcomas

Primary tumour (T)	TX	Primary tumour cannot be assessed	
	T0	No evidence of primary tumour	
	T1	Tumour ≤5 cm in greatest dimension	T1a Superficial tumour*
			T1b Deep tumour
	T2	Tumour >5 cm in greatest dimension	T2a Superficial tumour
			T2b Deep tumour
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed	
	N0	No regional lymph node metastasis	
	N1	Regional lymph node metastasis	
Distant metastasis (M)	M0	No distant metastasis	
	M1	Distant metastasis	

* tumour entirely above deep fascia. From Sobin and Wittekind (2002)

Table 2. The International Union Against Cancer staging of soft tissue sarcomas

Stage IA	T1a	N0, NX	M0	Low grade
	T1b	N0, NX	M0	Low grade
Stage IB	T2a	N0, NX	M0	Low grade
	T2b	N0, NX	M0	Low grade
Stage IIA	T1a	N0, NX	M0	High grade
	T1b	N0, NX	M0	High grade
Stage IIB	T2a	N0, NX	M0	High grade
Stage III	T2b	N0, NX	M0	High grade
Stage IV	Any T	N1	M0	Any grade
	Any T	Any N	M1	Any grade

From Green et al (2002)

Table 3. Correlation between the International Union Against Cancer staging system and different histological grading systems of soft tissue sarcomas

International Union Against Cancer stages	TNM two-grade system	Three-grade system	Four-grade system
Stage IA	Low grade	Grade 1	Grade 1
Stage IB			Grade 2
Stage IIA	High grade	Grade 2	Grade 3
Stage IIB		Grade 3	Grade 4
Stage III			
Stage IV			

TNM = tumour, node and metastasis. From Green et al (2002)

Bone sarcoma

The management of bone sarcomas was transformed in the 1980s by the realization that both osteosarcoma and Ewing's sarcoma are chemosensitive; both are now treated by neoadjuvant chemotherapy followed by surgical excision.

The effect of the chemotherapy can be assessed by estimating the amount of necrosis caused in the primary tumour, and experience has shown that >90% necrosis is a favourable prognostic factor. Surgical excision of the primary tumour remains essential, and in most bone sarcomas some form of reconstruction will be needed.

There are four major methods of reconstructing a skeletal defect:

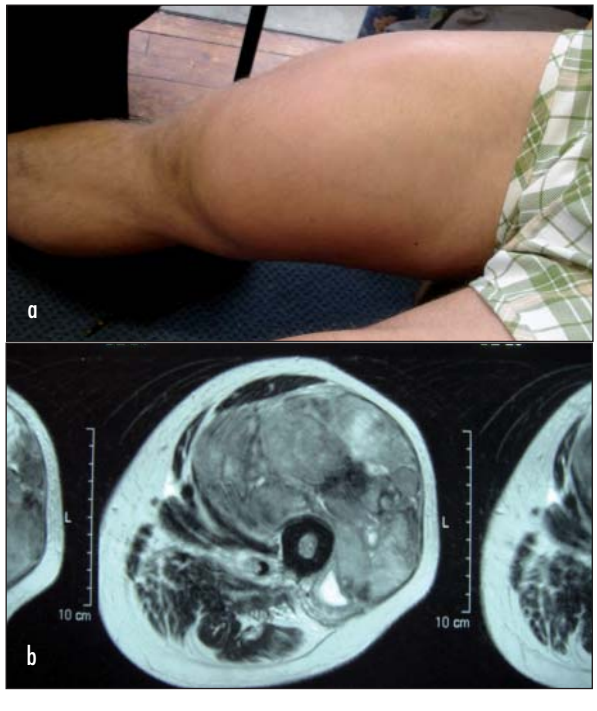
Resection arthrodesis

This was the early method of limb-sparing surgery before the routine use of chemotherapy for bone sarcoma. No attempt was made to restore motion at resected joints, but restoration of skeletal stability and long-term durable reconstruction were achieved (Enneking, 1977).

Osteoarticular or massive allograft

This was introduced in the 1970s as a biological solution for restoring segmental defects of bone after major resection, but this method has significant early and late complications, such as infection, non-union, joint instability and fractures; the overall complications rate can exceed 50% (Gebhardt et al, 1991). There is a modern trend to use the patient's own tumour bone, remove it, sterilize it outside the body by radiotherapy, microwave or pasteurising, and then reimplant it. This technique means that the patient's own bone is reimplanted, and appears to have significantly less complications.

Figure 2. a. This 58-year-old man claimed to have only noticed a swelling in his thigh for 4 weeks. b. He had a 25 x 14 x 12 cm tumour in his quadriceps almost completely encircling the femur, as shown on the magnetic resonance image. It was a high-grade soft-tissue sarcoma. He underwent excision of the quadriceps with the underlying periosteum of the femur, followed by 66 Gy of radiotherapy.



Allograft-prosthetic composite

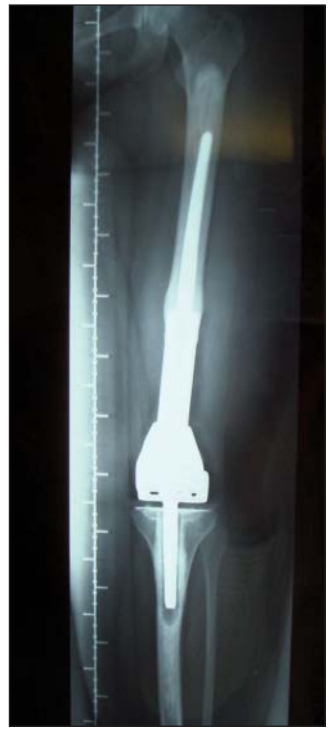
This was thought to provide the benefit of a biological reconstruction along with the stability achieved by cemented endoprostheses. Experience has shown that this method has the same high rate of complications as standard allograft reconstruction (Hejna and Gitelis, 1997).

Endoprosthesis

This is a highly successful and durable method for the restoration of skeletal integrity and joint function. The use of a cemented stem provides immediate fixation, early mobilization and rehabilitation (Roberts et al, 1991; Capanna et al, 1994). Modern refinements including the use of hydroxyapatite collars and rotating hinge knee joints have improved prosthesis survival significantly. This is the preferred technique of reconstruction after resection of bone sarcoma (*Figure 3*).

Today all the major joints with their adjacent segmental bone can be reconstructed safely and reliably with custom-made or modular endoprosthesis replacement, routinely used for the proximal and distal femur, proximal tibia, proximal humerus, pelvis and total femur. The main complications remain infection and wear of the prostheses, and in younger patients revision surgery is almost inevitable.

The prognosis for bone sarcomas is now about 60% survival at 5 years, but will vary depending on the size and location of the tumour as well as on the response to chemotherapy, if used.



Conclusions

Patients with bone or soft tissue sarcomas should be treated at specialist centres. A high level of suspicion and investigation of undetermined lumps should lead to earlier diagnosis and improved outcomes. BJHM

Figure 3. This patient was treated with chemotherapy and underwent resection of the bone and insertion of a distal femoral replacement.

Conflict of interest: none.

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KEY POINTS

- There are about 450 bone sarcomas and 2000 soft tissue sarcomas a year in the UK.
- As bone and soft tissue sarcomas are rare, delays in their diagnosis are common.
- The median size for both bone and soft tissue sarcomas at time of presentation is 10 cm.
- Bone and soft tissue sarcomas disseminate almost exclusively through the blood, with the lung being the most common site of metastasis.
- Magnetic resonance imaging is the method of choice to evaluate soft tissue tumours; computed tomography is the imaging modality of choice to evaluate the extent of bone destruction, but is mainly used to evaluate the lungs for metastatic disease.
- Limb-salvage surgery is possible in over 90% of patients with bone and soft tissue sarcomas.
- Chemotherapy is useful for Ewing's sarcoma and osteosarcoma, but not for most soft-tissue sarcomas or chondrosarcomas; radiotherapy is used for most soft tissue sarcomas and some bone sarcomas.
- Prognosis is related to size at diagnosis and response to treatment.
- Sarcomas should be treated in specialist sarcomas centres by a sarcoma multidisciplinary team.