BONE AND SOFT TISSUE TUMORS

Traditionally bone and soft tissue tumors have been treated separately.
This separation will be maintained in the following presentation.
Soft tissue sarcomas will be treated first and the sarcomas of bone will follow.

DEFINITION

Soft tissue pathology deals with tumors of the connective tissues.
The concept of soft tissue is understood broadly to include non-osseous tumors of extremities, trunk wall, retroperitoneum and mediastinum, and head & neck.
Excluded (with a few exceptions) are organ specific tumors.

EPIDEMIOLOGY

- Sarcomas are rare tumors compared to other malignancies: 8,700 new sarcomas in 2001, with 4,400 deaths.
- The incidence of sarcomas is around 3-4/100,000.
- Slight male predominance (with some subtypes more common in women).
- Majority of soft tissue tumors affect older adults, but important sub-groups occur predominantly or exclusively in children.
- Incidence of benign soft tissue tumors not known, but probably outnumber malignant tumors 100:1.

SOFT TISSUE TUMORS

- Histological classification of soft tissue tumors
- Nowhere in the picture.....
The etiology of soft tissue sarcomas is poorly understood, and what is known apply only to a small fraction of the group. The known etiologic agents are ionizing radiation, oncogenic viruses, and chemicals. These agents are able to cause genetic alterations that can lead to tumorigenesis.

- Radiation induced sarcomas develop in 1% of patients who have undergone therapeutic irradiation.
- The interval between irradiation and diagnosis of sarcoma varies between 5 and 10 years.
- The majority of radiation-induced sarcomas are high grade and poorly differentiated (MFH, FS, OS, and AS).

Host factors may also play a role in the development of soft tissue sarcomas.

- Immunosuppression, besides Kaposi’s sarcoma, may be associated with sarcomas.
- Lymphedema, congenital or acquired (post-mastectomy) is a rare cause of extremity-based AS.

- Herbicides (“agent orange”) and peripheral soft tissue sarcomas
- Retained metal objects (shrapnel, surgical devices) and AS and MFH
- Vinyl chloride, inorganic arsenic, Thorotrast, anabolic steroids linked to AS and MFH.

In both instances the connection between viral infection and sarcoma is more common in immunosuppressed hosts.

- Human herpes virus 8 (HHV8) linked to Kaposi’s sarcoma
- Epstein-Barr virus (EBV) linked to subtypes of leiomyosarcoma
**CLASSIFICATION**

- All tumors are derived from stem cells that are programmed to differentiate into various mature cell types.
- Some of the stem cells probably belong to local, organ-specific pools, as underscored by the fact that many tumors resemble tissues present in the region.
- Other involved stem cells may be bone marrow derived.

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**CONGENITAL SYNDROMES ASSOCIATED WITH BONE AND SOFT TISSUE TUMORS**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Gene(s)</th>
<th>Locus(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmoid tumors</td>
<td>AD</td>
<td>APC</td>
<td>5q21</td>
</tr>
<tr>
<td>Familial infiltrative fibromatosis</td>
<td>AD</td>
<td>EXT1</td>
<td>8q24</td>
</tr>
<tr>
<td>Langer-Giedion syndrome</td>
<td>AD</td>
<td>EXT1</td>
<td>8q24</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>Sporadic</td>
<td>TP53</td>
<td>17p13</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>AD</td>
<td>CHEK2</td>
<td>22q11</td>
</tr>
<tr>
<td>Lipomas</td>
<td>AD</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Symmetrical lipomatosis</td>
<td>Sporadic</td>
<td>-</td>
<td>18q21</td>
</tr>
<tr>
<td>Familial expansile osteolysis</td>
<td>AD</td>
<td>-</td>
<td>5q31</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>AD</td>
<td>-</td>
<td>9p21-22</td>
</tr>
<tr>
<td>Diaphyseal medullary stenosis</td>
<td>AD</td>
<td>-</td>
<td>10q23</td>
</tr>
<tr>
<td>Cowden disease</td>
<td>AD</td>
<td>-</td>
<td>7q33</td>
</tr>
<tr>
<td>Costello syndrome</td>
<td>AD</td>
<td>-</td>
<td>17q23-24</td>
</tr>
<tr>
<td>Carney complex syndrome</td>
<td>Sporadic</td>
<td>-</td>
<td>2p16</td>
</tr>
<tr>
<td>Bannayan-Riley-Ruvalcaba syndrome</td>
<td>Sporadic</td>
<td>-</td>
<td>11p15</td>
</tr>
<tr>
<td>Albright hereditary osteodystrophy</td>
<td>AR</td>
<td>-</td>
<td>10q23</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>AR</td>
<td>WRN</td>
<td>8p11-12</td>
</tr>
<tr>
<td>Venous malf. with glomus cells</td>
<td>Sporadic</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Uterine leiomyosarcoma</td>
<td>AR</td>
<td>SMARCB1</td>
<td>22q11</td>
</tr>
<tr>
<td>Embryonal rhabdomyosarcoma</td>
<td>AR</td>
<td>RB1</td>
<td>13q14</td>
</tr>
</tbody>
</table>

