Update and review of the management of bone tumours

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Abstract

Bone tumours are a rare group of heterogeneous malignancies. Osteosarcoma and Ewing's sarcoma are the commonest of these, usually occurring in the absence of an underlying cause. Peak incidence occurs in adolescence. Patients and families commonly report delays prior to referral for appropriate investigation. There must be a high index of suspicion for those presenting with increasing, unexplained or persistent bone pain or tenderness, particularly pain at rest or limp. Rapid referral to a specialist oncological orthopaedic surgeon in a cancer centre is essential for suspected spontaneous fracture or suspicious radiographic appearances. Bone tumours should be managed within a multidisciplinary team in a cancer centre. Bone tumours are treated as a systemic disease and treatment incorporates neoadjuvant chemotherapy, primary tumour therapy (surgery radiotherapy or radiotherapy alone) followed by adjuvant chemotherapy. Treatment within a clinical trial is considered standard of care. Several new agents are the subject of ongoing research. Children and young adults with bone tumours require lifelong monitoring for potential late complications of treatment.

Keywords cancer centre; chemotherapy; Ewing's sarcoma family of tumours; long-term follow-up; metastases; multidisciplinary team; osteosarcoma; radiotherapy

Definition

The term ''bone tumour'' encompasses a heterogeneous group of malignancies. Osteosarcoma and Ewing's Sarcoma are the most common of these. Osteosarcoma is a tumour derived from mesenchymal bone tissue, whilst Ewing's sarcoma is one of the Ewing's Sarcoma Family of Tumours (ESFT), which are thought to be derived from neural crest cells.

Epidemiology and pathogenesis

Bone tumours are rare. However, they most commonly arise in children and adolescents, with the peak incidence between 14 and 18 years. In the UK, 400 new cases of bone tumours (all ages) are diagnosed each year. In the US, 650–700 children and young adults less than 20 years are diagnosed with bone tumours.

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Bone tumours occur most commonly during periods of maximum somatic growth, corresponding with a peak incidence in adolescence. They are more common in males than females. Bone tumours usually develop in the absence of an obvious underlying cause; however, about 10% of osteosarcomas do have predisposing factors. Individuals with retinoblastoma gene germline mutation (RB1) are at an increased risk of osteosarcoma, and RB1 mutations can also be found in sporadic osteosarcoma. Osteosarcoma is one of a number of cancers that can arise in individuals with a dominantly inherited germline mutation of the p53 tumour suppressor gene (known as Li-Fraumeni syndrome) so a family history of early onset breast cancer or malignancy in children or young adults should raise suspicions. P53 mutations can again also be found in sporadic osteosarcoma. Previous treatment with radiotherapy predisposes to osteosarcoma within the radiotherapy field.

There is no clear inherited predisposition to Ewing's sarcoma. However, these tumours are rare in some racial groups which suggests that there may be an underlying genetic process. Almost all Ewing's sarcomas have either a typical translocation in the tumour cells or a close variation. About 90% of Ewing's sarcomas have a translocation involving a gene on chromosome 22 (EWS) fusing with a gene on chromosome 11 (Fli1) to give a new fusion gene (EWS-Fli1) that promotes the malignant phenotype (see Figure 1). This provides a potential target for treatment.

Distribution (see Figure 2)

Over 90% of osteosarcomas occur in the metaphyseal (growing) regions of long bones, most commonly the distal femur, proximal tibia and proximal humerus. Ewing's sarcoma arises throughout the skeleton, commonly the diaphyseal regions of the long bones and the flat bones of the axial skeleton. With this disease distribution, osteosarcoma patients tend to present earlier, whilst Ewing's sarcomas may progress undetected for months.

Historically, 20–25% of patients with osteosarcoma have detectable metastases found during initial staging investigations, whilst 30% Ewing's sarcomas have detectable metastases at presentation. As staging methods have improved, this proportion has increased. The commonest site for both osteosarcoma and Ewing's sarcoma metastases are the lungs. Osteosarcoma can metastasise to other bones whilst Ewing's sarcoma can metastasise to bones and bone marrow. Only rarely do they metastasise to other sites

