# Osteosarcoma

**Definition**
A primary malignant bone tumour characterised by the production of osteoid.

**Epidemiology**
Bimodal distribution; peaks in early adulthood and after fifty (due to Pagetoid sarcomas)
Second most common primary malignant bone tumour in NSW.
Third most common malignant tumour of adolescence after leukaemia and lymphoma.
Incidence is 1 per million in 6 year olds and 10.6 per million in 14 year olds. The peak incidence is in the second decade of life.
Males > females (1.5:1)

**Aetiology**
Radiation is a proven factor. More common in Hiroshima survivors, and workers exposed to radium.
Paget's disease is said to undergo malignant transformation in around 1%.
Retinoblastoma is a potent cause.
Li Fraumeni syndrome, Rothmund-Thomson syndrome.

**Molecular biology**
There are complex genetic aberrations in osteosarcoma but none are specific.
60% of tumours have an abnormality of the Rb22 tumour suppressor gene (13q), and a substantial proportion has abnormalities of the p53 gene[1] (17p).
The c-myc and c-fos proto-oncogenes are over expressed in osteosarcoma
Vascular endothelial growth factor is found in many osteosarcomas with pulmonary metastases

**Classification**
These tumours are classified according to the dominant element on histological examination:
1. Osteoblastic
2. Chondroblastic
3. Fibroblastic

There are some special types:
1. Periosteal
2. Parosteal
3. Telangiectatic
4. Low-grade central
5. Extraskeletal

**Clinical**
Most commonly involved bones are the distal femur, proximal tibia and proximal humerus.
Roughly half of osteosarcomas occur around the knee.
Rare distal to the ankle or wrist
The tumour involves the long bone metaphyses and may cross the physeal plate.
Osteosarcomas in older patients are more likely to involve the flat bones.
The most common symptom is pain (85%) which is worse at night and which increases in severity. The pain is probably due to microfractures through the involved bone but may also be due to compression or stretching of adjacent structures.
Other symptoms include lumps (palpable or visible) in 40%, limps and pathological fractures.
Swelling or an increase in pain in patients with Paget's disease implies malignant change.
There is an association with rickets/osteomalacia.

**Investigations**
**Lab**
The ESR is usually increased
There may be an increase in LDH and Alk phos.

[1] The p53 gene product functions as a cell cycle regulator and has the ability to induce apoptosis. It can also cause the cell cycle to pause to allow repair of faulty genetic material.

**Bone scan**
Demonstrates mets or multicentric tumour.

**Radiology**
**Plain XR**
Can have both osteolytic and osteoblastic areas; most tumours have a combination of these features.
The cortex is often breached and tumour radiating out can give rise to the characteristic sunburst spicules
Codman's triangle is another classic sign referring to the presence of reactive new bone at the angles of periosteal elevation
The tumour typically has a poorly defined zone of transition.

**CT**
Delineates extent of bony involvement. It is particularly useful in the imaging of pelvic tumours where fat planes allow better delineation between normal and tumour tissue.

**MRI**
Delineates extent of soft tissue involvement, and involvement of neurovascular structures. It is also very useful in delineating the level of marrow involvement and hence the level of resection.

**Staging**
Plain XR; CT; MRI; CXR; CT chest (can detect pulmonary nodules as small as 3mm); Bone scan (PET scan)
Cardiac function (gated heart pool scan) prior to anthracyclines.
Audiogram prior to cisplatin.
Consideration to sperm banking.

90% of osteosarcomas are 2B lesions.

**Pathology**
**Gross**
Usually the cortex is perforated and there is a large soft tissue mass
The tumour may vary from a soft fleshy mass to a firm fibrous mass.
The inner part of the mass is usually more heavily mineralised than the outer surface of the mass.
Intra-articular extension of tumour mass will be evident on gross inspection. If present, it tends to occur along the course of ligaments, such as the ACL and PCL.

**Microscopic**
The histopathologic features vary widely.
Lichtenstein stated the essential features as "(1) the presence of a frankly sarcomatous stroma and (2) the direct formation of tumour, osteoid and bone by this malignant connective tissue"

1. Osteoblastic
    a. Around 50% of tumours in Mayo series
    b. Osteoid is present as a fine lacework between individual tumour cells, or sometimes in the form of bony trabeculae which are usually thin and anastomosing
    c. Tumour cells have obvious features of malignancy such as nuclear hyperchromasia and abundant mitotic figures
2. Chondroblastic
    a. Around 25% of tumours in Mayo series
3. Fibroblastic
    a. Around 25% of tumours in Mayo series
    b. Tumour cells are spindle shaped and arranged in a herringbone fashion
    c. Matrix production is seen focally

Additionally:

1. Many tumours contain foci of giant cells
2. If one encounters a tumour that has all of the features of a GCT but that occurs in an unusual place such as the metaphysis of a growing child, serious consideration should be given to osteosarcoma
3. Paget's disease and osteosarcoma
    a. Occurs in less than 1%
    b. Pelvis is most commonly affected
    c. Long term survival is rare

   d. (Fibrosarcoma, chondrosarcoma and even GCT can all complicate Paget's)
4. Post chemotherapy changes
   a. Successful chemotherapy usually results in marked sclerosis and "cell dropout" with the entire tumour replaced with dense bone without tumour cells between the bony trabeculae

