Osteosarcoma, or osteogenic sarcoma, is the most common primary malignant bone tumor, accounting for approximately 20% of all cases. Osteosarcoma demonstrates a bimodal age distribution and most commonly occurs in the extremities. Approximately 75% of osteosarcoma diagnoses occur in patients less than 25 years of age; the average at diagnosis is 20 years. However, in patients 65 years and older, osteosarcoma often occurs secondary to irradiation or Paget's disease of bone. No histopathological difference between primary and secondary osteosarcoma has been identified, but primary osteosarcoma originates within normal bone, and secondary osteosarcoma originates within bone affected by a pathologic disease process.

Osteosarcoma derived from primitive osteoid-producing mesenchymal cells manifests heterogeneously; the degree of differentiation, location within the bone, and histological variation determine each osteosarcoma subtype. Each subtype varies in demographic distribution, biological behavior, and radiological appearance. High-grade conventional intramedullary osteosarcoma is the most common subtype. This subtype is a biologically complex and aggressive tumor involving a long bone's metaphysis, usually adjacent to a physis with the most significant growth, such as the proximal humerus, distal femur, or proximal tibia.

The most common presenting symptom of osteosarcoma is bone pain, initially with activity and then at rest. A reported history of a traumatic injury may or may not be present. Lesions are typically identified on radiographs of the affected limb; magnetic resonance imaging (MRI) is then utilized to characterize a lesion further, and a biopsy is required for definitive diagnosis.

The treatment of osteosarcoma typically requires some combination of wide excision, chemotherapy, and radiotherapy. Localized high-grade osteosarcomas are treated with neoadjuvant chemotherapy, radical surgical resection, and adjuvant chemotherapy. Approximately 10% to 20% of patients with osteosarcoma have evidence of metastases at their initial presentation; the most common metastatic site is the lungs. With the routine use of chemotherapy, approximately two-thirds of children and adolescents with osteosarcoma will achieve long-term cures.

Etiology

Primary Osteosarcoma

The etiology of osteosarcoma is currently unknown; studies traditionally have focused on multiple risk factors, including genetic predisposition, epidemiology, and the environment. Osteosarcomatous lesions typically demonstrate complex karyotypic mutations; several genetic aberrations have been identified in primary osteosarcoma. These mutations and their associated syndromes include:

- **Hereditary retinoblastoma**: Germline mutations in the RB1 gene are inherited in an autosomal dominant fashion and typically cause bilateral retinoblastoma by 1 year of age. This mutation imparts an increased risk of osteosarcoma later in life, especially in the setting of prior radiation treatment. Somatic RB1 mutations are associated with 30% to 75% of primary osteosarcoma cases.

- **Li-Fraumeni syndrome (LFS)**: Characterized by germline mutations in the TP53 tumor suppressor gene, LFS has been diagnosed in up to 5% of children with osteosarcoma. 12% of individuals with LFS will develop an osteosarcoma. Patients with Li-Fraumeni syndrome are also at increased risk of developing other types of cancer at a very early age.
- **Rothmund-Thompson syndrome**: Mutations in the RECQL4 gene are inherited in an autosomal recessive fashion and predispose to osteosarcoma as well as a characteristic infantile rash, dysplastic osseous structures, alopecia, premature cataracts, and chronic gastrointestinal distress.
- **Bloom syndrome**: The BLM gene maintains DNA stability during replication. When mutations in this gene are inherited in an autosomal recessive fashion, patients are predisposed to osteosarcoma, ultraviolet light-induced rashes, short stature, and sparse subcutaneous fat.
- **Werner syndrome**: Also known as adult progeria, mutations in the WRN gene induce premature aging, bilateral cataracts, osteoporosis, short stature, scleroderma-like skin changes, and a propensity for osteosarcoma. Patients with Werner syndrome tend to develop osteosarcoma later in life, typically around 35 to 57 years old, and in atypical locations, e.g., the feet.

Secondary Osteosarcoma

Secondary osteosarcoma is associated most commonly with Paget disease of bone and radiation exposure. Osteosarcoma has been induced in animal models with beryllium, alkylating agents, the Finkel-Biskis-Jinkins (FBJ) virus, and the Rous sarcoma virus. Case reports correlating an osteosarcoma diagnosis with a history of electrical burns, trauma, and joint arthroplasty have also been documented.

Epidemiology

The incidence of osteosarcoma is about 3.4 cases per million people per year. Osteosarcomas constitute <1% of all newly diagnosed malignancies in adults and nearly 4% of all newly diagnosed malignancies in children. Excluding hematological malignancies, osteosarcoma is the most commonly diagnosed malignancy in adolescents, with an incidence of 4.4 per million per year. Osteosarcoma does have a slightly increased incidence in males versus females. Approximately 20% of osteosarcoma are metastatic at presentation. Between 60% and 70% of metastatic disease is to the lungs; another 20% to 30% of metastatic lesions are skip or distant bony metastases.

Primary osteosarcoma is primarily a lesion of childhood and adolescence with a marked propensity for the knee. Secondary osteosarcoma reflects the varied nature of the predisposing condition with a broader age distribution, primarily within adulthood. Secondary osteosarcoma is much more likely to occur in flat bones, including the pelvis; this is likely due to the causative effect of Paget's disease of bone, which shares a similar anatomical preference.

Pathophysiology

Osteosarcoma frequently occurs near the metaphysis of the long bones of the appendicular skeleton. Rapid bone growth predisposes to the development of osteosarcoma; occurrence is most common during the pubertal growth spurt and near the growing physis. High-grade intramedullary osteosarcoma comprises approximately 80% of all osteosarcomas; 42% occur in the femur, 19% in the tibia, and 10% in the humerus. Between 75% and 90% of these long-bone tumors occur near the distal femoral, proximal tibial, or proximal humeral physis. Other commonly encountered anatomical sites for osteosarcoma development include the skull, jaw, and pelvis, primarily the ilium.

Osteosarcoma in adults is often secondary to another bone disorder. Approximately 1% of patients with Paget disease of bone develop osteosarcoma, although this risk may be decreasing as Paget disease is treated with bisphosphonates. Ionizing radiation is implicated in 3% of osteosarcoma cases, 4 to 40 years after exposure.

Histopathology

Osteosarcoma is a mesenchymal neoplasm that produces osteoid and woven bony matrix. The definitive diagnostic feature of osteosarcoma is malignant osteoid matrix production; the quantity and quality of the matrix will vary with histologic subtypes. Dense osteoid is characteristic of the sclerotic variant of osteoblastic osteosarcoma, while inconspicuous amounts of an osteoid matrix are seen in fibroblastic or small-cell osteosarcoma variants. Normal osteoid is histologically glassy, densely eosinophilic, and homogenous. Osteoid deposition by malignant cells may be filigree or lacelike, sclerotic with dense confluent sheets of the matrix, or thick and trabecular.

The 2020 World Health Organization Classification of Tumors of Bone recognizes the following subtypes of osteosarcoma:

- Low-grade central osteosarcoma
- Osteosarcoma not otherwise specified (NOS):
    - Conventional osteosarcoma
    - Telangiectatic osteosarcoma
    - Small cell osteosarcoma
- Parosteal osteosarcoma
- Periosteal osteosarcoma
- High-grade surface osteosarcoma
- Secondary osteosarcoma

Low-Grade Central Osteosarcoma

Low-grade central osteosarcoma comprises 1% to 2% of all osteosarcomas. This tumor occurs predominately in the long-bone metaphyses of young adults and is characterized by low mitotic

activity. Progression to a high-grade osteosarcoma has been documented in the setting of local recurrence. Immunohistochemically, amplification of MDM2 and CDK4 can help differentiate low-grade osteosarcoma from other benign intramedullary bone tumors.

Osteosarcoma Not Otherwise Specified (NOS)

Conventional Osteosarcoma

Conventional osteosarcoma (COS) is typically a central or intramedullary high-grade sarcoma involving the metaphysis of long bones, accounting for 75% to 80% of all osteosarcomas. Histologically, COS is composed of cells that are spindle to polyhedral in shape with variable nuclei and numerous mitotic figures. The osteoid matrix produced by tumor cells must be identified somewhere in the lesion, even if only in a minuscule amount. Historically, COS has been further subclassified histologically based on the predominant extracellular matrix as osteoblastic, chondroblastic, or fibroblastic.