Presentation

Bone sarcomas usually present with pain, often associated with a palpable mass. Patient and physician may attribute these symptoms and signs to a recent coincidental sports injury and diagnosis may be delayed whilst the patient is referred for physiotherapy. Patients and their families commonly report quite long delays prior to referral for appropriate investigation. A recent survey of patients showed that close to 50% of patients visited their GP more than 4 times prior to being referred. Suspicion should be aroused if the symptoms and/or signs are out of keeping with the nature of the injury, if there was no preceding injury, or if 'recovery' is delayed (see NICE guidelines in Table 1). Patients may also present with a pathological fracture. In addition, Ewing's sarcomas may be characterised by the presence of constitutional symptoms, for example pyrexia,

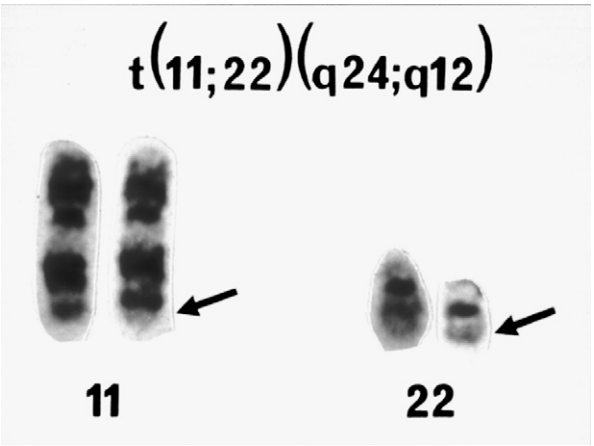


Figure 1 Characteristic translocation seen in Ewing's Sarcoma. About 90% of Ewing's sarcomas have a translocation involving a gene on chromosome 22 fusing with a gene on chromosome 11 to give a new fusion gene that promotes the malignant phenotype.

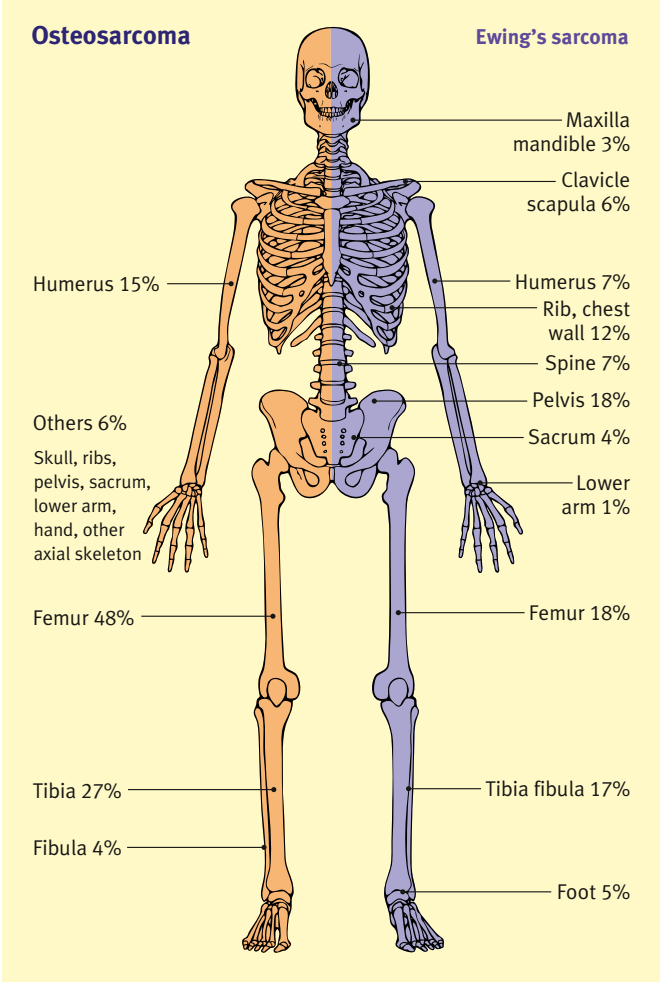


Figure 2 Primary tumour sites for osteosarcoma and Ewing's sarcoma. Over 90% of osteosarcomas occur in the metaphyseal regions of long bones whereas Ewing's sarcoma arises throughout the skeleton, commonly the diaphyseal regions of the long bones and the flat bones of the axial skeleton.

weight loss and lethargy. These symptoms predominate if diagnosis is delayed. Vertebral Ewing's tumours may also present with spinal cord compression.

Differential diagnosis

Differential diagnoses at presentation include sports injuries, osteochondritis or infection. X-ray appearances may suggest acute or chronic osteomyelitis. The investigations detailed below are utilised to differentiate between these diagnoses.

