Orthopaedic Oncology
OITE Review Course

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Introduction

In the evaluation of a patient with a bone tumor, there are several areas where data can be gathered that impact upon the differential diagnosis. These include the history, physical examination, and review of imaging studies. Ultimately, it may be determined that histologic confirmation is required at which time careful evaluation of lesional tissue will confirm a specific diagnosis.

The history associated with the presence of a musculoskeletal tumor defines the clinical context of the lesion. Age, Sex, duration of symptoms, presence and quality of pain, history of trauma, weight loss, smoking history and history of prior malignancy are all important historical factors. Critical to the early diagnosis of a skeletal tumor is an appreciation of the fact that the early symptoms associated with skeletal neoplasms mimic all types of ordinary musculoskeletal disorders. Any pain that extends beyond the expected duration associated with a tentative diagnosis should raise the suspicion of an underlying tumor. Night pain is another red flag again leading to the supposition of an occult lesion although many non-neoplastic conditions may also cause pain at night.

One of the most disorienting parts of a history in a patient with an occult tumor is a history of trauma. Frequently patients will experience some mild trauma to the affected area and then notice pain which would probably not have occurred in the absence of an underlying lesion. This is frequently not clear to the patient however who directly attributes the local symptoms and findings to the traumatic event. The history related in this way frequently fools a treating physician who then follows the local lesion until it becomes obvious that the true nature of the lesion goes well beyond a minor trauma. An example of this is the story related by a waiter who kicked a kitchen door to open it while carrying a heavy tray. The door was stuck and did not move resulting in an apparent calf injury. When the pain did not resolve, a compartment syndrome was suspected and it was not until several months later that tissue was obtained which revealed an underlying lymphoma. Similar is the history of an elderly female on full dose warfarin for a mechanical heart valve who bumped her thigh on a kitchen table and found
out months later that the large anterior thigh mass was a soft tissue sarcoma and not a simple hematoma. It is only through intellectual discipline and diligence that early diagnoses can be accomplished.

The easiest way to assemble a complete differential is to have memorized or available a reasonable list of common lesions to review as you contemplate each set of x-rays. Without such mental organization, it is difficult or impossible to assemble a comprehensive differential diagnosis of a particular lesion. The following three lists are separated into bone-forming, cartilage-forming and a “third list” of a variety of lesions. By going through these lists each time an x-ray is reviewed, one can make sure to include most relevant lesions in a specific differential diagnosis.

### TABLE 1 - Radiographic Differential Diagnosis:

<table>
<thead>
<tr>
<th>Bone Forming Tumors</th>
<th>Cartilage Forming Tumors</th>
<th>“Third List”</th>
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<tr>
<td>Osteoid Osteoma</td>
<td>Osteochondroma</td>
<td>Infection</td>
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<td>Stress fracture</td>
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In order to include or exclude lesions in a differential diagnosis it is imperative that the Orthopaedist have a clear image of each archetype lesion as well as an appreciation of the variability possible within the range of presentations. It is also important to keep in mind that not all bone forming tumors will show obvious bone formation on an x-ray and the same is true of chondroid lesions which also may show no obvious chondroid calcification on plain x-ray. The following is a short summary of the radiographic and clinical features associated with each of the common lesions and imaging studies showing a prototype or typical radiographic presentation:
**Osteoid osteoma:** Most common during the first two decades and appears as a small lytic nidus often with a “target” appearance surrounded by significant sclerosis (Figure 1). The nidus may be very tiny and difficult to find on x-ray. MRI scans will show extensive edema which may be confused with a marrow replacing neoplasm. CT scans with fine cuts (i.e. 1 mm) are the study of choice for finding the lesion (Figure 2). Bone scintigraphy shows focal intense uptake. Osteoid osteomas are associated with a classic pattern of constant pain relieved very well but for short periods by prostaglandin inhibiting drugs such as aspirin or ibuprofen.

**Osteoblastoma:** This is a rare neoplasm most often seen in the posterior elements of the spine or in the meta-diaphyseal region of long bones. It has a very variable appearance and may be blastic or lytic. It is rarely diagnosed correctly before histologic material is reviewed. The classic appearance is that of a calcified lesion in the posterior elements of the spine (Figure 3).
**Osteochondroma:** Osteochondromas are formed by radial growth of bone during childhood such that the lesion grows out away from the bone at an angle from the adjacent growth plate. The hallmark of an osteochondroma is that because it grows out from the underlying bone, the cortex of the bone is confluent with the cortex of the lesion and it pulls medullary bone up into itself (Figure 4). A tumor that is sitting on an intact cortex is never an osteochondroma. Osteochondromas can be sessile or pedunculated. Many that grow out of the flat bones or the proximal femurs can be very large and take on a “cauliflower” appearance. Secondary chondrosarcomatous degeneration should be suspected in any osteochondroma which grows after puberty or has a cartilage cap of greater than three centimeters during adulthood.

**Osteosarcoma:** These typically occur in the first three decades with a second peak beyond the sixth decade and present as permeative metaphyseal lesions with soft tissue extension and new bone formation (Figure 5). Periosteal reaction is common and frequently takes on a sunburst or “hair on end” appearance. Osteosarcoma needs to be in the differential of every aggressive lesion seen in bone in all age groups. It may appear as a purely lytic lesion with no radiographically apparent bone formation.
**Blastic metastasis:** These are most frequently seen with prostate and breast carcinoma and typically present as a permeative lesion with infrequent soft tissue extension.

**Paget’s disease:** This is a great mimicker and can take on a whole variety of appearances. Early Paget’s disease is lytic while late Paget’s disease is blastic showing coarse trabeculae and thickened cortices (Figure 6).

![Figure 6](image)

**Chondroblastoma:** This is an easy diagnosis. It typically appears as a painful lytic lesion in the epiphysis of a child (Figure 7) with significant edema seen on MRI scan. In older adolescents, it can occasionally grow across an old epiphyseal line to involve the adjacent metaphysis. This classic picture of a painful epiphyseal lytic lesion with abundant edema may cause this lesion to be confused with infection and even osteochondritis dessicans.

