Primary malignant tumours of the bone

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Abstract

Primary bone tumours are rare, with a prevalence of approximately 550 cases per year in the UK. Late presentation and identification of tumours delays diagnosis and negatively impacts on the survival of these patients. Characteristic clinical and radiological features of bone tumours should alert the physician to investigate further. Investigations should include blood tests and local and systemic imaging. MRI, CT and isotope bone scans are important in evaluating the tumour. The most common types of bone tumour are osteosarcoma, chondrosarcoma, Ewing sarcoma, spindle cell sarcoma of bone and chordoma. The important pathological features and treatment of each type of tumour are described in this article. Early contact with a supra-regional bone tumour unit is mandatory when a bone tumour is suspected, where a multidisciplinary approach to management is employed. Biopsy and surgical treatment should be carried out in these units wherever possible. Patients should be enrolled in international clinical trials, where feasible, to gather data that will ultimately improve outcomes. The survival rates from most bone tumours are 60–80% with appropriate treatment.

Keywords Chondrosarcoma; chordoma; Ewing sarcoma; osteosarcoma; primary bone tumour

Primary malignant bone tumours are rare, accounting for only 0.2% of all neoplasms. The UK and North America have an incidence of 8.2 per million, although higher incidences have been reported in some other regions of the world. This equates to over 550 new cases per year in the UK, with the most common tumours being chondrosarcoma (33%), osteosarcoma (32%), Ewing sarcoma (15%) and chordoma (5%).[1] Primary malignant bone tumours show a bi-modal age distribution and a male predominance (ratio 1.6–1.7:1). All bone tumours have similar presenting features, and require a standard series of investigations; however, each has individual characteristics that are important for treatment and prognosis. Early referral to a supra-regional bone tumour unit for specialist multidisciplinary treatment is essential to provide the best possible outcome.

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Presentation of primary bone tumours

Bone tumours commonly present with non-specific pain around a joint, which is typically nocturnal, dull and non-mechanical (not related to activity or weight bearing). They may also present with an unexplained limp. Late symptoms include swelling, mechanical pain and restriction of movement of the limb. Up to one-fifth of patients will present with either a pathological fracture or with a suspicious lesion on a radiograph taken for a reason unrelated to the tumour (suspicious radiological features are listed below). The mean size of a bone tumour at presentation is over 10 cm in the UK (compared with <2.5 cm for breast tumours), and mean time to diagnosis ranges from 4 months to 2 years depending on the type and site of the primary tumour.

Radiological features of a suspicious bone lesion

The following X-ray findings, although not pathognomonic of bone tumours, should give rise to a suspicion of a malignancy:

- cortical destruction
- periosteal reaction
- zone of transition (less well defined in more aggressive tumours)
- new bone formation, especially within soft tissues.

Differential diagnosis of bone tumours

A wide variety of conditions can mimic primary bone tumours and should be considered in the differential diagnosis for a suspicious bone lesion. These include:

- secondary bone tumours (most commonly from primary tumours of the breast, bronchus, kidney, prostate and thyroid)
- benign tumours of bone (osteoid osteoma, chondroblastoma, enchondroma, chondromyxoid, fibroma)
- infection (osteomyelitis, tuberculosis)
- developmental abnormalities, including fibrous defects (e.g. fibrous dysplasia, fibrocortical defects) and cystic defects (e.g. simple bone cyst)
- iatrogenic defects (e.g. iliac bone graft donor site)
- trauma (e.g. avulsion fractures)
- metabolic bone disease (e.g. osteomalacia, brown tumour of hyperparathyroidism)
- haematological malignancies (plasmacytoma/multiple myeloma, lymphoma).

Approach to a suspicious bone lesion

Following the identification of a suspicious bone lesion, the clinician must follow a systematic approach (outlined below) to ensure prompt and appropriate referral to specialist centres.

Focused history – Information should be sought about:

- pain – classically dull, nocturnal, not relieved by rest
- past medical history – infection, malignancy or predisposing conditions (e.g. Paget's disease, osteochondroma)
- systemic symptoms – weight loss, poor appetite, fever, anaemia
- symptoms of possible primary tumour (e.g. breathlessness, haemoptysis, haematuria, altered bowel habit).

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Detailed examination – to include:

- local examination to assess location, swelling, tenderness, joint contracture, skin condition
- regional examination, to include lymph nodes and assess for distal neurovascular compromise
- systemic examination, including the chest for signs of metastatic spread or primary tumour, and other sites of possible primary tumour (e.g. breast, prostate).