Telangiectatic Osteosarcoma

Telangiectatic osteosarcoma accounts for 2% to 12% of osteosarcomas. Histologically, telangiectatic osteosarcoma is characterized by numerous blood-filled sinusoids with septations containing cells with nuclear pleomorphism and numerous mitotic figures. The lesional tissue is also observed permeating into the surrounding marrow or cortex. (Image.Telangiectactic Osteosarcoma).

Small Cell Osteosarcoma

Small cell osteosarcoma constitutes only 1% of osteosarcomas. This condition is a histological combination of Ewing sarcoma and osteosarcoma and features numerous small round cells. Unlike Ewing sarcoma, spindling of tumor cells is seen with small-cell osteosarcoma. A minuscule volume of an osteoid matrix also distinguishes this as a variant of osteosarcoma.

Parosteal Osteosarcoma

Parosteal osteosarcoma accounts for <4% of osteosarcomas and occurs on the posterior distal femur in 75% to 80% of cases. A histopathological exam demonstrates “streamers of bone trabeculae” running in parallel and cellular fibrous tissue. Immature osteoid can be found within the bone spicules. Parosteal osteosarcoma is a low grade sarcoma. Immunohistochemical analysis shows both CDK4 and MDM2 amplification in a majority of parosteal osteosarcomas.

Periosteal Osteosarcoma

Comprising <1% of osteosarcomas, this subtype is found between the cortex and the inner periosteal layer of the bone. Histologically, periosteal osteosarcoma features ribbons of osseous trabeculae oriented in parallel, primarily composed of a chondroid matrix with a small amount of osteoid matrix. Periosteal osteosarcoma is considered intermediate-grade histologically.

High-Grade Surface Osteosarcoma

These are histologically identical to high-grade conventional and central variants and vary only in location. High-grade surface osteosarcomas are, by definition, confined to the bone's surface. Some of these osteosarcomas may represent dedifferentiated parosteal osteosarcoma.

Secondary Osteosarcoma

Secondary osteosarcomas arise in abnormal bone, most commonly in individuals older than 50 around the knee or hip joint. Secondary osteosarcomas accounts for only about 4% of osteosarcomas. The 2020 WHO classification subdivided secondary osteosarcoma into 6 subtypes: osteosarcoma in Paget's disease of bone, radiation-associated osteosarcoma, infarct-related osteosarcoma, osteosarcoma due to chronic osteomyelitis, implant-related osteosarcoma and osteosarcoma associated with disorders like fibrous dysplasia. The histology varies between subtypes, but the distinguishing features of osteoid production, variable nuclei with pleomorphism, and numerous mitoses are present.

Extraskeletal Osteosarcoma

Extraskeletal osteosarcomas are divided into the following histological types:

- **Low-grade**: This type of osteogenic sarcoma is histologically identical to low-grade surface parosteal variants and low-grade central variants, varying only in geography, potentially appearing at any extraskeletal location in the body, including the soft tissues of the thigh, buttocks, upper extremities, or retroperitoneum.
- **High-grade**: Histologically identical to high-grade conventional and central variants, differing only in geography, found at any extraskeletal location in the body.

History and Physical

Clinical History of Osteogenic Sarcoma

Symptoms of osteosarcoma may be present for a significant amount of time, sometimes weeks to months, before patients seek evaluation. Most commonly, the presenting symptom is **bone pain**, particularly with activity. A history of traumatic musculoskeletal injury may or may not be reported. Pain and swelling at the local site, usually at the growing ends of an extremity or long bones, are the most common presenting symptoms.

Around 10% of patients present with pathological fractures due to primary tumors or bony metastases (i.e., bone-to-bone spread). Systemic symptoms seen in lymphoma (e.g., fever and night sweats) are rare. Respiratory symptoms (e.g., frequent cough and hemoptysis) are also uncommon and, when present, indicate extensive lung involvement. Additional symptoms are unusual because metastases to other sites are extremely rare but typically pertain to the involved organ.