![Figure 7](image)
**Chondromyxoid fibroma**: A rare tumor usually seen as a lytic metahpyseal lesion with cortical thinning but no periosteal reaction (Figure 8). It is most frequent in the first three decades of life and is most commonly seen in the proximal tibia. It frequently has the appearance of a very large non-ossifying fibroma.

**Enchondroma**: This is a nest of cartilage tissue typically in a metathypseal region which is usually encountered as an incidental finding in adulthood (Figure 9). They are commonly discovered when an x-ray of the adjacent joint is obtained for reasons unrelated to the enchondroma itself. These lesions tend to be non-calcified or minimally calcified in young adults and usually show an increase in calcification but not an increase in size with follow-up over many years. The calcification has a typical stippled or “popcorn” pattern. They usually do not cause pain but they are typically hot on technicium bone scan. Unlike chondrosarcomas, enchondromas do not cause damage to the host bone in so much as they do not cause cortical thinning or expansion. They may cause some slight scalloping but the scallops seen on x-ray are usually short at less than one centimeter each. One exception to the look of enchondromas is seen when they occur in thin or small bones such as the fibular head or scapula. In these cases some expansion may be seen. It is helpful to keep in mind the notion that “enchondromas do not know what bone they are in.” As such when they grow to a typical size they may cause some cortical expansion in small or thin bones.
Chondrosarcoma: Unlike enchondromas, chondrosarcomas are active lesions which grow and alter the host bone over time (Figure 10). Working from the inside of the bone to the outside, the changes associated with chondrosarcoma include intralesional lysis, endosteal scalloping, cortical thinning and expansion. They also cause pain. Most will show chondroid calcification but some may appear purely lytic.

Infection: This is another great mimicker or other lesions and can take on a variety of appearances from geographic to permeative and from lytic to blastic. Periosteal reaction is common as are localized heat and erythema.

Metastasis: This is the most common cause of aggressive destructive lesions in adults and again can take on a variety of appearances from lytic to blastic. It frequently occurs as multiple lesions and may be the first presentation of the underlying neoplasm.

Round cell tumors: Pediatric round cell lesions include Ewing’s sarcoma and metastatic neuroblastoma. Ewing’s classically presents as a diaphyseal permeative lesion with “onion skin” periosteal reaction and a large associated soft tissue mass or it may be more metaphyseal and destructive (Figure 11). Twenty percent of patients will have associated systemic symptoms such as fever, chills and a high white blood cell count which may cause the lesion to mimic osteomyelitis.
Neuroblastoma (Figure 12) appears as a permeative lesion with medullary bone replacement and varying lysis. Adult round cell lesions include myeloma and lymphoma. Myeloma (Figure 13) occurs as solitary or multiple medullary lytic lesions with sharp margins but little reaction.

Lymphoma (Figure 14a and 14b) is typically a very permeative but minimally destructive lesion. The usual progression is that lymphomas fill up the medullary canal and then grow into the surrounding soft tissues while causing little destruction of the bone itself. X-rays may be remarkably normal while MRI scans show marrow replacement and often an associated soft tissue mass.
**Unicameral (Simple) bone cyst:** Most common in the proximal humerus, these are always central, full width lesions which may cause cortical thinning and minimal expansion but usually have no associated periosteal reaction. The widest portion of these lesions is usually no wider than the widest portion of the adjacent metaphysis (Figure 15).

![Figure 15](image)

**Aneurysmal bone cyst:** As the name implies, these lesions are usually very expansile or aneurysmal (Figure 16). They frequently have a delicate rim of expanded cortical bone which may be best seen on CT scan. Fluid-fluid levels are frequently seen but are not diagnostic of primary ABC as areas of secondary ABC formation may exist in other lesions such as Osteosarcoma, Giant cell tumor etc. These are usually found as eccentric metaephyseal lesions in patients in the first three decades.

![Figure 16](image)
**Non-ossifying fibroma:** These are usually eccentric metaphyseal lesions in children which grow to varying sizes (Figure 17). As growth of the patient continues and external remodeling occurs, lesions that were previously intramedullary in the metaphysis become intracortical in the metadiaphysis. This cortical disruption creates a mechanical insufficiency and causes the bone to replace the lesion with new bone formation as the lesion heals in.

**Fibrous dysplasia:** The classic fibrous dysplasia lesion occurs as a long lesion in a long bone with ground glass medullary calcification and cortical thinning but no periosteal reaction (Figure 18). Beyond that, fibrous dysplasia can have a very variable appearance and should be included in the differential of every benign appearing lesion in bone.
**Giant cell tumor:** This appears as a juxta-articular lytic lesion frequently with cortical thinning and expansion, possible soft tissue extension but usually no periosteal reaction (Figure 19). It is very rarely seen before growth plates are closed or after the age of 50 years.

**Langerhan’s cell histiocytosis:** This is an inflammatory condition which usually presents as intramedullary lysis in patients in the first three decades (Figure 20). The larger the lesion grows and the closer to a cortex it becomes the more likely it is to show some associated sclerosis. These lesions may also occur on the surface of a bone where they occasionally elicit an aggressive appearing periosteal reaction which simulates a malignant tumor radiographically. Histiocytosis must be considered in the differential of any intramedullary lesion in a young person.

**Metabolic conditions:** This category includes a wide variety of underlying diseases including osteoporosis, osteomalacia, renal osteodystrophy and any other metabolic condition affecting bone formation or healing.

**Trauma:** While obvious blunt trauma does not usually mimic tumors, stress fractures may mimic and be confused with lymphoma, osteoid osteoma, metastasis and infection to name just a few.
In addition to the lists above there are specific differentials that one should appreciate and which should come to mind in the presence of certain x-ray findings.

1. Sclerotic soap bubble lesion in the anterior cortex of the shaft of the tibia: adamantinoma vs. cortical fibrous dysplasia

2. Sclerotic lesion with a central lytic nidus: Osteoid osteoma vs. stress fracture vs. infection. Since many stress fractures or stress reactions involve intramedullary edema, they can mimic lymphomas which also cause intramedullary MRI changes and so lymphoma should always be considered in the differential of a stress reaction. Sequential MRI scans will demonstrate healing of a stress reaction but no healing of a lymphoma which may appear stable or progressive.

3. Cauliflower exophytic lesion: cauliflower osteochondroma vs. secondary chondrosarcoma arising in an osteochondroma. Remember to measure the thickness of the cartilage cap.

4. Multiple lesions in bone: metastases, myeloma, enchondromas, histiocytosis, fibrous dysplasia, non-ossifying fibromas

5. Lytic lesion in the humeral shaft in a child with no periosteal reaction: simple bone cyst

6. Lytic lesions in the sacrum: chordoma, chondrosarcoma, giant cell tumor, metastasis, myeloma

7. Calcified lesion on the surface of a bone: osteochondroma, periosteal osteosarcoma, parosteal osteosarcoma, myositis ossificans, periosteal chondroma, periosteal chondrosarcoma.

8. Aggressive meta-epiphyseal lesion in young patients (less than 30 years): Osteosarcoma, Ewing’s sarcoma, infection, ABC and giant cell tumor.

9. Aggressive meta-epiphyseal lesion in older patients (older than 30 years): osteosarcoma, chondrosarcoma, metastasis, adult round cell tumors, giant cell tumor

10. Lytic lesion in the epiphysis of a child with edema seen on MRI: Chondroblastoma vs. infection
Armed with this radiographic information, one should be able to assemble very complete differential diagnoses of most lesions encountered. As an exercise we can go through an unknown and try out this technique. Figure 21 shows an x-ray of a 19 year-old male with a six week history of progressive knee pain; worse at night and with weight bearing. The x-ray shows a juxta-articular lytic lesion in the proximal tibia with a moth eaten margin, cortical thinning but no periosteal reaction. A reasonable differential diagnosis using our “3 lists” and in light of the patient’s age includes: osteosarcoma, infection, Ewing’s sarcoma, giant cell tumor and aneurysmal bone cyst. Biopsy proved the lesion to be a giant cell tumor.

If the same x-ray was from a 50 year-old male the differential by age would include: osteosarcoma, chondrosarcoma, metastasis, myeloma, lymphoma and giant cell tumor. In either case, having a list of lesions to mentally review greatly increases the completeness of a radiographic differential and aides in including lesions which should be considered.

In terms of imaging studies other than x-rays, several factors should be understood.

**CT Scans:** The major value of a CT scan is to show bone detail. This includes bone formation as well as bone destruction. CT scans are the best study to see how much bone is destroyed and whether or not soft tissue calcification is present. It is not optimal for looking for the extent of a permeative lesion in bone, soft tissue extension from a bone lesion or the extent of a lesion in soft tissue.

**MRI scans:** MRI scans are excellent for showing the extent of a lesion in bone i.e. where it starts and stops. It is also excellent for showing the presence and extent of edema within bone and the presence or absence of an associated soft tissue extension. MRI is the study of choice for any soft tissue lesion. The
addition of contrast to an MRI scan can also help elucidate areas of cyst formation which do not contrast enhance (but may show rim enhancement) from areas of solid tumor which do enhance. One exception to this is chondroid lesions such as low grade chondrosarcoma which may also show rim enhancement with little internal enhancement and thus mimic a cyst. One must always be careful in differentiating between edema in bone and tumor in bone. As such, lymphoma frequently presents as high signal in marrow and must be in the differential of traumatic marrow lesions such as stress fracture.

**Technetium Bone Scan:** Bone scans are most useful when utilized as a skeletal survey tool to look for the total number of lesions present or when a singular lesion is suspected but not seen on initial x-ray. All active bone forming lesions are hot while some lytic lesions which engender no bone reaction may be normal or cold (e.g. myeloma). Sclerotic lesions which are normal on bone scan are usually old and inactive.

**Biopsy**
Once all imaging studies have been obtained, the next step in confirming a diagnosis is the biopsy. Not all lesions require a biopsy however, as many benign and inactive lesions may be diagnosed via imaging studies alone. The ideal biopsy is one which provides all tissue needed to establish a histologic diagnosis without affecting subsequent treatment options. The biopsy has been a source of much consternation and several series have been reported which enumerate the problems of biopsies done poorly. As a result, much confusion has arisen in regard to who should perform a biopsy, i.e. a community Orthopaedic surgeon or a specialized Orthopaedic Oncologist. A reasonable rule of thumb is that as a community Orthopaedist, if you encounter a lesion and you can determine by presentation and imaging studies that you will not treat it, then refer it without biopsy to a tumor specialist. A good example of this would be a 17 year old male who presents with a large painful mass about the distal femur and an x-ray which is classic for osteosarcoma. Most community Orthopaedic surgeons would not treat this lesion and so it
makes sense to send it directly to a subspecialist trained to biopsy this tumor. If, however, you understand
the principles of biopsy, decide that that you would treat the most likely diagnoses and have pathologists
on hand who can make the suspected diagnoses; then it is very reasonable to biopsy the lesion in the
community setting. Intrinsic in this decision to biopsy a particular lesion is the idea that the treating
surgeon should be very familiar with the guidelines concerning type of biopsy performed and biopsy
techniques.

Current biopsy options include both open and needle techniques. The advantage of percutaneous needle
biopsies is that they cause little soft tissue contamination and require little or no anesthesia. They are
frequently performed under CT scan or ultrasound guidance and can direct a biopsy needle into an
underlying lesion. The disadvantage of this technique however is that it provides only a small amount of
tissue for the pathologist to review. As such it can frequently be non-diagnostic. More importantly, it
must be remembered that primary bone tumors are notoriously heterogeneous thereby creating a great
potential for sampling error with closed techniques. Needle biopsies are optimal for initial sampling of
lesions in anatomically inaccessible areas such as the spine or pelvis. In most locations, however, the
carefully performed open biopsy is still the gold standard. The rules for open biopsy are as follows:

1. Use as small an incision as possible placed over the lesion

2. The incision should be longitudinal on the extremities and well planned on the trunk to be part of a
   resection incision.

3. While it is fine to use an extremity tourniquet above an extremity tumor, use of an Esmarch
   bandage over a tumor may rupture the tumor into the surrounding tissues and should be avoided.

4. Make a small incision into the capsule of a tumor so that it can be closed easily. This is especially
   important when there is no tourniquet used as bleeding may be appreciable and difficult to control
   with a large incision. It is a good rule to never make an incision into a tumor larger than the
   surgeon can fill with his or her fingertip so that bleeding can be effectively controlled. If excessive
bleeding is not encountered and if a larger incision is required, it may then be performed.

5. Try not to directly contaminate a neurovascular bundle when possible.

6. Try not to violate major flap structures (e.g. Gluteus maximus) or functionally important structures (e.g. Rectus femoris).

7. Utilize minimal retraction to limit soft tissue contamination.

8. It is better to go through a single muscle belly if it is large enough than to go between two structures which contaminates both.

9. Obtain good hemostasis by a meticulous multilayered water-tight closure. This is an essential step. Many large tumors put the closure under pressure and the vascularity commonly seen predisposes to subsequent drainage. Any wound complication will increase the risk of secondary infection and may delay subsequent chemotherapy or radiation.

10. Drains should not be used routinely. If needed they should be thin and brought out one to two centimeters beyond one end of the incision so that the drain track can be easily resected with the biopsy track.

11. Obtain a frozen section when feasible to insure that diagnostic material has been obtained. Tumors can often be very necrotic and it may take a large volume of tissue before diagnostic material is encountered. It is certainly easier to get more tissue while the patient is still prepped and draped in the operating room than several days later if the biopsy was insufficient.

12. Whenever feasible during a diagnostic open biopsy, the operating surgeon should accompany the specimen to the pathology department with imaging studies in hand. In this way, the pathologist can review the specimen and frozen section slides with the surgeon in light of the imaging studies and clinical history.

**Histologic Evaluation**

The histologic diagnosis of musculoskeletal tumors is very difficult and complicated. Good musculoskeletal pathologists require years of training and many more years of practice in order to develop
the skills needed for the correct diagnosis of difficult musculoskeletal tumors. Despite this, it is possible as an Orthopaedic Surgeon to develop a method for the systematic approach to histologic diagnoses which will orient you to the possible histologic differential diagnosis of a particular lesion and help you to participate in the diagnostic process for your patients. One of the difficulties encountered in musculoskeletal pathology is the large number of potential diagnoses. If all of these lesions are considered separately, it may become overwhelming for the Orthopaedist to try to place a specific lesion into a reasonable differential diagnosis. If one realizes, however, the trends and patterns that run through groups of histologic lesions as well as the relationship of histologic findings to a differential diagnosis based on available imaging studies, then the whole spectrum of histologic diagnoses, at least at an elementary level, is more understandable and less overwhelming.

**Bone Forming Tumors**

There are several lesions to be considered here including fracture callus, myositis ossificans, osteoid osteoma, osteoblastoma, fibrous dysplasia, parosteal osteosarcoma and osteosarcoma. These lesions typically contain woven bone and a spindle cell stroma, each of which need to be scrutinized to understand the nature of the lesion. It should be understood that in looking at bone forming lesions, it is the bone which differentiates reactive from neoplastic lesions and the stromal cells which differentiate between benign and malignant neoplasms. The first order then is to look at the bone produced by a specific lesion. Figure 22 shows a picture of lamellar bone with a surrounding round cell infiltrate (Ewing’s sarcoma) in which the lines of individual bone lamellae can be appreciated. Lamellar bone is rarely ever produced by tumors and is usually just native host bone caught up in a lesion or part of a mature bone reaction. On the other hand, woven bone can be either neoplastic or reactive and woven bone discloses this by the
presence or absence of osteoblastic rimming. Typically, woven bone with significant osteoblastic rimming is reactive (Figure 23) and indicative of fracture callus, periosteal reaction or myositis ossificans. In all of these lesions, spindled stromal cells may also be present and may have some mild atypia (especially in early myositis or early fracture callus). On the contrary, woven bone which shows no osteoblastic rimming (Figure 24) is usually neoplastic in origin and can be seen with both benign and malignant bone forming neoplasms. Neoplastic woven bone (i.e. with no osteoblastic rimming) seen in association with a benign spindle cell stroma is indicative of a benign bone forming neoplasm and this is again shown in figure 24. These include osteoid osteoma, osteoblastoma and fibrous dysplasia.

Also included in this histologic differential is parosteal osteosarcoma which is a grade one malignant tumor and as such presents with a stroma which shows little overt atypia. Thus the histologic differential diagnosis for lesions showing neoplastic woven bone and a bland spindle cell stroma include osteoid osteoma, osteoblastoma, fibrous dysplasia and parosteal osteosarcoma. The final pattern seen in bone forming lesions is the presence of neoplastic woven bone (again, woven bone with no osteoblastic rimming) in association with a malignant spindle cell stroma which constitutes osteosarcoma (Figure 25). The findings that make a spindle cell stroma appear malignant include: increased cellularity, spontaneous necrosis, the presence of significant atypia or pleomorphism and a high mitotic rate with many abnormal mitoses.
In summary the patterns to be understood in bone forming lesions are:

1. Reactive lesion: woven bone with osteoblastic rimming and a benign spindle cell stroma. (fracture callus, periosteal reaction, myositis ossificans)
2. Benign or low grade bone forming neoplasm: woven bone with no osteoblastic rimming and a bland appearing spindle cell stroma (osteoid osteoma, osteoblastoma, fibrous dysplasia, parosteal osteosarcoma)
3. Malignant bone tumor: woven bone with no osteoblastic rimming associated with a malignant spindle cell stroma (osteosarcoma)

These bone forming lesions mentioned above tend to look very different radiographically. Thus it is a radiographic differential integrated into the histologic differential with yields the final diagnosis.

**Cartilage Forming Tumors**

There are three patterns of cartilage tumors:

1. Benign cartilage (enchondroma) merging into low grade cartilage which merges into intermediate and high grade chondrosarcoma.
2. Chondroblastoma: cobblestone chondroblasts and intervening chicken wire calcification with immature cartilage.
3. Chondromyxoid fibroma: a benign spindle cell lesion with some areas of immature cartilage.