**CLASSIFICATION**

- Purpose of classification is to link similar tumors in order to understand their behavior, determine the most appropriate treatment, and investigate their biology.
- Soft tissue tumors are classified according to the cell type they resemble.

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**CLASSIFICATION**

- All tumors are derived from stem cells that are programmed to differentiate into various mature cell types.
- Some of the stem cells probably belong to local, organ-specific pools, as underscored by the fact that many tumors resemble tissues present in the region.
- Other involved stem cells may be bone marrow derived.
Refinements are coming from cytogenetics, molecular, and gene expression studies. The majority arise from - or show differentiation toward mesenchymal cells, but some show other differentiation (neuroectodermal, histiocytic). A small subset is of unknown histogenesis.

Tumors are also classified according their biologic potential. A three-tiered system is used:
- 1. Benign
- 2. Borderline (intermediate malignant)

Major Types of Soft Tissue Tumors

<table>
<thead>
<tr>
<th>MAJOR TYPES OF SOFT TISSUE TUMORS</th>
<th>Benign tumor</th>
<th>Malignant tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myofibroblast</td>
<td>Fibroma, myxoma</td>
<td>Fibrosarcoma, MFH</td>
</tr>
<tr>
<td>Adipocyte</td>
<td>Lipoma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Smooth muscle cell</td>
<td>Leiomyoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Skeletal muscle cell</td>
<td>Rhabdomyoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Endothelial cell</td>
<td>Hemangiona</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Schwann cell</td>
<td>Schwannoma, neurofibroma</td>
<td>MPNST</td>
</tr>
<tr>
<td>Cartilage cell</td>
<td>Chondroma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Intertitial cell</td>
<td>GIST</td>
<td>GIST</td>
</tr>
<tr>
<td>Histiocyte</td>
<td>JG, GCTTS, RDC</td>
<td>True histiocytic sarcoma</td>
</tr>
<tr>
<td>Unknown</td>
<td>No benign counterparts</td>
<td>ES, SS, ES, ASFS</td>
</tr>
</tbody>
</table>

Fibrous/myofibroblastic tumors
- Fibroma-benign
- Desmoid-borderline
- Fibrosarcoma-malignant

Lipomatous tumors
- Lipoma-benign
- Liposarcoma-malignant

Smooth muscle tumors
- Leiomyoma
- Leiomyosarcoma, low grade
- Leiomyosarcoma, high grade
**IMMUNOHISTOCHEMISTRY**

- Immunohistochemistry is the most practical way to evaluate the presence of certain protein and carbohydrate epitopes on tissue sections.
- Evaluation of cell- or tumor-type specific or cell-cycle related markers may have diagnostic significance.
- Very few markers are specific for one tumor type.
- No cell-cycle marker is able to separate benign and malignant tumors.

**GRADING**

- Grading is an element of any current staging system.
- Correct grading requires correct histologic typing of the sarcoma, as demonstrated by the inclusion of the histologic type as a grading variable.