Initial investigations – to include:

- plain film radiographs of the entire bone, including the joint above and below the lesion
- a chest radiograph to assess for evidence of metastases or primary tumour
- blood tests, including full blood count, erythrocyte sedimentation rate, C-reactive protein, electrolytes, bone profile (calcium, alkaline phosphatase and lactate dehydrogenase, which are raised in some bone tumours), tumour markers (prostate-specific antigen, carcinoembryonic antigen) and protein electrophoresis (specifically for plasmacytoma/multiple myeloma).

Staging tests: depending on results of the initial investigations, more advanced imaging studies, to allow staging of the tumour, may be indicated. Staging involves the identification of local and systemic spread, in order to guide treatment and predict prognosis.

- *Local staging* gives more information about the size, anatomical relationships (proximity to neurovascular bundles) and whether limb salvage surgery is possible. This comprises MRI of the whole bone with cross-sectional imaging. CT with three-dimensional reconstruction is occasionally required to assess the bone architecture or to assist manufacture of custom-made prostheses (especially in the case of pelvic tumours).
- *Systemic staging* gives information about distant spread of the tumour. Isotope bone scans are sensitive but not specific at detecting bone metastases (5% of tumours present with a skip metastasis often within the same or adjacent bone). CT of the chest allows detection of small (<5 mm) metastases.

The Enneking staging system is the most commonly used system for bone tumours (Table 1).

Biopsy: if any of the aforementioned investigations raise suspicion of a malignancy a referral should be made to a supra-regional bone tumour unit for a biopsy, which will be carried out according to the following principles:

- needle biopsy should allow an adequate amount of tissue for examination by an experienced bone tumour pathologist
- image guidance (fluoroscopy, ultrasound or CT) should be used to get a representative sample
- samples should be sent for microbiology, cytogenetics and histopathology
- the biopsy should not violate normal tissues, in order to prevent tumour spread
- the biopsy should be in line with the incision for definitive surgery, allowing excision of the biopsy tract (where seeding may have occurred).

Enneking staging system for osteosarcoma

Stage	Grade	Compartment	Distant metastasis
Ia	Low	Within bone	No
Ib	Low	Outside bone	No
IIa	High	Within bone	No
IIb	High	Outside bone	No
IIIa	Any	Within bone	Yes
IIIb	Any	Outside bone	Yes

Table 1

Classification of primary bone tumours

Although the clinical features and investigations are similar for all bone tumours, differences in epidemiology, predisposing factors, sensitivity to adjuvant treatment, and prognosis means that a basic understanding of the different types of bone tumour is required. The most important are examined individually below.

Osteosarcoma

Epidemiology: osteosarcoma is the most common primary malignant tumour of bone. In the UK, the prevalence is approximately 150 cases per year. There are two age peaks: in the second decade (frequently coinciding with the growth spurt) and over 50 years (likely due to malignant transformation of Paget's disease). Osteosarcoma is more common in males (ratio 1.4:1). Racial differences vary with age; osteosarcoma affects more Afro-Carribean patients in adolescence, and more Caucasian patients in older adulthood.[2]

Aetiology: the aetiology of osteosarcoma remains largely unknown, however, there is a widely accepted theory that loading stresses on rapidly dividing osteoblasts cause DNA mutations that lead to the disease. A number of predisposing factors have also been identified.

Radiation exposure – radiotherapy for a solid tumour accounts for at least 3% of osteosarcomas. The time delay between radiation exposure and osteosarcoma development is 10–20 years, therefore, the incidence is likely to increase as patients are surviving longer following their primary irradiation. These tumours typically develop at the edges of the original treatment fields making management difficult.

Paget's disease – this is a disease of disordered bone architecture as a result of increased osteoclast activity and a compensatory increase in osteoblast activity. Although considered the primary cause of osteosarcoma in older adults, malignant transformation affects only 1% of patients with Paget's disease. Histologically indistinct from other causes of osteosarcoma, these patients often have multiple bone involvement, giving a poor prognosis.

Genetics – a small number of genetic diseases resulting in mutations in tumour suppressor genes are known to be associated with a higher incidence of osteosarcoma. Two of these will be discussed briefly.

Li-Fraumeni syndrome is a familial syndrome of multiple neoplastic diseases including breast cancer, leukaemia, adrenocortical tumours, brain tumours, and soft tissue and bone sarcomas. The genetic defect lies within the *p53* tumour suppressor

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