In pattern one, it is essential to understand the spectrum of cartilage appearances that match the spectrum of histologic grading. Normal cartilage has two components, cells and matrix. Both are important in evaluating cartilage histologically.

Normal cartilage as in Figure 26 is sparsely cellular. The cells have small oval (pycnotic) nuclei and only one nucleus per cell. There is only one cell per lacuna and there are rare cells outside of lacunae. The matrix is well formed and regular with no areas that are loose or falling apart (myxoid change).

The changes that occur in cartilage as one goes from benign to low grade are as seen in Figure 27:

1. increased cellularity
2. the presence of plump nuclei
3. occasional binucleate cells
4. more than one cell in some lacunae
5. some cells outside lacunae
6. myxoid change in the matrix

This finding of “low grade cartilage” basically puts one in the spectrum of lesions ranging from cellular or active enchondroma to what some authors have called “grade ½ chondrosarcoma” to grade one chondrosarcoma. It is critical to appreciate that tumors in this range have a variable biologic potential in terms of their propensity to continue to grow. Throughout this range of lesion, pathologists have no effective means of predicting growth and so it would be arbitrary for them to attempt to artificially draw a line where cellular enchondroma ends and low grade chondrosarcoma begins. As such the term “low grade cartilage tumor” has become popular denoting the fact that the pathologist is acknowledging the position of the tumor in question somewhere within this spectrum of behavior. The key for the treating
A physician is to then look carefully at the clinical history and imaging studies and to make some assessment as to what would constitute a reasonable course of treatment. These options may range from careful observation to curettage to resection depending on a whole host of factors. These factors would include the presence or absence of pain, the age of the patient, the bone involved and the presence or absence of radiographic changes typical of chondrosarcoma as were listed previously.

As one goes further away from normal and closer to high grade malignant, the chondrocytes look less normal and behave in a less normal fashion. They develop dark, plump nuclei. The cellularity increases appreciably and mitoses become more common. The cells make less or no matrix or they start making abnormal matrix which may look nothing like recognizable chondroid (Figure 28).

At the end of this progression of dedifferentiation is high grade sarcoma, not otherwise specified, which is no longer recognizable as chondrosarcoma because it no longer has any chondroid phenotype. Associated with this histologic progression is a progressive increase in biologic potential in terms of local aggressiveness and metastatic behavior.

The second pattern in chondroid lesions is that seen in chondroblastoma. This lesion is usually suspected even before histologic material is available because of its characteristic radiographic and clinical features, i.e. a painful lytic lesion in the epiphysis of a child. Histologically one sees a pattern of “cobblestone” chondroblasts which are polygonal cells with well defined cell borders (Figure 29).
In association with these cells, a branching pattern of calcification labeled “chicken wire” is also common as is the presence of immature chondroid matrix. These histologic findings in association with an epiphyseal lytic lesion in a child yield a fairly straightforward diagnosis of chondroblastoma.

The final pattern seen in cartilage tumors is that seen in chondromyxoid fibroma. This is a rare lesion which is composed of benign spindle cells in a collagenous matrix (Figure 30). In association with this is seen varying amounts of immature chondroid. This histologic pattern seen in association with the typical radiographic findings helps to suggest this diagnosis.

At this point we have now covered the typical lists of bone and cartilage tumors while citing relatively simple trends and a few basic issues of pattern recognition. With the above information in hand, one can accurately diagnose many examples of bone and cartilage forming lesions by first assembling a radiographic differential via the radiology lists and then looking at the spectrum of histology of bone and cartilage forming lesions to put things together and decide on a specific diagnosis.

In order to test this technique, let us consider the following example. The x-ray shown in Figure 31 is from a forty year old female with a recent history of knee pain who has been in good health. The x-rays show an aggressive lytic lesion in the distal femur with cortical bone destruction and soft tissue extension. The radiographic differential of this lesion includes osteosarcoma, chondrosarcoma, metastasis, myeloma, lymphoma, and giant cell tumor.
The histology shows woven bone with no osteoblastic rimming compatible with neoplastic woven bone (Figure 32). Also seen histologically is a malignant spindle cell stroma. The final diagnosis is osteosarcoma with which the x-ray is also compatible. This straightforward approach to the differential diagnosis of these lesions may seem simplified and it is, but it is also based on the premise that the accurate diagnosis of typical cases can be simplified by understanding the trends which underlie the radiographic and histologic classifications. Obviously many cases present much more difficulty in interpretation and for which correct histologic diagnosis may be challenging or impossible even in the hands of renowned experts. Remember, this is not a system that will encapsulate and diagnose every musculoskeletal lesion but rather a framework by which one can develop an approach to these diagnoses.

**Round Cell Tumors**

A third group of bone lesions which can be understood by approaching those as a whole are round cell tumors. These include Ewing’s sarcoma and neuroblastoma in children as well as myeloma, lymphoma and small round cell metastatic carcinomas in adults. Also included in the differential diagnosis of this group are non-malignant lesions such as Langerhan’s cell histiocytosis and infection. The common thread between all of these lesions is that they are composed in part or in whole of small round cells. As such, when confronted with a round cell infiltrate in a histologic slide from a bone lesion, one must consider the following classes of disorders:

1. Infection (i.e. osteomyelitis)
2. Langerhan’s cell histiocytosis
3. Primary round cell tumors
4. Small round cell metastatic carcinomas

The histology of bone infection includes the presence of acute and chronic inflammatory cells. While
lymphocytes which tend to be associated with chronic inflammatory conditions may resemble lymphoid cells seen in lymphoma, polymorphonuclear leucocytes (polys) are usually easy to visualize and, when present in large numbers lead one to a diagnosis of infection. Thus when a round cell infiltrate is seen and most of the cells can be shown to be polys then infection is the likely diagnosis. Confirmation of course requires culture of an appropriate pathogenic bacterium.

Langerhan’s cell histiocytosis is also a type of inflammatory condition in bone. As the name implies it is composed of foci of proliferating histiocytes but also demonstrates varying numbers of small round cells including lymphocytes, neutrophils and, most notably, eosinophils. Histiocytes are difficult for non-pathologists to recognize. They are large cells with ill-defined cytoplasmic borders and an oval or indented nucleus.