**IMMUNOHISTOCHEMISTRY**

- Myofibroblastic tumors: SMA, HHF35
- Smooth muscle tumors: desmin, SMA, HHF35
- Skeletal muscle tumors: desmin, myogenin, Myo-D1, myoglobin
- Nerve sheath tumors: S-100 protein, CD34, EMA
- Fatty tumors: S-100 protein
- Synovial sarcoma: CK, EMA, S-100
- Epithelioid sarcoma: CK, CD34
- Carcinomas: CK, EMA
- Melanoma: S-100, HMB-45, Ammonase, Melan-A

Cam 5.2- synovial sarcoma

**GRADING**

- Grading applies best to excision specimen because biopsies may be non-representative of the correct grade.
- Preoperative treatments, such as radiation, chemotherapy, or embolization, can make grading inapplicable.
- Weak points of grading:
  - Subjective elements (number of mitoses, percent of necrosis, tumor differentiation)
  - Frequent vs. rare tumors

**GRADING SYSTEM SOFT TISSUE SARCOMAS (FFCC)**

<table>
<thead>
<tr>
<th>Score (1-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUMOR DIFFERENTIATION</td>
</tr>
<tr>
<td>well diff</td>
</tr>
<tr>
<td>mixed histogenetic types</td>
</tr>
<tr>
<td>poorly diff &amp; undiff histogenesis</td>
</tr>
<tr>
<td>MITOTIC COUNT</td>
</tr>
<tr>
<td>0-9/10 HPF</td>
</tr>
<tr>
<td>10-19/HPF</td>
</tr>
<tr>
<td>&gt;20/HPF</td>
</tr>
<tr>
<td>TUMOR NECROSIS</td>
</tr>
<tr>
<td>none</td>
</tr>
<tr>
<td>&lt;50%</td>
</tr>
<tr>
<td>&gt;50%</td>
</tr>
<tr>
<td>HISTOLOGIC GRADE</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>
**GRADING**

**DIFFERENTIATION SCORE 1**
- Well differentiated sarcoma (fibro-, lipo-, leiomyo-, chondro-)
- Well differentiated MPNST (neurofibroma with malignant transformation)

**DIFFERENTIATION SCORE 2**
- Conventional fibrosarcoma, leiomyosarcoma, angiosarcoma
- Conventional MPNST
- Myxoid sarcomas (MFH, liposarcoma, chondrosarcoma)
- Storiform-pleomorphic MFH

**DIFFERENTIATION SCORE 3**
- Sarcomas of undefined histog. (ASPS, SS, ES, CCS, undiff. Sarc., malign. rhabdoid tumor)
- Ewing family of tumors
- Pleomorphic sarcomas (lipo-, leio-)
- Round cell and pleomorphic liposarcoma
- Rhabdomyosarcoma (except botryoid and spindle cell)
- Poorly differentiated angiosarcoma
- Triton tumor, epithelioid MPNST
- Extraskeletal mesenchymal CS, and osteosarcoma
- Giant-cell and inflammatory MFH

**STAGING**

- The stage is an estimate of the extent or dissemination of a tumor (and in the current systems includes tumor grade).
- Staging is important for planning of treatment and prognostication.
- Clinical data and imaging studies are part of staging process.
- (Visceral sarcomas excluded)

**STAGING (G-TNM)**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>GRADE</th>
<th>PRIMARY TUMOR</th>
<th>LYMPH NODES</th>
<th>METASTASIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I - IV</td>
<td>LOW OR HIGH</td>
<td>T1 (&lt;5 CM) OR T2 (&gt;5 CM)</td>
<td>NEG/POS</td>
<td>ABSENT/PRESENT</td>
</tr>
<tr>
<td>IIA</td>
<td>LOW</td>
<td>T1a or T1b</td>
<td>NEGATIVE</td>
<td>ABSENT</td>
</tr>
<tr>
<td>IIB</td>
<td>LOW</td>
<td>T2a or T2b</td>
<td>NEGATIVE</td>
<td>ABSENT</td>
</tr>
<tr>
<td>IIA</td>
<td>HIGH</td>
<td>T1a or T1b</td>
<td>NEGATIVE</td>
<td>ABSENT</td>
</tr>
<tr>
<td>IIB</td>
<td>HIGH</td>
<td>T2a or T2b</td>
<td>NEGATIVE</td>
<td>ABSENT</td>
</tr>
<tr>
<td>II</td>
<td>ANY</td>
<td>ANY</td>
<td>POSITIVE</td>
<td>ABSENT</td>
</tr>
<tr>
<td>III</td>
<td>ANY</td>
<td>ANY</td>
<td>POSITIVE</td>
<td>PRESENT</td>
</tr>
</tbody>
</table>

