ESSR Consensus Document for Detection, Characterization, and Referral Pathway for Tumors and Tumorlike Lesions of Bone

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Abstract

Benign bone tumors are rare but are more common than primary malignant bone tumors. The early accurate diagnosis and reliable differentiation of these rare benign tumors and tumor mimickers from the even rarer malignant tumors with subsequent appropriate treatment or watchful waiting is crucial for the clinical outcome. Bone tumors are often a source of diagnostic and therapeutic uncertainty. Thus this European Society of Musculoskeletal Radiology consensus document is intended to help radiologists in their decision making and support discussion among clinicians who deal with patients with suspected or proven bone tumors. Evaluating these tumors starts with a patient history and physical examination. Radiography is the principal imaging modality and often can reliably diagnose a benign bone tumor by providing information about localization, matrix, aggressiveness, size, and (potential) multiplicity. In a significant number of cases, additional imaging is not necessary. Potentially malignant entities recognized by radiography should be referred for magnetic resonance imaging, which also serves as a preoperative local staging modality, with specific technical requirements. Indeterminate tumors, or tumors in which therapy depends on histology results, should be biopsied. For biopsy, we strongly recommend referral to a specialist regional sarcoma treatment center (RSTC), where a multidisciplinary tumor team, including a specialist pathologist, radiologist, and sarcoma surgeon, are involved. Additional staging modalities are entity specific and should be performed according to the recommendations of the RSTC.

Keywords
- bone tumor
- bone tumor mimickers
- consensus statement
- diagnostic algorithm
- imaging methods
- ESSR

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Rationale and Objective of the European Society of Musculoskeletal Radiology Consensus Document

The purpose of this article is to help general radiologists and clinicians working in health care settings other than dedicated sarcoma treatment centers to determine whether a bone tumor seen on imaging is aggressive or nonaggressive and to help with the further management and referral of these patients (►**Fig. 1**). In several instances and particularly when the initial assessment is suggestive of a benign bone lesion, it is entirely appropriate for a patient's imaging to be sent to a regional sarcoma treatment center (RSTC) for confirmation rather than the patient having to travel physically to the RSTC. But pathways should exist for prompt discussion of these cases and immediate clinical assessment of these patients where necessary. This article is a consensus document produced by the European Society of Musculoskeletal Radiology (ESSR) tumor working group. We use the term *bone tumor* here to refer to focal bone lesions identified on imaging that include bone neoplasms, tumorlike conditions, and also sequelae of infection.

