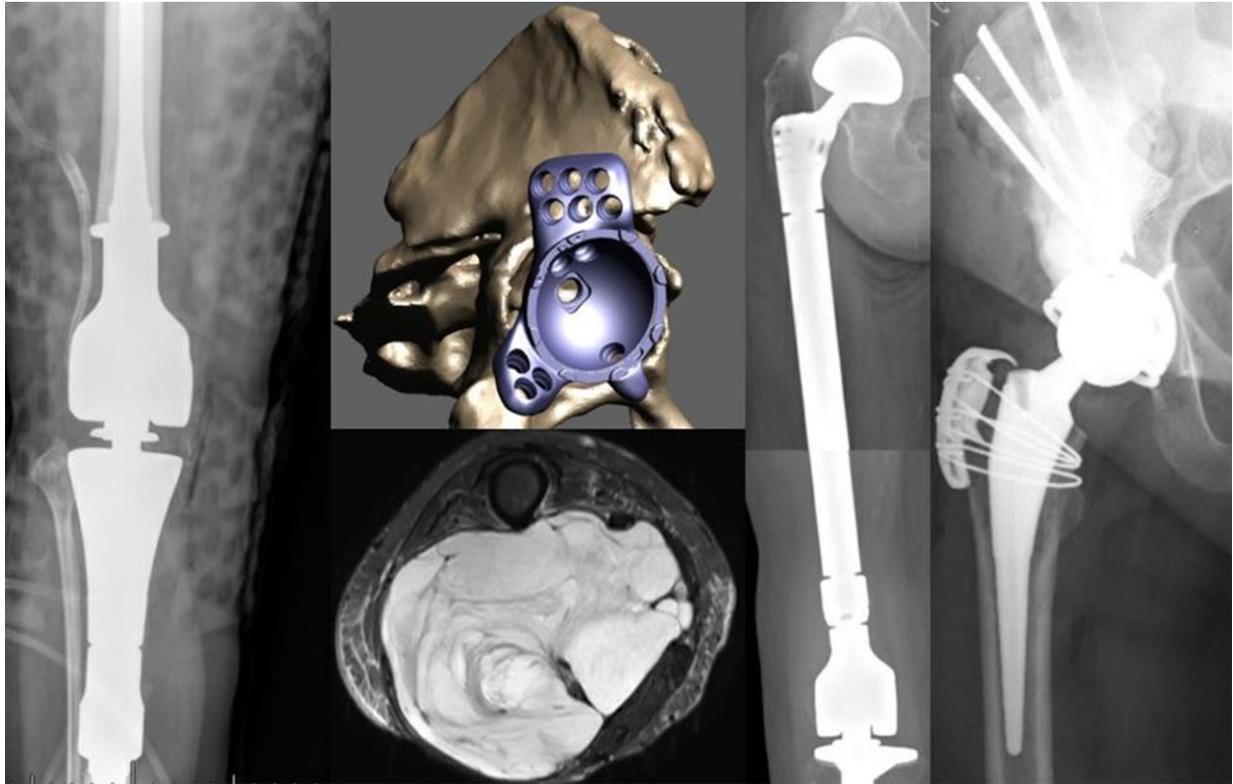


ONCOLOGY ONE

ORTHO NORTHEAST



JOHNSON'S REVIEW: ORTHOPEDIC ONCOLOGY

INTRODUCTION:

In general, the OITE (Orthopedic In-Training Exam) and Board Examination is trying to ensure safety and quality amongst general orthopedic surgeons. Many of the same topics are tested over and over again, so understanding the commonly asked questions is high yield. Remember, the examiners are not trying to trick you, although it may feel that way at times. All of the presented information within the question stem is generally relevant and trying to guide you to the correct answer. With some repetition it is possible to get every oncology question correct on OITE!

CONTENT:

1. Metastatic Disease
2. Malignant Primary Bone Tumors
3. Benign Primary Bone Tumors
4. Soft Tissue Sarcomas
5. Benign Soft Tissue Tumors
6. Common Associations and Tables

METASTATIC DISEASE

This is the most commonly tested topic on OITE, and rightfully so, as this is the most commonly encountered cancer case an orthopedic surgeon will see in clinical practice. Diagnosing unknown lytic lesions of bone in patients over 40 years of age is a critical topic and the most high-yield. **Always biopsy and/or have a definitive tissue diagnosis prior to any surgical treatment!**

Lytic bone lesion in a patient >40 years of age

- Differential = **Mets, myeloma, lymphoma, primary bone sarcoma** (say the rhyme) (and don't forget giant cell tumor of bone, Paget Disease, and brown tumor/hyperparathyroidism)
 - Primary bone sarcoma is approximately 1/500, but don't want to miss this
 - Delay in diagnosis and misdiagnosis are the most common causes of litigation against orthopedic surgeons in regards to sarcoma cases, not to mention associated patient morbidity.
 - **Most common reason for a lytic bone lesion in an adult (>40 years of age) = metastatic carcinoma**
- Breast, lung, prostate, kidney, and thyroid are most common visceral cancers to spread to bone (bone is third most common site of metastases after lung and liver)
- Pathology of tumor induced bone destruction due to **ratio of OPG:RANKL**
 - Osteolytic lesion = tumor release PTHrP, TGF, TNF that induces RANKL and the process repeats through a vicious cycle, thus breaking down bone
 - Osteoblastic lesion = endothelin-1 and proteases released by tumor cells inhibit RANKL inducing osteoblasts, thus forming bone
- Work up of unknown lytic bone lesion in patient >40 years of age
 - **This is one of the most commonly asked topics, MUST KNOW**
 - Thorough history and physical, labs (SPEP/UPEP, CBC, alk phos, LDH, PSA, TSH), CT chest, abdomen, and pelvis (looking for primary visceral tumor), radiographs of entire involved bone, whole body bone scan, and biopsy of most accessible location will obtain diagnosis in 85-90% of cases (Rougraff et al).
 - **Always have confirmed diagnosis of skeletal lesion prior to surgical treatment**, can be image-guided core needle biopsy or surgical biopsy (utilizing proper technique)