*a* superficial tumors of trunk and extremities (above fascia)
*b* deep tumors of trunk and extremities or intra-abdominal, intra-thoracic or retro-peritoneal
STAGING OF SARCOMAS

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>86</td>
</tr>
<tr>
<td>II</td>
<td>72</td>
</tr>
<tr>
<td>III</td>
<td>52</td>
</tr>
<tr>
<td>IV</td>
<td>10-20%</td>
</tr>
</tbody>
</table>

NEJM 2005; 353: 701-711

SOFT TISSUE SARCOMAS

- Gross examination
- Evaluation of inked margins
- Gross description and tumor measurements
- Photograph
- Sampling of tumor and margins
- Frozen sections for diagnostic or triaging purposes

SOFT TISSUE SARCOMAS-COMPREHENSIVE ANALYSIS

- Frozen tissue procurement
- Formalin fixation
- Cytogenetics
  (E.M.)

PARAMETERS TO BE INCLUDED IN REPORT OF A SARCOMA

- FINAL REPORT
  - 1. Tumor site, type of excision
  - 2. Depth of the tumor
  - 3. Tumor type and variant
  - 4. Grade (if possible)
  - 5. Tumor size
  - 6. Status of margins & L.N.
  - 7. Percent of necrosis
  - 8. Vascular invasion, if present

- ADDENDUM REPORT(S)
  - 1. Immunohistochemistry
  - 2. Electron microscopy
  - 3. Cytogenetics

MARGINS

- INTRALESIONAL: The surgical plane of dissection passes through tumor tissue.
- MARGINAL: The surgical plane of dissection passes through the pseudocapsule, without microscopic evidence of tumor.
- WIDE: The surgical plane of dissection passes outside the reactive zone and through normal tissue.
- RADICAL: The surgical margins are all wide and include the entire anatomical compartment(s) involved by the tumor.
- CONTAMINATED: A margin obtained by the surgical re-excision of the wound previously found to be microscopically intralesional in the same operative procedure.

IMAGING STUDIES

- The ultimate goal is:
  - 1. Detecting lesions
  - 2. Giving a specific diagnosis or a reasonable differential diagnosis
  - 3. Staging the lesion

- CT and particularly MRI allow detection and staging by delineating anatomical extent in virtually all cases.
- A relatively specific diagnosis can be given in approximately 25-50% of cases, according to the type.
Numerous cancer-specific genetic alterations have been described. Some of them (such as translocations, numerical changes, large deletions and gene amplifications) are seen at the cytogenetic level. Subtle changes (such as single base pair substitutions, small deletions) require molecular genetic detection.

Many chromosomal translocations and other genetic rearrangements lead to formation of oncogenic gene fusions or overexpression of normal genes. Many of these changes may be used for diagnosis or confirmation of diagnosis.

Nonrandom translocations were described first in hematopoietic malignancies. Identified in many types of sarcomas. Also identified in benign soft tissue tumors. Each translocation results in a specific gene fusion. Each gene fusion is present in most cases of a specific sarcoma category, and is not present in any other sarcoma type. These genetic events demonstrate consistency and specificity.

These translocations: 1. represent fundamental genetic steps in the development of these cancers 2. are useful markers for the diagnosis 3. may constitute new therapeutic targets.

Investigation of these translocation may: 1. clarify the molecular etiology of these cancers 2. help in identifying new markers for diagnosis and monitoring 3. lead to new therapeutic strategies against tumor-specific markers.
GENE FUSIONS IN SARCOMAS

1. These translocations disrupt genes located at the chromosomal breakpoints and juxtapose portions of these genes to create two reciprocal chimeric genes.
2. The breaks are confined to one or a few introns within the coding region of each gene.
3. The chimeric genes are transcribed to generate chimeric transcripts.
4. The chimeric transcripts are translated into chimeric proteins.