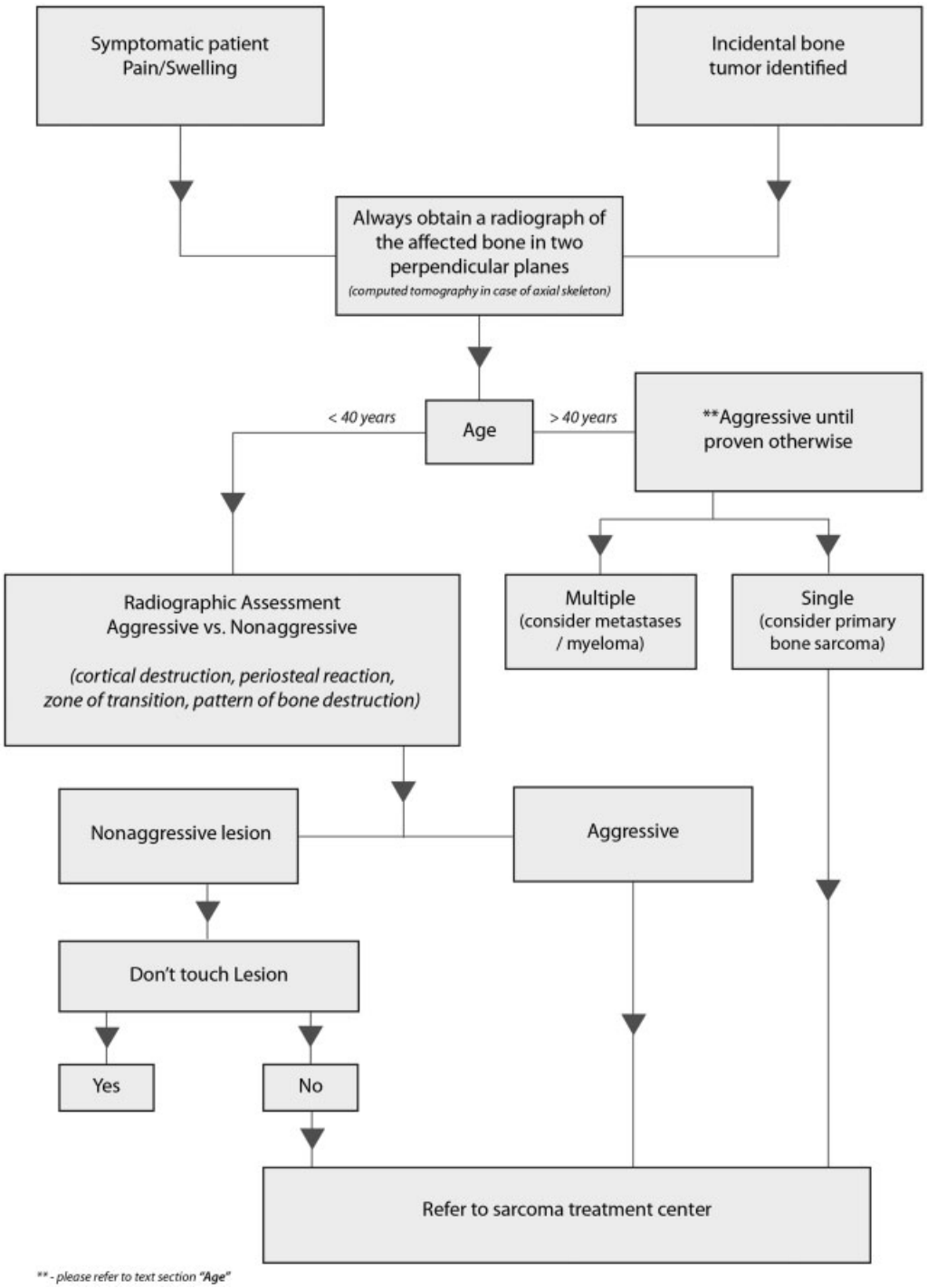

Fig. 1 Flowchart to aid assessment and referral of bone tumor detected on radiograph or computed tomography.

Incidence and Prevalence of Bone Tumors in Europe

Primary malignant bone tumors are rare in all European countries (►**Table 1**).[1] To put this into perspective, in the United Kingdom in 2013, the 582 new cases accounted for < 1% of all new cancer cases.[2] This equates to ~ 10 new bone sarcomas per million of the total population. In Germany, the annual incidence of sarcomas arising from the bone and joint cartilage from 1999 to 2012 ranged between 638 and 835 new patients.[3] In 2010 in Germany, 400 incident cases of malignant tumors were reported in men and 350 in women, with the mean age at diagnosis of 51 years for men and 57 years for women. A total of 239 men and 197 women died; the relative 5-year survival rate in 2009–10 was 62%.[4] The pattern of cancer diagnoses in children differs completely from that of adults. For example, children are mostly affected by embryonal tumors. The largest diagnostic groups are leukemias (33.8%), bone tumors add up to 4.4%, and soft tissue sarcomas to 5.8%.[4] In the Netherlands, the annual incidence of sarcomas arising from the bone and joint cartilage was 838 in 2013, 920 in 2014, and 973 in 2015,[5] and in Switzerland the total number of malignant bone tumors was 210 for men and 164 for women between 2006 and 2010.[6] In Sweden, Finland, and Denmark, the number of new malignant bone tumors between 2009 and 2013 was 136 for men and 106 for women. The proportion of bone cancer in relation to other cancers was 0.2% for men and 0.1% for women, the proportion of all cancer was 0.2%, and the number of persons living with the diagnosis per 100,000 inhabitants was 16 for men and 13 for women.[7] In the United States, primary malignant bone tumors had an incidence of 0.9/100.000 people compared with an estimated incidence of lung cancer equal to 56.2/100,000 people.[8] The National Cancer Institute estimated 3,300 new cases of bone and joint cancer in 2016 in the United States.[8]