Initial investigations

Initially, a plain radiograph of the affected area is essential to aid diagnosis but also to identify pathological fracture if present. The possible diagnosis can be further explored by MRI or CT scan of the affected area. Typical radiographic appearances of both tumours are shown in Figure 3. However, radiological appearance is only a guide and is no substitute for rapid referral. Rapid referral to a specialist orthopaedic surgeon in a tertiary centre is essential for suspicious radiographic appearances (see NICE guidelines in Table 1). Bone biopsy should only be carried out by a specialist oncological orthopaedic surgeon in a cancer centre.

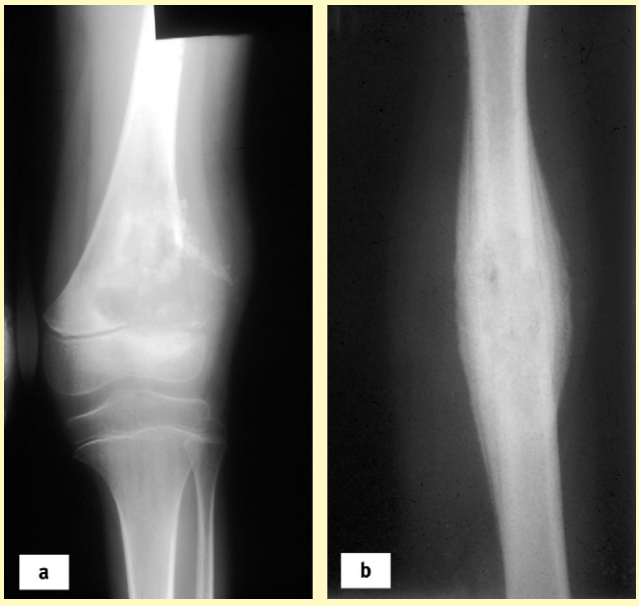
Diagnosis and pathology

Diagnosis for both osteosarcomas and Ewing's sarcomas is pathological and, as mentioned previously, biopsy should be performed by a specialist oncological orthopaedic surgeon in a cancer centre. Pathological diagnosis of osteosarcoma is made

NICE referral guidelines for suspected bone cancer and sarcoma (NICE 2005)

- A patient who presents with symptoms suggesting bone cancer or sarcoma should be referred to a team specialising in the management of bone cancer and sarcoma, or to a recognized bone cancer centre, depending on local arrangements.
- If a primary healthcare professional has concerns about the interpretation of a patient's symptoms and/or signs, a discussion with the local specialist should be considered.
- Patients with increasing, unexplained or persistent bone pain or tenderness, particularly pain at rest (and especially if not in the joint), or an unexplained limp should be investigated by the primary healthcare professional urgently. The nature of the investigations will vary according to the patient's age and clinical features (in older people metastases, myeloma or lymphoma, as well as sarcoma, should be considered).
- A patient with a suspected spontaneous fracture should be referred for an immediate X-ray.
- If an X-ray indicates that bone cancer is a possibility, an urgent referral should be made.
- If the X-ray is normal but symptoms persist, the patient should be followed up and/or a repeat X-ray or bone function tests or a referral requested.

Table 1



Plain radiographs demonstrating both the typical changes of an osteosarcoma including bone destruction and new bone formation occurring in the growing region of the femur **a** and the classical onion skin appearance of a Ewing's sarcoma with patchy bone destruction **b**.

Figure 3

by the identification of sarcomatous spindle cell stroma producing new bone (also known as osteoid). The more common, distinct pathological subtypes are osteoblastic osteosarcoma, chondroblastic osteosarcoma and fibroblastic osteosarcoma. A rarer subtype is small-cell osteosarcoma, which may be confused with Ewing's sarcoma.

Ewing's sarcoma is one of the small round blue cell tumours of childhood (as are neuroblastoma, rhabdomyosarcoma and lymphoma) and is also grouped with the other tumours in ESFT including primitive peripheral neuroectodermal tumours. Standard pathological examination may not discriminate between possible diagnoses but ESFT demonstrate typical CD99 staining on immunocytochemistry. The diagnosis is often confirmed by cytogenetics as more than 90% of Ewing's sarcomas are found to have the specific chromosomal translocation between chromosomes 11 and 22. ESFT includes both bone and soft tissue tumours that are histologically and cytogenetically indistinguishable.