FISH with dual color break-apart probe cocktail flanking the EWS breakpoint region at 22q12

GENE FUSIONS IN SARCOMAS

- The novel protein products have significantly altered functional properties.
- In many cases, one or both involved genes are transcription factors, and the chimeric product is a novel transcription factor.

BONE TUMORS

- The majority of tumors involving bone are secondary (or metastatic):
  - secondary (metastases) (95%)
  - primary (5%)

SOFT-TISSUE TUMORS SUMMARY

- Tumors of connective tissue.
- Rare (sarcomas: 3-4 cases per 100,000).
- Etiology unclear, with a few exceptions.
- Classified according to tissue they resemble.
- Biologically: benign, borderline or malignant.
- Grading and staging crucial elements to be added to diagnosis.
- Some of the lesions have specific translocations.

METASTATIC BONE TUMORS

- Carcinomas are the most common metastatic tumors to bone.
- Other neoplasms may also metastasize to bone (sarcomas, melanomas).
Secondary Tumors of Bone

- The carcinomas most frequently involved with bone metastasis originate from:
  - Lung
  - Breast
  - Prostate
  - G.I.
  - Kidney
  - Thyroid

BONE TUMORS

- The majority of bone sarcomas arise de novo.
- Some, however, develop in association with recognizable precursors.

BONE TUMORS

- Primary bone tumors are rare.
- Sarcomas account for 0.2% of all neoplasms (SEER Cancer Statistics Review, 1973-1996).
- Soft tissue sarcomas are 10 times more common than primary bone sarcomas.

BONE TUMORS

- In North America and Europe, the incidence rate for bone in males is approximately 0.8 new cases per 100,000 people a year.
- Osteosarcoma is the most common primary malignant tumor of bone (35%), followed by chondrosarcoma (25%) and Ewing sarcoma (16%).
- Chordomas and MFH represent 8 and 5% of the tumors in the group respectively.
BONE TUMORS

- Bone sarcomas as a group have a bimodal distribution.
- The first peak is in the second decade.
- The second peak occurs in patients older than sixty.

The clinical presentation of bone tumors is at the beginning non-specific, with pain and swelling presenting first. Later, limitation of movement and pathological fracture and general symptoms may occur. A long time may elapse until the tumor is diagnosed.

The imaging characteristics of some lesions are diagnostic. Even if not clear to the radiologist, the images may help somebody else down the diagnostic chain (e.g. the pathologist).

Some fancy words from the world of shadows:

Geographic with sharp margins and flocculent calcifications (Enchondroma)

Sclerotic margin and lytic (Chondroblastoma)

CONVENTIONAL X-RAY

STAGING

BIOPSY

TREATMENT

SUSPICIOUS FOR MALIGANACY

QUESTIONABLE RESULTS

CONVENTIONAL X-RAY

TREATMENT

MRM

BONE TUMORS

- Conventional radiographs are still important in the diagnosis of bone tumors.
- Many tumors are site-specific.
- Many tumors have a characteristic radiographic appearance.

1. Ewing sarcoma, lymphoma, myeloma
2. Osteoid osteoma, adamantinoma
3. Osteoid osteoma
d. Fibrous dysplasia
5. Chondromyxoid fibroma
6. Non-ossifying fibroma
7. Bone cyst, osteoblastoma
8. Osteochondroma
9. Osteosarcoma
10. Enchondroma, chondrosarcoma
11. Giant-cell tumor
12. Chondroblastoma

1. Ewing sarcoma, lymphoma, myeloma
2. Osteoid osteoma, adamantinoma
3. Osteoid osteoma
d. Fibrous dysplasia
5. Chondromyxoid fibroma
6. Non-ossifying fibroma
7. Bone cyst, osteoblastoma
8. Osteochondroma
9. Osteosarcoma
10. Enchondroma, chondrosarcoma
11. Giant-cell tumor
12. Chondroblastoma

BONE TUMORS

- The diagnosis is based on imaging and histological criteria.
BONE TUMORS

- Geographic with ill-defined margins: usually malignant (in this case a primary chondrosarcoma)

- The tumor need to be graded (grading is an important element of the staging and determines if the tumor is stage I or II).

- The TNM system follows a 2 tier grading system: low- and high-grade.