The incidence in several European countries and the United States seems quite similar (~ 10 per million). No significant change in the incidence of bone sarcomas has occurred for the last few decades. For example, since the late 1970s, bone sarcoma incidence rates have remained stable in Great Britain for males and females separately and for both sexes combined.[2] It is therefore uncommon for general practicing physicians or general radiologists to see many bone tumors in their working life. Benign bone tumors are, by far, more common than sarcomas. However, general clinicians and radiologists will encounter numerous patients with bone metastases and bone lesions due to hematologic conditions. Therefore, while encountering an osseous tumor, a skilled estimate of aggressiveness and knowledge about a further diagnostic algorithm is essential. The finding of a bone tumor was the main reason for seeking teleradiology advice at a referral center for musculoskeletal diseases in Munich, Germany, with 57% of all 322 submitted cases. Among these cases, 84% were diagnosed as benign.[9]

This article will help radiologists and clinicians determine whether a bone tumor is benign or malignant. It offers information about further imaging and the referral of patients with sarcomas and potential sarcomas. In view of the rarity of these tumors,[1] clinicians and radiologists across Europe must be aware of the location of their RSTC and/or national referral center. It is vital that the multidisciplinary team in the RSTC develop pathways for referral of these patients and communicate this information widely across local clinical settings.

Table 1 Incidence of bone tumors in various countries

Country (total population to the nearest million, 2013)	Incidence of bone tumors (year)
United Kingdom (64)	582 (2013)
Germany (81)	835 (2012)
Netherlands (17)	973 (2015)
Switzerland (8)	79 (2013)
Norway, Sweden, Finland, and Denmark (26)	242 (2013)
United States (317)	3,300 (2016 estimate)

History and Clinical Features

Patients with bone tumors may come to clinical attention for different reasons.[10] These patients can also present through varied settings including accident and emergency departments, orthopaedic clinics, rheumatologic centers, clinics, and referrals from community physicians. Many benign bone tumors are asymptomatic. However, patients may present with bone pain or swelling. Benign tumors such as osteoid osteomas and chondroblastomas can cause significant pain that brings the patient to clinical attention. Pain from osteoid osteomas is typically worse at night and relieved with anti-inflammatory medication such as salicylates, diclofenac, or ibuprofen. Pain could also be a mode of presentation when there is a pathologic fracture in the affected bone.

Sometimes patients come to our attention following trauma to the area and associated pain. The trauma itself is probably incidental in these cases. The presence of pain associated with a bone tumor may affect the decision to perform a biopsy in a lesion that might otherwise be treated conservatively. A large proportion of patients, however, come to medical attention when a bone tumor is identified incidentally on an imaging examination performed for other clinical reasons. For example, a computed tomography (CT) scan or a positron emission tomography (PET)/CT scan performed as part of staging for a visceral malignancy may demonstrate an incidental bone tumor. Similarly, a radiograph performed as a preoperative examination before a hip replacement might show an incidental bone tumor needing further analysis. For this reason, it is important for reporting radiologists to critically evaluate the bones on all imaging examinations performed for any reason.

Important considerations in history include recent trauma, rate of growth of the tumor, underlying oncologic history, and previous surgery. A standardized checklist,

primarily filled out by the patient and discussed with the radiologist, is considered advisable. Clinical examination should document pain related to the tumor, palpable swelling, skin alterations including warmth, tenderness to touch, and single/multiple tumors. This information should be available for the radiologist and is similar to the ESSR recommendations for soft tissue tumors in adults.[11]

Primary Imaging

The radiograph remains the most important tool for the detection, analysis, and interpretation of bone tumors.[12,13] CT may sometimes be needed in complex anatomical areas such as the spine, pelvis, shoulder girdle, and ribs because these areas of the skeleton are difficult to interpret on standard radiographs (►**Fig. 2**). Advanced imaging modalities such as magnetic resonance imaging (MRI), scintigraphy, and PET/CT are useful for subsequent local and distant staging, respectively, of the disease rather than the initial diagnosis. These additional imaging examinations aid in further assessment of the bone tumor and do not replace a radiograph/CT in characterization of the tumor.

It is therefore entirely reasonable for a general clinician/radiologist to obtain a radiograph in two perpendicular planes (and a CT scan in the case of axial skeletal tumors) for initial assessment of a bone tumor. This should be available before any interpretation of the tumor can take place (►**Fig. 3**). If a diagnosis of a benign tumor that does not need any further management can be made on the basis of this initial investigation, no further imaging is necessary. Some benign tumors such as chondroblastomas need specialist management and are best taken care of at the RSTC.

On initial assessment, clinicians may occasionally not be able to ascertain confidently whether a particular lesion is aggressive or nonaggressive, and these indeterminate lesions should be referred to the RSTC. All suspected bone sarcomas should also be referred to the RSTC. In particular, the radiologic report should clearly state the need for referral to the RSTC. A useful phrase in the report would be "urgent referral to the RSTC is advised." The radiologists at the RSTC may prefer to perform advanced imaging locally to suit their protocols. A biopsy in a suspected primary bone tumor should only be performed by the multidisciplinary team at the RSTC. In addition, all initial local staging examinations should be performed before biopsy. Staging investigations for distant disease/metastases, such as CT of the chest, are usually performed after biopsy.

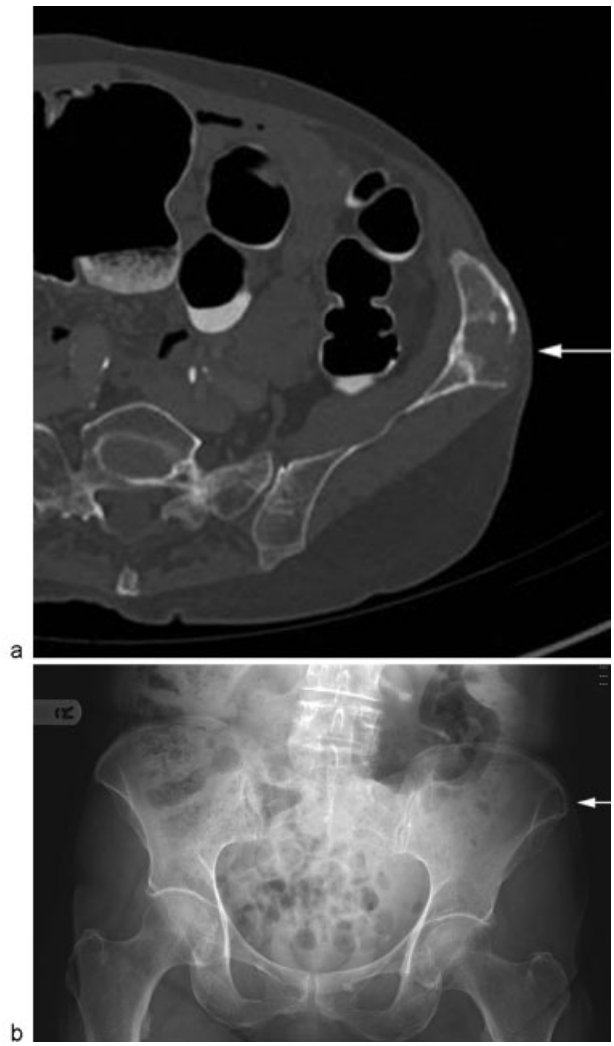

Fig. 2 (**a**) Axial computed tomography (CT) image shows an aggressive destructive bone lesion (arrow) in the left ilium during routine CT colonography. (**b**) Pelvic radiograph performed 2 months earlier was reported as normal demonstrating the difficulty in identifying, let alone assessing, the aggressiveness of bone tumors in the axial skeleton and flat bones. Retrospectively reduced density can be appreciated in the left ilium (arrow) when compared with the right.

Role of Imaging in Bone Tumors

Imaging plays a very important role in various stages of the diagnosis and management of bone tumors (►**Table 2**). The purpose of initial imaging in bone tumors includes detection

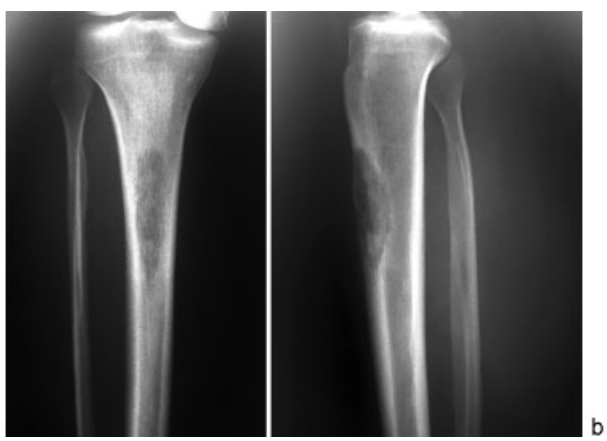

Fig. 3 (**a**) Anteroposterior radiograph of the proximal tibia shows a destructive tumor in the proximal tibia. On this projection, the tumor appears to be intra-medullary. However, a lateral radiograph (**b**) shows that the metastasis is, in fact, intracortical.