Staging and baseline investigations

In addition to plain radiograph, MRI of the primary site is useful to define intramedullary extension. CT thorax and isotope bone scan are necessary to investigate for metastatic disease. It is not yet clear if PET scanning will be additionally helpful in these tumours. If Ewing's sarcoma is suspected, two bone marrow biopsies and trephines must be performed. Any fluid or tissue sample must be sent for cytology, cytogenetics and histological assessment. FBC, U&Es, LFTs, bone profile, immunoglobulins, clotting profile, blood film, AFP/HCG/LDH, ESR and lactate dehydrogenase are essential baseline investigations, both to confirm normal organ function and to rule out other possible differential diagnoses. Baseline testing of cardiac function and renal function are also necessary because of the potential toxicities associated with the chemotherapy drugs most commonly used in treating these cancers.

Management

Bone tumours should always be managed within a multidisciplinary team (MDT) in a cancer centre. The MDT needs to encompass a diagnostic team (including pathologists, cytogeneticists and radiologists); a treatment team (including medical oncologists, clinical oncologists, specialist nursing teams and surgeons); and a supportive care team including rehabilitation specialists, psychosocial and educational support.

Chemotherapy is usually given via a central line (a Hickman line or a portacath). Community teams are involved in supporting patients at home between treatments and sometimes in carrying out blood tests required for evaluation prior to further chemotherapy. Throughout treatment, response of the primary and, if present, of distant metastatic disease, is evaluated using CT or MRI assessment. Renal and cardiac toxicities are evaluated using repeated GFR measurement and echocardiography respectively. Entry into an appropriate clinical trial must be considered standard of care for all patients with bone tumours. Management of bone tumours is constantly progressing and current standard treatment can at present be defined by the ongoing clinical trials described below. Typical pathways for osteosarcoma and Ewing's Sarcoma are shown in Figure 4.

Osteosarcoma

In the vast majority of cases, osteosarcoma needs to be treated with a combination of chemotherapy and surgery. Historically, treatment with surgery alone (usually amputation) led to overall survival of less than 20%. A series of trials in the late 1970s and 1980s at the Memorial Sloan-Kettering hospital developed the concept of neoadjuvant chemotherapy, in an effort to control both local and distant metastatic disease. This aided development of new approaches to limb sparing surgery instead of amputation, as well as developing ideas around the use of combination chemotherapy to reduce drug resistance, and the concept of switching drugs if patients have a poor response to initial chemotherapy (''salvage therapy''). Currently, disease-free survival rates of 60-70% are now commonly reported for patients receiving multiagent pre-operative chemotherapy followed by surgical resection and continuation of chemotherapy post-operatively.

The most active chemotherapy agents used in the treatment of osteosarcoma are cisplatin, doxorubicin and methotrexate. Ifosfamide given in combination with etoposide has also shown activity against osteosarcoma. It has been shown that those patients whose tumours respond well pathologically to pre-operative chemotherapy (defined as $<10\%$ viable tumour) have better 5 year survival rates than those who are poor responders ($\geq 10\%$ viable tumour): 5 year survival rates of 75–80% compared with 35–40% respectively.

Four of the major research groups in osteosarcoma (the North American Children's Oncology Group, the German-Swiss Cooperative Osteosarcoma Study Group, the European