- Moth-eaten and permeated are bad news (unless it's infection)

- Periosteal reactions (such as spiculated, Codman’s angle, onion skin) are witnesses of cortical destruction and soft tissue extension (usually bad news, unless infective)

| BONE TUMORS |
| BONE TUMORS |

| Stage IA | T1 | N0, NX | M0 | Low grade |
| Stage IB | T2 | N0, NX | M0 | Low grade |
| Stage II A | T1 | N0, NX | M0 | High grade |
| Stage II B | T2 | N0, NX | M0 | High grade |
| Stage III | T3 | N0, NX | M0 | Any grade |
| Stage IV A | Any | T | N0, NX | M1a | Any grade |
| Stage IV B | Any | T | N1 | Any M | Any grade |
| Any | T | Any | N | M1b | Any grade |

BONE TUMORS
- Stage I: low grade intra-compartmental (risk of metastasis <25%)
- Stage II: high-grade extra-compartmental (risk of metastasis >25%)
- Stage III: any grade, discontinuous tumor in the primary bone site
- Stage IV: any grade, metastatic

OSTEOID OSTEOMA
- On plain x-rays the lesion is characterized by dense cortical sclerosis surrounding a radiolucent nidus.
- CT scan best type of imaging study.

OSTEOID OSTEOMA
- Benign bone forming tumor.
- Small size, limited growth potential and disproportionate pain.
- Most common in long bones, but every bone may be affected.
- It may be painful on physical examination.
- It may be associated with redness of skin and swelling.
- Lesions close to a joint may be associated with joint effusion.
- Near diploid karyotype.
- Two cases with involvement of 22q13 and loss of distal part of 17q.
- Excellent prognosis following local excision (nidus has to be removed completely).

BONE-FORMING TUMORS

<table>
<thead>
<tr>
<th>Osteogenic tumors</th>
<th>Osteoid osteoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoblastoma</td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>Conventional</td>
</tr>
<tr>
<td></td>
<td>Telangiectatic</td>
</tr>
<tr>
<td></td>
<td>Small cell</td>
</tr>
<tr>
<td></td>
<td>Low grade central</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
</tr>
<tr>
<td></td>
<td>Parosteal</td>
</tr>
<tr>
<td></td>
<td>Periosteal</td>
</tr>
<tr>
<td></td>
<td>High grade surface</td>
</tr>
</tbody>
</table>

OSTEOID OSTEOMA
- Small, cortically based lesion, red and gritty, surrounded by sclerotic bone.
- The lesion is composed of a meshwork of osteoid trabeculae lined by plump osteoblasts.
OSTEOSARCOMA

- Malignant primary neoplasm of bone that produces osteoid (osteoid directly produced by the tumor cells).
- Intra-medullary origin (conventional type).
- Rare subtypes.
- Most common, non-hematopoietic tumor of bone (incidence 4-5 per million).

OSTEOSARCOMA

- Largely a disease of the young (60% <25 years)
- 30 % >40 years.
- In older people rule out predisposing conditions (e.g. Paget’s disease of bone, radiation)
- Long bones of appendicular skeleton are favored
- 91% metaphysis, 9% diaphysis

OSTEOSARCOMA

- Conventional:
  - Osteoblastic (50%)
  - Chondroblastic (<25%)
  - Fibroblastic (<1-2%)
  - Telangiectatic (<4%)
  - Small cell (1.5%)
  - Low grade central (<1%)
  - Parosteal (4%)
  - Periosteal (<2%)
  - High-grade surface (<<1%)
- Secondary (20% of OS in patients older than 40)

OSTEOSARCOMA

- Anaplastic, pleomorphic tumor.
- Production of osteoid.
- Cartilage and fibrous tissue may also be produced.

OSTEOSARCOMA

- Central: Low Grade, High Grade
- Surface: Low Grade, High Grade

OSTEOSARCOMA

- IHC not useful.
- Complex clonal chromosomal aberrations (including numerical and structural alterations).
- Recurrent involvement of 1p11-13, 1q11-12, 1q22-22, 11p14-15, 14p11-13, 15p11-13, 17p, 19q13.
- Imbalances of +1, -6q, -9, -10, -13 (retinoblastoma gene on chromosome 13) and -17.
- Gains in 3q26, 4q12-13, 5p13-14, 7q31-32, 8q21-23, 12q14-15 (MDM2 and PRIM1), and 17p11-12 (Li-Fraumeni syndrome).
- Over-expression of MET and FOS in >50% of OS, and MYC in <15%.
OSTEOSARCOMA
- Untreated is fatal (aggressive local growth and rapid hematogenous systemic metastasis).
- When treated with surgery alone, survival is limited.
- Age, gender, location, size, stage and laboratory tests traditional prognostic factors.
- The most reliable indicator of survival is the response to preoperative chemotherapy (good prognosis >90% tumor necrosis).
- In good responders survival in 80-90% of cases is not unusual.
- Bad responders, without change in chemotherapy, die in 80-90% of cases (but with change of regimen long-term survival can be greatly improved).

CARTILAGE-FORMING TUMORS

<table>
<thead>
<tr>
<th>Cartilage tumors</th>
<th>Osteochondroma</th>
<th>Enchondroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondroma</td>
<td>Enchondroma</td>
<td>Periosteal chondroma</td>
</tr>
<tr>
<td>Chondromyxoid fibroma</td>
<td></td>
<td>Multiple chondromasitis</td>
</tr>
<tr>
<td>Chondroblastoma</td>
<td>Chondroma</td>
<td>Central</td>
</tr>
<tr>
<td>Chondromyxoid fibroma</td>
<td></td>
<td>Periosteal</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td></td>
<td>Dedifferentiated</td>
</tr>
<tr>
<td>Osteochondroma</td>
<td></td>
<td>Mesenchymal</td>
</tr>
<tr>
<td>Chondroma</td>
<td></td>
<td>Clear cell</td>
</tr>
</tbody>
</table>

ENCHONDROMA
- Swelling of small bones of hands and feet, thinning of cortex and pathological fractures.
- Asymptomatic in long bones.
- Well margined lesions on imaging; lytic or mineralized.
- Usually in metaphysis, less common in diaphysis, rare in epiphysis.
- Hypocellular, avascular with abundant hyaline cartilage.

CHONDROSARCOMA (PRIMARY)
- Malignant neoplasm with pure hyaline cartilage differentiation.
- Primary or conventional chondrosarcoma (90% of CS) arises centrally in a previously normal bone.
- Third most common primary malignancy of bone after myeloma and osteosarcoma.
- Tumor of adulthood (majority of patients >50 years).
- Genetics:
  - Near diploid or pseudo-diploid karyotypes.
  - Simple numerical changes (-X, -Y, +5).
  - Rearrangements of 1p13-p22.
- Most commonly involved sites are: the pelvis, proximal femur and humerus, distal femur and ribs.
- Rare in the fingers (1%).
- Extremely rare in spine and craniofacial bones.
- Local swelling and pain.
- Metaphysis.
- Expansion of bone, thickening of the cortex with possible cortical erosion or destruction.
CHONDROSARCOMA (PRIMARY)

- Cut surfaces translucent, blue-gray to white (cartilage), lobular, solid to myxoid areas, cortical erosion and soft tissue extension possible.
- Lobules of cartilage separated by fibrous septa.
- Host lamellar entrapment.
- Three grades:
  1. Moderately cellular, otherwise indistinguishable from enchondroma.
  2. More cellular and atypical with more myxoid matrix.
  3. More cellular, atypical and myxoid than grade 2 lesions. Mitoses are easily detected.

The histological grade is the most important predictor of local recurrence and metastasis.
- 90% of patients with grade 1 lesions are alive at 5 years.
- Only 53% of patients with grade 2 and 3 lesions are alive at 5 years.
- 10% of recurrent tumors show increase in grade or dedifferentiate.
- Treatment is surgical (chemo and radiation resistant tumors).

Summary of bone sarcomas

- Tumors of connective tissue.
- Very rare (bone sarcomas: 1/10 of soft tissue sarcomas).
- Etiology unclear, with a few exceptions.
- Classified according to tissue they resemble.
- Biologically: benign, borderline or malignant.
- Grading and staging crucial elements to be added to diagnosis.
- No recurrent diagnostic translocation (unless a soft tissue equivalent exists, e.g. Ewing sarcoma).