- Biopsy will show carcinoma/epithelioid in clumps or glands i.e. carcinoma/adenocarcinoma
- **Scenarios to understand:**
 - Lytic bone lesions with no known primary diagnosis → do the Rougraff criteria
 - Lytic bone lesion with known primary cancer diagnosis, but no established or confirmed skeletal metastatic disease i.e. newly developed metastatic disease from previously known primary cancer → biopsy bone lesion to confirm diagnosis prior to surgical treatment
 - Lytic bone lesion with known primary cancer diagnosis and already confirmed skeletal metastatic disease → may proceed with surgical treatment as needed

Impending Pathologic Fracture

- Indications for prophylactic fixation
 - In general, not always easy to predict, but clinically, progressive weight-bearing pain with associated lytic lesion is high risk for fracture.
 - Should be familiar with scoring systems including Mirels and Harrington
 - **Mirels scoring system** is based off radiograph (not CT or MRI), score >8 indicates need for prophylactic fixation (not great for intermediate scores 7-8)

Variable	Score		
	1	2	3
Site	Upper limb	Lower limb	Peritrochanter
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size	<1/3	1/3–2/3	>2/3

- > 3 cm of craniocaudal cortical involvement and/or > 50% cortical involvement is high risk for pathologic fracture (helpful for 7-8 Mirel score)
- Prophylactic fixation is associated with better functional scores, less morbidity, less pain, shorter OR time, shorter hospital stay, and overall less costly when compared to pathologic fracture
- Avulsion fracture of lesser trochanter = pathologic lesions within femoral neck and impending fracture

Fracture prevention

- Denosumab (RANKL inhibitor) slightly more effective than bisphosphonates, but similar risk profile (studies suggest slight improved risk profile, but still included ON of the jaw and atypical subtroch fractures)
- Radiation is effective at reducing bone pain and risk of pathologic fracture

Surgical Treatment

- Goal is for immediate weight bearing, improved pain and function, and palliative purposes (except in isolated metastatic renal cell may utilize a curative intent)
- Multidisciplinary pre-operative medical optimization
- Ensure patient has adequate longevity (>3-6 months expected survival) to make surgery worth the risk. Discuss with medical oncology. PATHFX.org
- Longevity varies depending upon primary tumor type which may affect surgical decision making (metastatic lung carcinoma has poor prognosis, while breast cancer can have prolonged survival and may require more long lasting reconstruction)
- Typically utilize cemented implants as opposed to press-fit implant due to pathologic bone
- **Post-operative radiation is standard of care, should involve entire surgical field (entire femur after IM nail)**
- Amputation is very rarely utilized as the goal of surgery is palliation as patients have limit life span
- Upper Extremity
 - Scapula/clavicle: generally non-surgical
 - Proximal humerus: arthroplasty versus locked plating with cement augmentation
 - Humeral diaphysis: IM nail (utilize intercalary for segmental defects)

- Distal humerus: ORIF with cement augmentation versus arthroplasty
- Distal to elbow: ORIF with cement augmentation
- Lower Extremity
 - Ilium: generally non-surgical for non-weight bearing zones, may consider curettage and cementation as needed
 - Acetabulum: Harrington reconstruction or TM shell-cage construct
 - **Femoral neck and head: Hemiarthroplasty**
 - **Intertrochanteric and subtrochanteric: cephalomedullary nail +/- curettage and cementation versus arthroplasty depending upon amount of bony destruction. Arthroplasty associated with lower risk of reoperation, but is more invasive.**
 - THA associated increase risk of dislocation compared to hemi
 - Arthroplasty associated increase of risk of infection compared to IM nail
- Femoral diaphysis: IM nail +/- cement augmentation (utilize intercalary prosthesis for segmental defects)
- Distal Femur: ORIF with cement augmentation, IM nail, or arthroplasty depending upon amount of bone loss
- Distal to knee: IM nail, ORIF with cement augmentation (case-by-case)

Spinal Metastatic Disease

- Metastatic spine disease often involves anterior column, spares the intervertebral disc (unlike discitis/infection), and thoracic spine is most common location
- Risk factors for progressive neurologic deficit: osteolytic disease, pedicle involvement, posterior wall element involvement
- Indications for surgery: **neurologic compromise, progressive deformity, spinal instability intractable pain**
- Treat with post-op radiation
- **Thoracic spine is most common location for metastatic disease (proximal femur is second)**
- Generally requires decompression and fusion depending upon amount of and location of bone loss

Primary Tumor Specific Considerations

- It's important to understand all metastatic disease is not the same. Metastatic renal cell carcinoma is significantly different than lymphoma or prostate cancer etc.
- Acral metastasis (distal to elbow or knee) = lung or renal, likely spreads through capillaries/arterial tree, associated with poor prognosis
- **Vascular tumors that should undergo embolization prior to surgery = renal and thyroid**
- Osteoblastic = prostate, bladder
- Osteolytic = lung, renal, thyroid, GI
- Mixed = breast
- Sensitive to radiation = breast, prostate, lung, thyroid
- Not sensitive to radiation = Renal and GI
- Renal = tendency for exuberant local progression, radio-insensitive, consider wide excision/curative intent for isolated metastatic disease (may best to refer to ortho oncology), generally poor survival, but depends upon overall burden of disease
- Lung = acral mets, 0% rate of pathologic fracture healing, generally poorest prognosis average 6 month survival (may be improved with targetable mutation i.e. PDL1)
- Breast = sensitive to radiation, generally mixed lytic/blastic, can have prolonged survival average 24 months
- Prostate = low risk of pathologic fracture due to osteoblastic lesions, sensitive to radiation, can have prolonged survival average 40 months
- Thyroid = low rate of skeletal metastasis, but high rate of skeletal related events, very vascular so embolize pre-operatively, can have prolonged survival average is 48 months

- Myeloma = consider aggressive surgical fixation in newly diagnosed patients prior to bone marrow transplant (utilize skeletal survey for staging, may not show up on bone scan), generally a progressive disease, consider stabilizing entire bone
- Lymphoma = treat with chemo and radiation, rarely needs surgical fixation

PRIMARY BONE MALIGNANCY:

Staging of bone tumors:

MSTS (Enneking) staging system:

- Benign tumors put in Arabic numbers (**Benign is easy = easy as 123**) and malignant is Roman numbers (I, II, III)
- 1. Latent (enchondroma, NOF) 2. Active (ABC, Giant cell tumor, chondroblastoma) 3. Aggressive (giant cell tumor)

Surgical Staging System (SSS)

Stage	Grade	Site
IA	Low (G1)	Intracompartmental (T1)
IB	Low (G1)	Extracompartmental (T2)
IIA	High (G2)	Intracompartmental (T1)
IIB	High (G2)	Extracompartmental (T2)
III	Any (G) + Regional or distant metastasis	Any (T)

From Enneking WF, Spanier SS, Goodman MA: A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980:153:106-120.

AJCC Staging System:

Stage Grouping

Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
Stage IIA	T1	N0	M0	G2, G3
Stage IIB	T2	N0	M0	G2, G3
Stage III	T3	N0	M0	G2, G3
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

- T2 > 8 cm, T3 = discontinuous tumor, G1 = low-grade, G2 & G3 = high grade, N1 = lymph node mets, M = distant mets
- Higher stage = worse prognosis

Osteosarcoma

- Most common malignant bone tumor in children (Most common malignancy of bone is metastatic disease, and most common primary malignancy of bone is myeloma)
- Majority of cases occur in second decade of life and later peak in sixth decade of life
- Associated with RB1 (retinoblastoma gene), p53 mutation, Paget disease, prior radiation, Rothmund-Thomson syndrome
- Presents with progressive pain and swelling to affected area
- Most commonly affect metaphysis (opposed to Ewings which is most commonly occurs in diaphysis), with distal femur being most common location followed by proximal tibia, proximal humerus, and pelvis
- **Most commonly presents as stage IIB** with long term survival approximately 70% (5-year survival in patients with metastatic disease is 20%, localized pelvic osteosarcoma associated with 25% 5-year survival)
- **Poor prognostic factors:** metastatic disease, local recurrence, poor response to chemo (<90% necrosis), large tumor size, elevated serum alk phos and LDH, vascular invasion, positive surgical margins. Tumor stage is most important prognostic factor.
- Imaging demonstrates sun-burst (hair-on-end) matrix mineralization, Codman's triangle (periosteal reaction)

- **Always image entire bone** (skip lesions are the second most common location for mets after lung)
- Always Biopsy prior to treatment planning. Pathology demonstrates malignant osteoid
- **Staging include:** CT chest (rule out pulmonary mets), whole body bone scan (bony mets are second most common), and whole PET/CT is often included (PET probably won't be tested on, but CT chest and bone scan are gold standard)
- Treatment for high-grade osteosarcoma : **neoadjuvant chemo, wide surgical excision, followed by adjuvant chemotherapy**
- Chemo generally includes: Adriamycin (doxorubicin), methotrexate, and ifosfamide
- Adriamycin associated with cardiotoxicity
- Treatment for low-grade osteosarcoma (parosteal osteosarcoma) = Wide surgical excision only (chemo only works on rapidly dividing cells)
- Surgery should be wide surgical excision typically limb-salvage surgery, amputation if critical neurovascular structure compromised by tumor and unable to obtain adequate margins with limb-salvage surgery
- Osteosarcoma subtypes
 - Parosteal osteosarcoma: low-grade surface osteosarcoma, most commonly arises from posterior distal femur, 25-50 years of age, **"stuck on appearance,"** treat with wide excision only, 25% risk of dedifferentiation into high-grade osteosarcoma (**Be familiar with radiographic appearance**)
 - Periosteal osteosarcoma: rare, intermediate surface osteosarcoma, occurs in second decade of life, chemo is debatable but commonly used
 - High-grade surface osteosarcoma: rare, high-grade surface osteosarcoma, no intramedullary involvement
 - Telangiectatic osteosarcoma: rare, contains large, blood-filled spaces, similar radiograph appearance to ABC (**when see an ABC must rule out telangiectatic osteosarcoma**).