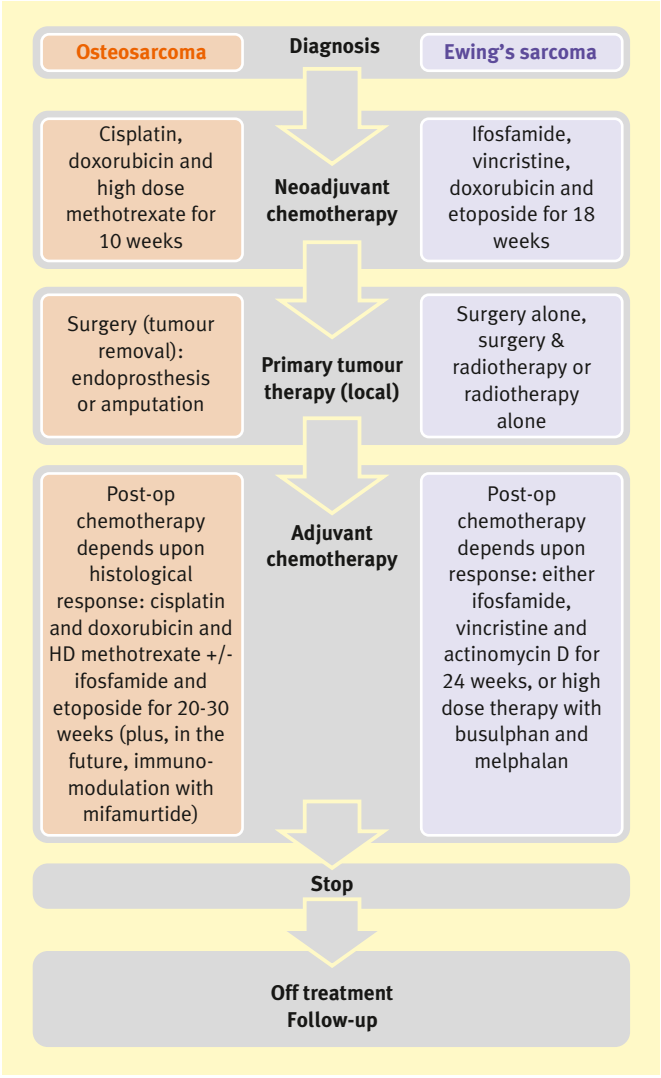


Figure 4 Typical treatment pathways in osteosarcoma and Ewing's sarcoma, illustrating their similarities and differences from diagnosis to follow-up.

Osteosarcoma Study Group and the Scandinavian Sarcoma Group) have collaborated to conduct a large intergroup randomised trial with widely inclusive eligibility criteria to address the question whether chemotherapy should be amended on the basis of pathological response to pre-operative chemotherapy: EURAMOS 1.

The trial is testing whether it is feasible to improve event free and overall survival for both the good and poor responders by the inclusion of additional chemotherapy agents into the post-operative treatment schedule? The control arm is methotrexate, doxorubicin and cisplatin (MAP). Good responders are randomised between MAP and MAP with pegylated interferon α-2b (given as maintenance after MAP). The rationale for using interferon in this setting is to maintain remission: interferon has repeatedly shown a growth inhibiting effect on both osteosarcoma cell lines and animal models *in vitro*. Poor responders are randomised between MAP and MAP with ifosfamide and etoposide (MAPIE). A few studies have previously evaluated the role of altering post-operative chemotherapy in poor pathological responders but there has been no randomised trial to evaluate ifosfamide and etoposide in this setting.

There is good evidence that axial, primary metastatic and secondary osteosarcomas can be cured if all disease sites are resectable, and are all therefore eligible for participation in EURAMOS 1. Patients with non-resectable disease have a poor prognosis but may have good palliation of symptoms with the chemotherapy regimens described above. For patients with relapsed osteosarcoma, a combination of chemotherapy and aggressive surgical resection of pulmonary metastases produces some long-term survivors.

Mifamurtide is a new immunomodulatory drug that should soon be available for routine use in the management of osteosarcoma. Recent evidence from a large American randomised controlled trial showed that in patients with non-metastatic disease it could be combined with surgery and chemotherapy to improve long-term survival.

Ewing's Sarcoma

Ewing's sarcomas were historically treated with local radiotherapy alone, leading to 90% of patients dying from metastatic disease. It is now established that this disease requires a combination of chemotherapy, surgery and radiotherapy to control both local and distant metastatic disease. For localised disease, 5 year survival rates of 55—65% have been documented. Several chemotherapy drugs have shown activity in this situation including doxorubicin, etoposide, vincristine, actinomycin D, cyclophosphamide and ifosfamide. Known prognostic factors in this patient group include the tumour volume, tumour site (pelvic/non-pelvic, axial/extremity, bone/soft tissue), age, pathological response to chemotherapy and factors relating to availability of treatment options locally.

Patients with metastatic Ewing's sarcoma have a worse outcome. Those with pulmonary metastases have a survival of close to 40% but only 10—20% disease-free survival has been reported in patients who present with bone or bone marrow metastases and receive standard combination chemotherapy. Prognostic factors in patients with metastatic disease include response to chemotherapy and site of metastatic disease.

