Bone: Conventional osteosarcoma

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Identity

![Diagram of Bone: Conventional osteosarcoma]

Unusual histological forms with the same clinical behavior (<1%)

- SCLEROSING OSTEOBLASTIC
- OSTEOSARCOMA RESEMBLING OSTEOBLASTOMA
- CHONDROMYXOID FIBROBLASTIC
- CHONDROBLASTIC
- CLEAR CELL
- MALIGNANT HISTIOCTOMA- LIKE
- GIANT CELL
- ETHELIOID
**Alias**
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 of post-radiation sarcomas) and extra medullary osteosarcomas (Parosteal, 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
Conventional osteosarcomas are classified in terms of predominant ECM:
- Osteoblastic osteosarcoma: predominantly bony/osteoid matrix (50%),
- Chondroblastic osteosarcoma: predominantly chondroid matrix (25%),
- Fibroblastic osteosarcoma: predominantly spindle cell matrix, low osteoid (25%),
- Unusual histological forms with the same clinical behavior (<1%),
  Intermediary forms may occur, consisting of mixed ECM types.

Clinics and pathology

Disease
Conventional osteosarcoma is a high grade malignant primary central osteosarcoma 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. Benign bone-forming neoplasms very rarely undergo malignant transformation. Potentially possible progenitor cells are osteoblasts and/or undifferentiated mesenchymal stem cells (MSCs). Because of their ability to produce bony matrix components and to differentiate respectively as OSs are mainly characterized by their bony extracellular matrix and the large morphological variety and differentiation patterns.

Epidemiology
Osteosarcoma is the most common primary malignant bone tumor of non-haematopoietic origin with an incidence of 4-5 per million population. 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 3:2, 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 affects most often the ends of the long bones, in particular the distal femur, proximal tibia and proximal humerus. It is often a fleshy or hard tumour over 5 cm localized at the metaphysis (>90%) or diaphysis (<10%) and very rarely the epiphysis of the bone. Conventional Osteosarcomata frequently penetrates the cortex and is associated with a soft tissue mass. As mentioned at the classification part, osteosarcomas can be osteoblastic in which some have a grey-tan and granular (pumice-like) appearance, while others become denser and look more yellow-white. Chondroblastic osteosarcomas have a white appearance with mineralized and non-mineralized matrix.
Radiography: The overall radiographic appearance of conventional osteosarcoma is a mixed lytic/blastic lesion with cortical destruction and tumor expansion into soft tissue. To evaluate the extent of the tumor preoperatively CT scan, MRI and DEMRI (dynamically enhanced MRI) may be helpful. Furthermore DEMRI is useful to monitor the effect of neoadjuvant chemotherapy.
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Cytology

At least two cell types are seen in most high grade osteosarcoma cases which are often spindle shaped and highly anaplastic. Other cell types seen are epithelial, plasmacytoid, fusiform, ovoid, small round cells, clear cells and giant cells. Aspiration cytology should always be combined with X-ray analysis and histochemical detection of alkaline phosphatase to be sure of osteosarcoma diagnosis.

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. The nature of this extra cellular matrix determines the subtype of conventional osteosarcoma as outlined above. Not often mentioned is the angiocentric growth pattern of conventional osteosarcoma explaining the high rate of metastasizing trough the bloodstream ending primarily in the lungs. Metastases are mostly similar in histology to the primary tumor with respect to growth rate and ECM, but exceptions occur. Immunohistochemical staining of alkaline phosphatase which shows osteoblastic nature of the tumor is combined with cytology and x-ray a useful diagnostic marker. However other useful diagnostic and prognostic markers are rare, based on small studies or differently interpreted in the literature.

Treatment

Conventional osteosarcoma is considered to be a systemic disease and universally fatal if untreated. The present 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 and therapy targets at signal transduction pathways are the subjects of today's research for sarcoma treatment. However for osteosarcoma such targeted drugs have not yet been identified.

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 (RB, p53 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 by Huvos grade I to IV. In those patients whose tumors have >90% tumour necrosis (Huvos gr. IV) long-term survival is generally 80-90%. However within the group of "non-responders" (necrosis <90%) the survival is extremely poor, usually <15% (alternative regimens of chemotherapy may improve prognosis here). New therapies are not only needed for this group, but also to replace or to reduce the current high dosage chemotherapy.

Genetics

Note

In contrast to many other tumors of childhood e.g. Ewing sarcoma and hematological malignancies, which are mostly characterized by balanced chromosomal translocations or germline mutations, conventional OSs show extreme genetic instability. Osteosarcoma cells
obtain remarkably high additional chromosomal changes upon in vitro culturing. This has hampered the identification of specific genetic alternations that are causal for osteosarcoma genesis.

**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 and 17p 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's involvement in the degradation of the p53 protein.

**Genes involved and proteins**

**Note**
TP53 and RB1, two well known tumor suppressor genes, are altered in Osteosarcoma and will be discussed in more detail. Also other genes (table) as MDM2, CDK4/p16, cMYC and CHK2 have been reported to show alternations in Osteosarcoma but are not completely studied yet.

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Location</th>
<th>Alternation</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPS3</td>
<td>17p</td>
<td>Amplification</td>
</tr>
<tr>
<td>c-MYC</td>
<td>8q</td>
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<td>N-MYC</td>
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<td>c-FOS</td>
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<tr>
<td>CDK4</td>
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<tr>
<td>MDM2</td>
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</tr>
<tr>
<td>TP53</td>
<td>17p</td>
<td>Mutation</td>
</tr>
<tr>
<td>RB1</td>
<td>13q</td>
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<tr>
<td>RECQL4</td>
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<tr>
<td>CDKN2A/p16</td>
<td>9p</td>
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<tr>
<td>CHK2</td>
<td>22q</td>
<td>Mutation</td>
</tr>
<tr>
<td>EZR (ezrin)</td>
<td>6q</td>
<td>Amplification</td>
</tr>
</tbody>
</table>

**TP53 (tumor protein p53)**

**Location**
17p13.1

**Note**
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. 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 CHK2 gene act on the same pathway by mediating p53 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 p53 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 1)**

**Location**
13q14.2

**Note**
In accordance with p53, 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 RB 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. When pRB is ineffective at this role, mutated cells can continue to divide and may become tumorigenic.

**To be noted**

**Note**
Result of the chromosomal anomaly:
Except the characteristic hyperploidy of conventional osteosarcoma, the neoplastic cells protect their chromosomes from erosion by two mechanisms called alternatively lengthening of telomeres (ALT) and telomere maintenance by activation of the enzyme telomerase, coded as TERT.

Hereditary genetics:
RB1, TP53 and RECL2 mutations are correlating with a higher chance of osteosarcoma for the carriers. Also several tumor syndromes as Li-Fraumeni, Retinoblastoma, Rothmund-Thomson and Paget's disease of bone include osteosarcoma in their spectrum.

**References**


This article should be referenced as such: