Osteosarcoma is the most common bone malignancy in children. The suggested association between rapid bone growth and osteosarcoma is based on the following:
- occurrence peaks during adolescence and young adulthood.
- development of the malignancy earlier in girls than boys, corresponding with an earlier adolescent growth spurt and advanced skeletal age.
- predilection of osteosarcoma for the metaphyseal part of the rapidly growing bones during adolescence (distal femur, proximal tibia, and proximal humerus).
- equal incidence of osteosarcoma between boys and girls before puberty; higher rates in boys after puberty, corresponding to their growth spurt.

Osteosarcoma arises from the osteoblasts, and the proliferating cellular stroma produces osteoid tissues (immature bone).

**Risk Factors:**

In addition to exposure to ionizing radiation, (A – 1) genetic susceptibility syndromes are known to increase the risk for osteosarcoma. The strongest genetic predisposition is found in patients with hereditary retinoblastoma and patients whose families are known to have Li-Fraumeni Syndrome (TP53 germline mutation).

Precursor benign bone lesions such as Paget’s disease and osteochondroma are also considered to be risk factors for osteosarcoma development. Although there is no evidence that bone trauma is associated with the development of osteosarcoma, traumatic injury can lead to a medical examination that discloses osteosarcoma.

**Clinical Signs and Symptoms:**

Patients with osteosarcoma often have symptoms for 3 to 6 months prior to diagnosis. In many cases, the pain is dull and often involves the long bones; patients and parents usually attribute the pain to growth spurts (growing pains).
- Pain that is dull, aching, and constant with an average duration of 3 months prior to diagnosis; pain usually occurring in and around the involved area, often associated with a soft tissue mass and swelling. Pain is aggravated by activity and weight bearing.
Bone Tumors – Osteogenic Sarcoma (Osteosarcoma)

- Pain in other bony sites might represent metastatic lesions. The most common metastatic sites are the lungs and other bones.
- Soft-tissue mass causing asymmetry between extremities.
- Local edema, swelling, tenderness, decreased range of motion and pulsations/bruits may be present on examination.
- Altered gait or function to compensate for the pain, swelling and decreased range of motion.
- Visible metastatic disease in 20% of patients, usually pulmonary; most often patients do not have respiratory symptoms in the absence of extensive lung involvement.

Diagnostic Workup:

- Complete history of the illness including location, duration, and intensity of pain; limping or refusal to bear weight; presence of mass.
- **A – 2 Physical exam** including observation of soft-tissue mass, abnormal gait, limited range of motion, asymmetry between the affected and non-affected limb (shape, circumference), warmth and tenderness associated in the affected limb
- Radiography of the extremity often includes a **(A – 3) sunburst pattern**, mixed regions of the sclerosis and **(A – 4) lytic lesions of bone**; and Codman’s triangle (an isolated cuff of reactive subperiosteal new bone at the boundary of any benign or malignant mass that rapidly elevates the periosteum). Skeletal x-rays can show the presence of pathological fractures.
- Chest x-ray to assess for possible metastatic disease.
- Bone scan to assess for increased **(A – 5) uptake of radioisotope at tumor sites** or areas of healing bone.
- CT scan of chest to determine presence and extent of pulmonary lesions.
- MRI scan to assess for **(A – 6) soft tissue, nerve, & vessel involvement**; tumor boundaries.
- Lab studies for serum alkaline phosphate (elevated in 40% of patients).
- Arteriography may help determine the extent of blood or vascular flow to the tumor.
- Fine-needle, core, or open incisional biopsy can determine histology; however open biopsies are preferred.

Osteosarcomas are grouped into the following categories:

**Localized osteosarcoma:** affects only the bone it developed in and the tissues next to the bone, such as muscle, tendon, etc.
Metastatic osteosarcoma: spreads to other parts of the body such as the lungs or to other bones not directly connected to the bone the tumor arose in. Most often the tumor spreads to the lungs (85%); however, it can also spread to other bones, the brain, or other internal organs. In general, metastatic osteosarcoma is correlated with poor prognosis, although cure is still possible if the metastasis is amenable to surgery and chemotherapy treatments.

Recurrent osteosarcoma: the malignancy has come back (recurred) after it has been treated. It may come back in the tissues where it first started; or it may come back in another part of the body.

Progressive disease refers to a tumor that continues to grow despite treatment.

Grading

Based on the cellular histology, osteosarcoma is also divided according to the grade (the likelihood that the cells will spread, based on their appearance).

Low Grade Tumors (G1) – cells look normal, are slow-growing and less likely to spread; parosteal and intramedullary low grade.

High Grade (G2) - cells look very abnormal, are likely to grow more quickly, and are more likely to spread. These osteosarcomas have different names based on their appearance under the microscope.

- osteoblastic
- chondroblastic
- fibroblastic
- mixed
- small cell
- telangiectatic
- high-grade surface

Classification According to Site/Location/Extent of Disease:

Intracompartmental (T1) - the tumor has remained in place
Extracompartmental (T2) – the primary tumor has extended into nearby structures.

Staging:

Osteosarcoma is commonly (A – 7) staged. The following are several staging systems commonly used:

1. Enneking Staging System – used to formally stage osteosarcoma. The system is based upon the tumor grade (G), the extent of the primary (original) tumor (T), and whether there is metastasis (M).

2. American Joint Committee on Cancer (AJCC System) – based upon the tumor grade, size and location as well regional and distant metastasis.
3. Musculoskeletal Tumor Society (MSTS) – based on tumor grade and extent of the primary tumor (extra or intra compartmental) and metastasis.

**Prognostic Considerations:**

Several characteristics of the disease have prognostic factors: the presence of metastasis greatly affects survival time, and the location of the tumor determines not only the outcome but could also direct the treatment modality. Axial tumors (pelvis, spine) are often correlated with poor prognosis because of the limitations imposed by the tumor location on surgical resection procedure. Other poor outcome predictors include age (<10 years), and levels of tumor markers (increased serum and tumor alkaline phosphatase (ALK) and lactase dehydrogenase (LDH) correlates with poor outcomes). Tumor histology such as a high grade, telangiectic variant correlates with poor outcomes.

Patients who have low grade tumors, normal LDH, or whose tumors have had complete necrosis after preoperative chemotherapy have a better prognosis. In addition, patients who are 10 years and older, and patients with small tumors also have better outcomes.

**Treatment:**

Treatment for osteosarcoma includes chemotherapy and surgery. Chemotherapy is given preoperatively to shrink and contain the tumor, thus facilitating surgery; and postoperatively, in order to destroy microscopic metastases.

The goal of (A – 8) surgery is to obtain a wide margin of resection (a zone of 5 mm or more of normal, healthy tissue around the tumor). Factors that could influence the surgical procedure are tumor type and location, patient’s age, response to preoperative chemotherapy, and the preferences and decisions of the surgeon, patient, and family.

The encouraging impact of pre-operative and post-operative chemotherapy on the natural history of osteogenic sarcoma made (A – 9) chemotherapy a standard component of treatment for children with bone tumors. New chemotherapy agents and methods of drug administration have demonstrated improved local disease control and its efficacy as adjuvant therapy for less mutilating surgical procedures.

**Future Directions:**

Advances in technology and surgical techniques are providing less invasive surgical procedures and better functional outcome for osteosarcoma patients. New drugs and better combinations are also currently being investigated for their efficacy and impact on survival. In addition, clinical investigations are now underway to test monoclonal agents that target important receptors (e.g. EGFR, VEGF) and hematopoetic growth factors to ameliorate toxic effects of high dose chemotherapy, especially for metastatic bone cancers.

Other clinical investigations include identifying osteosarcoma biomarkers that can be used for early detection/diagnosis, treatment modifications, predicting disease outcomes.
Bone Tumors – Osteogenic Sarcoma (Osteosarcoma)

Helpful Web Links:

CancerIndex.org
http://www.cancerindex.org/clinks3t.htm
http://www.cancerindex.org/ccw/faq/osteo.htm

Cancerbacup.org
http://www.cancerbacup.org.uk/Cancertype/Childrenscancers/Typesofchildrenscancers/Osteosarcoma

The Penn State Children’s Hospital
Penn State Hershey Medical Center, Hershey, PA
A to Z Topics
http://www.hmc.psu.edu/childrens/healthinfo/o/osteosarcoma.htm

Bonetumor.org, Newton, MA
http://bonetumor.org/tumors/pages/page23.html
http://bonetumor.org/tumors/pages/page18.html

St. Jude Children’s Research Hospital, Memphis, TN
http://www.stjude.org/disease-summaries/0,2557,449_2167_2995,00.html

American Cancer Society
http://www.cancer.org/docroot/cri/cri_2_3x.asp?dt=52

Related www.Cure4kids.org Seminars

Seminar #95 Current Concepts in Bone Graft Substitutes for Limb Sparing Surgery
Stephen Gitelis, MD and Ross Wilkins, MD, MS
http://www.cure4kids.org/seminar/95

Seminar #236 Plastic Surgery in Limb Salvage
Bhaskar Rao, MD, Yuko Araki, MD, Beth McCarville, MD, Jesse J. Jenkins, III, MD and Robert Wallace, MD
http://www.cure4kids.org/seminar/236

Seminar #249 Surface Osteosarcoma
Monika Metzger, MD, Sue C. Kaste, DO, Jesse J. Jenkins, III, MD and Michael D. Neel, MD
http://www.cure4kids.org/seminar/249

Seminar #403 Pulmonary Lesions in Osteosarcoma
Fariba Navid, MD, Fredric Hoffer, MD, Joseph D. Khoury, MD, Michael Absalon, MD, PhD and Patricia Flynn, MD
http://www.cure4kids.org/seminar/403

Seminar #463 Limb Salvage Surgery for Children with Cancer
Michael D. Neel, MD
http://www.cure4kids.org/seminar/463
Appendix

A – 1 Risk for Childhood Osteosarcoma

Teens (especially boys) who are taller than average
Children with inherited syndromes – retinoblastoma, Li-Fraumeni syndrome
Children who have received radiation treatments
Presence of benign bone tumors such as Paget’s Disease

A – 2 Physical Assessment Findings:

Swelling, tenderness, warmth, pain, asymmetry of the extremities, palpable soft tissue, shiny, stretched skin.
Associated symptoms include deficits in range of motion, changes in gait, weight loss, and possible nerve involvement.

Used with permission.
Mayo Clinic, Rochester, MN
Mayo Foundation for Medical Education and Research
http://www.mayoclinic.org/osteosarcoma/details-osteosarcoma.html
A – 3 Sunburst Lesion

Osteogenic Sarcoma
(Osteosarcoma)

The pathologist must see malignant cells making their own osteoid.

PathosWeb, Dino LaPorte MD
http://www.pathguy.com/lectures/ostesarc.gif
A – 4 Radiographic Studies

X-ray finding: opacity and lesion in the distal right femur.

[Link to eMedicine.com page](www.emedicine.com/orthoped/topic512.htm)
A – 5   Bone Scan

Increased uptake in right distal femur
Bone Tumors – Osteogenic Sarcoma (Osteosarcoma)

A – 6    Magnetic Resonance Imaging

Carlos Rodriguez-Galindo, MD, St. Jude Children's Research Hospital
A – 7 Stage:

A commonly used staging system for osteosarcomas is described below:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>TNM and Grade (G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I A</td>
<td>Tumor is confined to the bone and is less than 8 cm, and is low grade.</td>
<td>T1, N0, M0, G1 - G2</td>
</tr>
<tr>
<td>Stage I B</td>
<td>Tumor is confined to the bone, is larger than 8 cm, and is low grade</td>
<td>T2, N0, M0, G1 - G2</td>
</tr>
<tr>
<td>Stage II A</td>
<td>Tumor is confined to the bone, is less than 8 cm, and is high grade</td>
<td>T1, N0, M0, G3 - G4</td>
</tr>
<tr>
<td>Stage II B</td>
<td>Tumor is confined to the bone, is larger than 8 cm, and is high grade</td>
<td>T2, N0, M0, G3-G4</td>
</tr>
<tr>
<td>Stage III</td>
<td>Tumor is confined to the bone but has &quot;skipped&quot; to other sites on the bone; can be any grade</td>
<td>T3, N0, M0, Any Grade</td>
</tr>
<tr>
<td>Stage IV A</td>
<td>The tumor has spread to the lung.</td>
<td>Any T, N0, M1a, Any G</td>
</tr>
<tr>
<td>Stage IV B</td>
<td>The tumor has spread to lymph nodes and distant sites, OR Any T, Any N, M1b, Any G: The tumor has spread to distant sites other than the lung</td>
<td>Any T, N1, Any M, Any G</td>
</tr>
</tbody>
</table>
**A – 8 Surgical Procedures for Osteosarcoma**

**Amputation** – surgical removal of the limb. This has risk for decreased quality of life and impacts functional capacity of the patient. Also, patients are at risk for phantom limb syndrome. This procedure is commonly used in expendable bones such as the fibula, rib, toes, or ulna.

Leg amputation with prosthesis

![Leg amputation with prosthesis](image)

Michael Neel, MD; Bhaskar Rao, MD, St. Jude Children's Research Hospital

**Limb Salvage Procedures** – the extremity is spared; only the diseased area and the tumor are removed.

**Replacement Procedures** – after the diseased bone and proximal joint is removed, an endoprosthetic device (total knee, hip joint; repiphysis prosthesis) is implanted; infection of the allograft, bone and surrounding soft tissues may occur necessitating additional surgeries and even amputation procedures. Mechanical failure from routine use is also common and expected; the patient may need replacement procedures.

![Replacement procedures](image)

Michael Neel, MD; Bhaskar Rao, MD, St. Jude Children's Research Hospital
**Rotationplasty** – always involve the distal femur, proximal tibia or the knee. The tumor is removed, the distal limb is attached to the proximal limb with the foot facing backward. The foot then acts like the knee joint and is used to attach the prosthesis. The patient is able to control the movement of the prosthesis.

A – 9 **Chemotherapy Agents Used in Osteosarcoma**

- Doxorubicin (Adriamycin)
- Cisplatin (Platinol)
- Methotrexate – also given at high doses
- Ifosfamide (Ifex)
- Etoposide (VP-16)