The ongoing randomised trial aiming to improve outcome in patients with Ewing tumours (EURO-E.W.I.N.G.99) is the result of collaboration between a number of major European and International Ewing tumour study groups. It has several aims including increasing the intensity of induction chemotherapy, aiming to improve the pathological response and survival in this patient group whilst not increasing toxicity to such a degree that subsequent treatment cycles are delayed. All patients receive a standard 4 drug induction programme (VIDE: vincristine, ifosfamide, doxorubicin and etoposide) for 6 cycles over 18 weeks. In patients with non-metastatic tumour and a good response to standard VIDE induction chemotherapy, VAI (vincristine, actinomycin D and ifosfamide) and VAC (vincristine, actinomycin D and cyclophosphamide), consolidation chemotherapies are compared. Patients who receive radiotherapy as primary treatment with <200 ml residual tumour are also treated within this group. In patients with non-metastatic disease who have a poor histological response to either VIDE induction chemotherapy or patients who have large tumours (>200mls) and receive radiotherapy as primary treatment, VAI consolidation chemotherapy is compared with high-dose

chemotherapy (Busulfan-Melphalan) and PBPC rescue. For patients with either pulmonary or pleural metastases at diagnosis, VAI chemotherapy and whole lung irradiation is compared with high dose therapy (Busulfan-Melphalan) and PBPC rescue. For patients who have metastases at other sites (e.g. bone or bone marrow), several options are investigated within this trial.

Selecting the correct local therapy in Ewing's sarcoma is crucial in order to maximise survival whilst trying to limit long-term morbidity. A comparison of patients treated in the UK or Germany in a randomised trial has shown that the German patients had a 10% better survival rate than those from the UK. A careful analysis has demonstrated that this difference is almost entirely accounted for by differences in local therapy. The German patients were 3 times more likely to have had both surgery and radiotherapy than the UK patients. Twice as many UK patients had only one modality. It is clear that poor local control, i.e. local relapse, eventually leads to systemic relapse and usually death. Decision making about local therapy is highly specialised and attempts are currently underway in the UK to develop a national quality-controlled scheme for this.

Unfortunately, most patients with relapsed Ewing's Sarcoma will die of their disease. Appropriate chemotherapy regimens for this clinical situation are the subject of ongoing research but recent evidence suggests that the combination of irinotecan and temozolamide may induce a response in up to 65% of patients. There are a number of newer agents including insulin-like growth factor receptor-1 antibodies, small molecules and mTOR inhibitors which are showing some early promise in the treatment of Ewing's sarcoma and osteosarcoma but have yet to be subject to randomised trials.

Prognosis and explanation to patient

There has been little change in outlook for osteosarcoma in the past 20 years in the UK (Figure 5) despite ongoing clinical trials. Ewing's sarcoma, however, has shown some improvement in overall survival over this same period of time (Figure 6). For all bone tumours, patients presenting with metastatic disease have a much poorer outlook than those presenting with a primary tumour alone. However, every patient is different and it must be made clear to each patient that their management plan and prognosis depend upon many factors including tumour type, stage and disease site(s). It should also be made clear that bone tumours are treated as a systemic disease, usually incorporating a combination of chemotherapy, surgery and (in the case of Ewing's sarcomas) possibly radiotherapy.

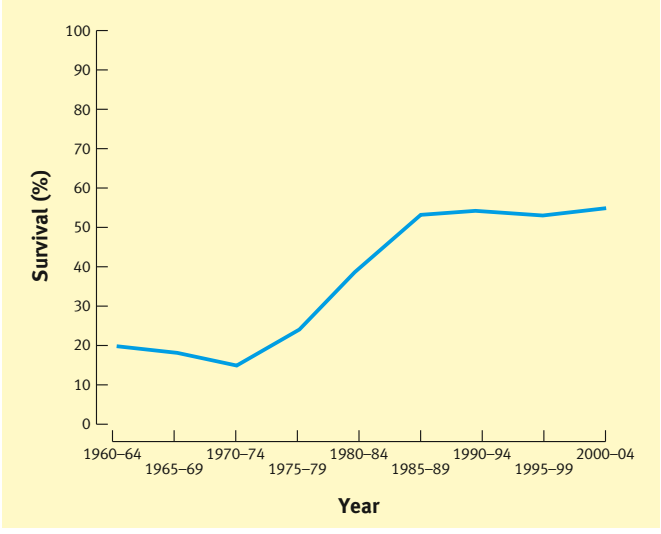


Figure 5 UK osteosarcoma survival 1960—2000, illustrating improvement until the mid-1980's since when there has been negligible change.