Table 2 Relevance of various radiologic investigations in the assessment of solitary bone tumors

Clinical features: Pain in a tumor may necessitate biopsy in an otherwise benign looking tumor. **Age** and **location:** Most important consideration.
Radiographs: Most specific imaging examination but may be negative in early stages of tumor
Location of tumor: Part of body (hand/tibia/femur, etc.)
Epiphysis/metaphysis/diaphysis
Medullary/cortical/surface
Aggressive versus nonaggressive tumors: Most important part of the assessment
Matrix: Fibrous/Chondroid/Osseous
Osteolytic versus osteosclerotic
Computed tomography
To assess tumors difficult to interpret on radiographs such as axial skeleton, shoulder girdle, ribs, and flat bones
Sometimes to assess matrix mineralization, cortical destruction, soft tissue extension
Magnetic resonance imaging: Standard T1- and T2-weighted spin-echo images ± fat suppression ± intravenous contrast
Intralesional matrix assessment (fat, blood, fluid levels, chondroid matrix)
Cortical destruction and soft tissue extension
Joint and/or neurovascular invasion
Nuclear medicine investigations
Technetium whole-body scintigraphy to look for other skeletal lesions, not for local staging
FDG/fluoride PET not indicated for initial work-up of bone tumors
Several incidental lesions may be picked up especially with fluoride PET
Biopsy
Should only be performed at, or under the guidance of the regional sarcoma treatment center for all suspected primary bone tumors

and diagnosis with the objective of arriving at a short differential diagnosis. Once a bone tumor is detected, further imaging may also be necessary for local and distant staging of the disease. Imaging guidance (usually CT) offers the ability to target the best part of the tumor for biopsy and arrive at a conclusive histologic diagnosis. When neoadjuvant therapy such as chemotherapy and radiotherapy is used, imaging may also be necessary to assess response to therapy and restage the tumor. Once initial treatment has been performed, imaging is also needed for follow-up and detection of a recurrence. Radiography, CT, MRI, and nuclear medicine techniques (such as scintigraphy, fluorodeoxyglucose [FDG]-PET, and sodium fluoride [NaF]-PET) have different and complementary roles in the management of bone tumors. The temptation to make a bone tumor diagnosis on MRI scan alone should be avoided because mistakes can often arise in characterizing bone tumors on MRI.

Terminology

Radiographs can only distinguish among four different densities: soft tissue, fat, air, and calcium (bone, mineralization, and cement).[12] Fat and air are unlikely to be encountered on radiographs of bone tumors even though fat can be seen as part of several bone tumors macroscopically and microscopically. Large intraosseous lipomas may occasionally demonstrate obvious fat density on radiographs. Periosseous or periarticular fat pads may be displaced secondarily due to soft tissue involvement. So most bone tumors either show a soft tissue density or calcific (bony or mineralized) density on radiographs. It is recommended to designate bone tumors as either "aggressive" or "nonaggressive" rather than "malignant" or "benign." Although most malignant tumors appear aggressive on radiographs and most benign tumors appear nonaggressive, this is not always the case. For example, it is not uncommon for a benign eosinophilic granuloma, one of the variants of Langerhans cell histiocytosis, to look aggressive, whereas a malignant tumor such as a plasmacytoma can appear nonaggressive (►**Fig. 4**).

