

# Solid Tumour Section

## Review

## Bone: Conventional Osteosarcoma

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### Abstract

Review on Osteosarcoma, with data on clinics, and the genes involved.

#### Keywords

Osteosarcoma

### Identity

#### Other names

Osteosarcoma, not otherwise specified; Chondroblastic osteosarcoma; Fibroblastic osteosarcoma; Osteofibrosarcoma; Central osteosarcoma; Conventional central osteosarcoma; Medullary osteosarcoma; Intracortical osteosarcoma; Classical osteosarcoma; Osteogenic sarcoma; Osteoblastic sarcoma; Central osteogenic sarcoma; Conventional central osteosarcoma; Sclerosing osteosarcoma.

#### Note

Some of the above mentioned aliases are based on the anatomical location (Medullary osteosarcoma, Intracortical osteosarcoma), histological, with respect to the constitution of the extra cellular matrix (ECM) and/or radiological appearance (Chondroblastic osteosarcoma, Fibroblastic osteosarcoma, Osteoblastic sarcoma, Sclerosing osteosarcoma) of the tumor. Others are referring to the characteristic appearance of osteosarcoma without further specifying (conventional, central). Secondary osteosarcomas (mainly linked with Paget's disease of bone or post-radiation sarcomas) and extra medullary osteosarcomas (Parosteal osteosarcoma, Periosteal osteosarcoma) share many

features with conventional osteosarcoma, but also have additional characteristics. Some of these subtypes of osteosarcoma are discussed in the chapter osteogenic tumors.

### Classification

#### Note

Conventional osteosarcomas are classified in terms of predominant ECM:

**Osteoblastic osteosarcoma:** predominantly bony/osteoid matrix

**Chondroblastic osteosarcoma:** predominantly chondroid matrix

**Fibroblastic osteosarcoma:** predominantly spindle cells, low osteoid

**Unusual histological forms** with the same clinical behavior. Intermediary forms may occur, consisting of mixed ECM types.

### Clinics and pathology

#### Disease

Conventional osteosarcoma is a high grade malignant primary central sarcoma of bone characterized by the presence of osteoid extracellular matrix.

#### Etiology

There are no benign precursors of osteosarcoma identified till now, however an association between Paget's disease of bone and post-radiation sarcoma with secondary osteosarcoma is suggested. Patients with genetic syndromes including Li-Fraumeni syndrome (TP53 mutation), hereditary

retinoblastoma (RB1 mutation), and Rothmund-Thompson (RECQL4 mutation), have a higher chance of developing osteosarcoma. Benign bone-forming neoplasms very rarely undergo malignant transformation. Currently there is no consensus on the progenitor cell of osteosarcoma. Mesenchymal stem cells (MSCs) potentially are the progenitor cells as these cells have the capability to differentiate towards the osteogenic lineage. In a model of murine MSCs that spontaneously transformed during ex vivo expansion, the transformed MSCs formed osteosarcoma in mice when these MSCs were injected. Although spontaneous malignant transformation is not described for human MSCs to this date, human MSCs transformed upon RB1 knockdown and MYC overexpression. After injection into mice these transformed human MSCs also lead to osteosarcoma formation. However, a more differentiated precursor cell such as an osteoblast could also be the progenitor cell of osteosarcoma. Conditional deletion of RB1 and TP53 in differentiated bone marrow derived murine MSCs transformed these cells and formed osteosarcoma in mice. Undifferentiated murine MSCs with deletion of RB1 and TP53 formed leiomyosarcoma leiomyosarcoma and not osteosarcoma. As there is evidence that both osteoblast and undifferentiated MSCs can be the progenitor cells of osteosarcoma, it is also likely that both cell types are the precursor.