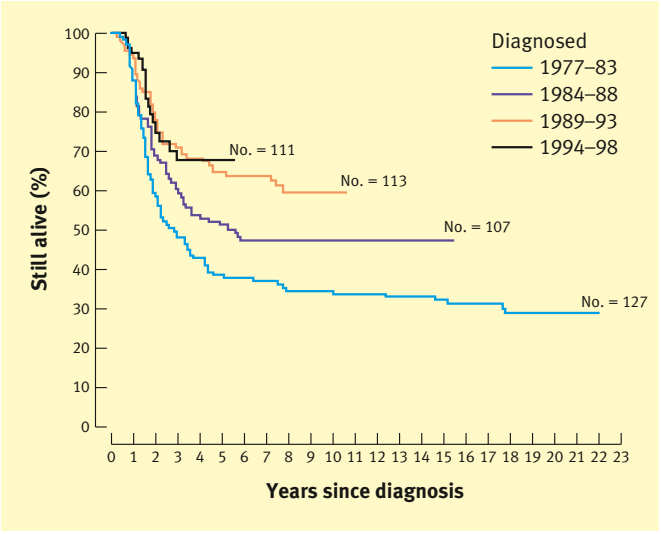


Figure 6 UKCCSG data demonstrating improving survival rates for Ewing's Sarcoma between 1977 and 1993.

Follow up

At the end of treatment, imaging of all disease sites is essential, alongside assessment of cardiac and renal function. Following completion of treatment, patients need regular review with appropriate expertise. In this period, CXR and blood tests including renal function, electrolytes and LFTs are required at each clinic visit. Patients who receive treatment for bone tumours in childhood require lifelong monitoring either in a long-term follow-up clinic or in the community (with paediatric oncology support). It is essential to monitor for and manage potential complications of treatment. Anthracyclines can cause cardiac damage later in life even without obvious damage at the time of treatment. Renal toxicities may develop early with electrolyte loss most commonly, but may also develop many years later, leading to an increased risk of hypertension in middle age. There is a potential in both sexes for infertility. Sperm banking should be offered to all boys before they start chemotherapy. Unfortunately, there is no current established method of ovarian tissue storage. Girls may suffer temporary or permanent cessation of menstruation after chemotherapy. They may also develop premature ovarian failure and the inherent problems this may entail later in life, including osteoporosis and coronary artery disease.

Rehabilitation

Patients who have completed a combination of complex chemotherapy, surgery and possibly radiotherapy often require continued rehabilitation for a number of months or years afterwards. The functional and cosmetic outcomes from

endoprosthetic replacement or limb amputation are very variable. Physiotherapy to minimise physical disability is essential. The majority of young people treated for bone sarcomas can have a full and fulfilling life.

Prevention

There are no interventions known to decrease the likelihood of developing bone tumours. Prevention of disease complications and disabilities is the subject of ongoing evaluations. These include minimising debilitating surgery by improving neo-adjuvant chemotherapy, and reducing short- and long-term chemotherapy-related toxicities. ◆

Practice points

- There must be a high index of suspicion for young people presenting with increasing, unexplained or persistent bone pain or tenderness, particularly pain at rest (especially if not in the joint), or an unexplained limp, and should be investigated urgently, initially with a plain radiograph.
- Rapid referral to a specialist oncological orthopaedic surgeon in a Cancer Centre is essential for suspected spontaneous fracture or suspicious radiographic appearances, as both bone biopsy and any subsequent surgery must only be carried out by a specialist oncological orthopaedic surgeon.
- Children and Young Adults with bone tumours should be managed in the context of a multidisciplinary team within a Cancer Centre.
- Treatment within a clinical trial is standard of care and must be considered for all patients.
- Children and Young Adults who receive treatment for bone tumours require lifelong monitoring to identify and manage any late complications of treatment.

FURTHER READING

Automated childhood cancer information system. Avaliable at: http://www-dep.iarc.fr/accis.htm.

Avaliable at: www.teenagecancertrust.org/ find- your- sense-of-tumour.

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EURO-EWING99 trial protocol.

EURAMOS1 trial protocol.

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NICE guidance on cancer services: Improving outcomes in children and young people with Cancer (August 2005) and Improving outcomes for people with sarcoma (March 2006).