Eosinophils are easy for even Orthopaedists to recognize as they are small round cells with bilobed nuclei and red cytoplasm. Figure 33 demonstrates the presence of both of these cell types in this example of Langerhan’s cell histiocytosis. So, when diagnosing histiocytosis, Pathologists look for histiocytes and Orthopaedists look for eosinophils.

Pediatric round cell tumors occurring in bone include Ewing’s sarcoma and metastatic neuroblastoma. Ewing’s sarcoma is a malignant tumor of unknown histogenesis composed of uniform sheets of small round blue cells. These cells show round or oval nuclei of uniform size with poor delineation of cytoplasm. Stains for intracellular glycogen are typically positive. Neuroblastoma occurring in bone is usually a metastasis from a primary tumor in the midline. The cells of neuroblastoma look similar to those of Ewing’s sarcoma but show the presence of pseudo-rosettes.
These are circles of round cells surrounding a pink ground substance as seen in figure 34. So, in pediatric round cell tumors, small round blue cells with no pseudo-rosette formation is typical of Ewing’s sarcoma while similar appearing cells which also show pseudo-rosette formation are typical of neuroblastoma.

Adult round cell tumors include myeloma, lymphoma and small round cell metastatic carcinomas. Myeloma is, for the most part, easily recognizable (when well differentiated) by the fact that it is composed of sheets of plasma cells. Plasma cells (Figure 35) have a single round or oval nucleus with eccentric cytoplasm.

The cell outlines are distinct and the nuclei often show prominent clumping of chromatin which produces a “clock face” or “wheel spoke” appearance. Thus, sheets of recognizable plasma cells define myeloma. Lymphoma and small round cell carcinoma metastases are much more difficult to differentiate by routine light microscopy and may require immunohistochemical stains for final verification. As such metastases usually stain positive for cytokeratin while lymphomas will stain for lymphoid markers such as leukocyte common antigen or B or T cell markers. So with adult round cell tumors, sheets of plasma cells indicate myeloma while round cells which are not plasma cells and look more lymphocytic are either lymphoma or a small round cell carcinoma.

The final group of lesions which can be considered together are bone cysts. These include unicameral or simple bone cysts and aneurysmal bone cysts. As previously noted, these lesions appear different radiographically.
Histologically, unicameral bone cysts appear as a thin layer of fibrous tissue lining large empty spaces (Figure 36). Benign giant cells, hemosiderin pigment and a few chronic inflammatory cells may also be present. Aneurysmal bone cysts have a different histologic appearance and feature the presence of blood filled cavernous spaces whose walls lack the normal features of blood vessels as seen in Figure 37. There is some overlap between these two lesions however and some cysts will have characteristics of both. This is most evident in the case of cysts directly abutting the growth plate in skeletally immature individuals, especially in young children. In these instances, the cyst is often central as opposed to eccentric and often not very expansile.

Still these lesions can have a very aggressive course. They tend not to respond to percutaneous treatments and often require open treatments associated with aneurysmal bone cysts such as curettage, bone grafting and embolization. In these cases, great care needs to be directed toward preservation of the adjacent growth plate.

Other Lesions

To complete our review of common tumors and tumor-like conditions, there a several lesions with which the Orthopaedist should be familiar which need to be considered individually.

Benign giant cell tumor of bone: Giant cell tumor of bone is a truly fascinating lesion with a variable biologic potential. While this is typically an aggressive benign lesion, two percent of patients with histologically benign giant cell tumor of bone will experience pulmonary metastases and a number of these patients will die from progressive metastatic disease. In others, however, the metastases will not
pursue an aggressive course. The diagnosis of benign giant cell tumor is usually fairly simple when the histologic findings are coupled with typical radiographic changes. The x-rays usually show a juxta-articular lytic lesion with a moth eaten margin, cortical thinning or erosion but no periosteal reaction. Histologically, the lesion is composed of multinucleate giant cells and mononuclear stromal cells. The characteristic finding is that the nuclei of the giant cells look identical to the nuclei of the stromal cells (Figure 38). Mitotic figures may be found in all of these lesions and may be prominent in some. Small areas of woven bone may also be seen along with areas of spindle cells with spindled nuclei. While the diagnosis of most of these lesions is straightforward, there are some giant cell rich osteosarcomas which are indistinguishable from benign giant cell tumor. In these lesions, it is often only a malignant pattern of subsequent growth and metastasis that elucidates the true nature of the neoplasm. As a result, it is always a good question when looking at a probable benign giant cell tumor of bone to at least mentally touch on the possibility of giant cell rich osteosarcoma; realizing that the ultimate differentiation may be difficult to impossible.

**Non-ossifying fibroma (Metaphyseal fibrous defect):** This is a common lesion which only rarely requires surgical intervention. Most of these lesions are incidental findings and require no specific treatment other than occasional x-rays to document stability and healing. On occasion, however, these may be large enough to cause mechanical pain and limit the ability of the child or adolescent to participate in desired activities. In these cases or when the specific diagnosis remains elusive, open biopsy with curettage and some form of bone grafting is reasonable. Following surgical excision and grafting, these lesions will typically heal completely in about eight weeks whereas this would commonly take two years or more with no intervention.
Histologically, these lesions have a characteristic appearance showing benign spindle cells with good number of benign giant cells mixed in (Figure 39).

**Adamantinoma:** This is a characteristic lesion usually seen in the anterior cortex of the midshaft of the tibia. This usually appears as a “soap bubble” sclerotic lesion and can mimic cortical fibrous dysplasia. Cortical fibrous dysplasia occurs predominately in males in the first two decades while adamantinoma occurs in both sexes and all ages though typically during the first four decades. Histologically, adamantinoma is a low grade spindle cell sarcoma with islands of epithelial cells that may resemble cutaneous basal cells (Figure 40). A second pattern consists of islands of neoplastic cells surrounded by columnar cells in a palisading fashion. These findings are usually fairly diagnostic when seen with the usual presentation via imaging studies.