Physical Examination Findings

Physical examination findings of osteogenic sarcoma are typically focused on the location of the primary tumor, including:

- A palpable, tender mass
- Decreased range of motion of adjacent joint, with possible effusion
- Pain on weight-bearing or inability to bear weight
- Local or regional lymphadenopathy (unusual)
- Respiratory findings with metastatic forms

The preoperative neurological deficit in vertebral osteosarcoma can be assessed according to the Frankel grading system. The classification given by Tomita et al is based on the location and grade of spinal tumors to help determine prognosis and the optimal surgical approach.

Evaluation

National Comprehensive Cancer Network 2020 Guidelines for Osteogenic Sarcoma Evaluation

The National Comprehensive Cancer Network (NCCN) recommends diagnostic laboratory, imaging, and histological studies following the initial clinical assessment.

Laboratory Analysis

Serum tests, including a **complete blood count, alkaline phosphatase (ALP), and lactate dehydrogenases (LDH)**, are assessed in the initial workup because they provide evidence for diagnosis and prognosis. ALP levels will be high due to the increased osteoblastic activity associated with osteogenic sarcoma. Extremely high levels have been linked to heavy tumor burden and are generally considered a poor prognostic indicator. During initial evaluation, serum LDH is frequently higher in patients with metastatic disease than localized disease.

Furthermore, evaluating the levels of the biomarkers later in the treatment process is also essential, as levels may decrease with successful therapy or rise with residual disease or recurrence. The NCCN also recommends that genetic evaluation and counseling be considered for patients diagnosed with osteogenic sarcoma with a family or personal history of bone sarcomas.

Primary Tumor Site Diagnostic Imaging

The following imaging modalities are preferred for evaluation of osteosarcoma:

- **Radiographs**: Radiographs of the entire bone affected should be obtained. The radiographic findings vary depending on the type of osteosarcoma. A radiograph of conventional osteosarcoma usually demonstrates medullary and cortical bone destruction with mixed lytic and blastic appearance. High-grade osteosarcoma will often be described as having a permeative or moth-eaten appearance with a "sunburst" configuration due to aggressive periostitis or "codman triangle" configuration due to

elevation of the periosteum away from the bone. Telangiectatic osteosarcoma, on the other hand, is usually purely lytic, while low-grade intramedullary osteosarcoma may appear as a purely sclerotic lesion. Parosteal osteosarcoma is a lobular sclerotic mass stuck onto the bone, while periosteal osteosarcoma is less sclerotic with cortical involvement and periosteal reaction. (see Image. Osteogenic Sarcoma).

- Magnetic resonance imaging (MRI): MRI is an indispensable tool for defining the extent of a tumor inside and outside the bone. The entirety of the involved bone, as well as 1 joint above and 1 below the tumor, should be included in the study so that "skip" lesions are not missed. MRI can accurately and precisely delineate the degree of tumor in the adjacent soft tissues, joint involvement, whether or not the tumor crosses the physis, and proximity to the nearest neurovascular bundle. Nearly every aspect of treatment is assessable with MRI, from presurgical assessment for limb-sparing resection to the degree of chemotherapy response in the form of tumor necrosis, shrinkage, and improved capsulation.
  Traditional sequences acquired in MRI of osteogenic sarcoma may demonstrate the following:
    - **T1-weighted Images**
      - Non-ossified soft tissue component: intermediate signal intensity
      - Osteoid components: low signal intensity
      - Peritumoral edema: intermediate signal intensity
      - Scattered foci of hemorrhage: variable signal intensity based on chronicity
    - **T2-weighted Images**
      - Non-ossified soft tissue component: high signal intensity
      - Osteoid components: low signal intensity
      - Peritumoral edema: high signal intensity
      - Telangiectatic osteosarcoma: multi-cystic expansile lesion with fluid-fluid levels and septa that enhance with contrast.
      - Parosteal Osteosarcoma: lobular mass with a clear line between portions of the sarcoma and the underlying cortical bone.
      - Periosteal Osteosarcoma: areas of cortical erosion but rarely intramedullary involvement and no corticomedullary continuity.
      - Extraskeletal Osteosarcoma: Soft tissue mass with internal calcification.