UPS (Undifferentiated Pleomorphic Sarcoma) of Bone (Formerly known as MFH – Malignant Fibrous Histiocytoms)

- Occurs in older patients >40 years of age with lytic and permeative lesion of long bones involving metaphysis (often looks similar to metastatic disease on imaging!)
- Staging and Treatment is similar to osteosarcoma (chemo, surgery, chemo)
- Prognosis is worse than standard osteosarcoma (adults don't tolerate chemo as well as children)
- Secondary UPS from preexisting lesion (like Paget's, bone infarct, or radiation) has even worse prognosis

Fibrosarcoma of Bone:

- Rare, most common in patients > 40 years of age
- Most commonly in femur, lytic lesion of metaphysis, 25% occur with preexisting lesion
- Pathology demonstrates herringbone pattern
- Staging and treatment is similar to osteosarcoma (chemo, surgery, chemo)
- Slightly worse prognosis compared to osteosarcoma

Chondrosarcoma:

- Occurs in adults > 40 years of age
- Stage and grade associated with prognosis
- **Worse prognosis with pelvic and axial tumors**
- **Increased telomerase activity (detected by PCR testing) associated with increased grade of tumor and risk of local recurrence**
- Low-grade chondrosarcomas (atypical cartilage tumors) can be difficult to differentiate from enchondroma
 - Generally are > 8 cm, demonstrate endosteal scalloping, and associated with pain
 - If there is cortical breakthrough or soft tissue component think of higher grade tumor
 - Generally do not metastasize (some use nomenclature of atypical cartilage tumor)

- Treat with curettage and bone grafting (15% risk of recurrence and 5% risk of differentiation into high-grade chondrosarcoma)
- Treat low-grade chondrosarcoma of pelvis with wide excision (no such thing as a low-grade chondrosarcoma of the pelvis)
- High grade chondrosarcoma or any pelvic chondrosarcoma treat with wide excision
- **No role for chemo or radiation, surgery only!** (Always exceptions like metastatic disease, mesenchymal chondrosarcoma, and dedifferentiated chondrosarcoma)
- Clear cell chondrosarcoma
 - Rare tumor involving the epiphysis (proximal femur and humerus are most common)
 - Treat with wide excision (no chemo or radiation)
 - Overall good prognosis
- Mesenchymal chondrosarcoma
 - Very rare chondrosarcoma subtype (probably won't test on it)
 - Treat with chemo and wide surgical excision
 - Poor prognosis

Round Cell Tumors:

Ewing Sarcoma/ Primitive Neuroectodermal Tumor (PNET)

- Second most common primary bone tumor in children (80% < 20 years of age)
- **t11:22 (EWS/FLI1 fusion gene)**
- Pain is most common presenting symptom
- Staging: Bone marrow biopsy, CT chest, whole body bone scan, x-ray and MRI of entire involved bone, +/- whole body PET/CT
- Differential = infection, EG, Lymphoma, osteosarcoma
- Path = **small round blue cells, CD99 positive, t11:22 EWS/FLI1 fusion**
- Treat with neoadjuvant chemo, wide surgical excision, Radiation is controversial but can be used for local control alone or with surgery
- Worse prognosis with higher grade tumor, higher stage tumor, <90% necrosis, large tumor volume, pelvic tumors, metastatic disease

Chordoma

- Slow-growing primary bone malignancy of notochordal rest cells, occurring in axial spine (**sacrum** or base of skull/c-spine)
- Females 3:1, > 40 years of age, sacrum most common
- Pathology demonstrates **physaliferous cells with intracellular vacuoles**
- Treatment is wide surgical excision (radiation is controversial sometimes is utilized, but generally is not sensitive to radiation)

Adamantinoma

- Rare, slow-growing malignant tumor with predilection of **anterior tibia**
- 90% in tibial diaphysis
- "soap bubble" appearance with well-circumscribed multiple lytic lesions with dominant expansile lesion
- Pathology demonstrate **nest of epithelial cells** in columnar appearance and **keratin-positive**
- Treat with **wide excision only** (chemo and radiation not indicated), typically requires intercalary allograft
- Overall good prognosis about 87% at 10 years

BENIGN BONE TUMORS

Bone forming Benign Bone Tumors:

Osteoid Osteoma

- Painful bone forming cortically based tumor
- 5 – 30 years of age, **Central nidus seen on radiographs (confirmed by CT)**
- Release prostaglandins (**PGE-2**) and cyclooxygenases (pain improved with NSAIDs)
- Associated with night pain
- 10-15% occur in spine (posterior elements) and can cause painful scoliosis (nidus at center of concavity)
- Nidus is < 1 – 1.5 cm (if bigger think osteoblastoma)
- **Treat with RFA** (unless near spinal cord or nerve roots then treat with extended curettage)
- Osteoblastoma is larger, generally more aggressive, more commonly involves metaphysis and spine, typically treated with curettage and bone grafting or wide excision

Parosteal Osteoma

- Rare, deposition of reactive bone on the surface of the cortex
- Multiple osteomas associated with Gardner syndrome (colonic polyps, fibromatosis, cutaneous and subcutaneous lesions)
- Rule out parosteal osteosarcoma

Bone Island

- Cortical bone within the intramedullary space, asymptomatic
- Osteopoikilosis is a hereditary syndrome, with multiples bone islands

Cartilage Tumors

Enchondroma

- Benign tumor comprised of mature hyaline cartilage within the medullary space
- Rings and stippled calcifications within the medullary space “popcorn calcification”, lytic expansile lesions when involving the bones of the hand
- Differential = bone infraction or chondrosarcoma
- All ages, most common in 20-50 years of age
- Possibly related to incomplete endochondral ossification (fragments of epiphyseal cartilage displace into metaphysis)
- Should be asymptomatic, commonly incidentally discovered when obtaining radiographs of a painful joint (ie pain due to rotator cuff, OA, meniscus tear etc)
- ½ occur in the hand (most common bone tumor of the hand)
- Rare in the spine or pelvis
- <1% risk of malignant transformation
- Generally 1-10cm in size, may cause < 50 % endosteal erosion
- **Lesions that are > 5 cm, cause deep endosteal scalloping (>50% cortical depth), and are painful should raise concern for chondrosarcoma**
- **Imaging is critical for determining malignancy (biopsy is unreliable)**
- Bone scan not helpful in differentiating malignancy from benign lesion
- Treat with serial radiographs (every 6 months for 2 years per MSTs)
- If pathologic fracture in small tubular bones, treat with splint allow fracture to heal, then curettage and bone graft
- **Ollier’s Disease:** multiple enchondromas, varying degrees, associated with growth abnormalities and deformity, 15-30% lifetime risk of malignancy (chondrosarcoma)
- **Maffucci Syndrome:** multiple enchondromas and soft-tissue angiomas/phleboliths, up to 100% risk of developing chondrosarcoma, also have increased risk of visceral malignancy