**Chordoma:** This is a low grade sarcoma which is thought to be a notochord remnant tumor. It occurs usually in the spine with the sacrum being the most common location followed by the base of the brain. Other areas of the spine can also rarely be affected. In the sacrum, the lesion classically presents as a midline lesion with bone destruction and most will have an associated anterior mass. Clinically, these lesions present with low back pain of varying duration and frequently with a history of referred pain or numbness involving the rectum and perineum. It is essential for the clinician to recognize that normal sciatica does not cause pain in a perineal distribution and that pain or numbness referred to this area is indicative of a pelvis tumor compromising the sacral plexus until proven otherwise.
Histologically, chordoma has a typical presentation (Figure 41) showing a myxoid or loose appearing mucinous lesion with strands or chords of syncytial cells where the cell margins are indistinct and the cells flow together. Also seen are physaliferous or “foam” cells which are large multivacuolated cells which take on a “foamy” appearance.

All of these cells float in a mucinous matrix which gives the tissue a very runny texture grossly. While this lesion is usually characteristic, the histologic pattern may occasionally mimic chondrosarcoma.

**Immunohistochemistry**

One of the major advances in diagnostic pathology that has occurred over the past two decades has been the development of sophisticated immunohistochemical techniques. These stains have greatly improved the diagnostic acumen of tissues seen via light microscopy and have added a new area of classification based on specific cell proteins. While it is beyond most Orthopaedic surgeons to have a detailed knowledge of this field, these stains are commonly referred to in pathology reports of musculoskeletal lesions and so should be familiar at a basic level to all Orthopaedic surgeons.

Immunohistochemical stains bind to intermediate filament proteins (IFP’s) which are basic structural components of all human cells. These proteins include six distinct moieties which are separated biochemically and include vimentin, desmin, keratins, neurofilament proteins (NFP’s), glial fibrillary proteins (GFAP’s) and lamins (nuclear envelope proteins). In terms of cell function, the IFP’s serve a nucleic acid binding function and may also act as modulators of nuclear function at a translational or transcriptional level. It should be emphasized that while certain tumors have typical immunohistochemical profiles, this can be variable from tumor to tumor as individual tumors exhibit specific genotypes and phenotypes.
**Keratins:** These are commonly seen in epithelial tissues and epithelial cells. From a bone tumor standpoint, keratins are the classic marker of metastatic carcinomas. They may be seen however in almost any form of sarcoma in rare instances. Keratins are also commonly seen in those sarcomas which show some epithelial differentiation including synovial sarcoma, adamantinoma and epithelioid sarcoma where they can be seen to label cells in the epithelial component of these lesions.

**Vimentin:** This is the typical stain of all tumors of mesothelial origin. It thus stains almost all sarcomas but it is usually negative in carcinomas. Its presence is widespread among sarcomas so that it is not very useful in distinguishing between specific sarcoma types.

**Desmin:** This is typically found in muscle cells and in tumors with myo-differentiation. These tumors most commonly present in soft tissue and include rhabdomyomas, rhabdomyosarcomas, leiomyomas and leiomyosarcomas. They are also occasionally seen to be present in desmoid tumors and in primitive neuroectodermal tumors.

**Actins:** As with desmins, actins are indicative of myogenous differentiation and are seen in tumors showing these changes which parallel desmin in muscle-restricted immunoreactivity.

**S-100:** This protein derives its name from the fact that it is soluble in 100% solution of ammonium sulfate. It has a wide distribution in human tissues. The stains are most commonly associated with neural, chondroid or melanocytic differentiation.

**Factor VIII related antigen.** Also called Von Willebrand factor, factor VIII stains in lesions with vascular differentiation. It is typically seen in benign and low grade vascular lesions such as hemangiomas and hemangioendotheliomas while not commonly being present in high grade angiosarcomas.

**Soft Tissue Tumors**

As in the case of bone lesions, soft tissue tumors can be quite confusing when approached as a large number of unrelated topics. Again, however, a systematic approach to the diagnosis of these lesions
reveals a limited number of clinical presentations. Histologically, however, they do form a large and diverse group with fewer trends in the histology than shown in bone tumors.

**Clinical Presentations**

Most soft tissue tumors present with pain and/or a mass. As noted previously, there may be a history of trauma as patients tend to relate mass lesions with trauma to that site, however trivial. It is also remarkable that even very large soft tissue masses including sarcomas can reach tremendous size and yet cause minimal if no symptoms. Many patients falsely assume that because the lesion is painless it must also be harmless. This is obviously not the case but is often responsible for long delays in diagnosis of the part of the patient or, less frequently, the physician. Ironically, the lesions in soft tissue which are most commonly painful are the benign soft tissue tumors including desmoid tumors, hemangiomas, benign nerve sheath tumors and soft tissue infections.

**Imaging Studies**

**X-RAY:** Most soft tissue masses are seen poorly or not at all on plain x-rays. Those which show calcification will be more apparent, however. While the most common lesion to present with soft tissue calcification is myositis ossificans, synovial sarcoma can present this way also. The calcification seen in synovial sarcomas can vary considerably from minute, almost imperceptible calcifications to very dense calcification which may mimic a benign lesion (Figure 42).

**MRI SCANS:** These are the gold standard for the evaluation of lesions in soft tissue. MRI scans are very useful in showing where a lesion is but are less useful in showing what a lesion is. There are some notable exceptions, however. The classic MRI finding in most soft tissue tumors is a lesion that is well This is not so. Most soft tissue sarcomas are very distinct while often showing a bit of edema in the
compartment in which they occur. On the contrary, many benign lesions are poorly marginated on MRI
scans and these include desmoid tumors, hemangiomas, inflammation, injury and infection. The following
lesions have a characteristic MRI appearance:
circumscribed and showing dark signal on T1 and high signal on
T2, fat suppressed T2 or STIR views (Figure 43). The possible
etiology of such a lesion includes benign tumor, malignant
tumor, abscess, cyst and hematoma. It is often wrongly thought
that soft tissue sarcomas are grossly invasive while benign
lesions are radiographically distinct and “encapsulated”.

**Lipoma:** This is one of the few histologic diagnoses that can be
made confidently on the basis of MRI and clinical findings
alone. Benign lipomas appear as masses of uniform fat density
and so parallel the appearance of normal subcutaneous fat on all
sequences. Thus they are bright on T1 and T2 views (Figure 44)
but suppress as does the normal fat on fat-suppressed T2 and
STIR views. Therefore a mass seen on MRI as a uniform fat
density with no interstitial markings is diagnostic of benign
lipoma.