Bone tumors may demonstrate internal calcified/mineralized density related to either a chondroid matrix or an ossified tumor matrix. Chondroid matrix typically appears as "rings and arcs," "popcorn-like," or "flocculent" type of mineralization, and ossified matrix appears as a dense "cloudy" type of matrix (►**Fig. 5**). It is important to differentiate between the two types of matrix mineralization because the differential diagnosis varies with each type. It is sometimes difficult to differentiate, and it is entirely reasonable to use the term *mineralization* in these cases. Tumor mimics resulting from various causes such as anatomical and developmental variants, trauma, infection, or osteonecrosis should be considered during bone tumor assessment and classified as bone tumor mimickers.[14]

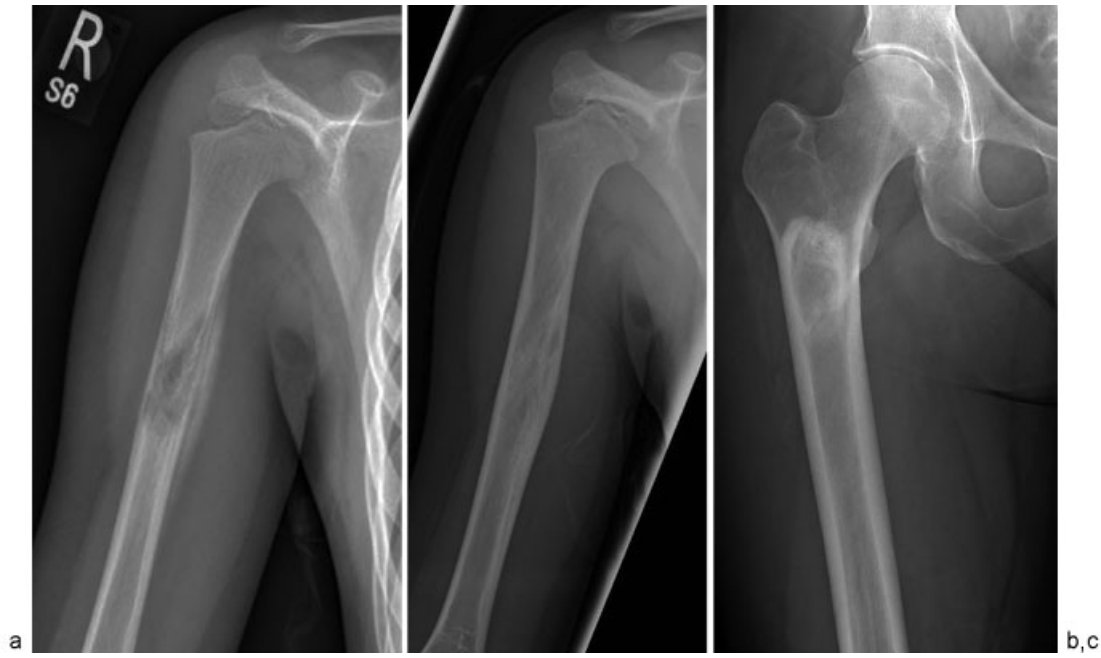

Fig. 4 (**a**) Radiograph of the humerus in a 6-year-old boy shows an aggressive humeral diaphysis tumor that has healed on radiograph taken 8 months later (**b**) with conservative treatment, in keeping with eosinophilic granuloma. Note also that the lamellated periosteal reaction to the tumor in (a) has changed to a solid periosteal new bone formation following healing in (b). (**c**) Radiograph of the femur in a 49-year-old shows a lucent tumor with thick sclerotic margins and nonaggressive appearance. Biopsy showed it to be a myeloma.

Principles of Assessment

Although the assessment of a bone tumor on radiographs is based on certain rules described later in this article, none of these rules are absolute, and there are some exceptions. It is thus important that at the end of the radiographic assessment, the radiologist arrives at a short differential diagnosis of two or three possibilities that should be discussed with the clinician. Most tumors can be included in the differential diagnosis and never be wrong. But if the differential diagnostic list is very long, it becomes useless to the referring clinician. If the differential diagnosis list is short and accurate 80% of the time, in our experience it is good enough for the referring clinician.[13,15] The most important part of the assessment is to identify those tumors that need further management rather than arriving at a specific diagnosis. However, even when the diagnosis is clear, several tumors still need biopsy to help with further management and therefore need referral to the RSTC.