### Epidemiology

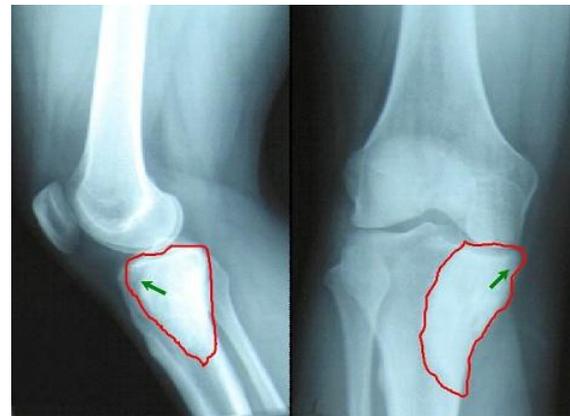
Osteosarcoma is the most common primary malignant bone tumor of non-haematopoietic origin with an incidence of 4 per million people aged between 0-24 years or >60 years and 1.7 per million people in the age group 25-59. There is no association with ethnic group or race. The disease mostly affects children and young adults (70%), but a secondary smaller peak incidence (30%) is seen in patients over 40 years of age. However for these late onset osteosarcomas a predisposing condition, as Paget's disease or post-radiation sarcoma can often be causal. Males are more frequently affected than females in a ratio of 1.35:1, possibly because of the more irregular growth spurt in young males than in females.

### Clinics

Symptoms, mainly deep pain, develop over a period of weeks to a few months until they become unbearable. This non-specific pain either combined with a palpable mass or not is the cardinal symptom of conventional osteosarcoma. Also edema and localized warmth may be included to the symptoms as is the limitation of the patient's motions. Pathological fractures occur in 5-10% of the patients.

**Macroscopy:** Conventional osteosarcoma can arise in any bone, but most often affects the ends of the long bones, in particular the distal femur (30%), proximal tibia (15%) and proximal humerus (15%). It is often a fleshy or hard tumour 5-10 cm in size localized at the metaphysis (90%) or diaphysis (9%) and very rarely the epiphysis of the bone. Conventional osteosarcoma frequently penetrates the cortex and is associated with a soft tissue mass.

**Radiography:** The overall radiographic appearance of conventional osteosarcoma is a mixed lytic/sclerotic lesion with cortical destruction and tumor expansion into soft tissue. Sometimes a so-called Codman's triangle is observed when the tumor raises the periosteum away from the bone. To evaluate the extent of the tumor preoperative CT scan, and (dynamic) MRI may be helpful. Furthermore dynamic MRI is useful to monitor the effect of neoadjuvant chemotherapy.

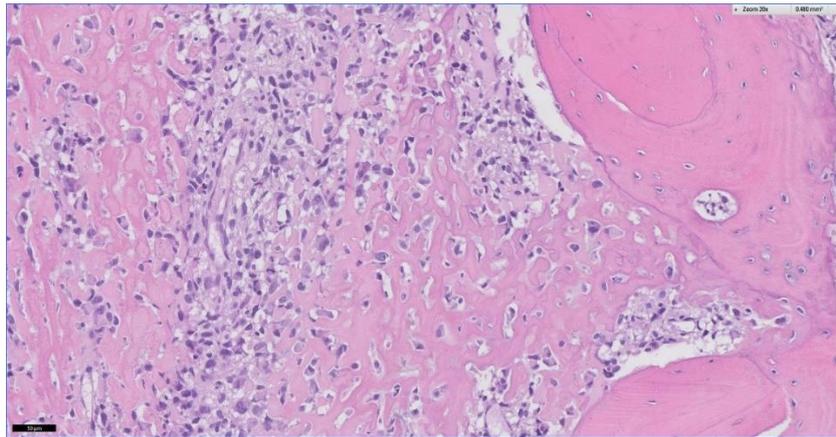


**Figure 1. Radiographic picture of an osteosarcoma** located at the proximal part of the tibia. The red circled area shows the characteristic osteogenic view with some osteolytic parts (green arrows).

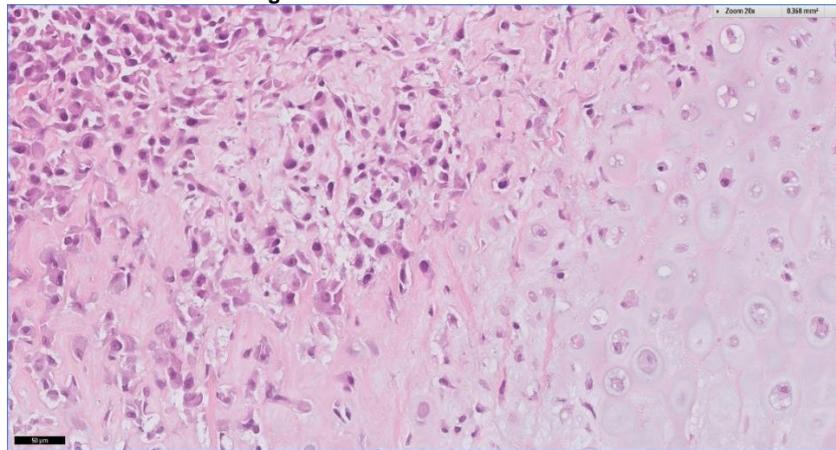
### Cytology

Cells are often highly anaplastic, and can be epithelioid, plasmacytoid, fusiform, ovoid or small and round cells. Giant cells can be seen.