**Natural history**
There is a pronounced tendency for early and widespread haematogenous spread.
Death is via pulmonary mets

**Management**
Neoadjuvant therapy prior to surgery
Benefits of neoadjuvant chemotherapy:
1. May prevent development of resistant clones in tumours with rapid doubling times
2. May kill microscopic metastases
3. May shrink primary tumour and allow limb salvage
4. May sterilise microscopic tumour foci in the reactive zone around the tumour.
5. Allows time for surgical planning, design or fabrication of custom prostheses, procurement of allograft.
6. Gives prognostic information – necrosis of a high proportion of tumour in the surgical specimen is encouraging prognostically.

Agents known to be effective against osteosarcoma include doxirubicin, cisplatin, ifosfamide, high dose methotrexate and cyclophosphamide.

At operation either a wide marginal excision or radical excision is performed. Wide marginal excision may allow limb-sparing surgery. Limb sparing surgery is indicated for patients in whom wide margins can be obtained without sacrificing so much tissue that the remaining limb is non functional. Nerves are the limiting factor. The overall reconstruction should function at least as well as a prosthesis.

If the margins are poor the patient should undergo immediate amputation, because local recurrence is an almost guarantee of death within 15 months.

Operative specimens provide an opportunity to assess the response to chemotherapy.

Patients appear to adapt equally well to amputation and limb sparing surgery psychologically.

**Prognosis**
The *probability of disease free survival is dependent on the presence of clinically detectable mets on presentation.*
*Mets – 11% 5 ysr*
*No mets – 69% 5 ysr*
Other prognostic factors:
-Tumours of the appendicular skeleton do better. The five year survival rate is around 30% for patients with pelvic tumours.
-Patients with elevated LDH and Alk phos at presentation do worse.
-Patients who express P glycoprotein have a poorer survival rate – this is a product of the multidrug resistance protein
-Patients with a >90% kill from neoadjuvant chemotherapy do better.
Limb sparing surgery is possible in around 90%.

**Osteosarcoma variants**
**Telangiectatic osteosarcoma**
1. 3.6% of all osteosarcomas
2. XR show purely lytic lesion
3. Grossly, the tumour looks like a bag of blood.
4. Histologically, looks like an ABC with cavernomatous spaces separated by septae, but with septae filled with pleomorphic malignant cells.
5. Benign giant cells are always present
6. High grade tumour
7. Similar prognosis to conventional osteosarcoma.

**Low-grade central (intramedullary) osteosarcoma**

1. Patients are a little older
2. Involves larger leg bones (distal femur and proximal tibia)
3. While half the XR appear malignant, the other half have a well defined zone of transition
4. Consists of spindle cells with little cytological atypia. Mitotic figures are uncommon. The fibrous nature and low grade of the tumour may allow confusion with fibrous dysplasia.
5. Excellent prognosis

**Periosteal osteosarcoma**

1. Schajowicz calls this juxtacortical chondrosarcoma and Jaffe referred to it as cortical osteosarcoma
2. Rare, comprising around 1.5% of tumours in the Mayo series
3. Tends to be more common in females and involve the diaphysis of long bones, particularly the tibia.
4. XR show a sunburst appearance merging into the surrounding tissues. The lesion appears to sit in a saucer-shaped depression in the cortex. It rarely grows into the medullary canal.
5. Microscopically this tumour is a moderately differentiated chondroblastic osteosarcoma
6. Appears to be an excellent prognosis with surgery alone.

**Parosteal osteosarcoma**

1. This is a distinctly less malignant osteosarcoma with a vastly different clinical behaviour
2. Makes up 4% of osteosarcomas
3. More common in females.
4. The tumour is well differentiated and arises from the cortex
5. Occurs in a slightly older age group than standard osteosarcoma
6. Most common site is the posterior distal portion of the femoral shaft
7. The tumour is densely mineralised, and is attached to the underlying cortex by a broad base. It tends to encircle the underlying bone but is often separated from it by a lucency. The term “pasted on” may be used to describe the appearance. The tumour does however enter the medullary canal in almost half of cases, but this doesn’t affect long term survival.
8. Histologically, relatively normal appearing anastomosing trabecular bone is separated by a hypocellular spindle cell stroma. The fibrous nature of the tumour and low grade may lead to confusion with fibrous dysplasia.
9. There may be a cartilaginous cap
10. May undergo dedifferentiation into a highly malignant tumour
11. Treatment is with surgical excision alone with a 93% long term survival rate.

**High grade surface osteosarcoma**

1. Extremely rare tumour, occurs in 2$^{nd}$ and 3$^{rd}$ decades of life.
2. Diaphyseal surface of long bones (particularly femur)
3. High grade malignancy, essentially identical to classic osteosarcoma