Biopsy

A **biopsy** is necessary after the physical exam, laboratory analysis, and diagnostic imaging confirm the presence of a lesion consistent with osteosarcoma. The final surgical procedure must include resection of the biopsy tract, which can be tattooed for easy identification to avoid recurrence due to potential seeding of this tract with cancer cells. Ideally, the surgeon who undertakes the biopsy should be the same individual who completes the resection so they are familiar with the path and extent of the biopsy. An open approach to biopsy was previously considered the best option owing to a high accuracy rate.

In recent years, however, research has determined that an open approach correlates with an increased risk of complications such as infection, improper wound healing, and seeding of the site by tumor cells, as previously discussed. As such, **core biopsy** has replaced the traditional open approach, mainly because of the reduced risk of contamination of the surgical bed with tumor cells but also due to lower cost and decreased recovery time. Attempting limb-sparing procedures in patients with the perceived potential to save local tissue safely is crucial.

Core needle biopsy is achieved via a single deep stab with a needle through a trocar, which traverses a single tissue plane in a location that will be included in the final resection. Multiple cores are necessary from the representative region of the mass to the soft tissue portion in the lesion's periphery. The necrotic central region will yield little viable tissue, and the "Codman triangle" region will yield only reactive bone. Importantly, recent studies have shown that fine-needle aspiration is not an efficacious approach to biopsy because it does not yield an adequate tissue sample for an accurate diagnosis. Following the biopsy, pathologists should analyze tissue samples in fresh or frozen format for definitive diagnosis, grading, and histological subtyping, affecting medical and surgical treatment strategy.

Tumor Staging

The following imaging modalities are preferred for osteosarcoma staging:

- **Chest computed tomography (CT)**: Modality of choice for evaluating for pulmonary metastasis.
- **Nuclear imaging**
    - **Positron emission tomography/CT**: Positron emission tomography (PET)/CT is a nuclear medicine imaging modality that detects highly metabolic lesions. It is utilized to evaluate for metastatic disease, especially in the skeleton.
    - **Radionuclide bone scan**: Technetium 99 methylenediphosphonate (Tc99 MDP) bone scan is an effective and less expensive, though less sensitive, imaging modality for detecting bony metastasis.

Pretreatment Chemotherapy Evaluation

Chemotherapy may result in auditory, renal, and cardiac toxicity, making baseline assessment of these parameters extremely important. Pure tone audiometry, baseline renal function testing, and echocardiographic evaluation might be warranted. Additionally, because osteogenic sarcoma is most prevalent in children and young adults, fertility consultation with an interdisciplinary team, including reproductive specialists, is recommended, as chemotherapy and radiation therapy may affect fertility.

Treatment / Management

Osteogenic Sarcoma Management Guidelines

The NCCN advises clinicians to refer patients to a tertiary care center with osteogenic sarcoma specialists and interprofessional teams for optimal management of this condition. Furthermore, **multimodality therapy consisting of neoadjuvant chemotherapy, followed by surgery and chemotherapy in the adjuvant setting, is considered the treatment of choice**. Generally, clinicians performing wide excision should expect to achieve histologically negative margins. The combination of chemotherapy with surgical procedures and advanced imaging modalities has increased limb salvage rates from 53% in the 1980s to greater than 90% in recent times. Along with the advancement in psychological and cosmetic outcomes, limb salvage procedures have comparable overall survival and local recurrence rates to amputation. The utility of neoadjuvant chemotherapy has been attributed to subclinical micrometastatic disease. Enrollment in a clinical trial should be considered in all cases.