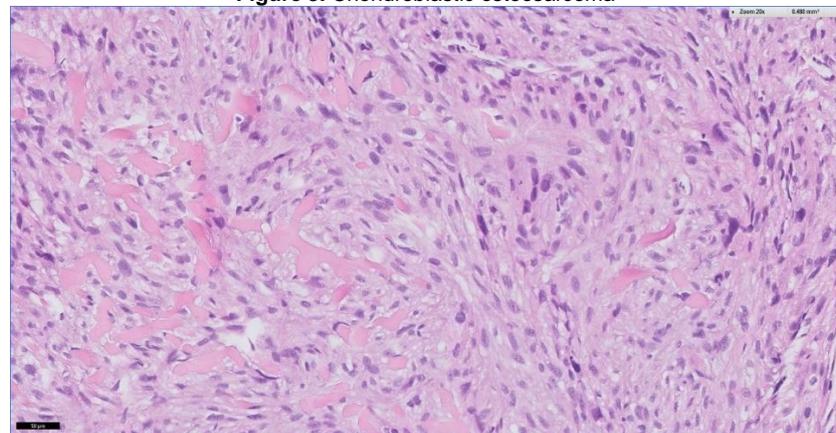
**Microscopy:** The main hematoxylin and eosin stain (HE) based characteristic of osteosarcoma is the identification of osteoid which is dense, pink, amorphous extra cellular material containing large amounts of collagen type I. Metastases are mostly similar in histology to the primary tumor with respect to growth rate and ECM, but exceptions occur. Histochemical staining of alkaline phosphatase can demonstrate the osteoblastic nature of the tumor. Novel immunohistochemical markers SATB2 and DMP1 demonstrate osteogenic differentiation, but these are not entirely specific for osteosarcoma.



**Figure 2.** Osteoblastic osteosarcoma



**Figure 3.** Chondroblastic osteosarcoma



**Figure 4.** Fibroblastic osteosarcoma

### **Treatment**

Conventional osteosarcoma is considered to be a systemic disease and universally fatal if untreated. The current treatment is a combination of chemotherapy and surgery. Patients receive multi-component neoadjuvant chemotherapy which facilitates limb-sparing surgery instead of amputation by decreasing tumor mass and suppressing micrometastases. Most often patients are also given chemotherapy after surgery at high doses to prevent metastatic spread. The most effective cytostatics in osteosarcoma are

doxorubicin, cis-platinum and methotrexate. Drugs directed at receptor tyrosine kinases, such as drugs targeting IGF1R (insulin-like growth factor 1 receptor), are the subjects of today's research for osteosarcoma treatment.

### **Prognosis**

The multi-disciplinary approach of neoadjuvant chemotherapy, surgery and adjuvant chemotherapy has improved the survival of the patients from 10%-20% up to 60%-70% in the past 20 years. Many potential markers (RB1, TP53 etc.) have been evaluated to predict patients prognosis, but till now

the histological response to chemotherapy is the most sensitive indicator of survival. This response is determined by histological examination of multiple sections from the resected tumor and grading the percentage of tumor necrosis. In those patients with a good response (defined as >90% tumour necrosis) long-term survival is generally 80-90%. However within the group of non-responders (necrosis <90%) the survival is usually 40-60%.

## Genetics

### Note

Many other tumors of childhood e.g. Ewing sarcoma and hematological malignancies are mostly characterized by balanced chromosomal translocations or germline mutations. In contrast, conventional osteosarcoma shows extreme genetic instability, especially numerical aberrations and non-recurrent inter- and intra-chromosomal rearrangements. About 50% is characterized by chromothripsis, a single cataclysmic event resulting in genomic rearrangements. The chromothripsis breakpoints often show clusters of point mutations, known as kataegis. Furthermore, around 80% of osteosarcomas show loss of heterozygosity and genomic instability signatures that are characteristic for BRCA-deficient tumours.