Osteochondroma

- The most common benign tumor
- Hamartomatous proliferation of bone and cartilage, likely due to trapped growth-plate cartilage that herniates through the cortex beneath periosteum (sometimes believed to be due to a defect in the perichondrial not of Ranvier)
- Most are solitary
- Grow until skeletal maturity (follow same local and systemic hormones that dictate the growth plates)
- Can be sessile or pedunculated, generally grow/point away from the joint, **medullary space and cortex is continuous with the bone of origin**
- **Risk of malignant transformation is <1%**
- In adults lesions that are getting larger and painful are concerning for malignant transformation, cartilage cap > 2cm (on MRI) is concerning for malignant transformation
- Conservative treatment for asymptomatic lesions, complete excision for those that are symptomatic (excision prior skeletal maturity associated with increased risk of recurrence)
- Multiple Hereditary Exostosis (MHE)
 - **Autosomal Dominant**, multiple osteochondromas
 - **Due to mutation of EXT 1 (most severe), 2, and 3 (least severe) tumor suppressor genes**
 - Associated skeletal deformities and short stature
 - **Risk of malignant transformation is about 5-10%**, most commonly low-grade chondrosarcoma, pelvis is most common location

Chondroblastoma

- Some call “pediatric giant cell tumor”
- 80% < 25 years of age, arises in epiphysis
- **Lytic lesion of the epiphysis** (differential = giant cell tumor, Brodie’s abscess, and clear cell chondrosarcoma)
- Associated pain, loss of range of motion, limp
- Knee is the most common location followed by shoulder and hip
- <1% develop “benign” pulmonary metastasis
- **Chicken wire and cobblestone appearance on pathology**
- 1/3 have secondary ABC
- Treat with curettage and bone grafting

Chondromyxoid Fibroma

- Very rare, occurs in long bones of lower extremity
- Lucent, eccentric lesion, with scalloped and sclerotic rim
- Treat with curettage and bone grafting

Fibrous Tumors

Nonossifying Fibroma (NOF)

- Also known as metaphyseal fibrous defect (MFD) or cortical defect
- Most common pediatric bone lesions, most common in ages 5-15, up to 30% of children with open physes
- Not a true neoplasm, due to failure in ossification
- Eccentric, lytic, cortically based lesion with sclerotic rim
- Diagnostic on radiographs, no need for MRI
- Treat observation, spontaneously regresses (become sclerotic in skeletal maturity)
- For pathologic fractures, initially treat non-op allow fracture to heal, then observe or curettage and bone graft depending upon symptoms

- Jaffe-Campanacci syndrome: multiple NOFs, café au lait pigmentation, mental retardation, heart and eye abnormalities
- Neurofibromatosis: associate with multiple NOFs

Fibrous Dysplasia

- Hamartomatous proliferation of fibro-osseous tissue within bone
- Usually < 30 years of age
- Radiographs demonstrate “ground glass” or “shower door” appearance with cortical thinning and bowing deformity (Shepard’s crook deformity of proximal femur)
- Pathology = fibrous tissue with irregular and poorly mineralized bone forming “Chinese letters” or “alphabet soup” appearance
- Focal or multifocal inability to produce mature lamellar bone (remains as immature, poorly mineralized trabeculae)
- Due to mutations of GS-alpha on chromosome 20q13 causing sustained activity of adenylate cyclase cAMP
- Tissue expresses fibroblast growth factor (FGF-)23 which may cause hypophosphatemia in patients with McCune-Albright Syndrome
- McCune-Albright Syndrome
 - multifocal fibrous dysplasia, precocious puberty, and coast of Maine (bumpy border) skin lesions
 - unilateral bone lesions and skin lesions
- Most common cause of oncogenic osteomalacia (renal phosphate wasting due to FDF-23)
- Mazabraud syndrome: Fibrous dysplasia (usually polyostotic) and intramuscular myxomas
- Treatment: observe for asymptomatic patients, for significant deformities and fractures curettage and bone grafting with internal fixation, high-risk of recurrence with curettage and bone grafting (use cortical bone not cancellous bone)
- About 1% risk of malignant transformation (UPS, osteosarcoma, or fibrosarcoma)

Osteofibrous Dysplasia

- Non-neoplastic fibro-osseous lesion
- Predilection for anterior tibia, can cause anterolateral bowing, pseudoarthrosis occurs in 10-30%
- Radiographs: eccentric, well-defined diaphyseal anterior tibial lytic lesion, with multiple lucent areas with surrounding sclerosis, typically no periosteal reaction, confined to anterior cortex, may expand the cortex
- Differential = adamantinoma
- Pathology = fibrous stroma with islands of woven bone with prominent rimming osteoblasts (unlike fibrous dysplasia)
- Treatment= avoid surgery if possible, bracing as needed, may regress with skeletal maturity