**Atypical Lipoma:** This tumor has also been labeled “well-
differentiated liposarcoma” and “lipoma-like well differentiated
liposarcoma”. It is a fat containing lesion characterized by
lobules of fat signal on MRI with surrounding layers of fibrous
tissue which show as thin layers of high signal (Figure 45). The
critical difference here between this lesion and higher grade
liposarcoma is that the lobules in this lesion look fatty on MRI.
Ordinary liposarcoma looks like the typical non-lipomatous lesion which shows dark on T1 and bright on T2, fat suppressed T2 and STIR views. While atypical lipomas do not metastasize, they do carry a 10% risk of malignant transformation, usually to high grade liposarcoma.

**Myositis ossificans:** The hallmark of late lesions radiographically is the presence of well formed and benign appearing calcification in soft tissue (Figure 46) which often is more prominent peripherally and is thus termed “egg shell calcification”. Early lesions show little or no calcification but do show tremendous inflammation and edema in the adjacent soft tissues. In theses cases the edema greatly exceeds in volume the area of the lesion itself.

**Hemangioma:** These are typically diffuse heterogeneous lesions with serpiginous borders (Figure 47). The classic findings of a hemangioma include the presence of a painful lesion in soft tissue which presents with a soft tissue mass seen on MRI scan but with no mass effect. Atrophy from the underlying pain and smooth soft tissue calcifications (phleboliths) are common.

**Histology of Soft Tissue Tumors**

The histology of soft tissue tumors shows less in the way of common trends than does the histology of bone lesions. There are many specific tumors to consider and the range of lesions goes beyond the scope of this manuscript. Several excellent texts are available and these provide a comprehensive review of the basic and also the more sophisticated aspects of soft tissue tumor histology.
Treatment of Musculoskeletal Tumors

There are several potential treatment options for musculoskeletal tumors. For those lesions in bone, these range from simple curettage to aggressive intralesional excision to wide and radical resection. Simple curettage is sufficient for lesions which tend to be self limited such as nonossifying fibroma and eosinophilic granuloma. Aggressive benign lesions such as giant cell tumor, aneurysmal bone cyst, chondromyxoid fibroma and osteoblastoma require a more aggressive surgical technique. This usually entails several steps which together allow the surgeon to control the tumor bed and result in a high likelihood of local control. These steps for aggressive intralesional excision are shown in Table 2. It is only through the meticulous and methodic application of these steps that eradication of the underlying lesion can be attained with high frequency.

TABLE 2

<table>
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<tr>
<th>SURGICAL STEPS FOR EFFECTIVE INTRALESIONAL SURGERY</th>
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The treatment of sarcomas of bone and soft tissue are summarized in Table 3.

**TABLE 3**

<table>
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<tr>
<th>SARCOMA TREATMENT MODALITIES</th>
<th>RADIO-RESISTANT</th>
<th>RADIO-SENSITIVE</th>
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<tr>
<td>Surgery</td>
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<td>- Chondrosarcoma</td>
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<td>- Low Grade Soft Tissue Sarcomas</td>
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<td>- Chordoma</td>
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<tr>
<td>- Adamantinoma</td>
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<tr>
<td><strong>HIGH GRADE</strong></td>
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</tr>
<tr>
<td>Surgery + Chemotherapy</td>
<td>Surgery + Radiation + Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>- Osteosarcoma</td>
<td></td>
<td>- High Grade Soft Tissue Sarcomas</td>
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<td>- Ewing’s Sarcoma</td>
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<td>- Other High Grade Bone Sarcomas</td>
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Low grade bone sarcomas such as chondrosarcoma, chordoma and adamantinoma respond only to surgery and so that is the only modality utilized in their treatment. High grade bone sarcomas such as osteosarcoma and Ewing’s sarcoma respond well to chemotherapy and this is therefore a consistent part of these treatment protocols. Other high grade bone sarcomas such as malignant fibrous histocytoma in bone, high grade chondrosarcoma and dedifferentiated chondrosarcoma present a challenge due to their significant metastatic rate. While there is less data than is present for osteosarcoma, chemotherapy is commonly utilized in an attempt to both increase resectability and decrease the appearance or progression of systemic spread. Radiation is still a possible local treatment for Ewing’s sarcoma but has been largely replaced by surgery due to the potential for post-radiation morbidity and malignant transformation. Despite this radiation is still utilized and reasonable in cases where resection carries unacceptable morbidity or when surgical margins are closer than desired. This also applies to other high grade bone sarcomas as a treatment plan for each should be individualized to each patient in light of the potential benefits of each treatment option.

Low grade soft tissue sarcomas respond well to a combination of wide resection surgery and local radiation. The radiation can be given either pre-operatively or post-operatively. In either case, there is no
difference in local control as long as the treatments are well planned. The major advantage to pre-operative radiation is that the presence of the lesion IN SITU allows the radiation oncologist to concentrate his field on the lesion and can usually treat a smaller field size than in cases where the lesion has been removed previously. Radiation also has many beneficial effects on the local tumor which commonly will decrease in size and vascularity as well as increase in firmness thereby greatly facilitating resection. The disadvantage of preoperative treatment is that it necessitates operating through tissues that have been damaged by receiving usually 50 centigray (5000 rads) of radiation. This carries a 20% risk of major wound complications in most series.

High grade soft tissue sarcomas still present a major challenge to the oncology team. Local control can be accomplished with radiation and wide resection as with the low grade malignant lesions. Ideally, the high grade lesions should also receive systemic treatment in the form of chemotherapy in light of the higher rate of metastasis associated with high grade histology. While these patients are commonly treated with protocols which include multi-drug chemotherapy, the results of this treatment in terms of improved survival are not as dramatic as we would hope. Chemotherapy for high grade soft tissue sarcomas continues to be a controversial topic and one where much research has been directed. Hopefully, new findings regarding the molecular and genetic bases of these diseases with spawn new drug treatments for all types of sarcomas and further improve the survival of these patients.