## Cytogenetics

### Note

Conventional osteosarcomas are almost always hyperploid and show more amplifications than losses of genetic material. In the literature there is a general consensus about the gain of the chromosome arms 8q, 17p and 6p while many other (sporadic) observations are also reported. The amplified region at 17p contains COPS3 gene which is suggested to be the target of this amplification because it is involved in the degradation of the p53 protein. The chromosomal region 6p12-21 contains the RUNX2 gene, involved in terminal osteoblast differentiation. Furthermore, deletion or loss of heterozygosity at chromosome arm 3q13, where the LSAMP gene is located, correlates with disease progression and poor survival.

## Genes involved and proteins

### Note

TP53 and RB1, two well known tumor suppressor genes, are most commonly altered in osteosarcoma and will be discussed in more detail. Also other genes (table) as MDM2, CDKN2A (p16), MYC and CHEK2 have been reported to show alternations in osteosarcoma but are not completely studied yet. Recent next-generation sequencing (NGS) studies

allowed for the identification of new genes involved in osteosarcoma. In particular genes involved in the IGF1R-signaling pathway were discovered in different NGS-studies, where it was shown that around 14% of osteosarcomas show amplification of the IGF1 receptor. Furthermore, around 24% of osteosarcomas contain genomic alterations in members of the PI3K/mTOR pathway. Other genes that were found in multiple NGS-studies are included in the table.

Gene name	Location	Alteration
COPS3	17p	Amplification
MYC	8q	Amplification
MYCN	1p	Amplification
FOS	14q	Amplification
CDK4	12q	Amplification
MDM2	12q	Amplification
TP53	17p	Mutation
RB1	13q	Mutation
RECQL4	18q	Mutation
CDKN2A	9p	Mutation/deletion
CHEK2	22q	Mutation
EZR	6q	Amplification
ATRX *	Xq	Mutation/deletion
PTEN	10q	Mutation

\* Although the ATRX gene is located on the X chromosome, there was no gender bias for mutations in this gene.

### TP53 (Tumour protein p53 (Li-Fraumeni syndrome))

#### Location 17p13.1

TP53 mutation (which is detected by increased levels of immunohistochemical staining because of the higher half life time caused by the mutation or sequencing) is detected in approximately 20% of high-grade central OSs. Recent next-generation sequencing studies that can detect structural variations conclude that the number of TP53 alterations is much higher, namely around 90%. Most often there are translocations in the first intron of TP53, resulting in gene inactivation. As structural alterations cannot be detected by immunohistochemical staining, this can explain the lower number of TP53 alterations found by traditional methods.

The mutation shows correlation with an increased genomic instability of the tumor but not with clinical outcome. Also amplification of the MDM2 gene (about 6%) and loss of the CHEK2 gene act on the same pathway by mediating TP53 degradation.

#### Protein

TP53 plays an essential role in the regulation of cell cycle, specifically in the transition from G0 to G1. TP53 protein contains DNA-binding, oligomerization and transcription activation domains. It binds as a tetramer to a p53-binding site and activates expression of downstream genes that inhibit growth and/or invasion. Mutants of TP53 mainly fail to bind the DNA binding site and lose the tumor suppressor activity. Alterations of the TP53 gene occur not only as somatic mutations in human malignancies, but also as germline mutations in some cancer-prone families known as Li-Fraumeni syndrome.

### **RB1 (retinoblastoma)**

#### **Location 13q14.2**

In accordance with TP53, in the RB1 pathway also other genes are reported to have alternations especially when RB1 is not affected. For example CDKN2A (p16) gene has been shown to be mutated in OSs that have no RB1 mutations. The group of patients that show CDKN2A (p16) loss without TP53 or RB1 alternations are thought to have even worse survival compared to the rest of the patients.

#### **Protein**

pRB (protein name of the RB1 gene) is usually present as a phosphoprotein inside cells and is a target for phosphorylation by several kinases. One highly studied function of RB1 is to prevent the cell from dividing or progressing through the cell cycle. The blockade in cell cycle progression is facilitated by p16 that inhibits CDK4/ CDK6 dependent phosphorylation. When pRB is ineffective at this role, mutated cells can continue to divide and may become tumorigenic.

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