Langerhans Cell Histiocytosis

- Most common in children <20 years of age, known as the great mimicker
- Due to abnormal proliferation of macrophages (histiocytes)
- Differential diagnosis = Ewings, leukemia, and osteomyelitis
- Varying forms and severity of disease
 - Eosinophilic granuloma = bone lesions only, often solitary bone lesion, no visceral involvement, most common
 - Hand-Schuller-Christian disease = widely disseminated disease with triad of diabetes insipidus, exophthalmos, and lytic bone lesions, ages 2 – 10 years
 - Letterer-Siwe disease = fulminant, multi-organ involvement, with hepatosplenomegaly, presents in infancy, usually fatal

- Hashimoto-Pritzker disease = aka congenital self-healing reticulohistiocytosis, a spontaneously resolving form associated with skin eruptions within first months of life
- Punched out lytic lesions, skull, spine, pelvis, or ribs are most common
- Vertebra plana is classic (although only seen in 15% of cases with spinal involvement, however 90% of patients with vertebra plana have LCH) → 90% get better with bracing, rarely needs surgery
- Skeletal survey is best (bone scan unreliable, only shows 35% of lesions)
- Pathology shows eosinophils and langerhan cells (histiocytes) which are kidney bean shaped cells
- Electron microscopy demonstrated Birbeck bodies
- Solitary lesions treated with curettage and bone grafting (or steroid injections)
- Systemic treatment (methotrexate and vinblastine) for disseminated disease

Cystic Bone Tumors

Unicameral Bone Cyst (Simple bone cyst)

- Serous fluid-filled bone lesion, usually seen in patients < 20 years of age
- Possibly a result of temporary failure of medullary bone formation near epiphyses
- Commonly presents with pathologic fracture
- Proximal humerus and femur are most common location
- Lytic, centrally located lesion that starts metaphyseal and moves down diaphysis with skeletal growth
- Bone expansion generally no wider than physis (unlike ABC)
- “Fallen Leaf Sign” cortical fragment that falls to bottom of lesion, pathognomonic for cystic lesion (fracture fragment couldn’t fall through a solid tumor)
- MRI post contrast demonstrated peripheral enhancing lesion (no solid component)
- Pathology = thin fibrous cyst membrane, no endothelial cells
- Often self resolves with skeletal maturity, after fracture 15% will resolve
- Treatment includes steroid injection, percutaneous bone grafting, or open curettage and bone grafting (more aggressive with surgery for lower extremity lesions at risk of hip fx etc)

Aneurysmal Bone Cyst

- Destructive, expansile, reactive bone lesion filled with blood-filled channels
- Most common < 20 years of age
- Can be secondary in 30% of cases (chondroblastoma, giant cell tumor, CMF, Osteoblastoma, FD)
- Primary ABCs are due to translocation and upregulation of USP6 (ubiquitin-specific protease) (aka TRE17) leading to up regulation and induction of MMP-9 (matrix metalloproteinase 9)
- Lytic expansile lesion, generally wider than metaphysis and physis (as opposed to UBC)
- MRI = fluid-fluid levels (serum and blood)
- Most rule out telangiectatic osteosarcoma
- Pathology = blood-filled cyst with giant cells
- Treat with curettage and bone grafting, local recurrence up to 30% may be improved with adjuvants such as phenol or argon beam
- Increased risk of local recurrence with younger age and open physes
- Embolization may be helpful for spinal or pelvic tumors
- Wide excision may be needed if there is severe bone loss/destruction

Miscellaneous Tumors

Giant Cell Tumor of Bone

- Benign, aggressive bone tumor, consisting of undifferentiated mononuclear cells

- Most common in 20 – 50 years of age (> 90% older than 20, as opposed to chondroblastoma)
- Lytic lesion of the epiphysis which extends into the metaphysis, knee is most common location
- Often has secondary ABC component
- If arising from spine usually anterior vertebral body
- Pathology = multinucleated giant cells the look the same as the cells of the stromal background (the stromal cells are the true neoplastic cells!)
- Treat with extended curettage and bone grafting or cementation, high local recurrence rate up to 30% local adjuvants (phenol, argon) may decrease local recurrence
- Locally aggressive lesions with joint destruction may require wide excision and endoprosthesis
- Denosumab may help with bone reconstitution prior to surgical treatment
- Approximately 2% of cases develop pulmonary metastases (always get chest imaging after diagnosis established)

SOFT TISSUE SARCOMAS

- Approximately 11,000 cases per year in the United States
- Commonly present as a painless enlarging soft tissue mass
- Over 100 subtypes of soft tissue sarcoma
- Malignancy of mesenchymal origin (connective tissue)
- Over 50% of soft tissue sarcoma undergo unplanned excision, improper biopsy, and/or have delayed diagnosis
- Unplanned excision associated increase risk of local recurrence, need for more morbid surgery (skin flap or amputation), and in some scenarios (deep, large, high grade tumors) associated with worse overall prognosis
- Any concerning mass clinically should undergo MRI with and without contrast
- On MRI a determinate mass is diagnostic on MRI (ie lipoma, hemangioma) while an indeterminate mass cannot be diagnosed on MRI and requires biopsy (ie sarcoma)
- Sarcoma can present as hematoma (should be concerned if MRI demonstrated hematoma and there is no history of trauma, skin ecchymosis, or blood thinners)
- Always biopsy and have definitive diagnosis prior to treatment
- Image guided core needle biopsy with referral to sarcoma treatment center/orthopedic oncology for proper biopsy
- If surgical biopsy performed utilize longitudinal incision along extensile approach
- Once definitive tissue diagnosis obtained staging studies should be obtained = CT chest without contrast (whole-body PET/CT is a consideration per guidelines), and physical exam of lymph nodes (however lymph node spread is rare)
- Most commonly metastasizes to the lungs
- Sarcoma less commonly goes to lymph nodes (CARES= Clear cell sarcoma, Angiosarcoma, Rhabdomyosarcoma, and Epithelioid sarcoma, Synovial sarcoma increased predilection for lymph node metastases)
- Prognosis is worse with tumors > 5 cm, increasing grade, and increasing stage (stage is most predictive of prognosis as it takes into account all factors)
- General treatment for soft tissue sarcoma = wide surgical excision and radiation therapy (systemic chemotherapy is considered for chemo-sensitive subtypes, and large, high-grade, deep soft tissue sarcomas)
- Soft tissue sarcoma subtypes to be aware of:
 - UPS (undifferentiated pleomorphic sarcoma) = formerly known as MFH, pathologic diagnosis of exclusion as unable to classify into any other subtype, most common high-grade sarcoma in adults
 - Liposarcoma
 - Atypical lipomatous tumor (ALT)/Well-differentiated liposarcoma (WDL) = no potential for metastasis, high risk of local recurrence (20-30%) compared to lipoma, and low risk of