The National Cancer Institute (NCI) recommends the following management guidelines based on the grade and resectability of a tumor:

- **Low-grade osteosarcoma without metastasis**
    - **Intramedullary and surface**
        - Wide excision alone (i.e., no neoadjuvant chemotherapy)
        - If postsurgical pathology demonstrates low-grade features, then adjuvant chemotherapy is not recommended.
        - If postsurgical pathology demonstrates high-grade features, consider adjuvant chemotherapy.
    - **Periosteal**
        - Consider neoadjuvant chemotherapy
        - Wide excision
        - If postsurgical pathology demonstrates is consistent with biopsy (low-grade features only), no adjuvant chemotherapy is recommended.
        - If postsurgical pathology demonstrates high-grade features, adjuvant chemotherapy is recommended.
- **High-grade intramedullary or surface osteosarcoma without metastasis**
    - Neoadjuvant chemotherapy; then restage the lesion
    - If restaging suggests the lesion is resectable, perform a limb-sparing wide excision.
        - **Positive margins**
            - If a favorable response to preoperative neoadjuvant chemotherapy (<10% viable tumor on postsurgical pathology) was seen, then continue the same neoadjuvant chemotherapy regimen and consider additional surgical resection with or without radiation therapy.
            - If an inadequate response to preoperative neoadjuvant chemotherapy (e.g., >10% viable tumor on postsurgical pathology) is noted, then continue the same neoadjuvant chemotherapy regimen or consider a new regimen and consider additional surgical resection with or without radiation therapy.
        - **Negative margins**

        - If a good response to preoperative neoadjuvant chemotherapy (i.e., <10% viable tumor on postsurgical pathology) was observed, continue the same neoadjuvant chemotherapy regimen. No further resection is required.
        - If an inadequate response to preoperative neoadjuvant chemotherapy (i.e., ≥10% viable tumor on postsurgical pathology) is noted, continue the same neoadjuvant chemotherapy regimen or consider a new regimen. No further resection is required.
    - If restaging suggests the lesion is unresectable, then continue chemotherapy and consider radiation therapy.
- **Any grade with metastasis at presentation, follow guidelines for high-grade osteosarcoma plus the following**:
    - If metastases are resectable (e.g., pulmonary, visceral, or skeletal sites), a metastasectomy should be performed (see Image. Pulmonary Metastasis of Osteogenic Sarcoma).
    - If metastases are unresectable, then consider chemotherapy and radiation therapy, after which the primary site requires reassessment for local control.

Follow-up and Surveillance

Surveillance schedule

- Every 3 months for postoperative years 1 and 2
- Every 4 months in postoperative year 3
- Every 6 months in postoperative years 4 and 5
- Yearly for postoperative years 6 and beyond

Surveillance visits should include:

- Physical exam with assessment of function
- Contrast-enhanced CT with or without MRI of the postoperative site and chest
- Consider PET/CT or bone scan
- Complete blood count with additional laboratory tests as clinically indicated (e.g., alkaline phosphatase levels)

If a relapse is detected, chemotherapy with resection, if possible, should be resumed in conjunction with the following guidelines:

- Evaluate tumor treatment by performing radiographs of the original tumor site, CT or MRI with contrast of the site of relapse, and CT of the chest to assess for pulmonary lesions
- In tumors responsive to treatment (i.e., <10% viable tumor on postsurgical pathology), continue surveillance (i.e., restart OSTEO-4 guidelines)
- In tumors with a poor response to treatment (i.e., ≥10% viable tumor on postsurgical pathology) or continued progression of the disease, management strategies include:
    - Resection (if possible)

- Clinical trial
- Palliative radiation
- Best supportive care

Recurrent Osteogenic Sarcoma

In individuals with recurrent disease with or without metastasis, surgical resection is preferred if possible; primarily, adjuvant chemotherapy is given. A 5-year survival rate of 33% may be obtained in patients with a second surgical remission. (Please refer to the Medical Oncology section for more information on chemotherapy regimens). In patients who are not candidates for surgery, chemotherapy with or without radiation is preferred. In those with metastasis, dismal 5-year survival rates of 20%, which has remained unchanged over the past 25 years, underline the need to explore newer approaches.

Supportive Management and Palliative Medicine

The management of chemotherapy-related complications such as nausea and vomiting, anemia, neutropenic fever, fatigue, neuropathy, and cardiotoxicity, provision of symptom-directed therapy, and counseling regarding goals of care discussions have shown improvement in the quality of life. The provision of continuity of care through home care and round-the-clock telephonic liaison might assume special significance, depending on environmental circumstances (e.g., the COVID-19 pandemic). Hospice should be considered early.