transformation into dedifferentiated liposarcoma. In the extremity termed ALT due to excellent prognosis, and WDL in the pelvis due to more challenging prognosis. **Differentiated form lipoma with MDM2 amplification on FISH.** MRI similar to lipoma, however large (>10 cm, thick fibrous septae, and deep)

- Dedifferentiated liposarcoma = ALT/WDL that has dedifferentiated into high grade sarcoma, demonstrated MDM2 amplification
- Myxoid/round cell liposarcoma = adults 30 – 60 years of age, demonstrated **t(12;16)** translocation, known for atypical metastases staging and surveillance studies consider CT chest, abdomen, and pelvis as well as spine MRI
- Pleomorphic liposarcoma = rare, generally patients > 60 years of age, malignant lipoblasts with areas similar to UPS
- Synovial Sarcoma
 - Misnomer, tends to occur around joints (juxta-articular, not intra-articular), but has nothing to do with synovium
 - **Most common soft tissue sarcoma of foot and ankle**
 - **Most common soft tissue sarcoma of young adults**
 - Pathology can be monophasic or biphasic (epithelioid/glandular and spindle cell areas)
 - Cytogenetics **demonstrate t(x;18)(p11.2;11.2) producing SYT-SSX1 (may have worse prognosis) and SYT-SSX2 fusion proteins**
- Leiomyosarcoma
 - Cell of origin is smooth muscle (uterine wall and veins of retroperitoneum, pelvis, and superficial extremities)
 - Actin and vimentin positivity on immunohistochemistry
- Malignant Peripheral Nerve Sheath Tumors (MPNST)
 - Associated with NF1 (about 10-13% lifetime risk)
 - Aggressive and fast growing with poor survival (30-40% at 5 years)
- Clear Cell Sarcoma
 - Aka malignant melanoma of soft parts
 - Cytogenetics demonstrates **t(12;22)**
 - Associated with lymph node metastasis
- Angiosarcoma
 - Typically older patients > 60 years of age, and often arise from the skin
 - Generally aggressive
 - May have sensitivity to taxol and VEG-f inhibitors
- Epithelioid sarcoma
 - **Most common soft tissue sarcoma of the hand**
 - Generally slow growing can be mistake for clinically benign lesions
 - Typically occur in patients < 40 years of age
 - Tendency for lymph not metastasis (role of sentinel lymph node dissection is unclear)
- Dermatofibrosarcoma Protuberans (DFSP)
 - Low-grade, dermal sarcoma of young adults
 - Painless enlarging skin plaques and lesions
 - Treat with wide excision only
 - Rarely develop into high-grade fibrosarcoma
- Ewing sarcoma (extraskeletal) and PNET (primitive neuroectodermal tumors)

- Treat with wide surgical excision and radiation
- Chemosensitive and generally treated with high-dose chemotherapy
- Fibrosarcoma
 - Herring bone pattern on histology
- Rhabdomyosarcoma
 - **Most common soft tissue sarcoma in children**
 - 4 types
 - Embryonal: infants and young children
 - Alveolar: adolescents and young adults
 - Botryoid: “bunch of grapes” typically vaginal
 - Pleomorphic: older adults
 - Cytogenetics demonstrates **t(2;13) creating fusion protein Pax-3-FKHR** (associated with increased risk of metastases)

BENIGN SOFT TISSUE TUMORS

- Clinical evaluation is critical to determine if there is concern for malignancy
- Tumors that are large (>5cm), deep to fascia, or enlarging are concerning for malignancy and should have MRI with and without contrast
- Tumors that are static, < 3.2 cm, and subcutaneous have 6% risk of being malignant
- Masses that fluctuate in size are almost never malignant
- Intra-articular masses are almost never malignant (except if there direct invasion from bone)
- Ultrasound helpful to determine if mass is solid or cystic (also helpful to evaluate for flow in vascular tumors)

Lipoma

- Benign tumor of adipose tissue
- Pathology = **mature adipocytes**
- Determinate lesion (no biopsy needed as it is diagnostic on MRI which demonstrates homogenous mass that is **isointense to fat on all sequences and lacks significant post-contrast enhancement**)
- Treat with observation versus marginal surgical excision

Atypical lipomatous tumor

- Similar to lipoma on MRI except large, deep, and thick fibrous stranding
- Differentiated from lipoma after marginal excision with **MDM2 amplification**
- Increased risk of local recurrence 20-30% and low risk of dedifferentiation into high-grade liposarcoma

Venous malformation (often referred as intramuscular hemangioma)

- Common in patients < 30 years of age
- Lesion fluctuates in size
- Pain worse after activity (lesion is encouraged with blood)
- Phleboliths seen on radiographs and MRI demonstrates “ bag of worms”
- Symptomatic lesions treated with **sclerotherapy**
- Surgical excision associated with high risk of recurrence

Peripheral nerve sheath tumor

- Schwannoma
 - “Bright like a lightbulb” on T2 sequence
 - Positive Tinels sign

- Pathology = spindle cells (Antoni A) and hypocellular area (Antoni B), the combination together makes Verocay bodies (palisading formation)
- Symptomatic lesions treated with marginal excision
- Neurofibroma
 - Most commonly arise sporadically, but can occur in NF1 and NF2
 - Rapidly enlarging neurofibroma may suggest MPNST
 - MRI = target sign
 - Surgical excision for symptomatic lesions (high risk of nerve injury than schwannoma as tumor arises from nerve fibers)

Intramuscular myxoma

- Myxoid is Greek for mucus
- Myxomatous tumor of muscle
- T2 hyperintense lesion
- Mazabraud syndrome = multiple myxomas and fibrous dysplasia
- Marginal excision for symptomatic lesions

Desmoid tumor (extra-abdominal fibromatosis)

- Benign locally aggressive tumor
- High risk of local recurrence with surgical excision
- Same family as superficial lesions (dupuytren contracture and Ledderhose disease)
- More common in patients with FAP (familial adenomatous polyposis)
- Typically dark and dark on T1 and T2 (fibrous tumor)
- Treatment is challenging and evolving, watchful waiting for stable lesions
- Wide surgical excision for enlarging tumors
- Consider tyrosine kinase inhibitors for refractory disease or unresectable disease
- Radiation in some clinical scenarios

Synovial Chondromatosis

- Metaplastic proliferation of hyaline cartilage nodules within synovial membrane
- Hip and knee most common, typically 30-50 years of age
- Open or arthroscopic synovectomy

Pigmented Villonodular Synovitis (PVNS)

- Aka tenosynovial giant cell tumor of tendon sheath (diffuse type)
- Most common neoplastic cause of joint erosion/destruction
- Recurrent hemarthrosis leading to early osteoarthritis
- GRE sequence on MRI demonstrated bloom artifact (metal artifact from hemosiderin)
- Treat with open or arthroscopic synovectomy
- TKA for degenerative knee
- Tyrosine kinase inhibitors may be considered for severe disease

Myositis Ossificans

- Often due to trauma of skeletal muscle (can present without history of trauma)
- Injury leads to calcification and ossification of soft tissue
- Zoning pattern with peripheral calcification (as opposed to Extraskeletal osteosarcoma)
- Not attached to nearby bone (as opposed to surface osteosarcoma)
- Self-limiting process
- Marginal excision for symptomatic lesions, only after lesion is mature (6 to 12 months)

COMMON ASSOCIATIONS AND TABLES:

Treatment of Bone Sarcomas (remember chemo and radiation only work on cells that divide fast i.e. not low-grade tumors)

- Osteosarcoma (also include UPS, fibrosarcoma of bone, high-grade surface osteosarcoma): chemo, surgery, chemo
- Parosteal osteosarcoma: wide surgical excision
- Ewings: chemo, surgery, chemo (+/- radiation)
- Chondrosarcoma: wide surgical excision only
- Chordoma: wide surgical excision
- Adamantoma: wide surgical excision

Treatments of Soft Tissue Sarcoma

- Wide surgical excision and radiation therapy (chemo is considered in chemosensitive subtypes (myxoid liposarcoma), metastatic disease, and high grade, deep, large tumor >5cm)
- DFSP: wide surgical excision

Staging of Bone Sarcomas

- MRI with and without of entire bone involved, CT chest without, Whole bone scan, whole body PET/CT, labs (alk phos, LDH)

Staging of Soft Tissue Sarcoma

- MRI of entire tumor, CTR chest without, lymph node physical examination, consider whole body PET/CT

Work Up of Unknown Lytic Lesion of Bone in Patient > 40 Years of Age

- X-ray of involved bone, CT with chest, abdomen, and pelvis, whole body bone scan, labs (SPEP/UPEP, PSA), biopsy of most accessible location

Common Sarcoma Translocations

Diagnosis	Translocation	Gene/Fusion Protein
Ewing's	t(11;22)	EWS-FL1
Rhabdomyosarcoma	t(2;13)	Pax3-FKHR
Myxoid Liposarcoma	t(12:16)	TLS-CHOP
Synovial Sarcoma	t(x;18)	SYT-SSX1, 2, or 3
Clear Cell Sarcoma	t(12;22)	EWS-ATF1

Epiphyseal Bone Tumors

- Chondroblastoma
- Giant cell tumor
- Clear cell chondrosarcoma

Diaphyseal Tumors

- Ewing's
- Langerhans Cell Histiocytosis
- Lymphoma

Infection

Intra-articular Tumors (almost never malignant)

PVNS

Synovial chondromatosis

Lipoma arborescens

Imaging of Soft Tissue Tumors

PVNS = Blooming artifact on GRE sequence

Lipoma = isointense to subcutaneous fat on all sequence without significant post-contrast enhancement

Atypical lipomatous tumor = lipoma that is large, deep, and thick (>4 mm) fibrous stranding

Peripheral nerve sheath tumor = "Bright like a light bulb" on T2, "target sign," "string sign"

Intramuscular hemangioma = "salt and pepper" with flow on ultrasound

Myositis ossificans = peripheral calcifications

Soft tissue sarcoma = Dark on T1 and Bright on T2 with heterogeneous post-contrast enhancement