Differential Diagnosis

The differential diagnosis for a meta-diaphyseal bone lesion in a pediatric patient includes benign entities, e.g., osteoblastoma, osteoid osteoma, osteomyelitis, fracture callus, or Langerhans cell histiocytosis, and malignant conditions (e.g., Ewing sarcoma and lymphoma).

- **Osteoblastoma and osteoid osteoma** are usually well-circumscribed, with a peripheral rim of reactive bone consisting of a loose fibrous stroma with a vascular component, rimming of bone trabeculae, and absence of atypical mitoses.
- **Callus formation** is usually associated with a history of accompanying trauma, organized matrix deposition, presence of granulation tissue-like stroma, presence of hyaline cartilage with woven lamellar bone, and presence of transition area from immature osteoid to that of osteoblasts lined bony spicules.
- **Langerhans cell histiocytosis of bone** usually presents as a painful osteolytic lesion, and tissue biopsy demonstrates a clonal proliferation of cells that express CD1a, CD207, CD68, and S-100.
- **Ewing sarcoma** classically appears in the diaphysis of long bones but can occur in the metaphyseal region and have similar radiologic findings, e.g., Codman triangles. Histologically, Ewing sarcoma has a clonal population of small round blue cells characterized by the EWS-FLI1 translocation.

Among the differentials for morphologic variants, **telangiectatic osteosarcoma** must be differentiated from aneurysmal bone cyst (ABC). Both lesions can have surrounding periosteal reaction and fluid-fluid levels on MRI, but ABCs do not typically have a soft tissue mass associated with them. Histologically, the septa in aneurysmal bone cysts contain cells with significantly less pleomorphism and nuclear hyperchromasia than in telangiectatic osteosarcoma and lack lacey malignant osteoid. ABCs are also associated with a specific USP6 gene rearrangement not seen in osteosarcoma. **Low-grade parosteal osteosarcoma** must be differentiated from osteochondroma, heterotropic ossification, and surface osteoma. Osteochondromas are characterized radiographically by corticomedullary continuity, which surface osteosarcoma lacks.

Surgical Oncology

Surgical Resection of Primary Site Osteosarcoma

The goal of surgical resection is a **negative margin or R0 resection** in which no tumor at the edges of the resection are present. This can be achieved through either **limb salvage surgery or amputation**, depending on the location and size of the sarcoma and patient preferences.

Limb Salvage Surgery

Limb salvage surgery is completed in about 75% of osteosarcoma cases. Because osteosarcoma is the most common primary osseous malignancy in the pediatric population, surgery presents a unique set of challenges. To achieve clear margins, excision may necessitate resection of the physis, leading to deformity or leg length discrepancy as the child matures. In the past, a tumor that traversed the growth plate was considered to be an indication for amputation because no means to restore function were available. With the advent of options that grow or expand with the patient, masses that cross the growth plate are no longer considered a contraindication to limb salvage.

After resectioning the sarcoma, limb salvage surgery often requires reconstruction of the defect created. The purpose of reconstruction is the restoration of function to the affected limb. In the case of non-weight-bearing bones like the fibula or clavicle, reconstruction is unnecessary because the excision of these structures does not impart functional deficit. For reconstruction, the following options are available:

- **Allograft or autograft bone reconstruction**
    - **Allograft bone replacement** utilizes bones collected from organ donors in the postmortem period. As with organ donation, potential donors undergo screening for infectious diseases. Once surgically grafted into the osteosarcoma patient, the native bone will grow into the allograft bone and heal. Rejection is rare because very few donor cells remain within the donated bone, and bones are relatively inert. The most serious complication that may arise with allograft reconstruction is the failure of fusion between the patient and allograft bone. Infection and fracture are also important complications requiring internal fixation or removal. A hybrid

reconstructive option is an allograft prosthetic composite, which combines an allograft bone fragment with a metallic prosthesis. Allograft prosthetic composite arthroplasty is useful for reconstructing weight-bearing joints such as the knee.