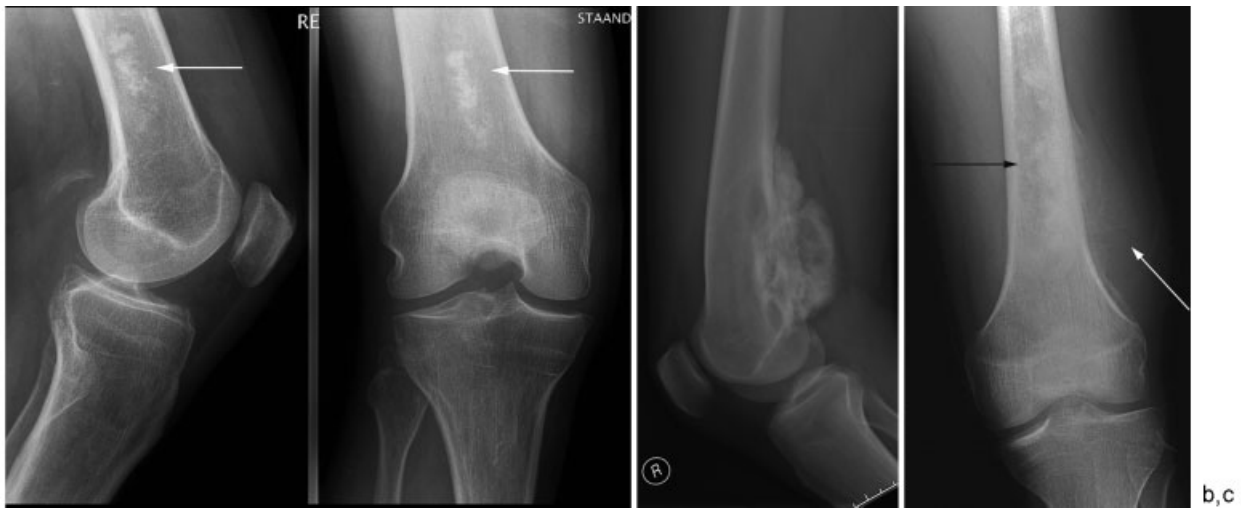

Fig. 5 (**a**) Radiographs of the knee show an enchondroma within the distal femur with internal "flocculent" calcification (arrows). (**b**) Lateral radiograph of the distal femur shows the ossified dense matrix of this parosteal osteosarcoma. (**c**) Frontal radiograph of the femur in a 16-year-old shows the dense ossified matrix (black arrow) in this osteosarcoma. Also note the aggressive periosteal reaction in (c) with a Codman's triangle and spiculation (white arrow).

Clinical Features: Relevance to Diagnosis

Patients with bone tumors can present with symptoms including swelling, pain, and limb dysfunction. In the spine, tumors can also present with neurologic dysfunction. Some rare tumors such as mesenchymal phosphaturic tumors can also present with systemic features related to osteomalacia. There are reports of bone tumors presenting with paraneoplastic syndromes, which is very unusual. Clinical features are not particularly useful to differentiate benign from malignant tumors with certainty. Although malignant tumors are more likely to be painful, some benign tumors such as osteoid osteomas, osteoblastomas, chondroblastomas, or osteomyelitis can also be very painful.[16] All bone tumors that affect cortical bone carry a risk of pathologic fracture, although because of the rapidity and extent of bone destruction, this is more common with malignant tumors. Nevertheless, fractures can occur with benign tumors and are well documented by their occurrence in simple bone cysts.

The presence of symptoms should always be carefully considered, especially before a tumor is deemed to be a benign so-called do-not-touch lesion. A biopsy may still be indicated in these symptomatic patients, even if a specific benign diagnosis is suspected on imaging. At the very least, these patients need to be followed up until symptoms settle. It is useful to perform certain biochemical investigations on all patients with bone tumors including serum calcium/phosphate and alkaline phosphatase. This helps identify tumors such as brown tumors resulting from hyperparathyroidism, which can be confused with giant cell tumors both on imaging and histology (►**Fig. 6**). Similarly, there are other tumors, such as a mesenchymal phosphaturic tumor, that can cause biochemical disturbances and oncogenic osteomalacia.

Symptomatic Patient, Radiograph Negative

A radiograph is not very sensitive at the early stages of a bone tumor. At least 50% of trabecular bone needs to be destroyed before the tumor becomes detectable on radiographs.[17] All patients with symptoms related to an area of the skeleton, not fully explained by clinical examination and laboratory investigations, need further imaging, even if the initial radiograph does not reveal a bone tumor. If a tumor is not visible on radiographs, it cannot be assumed that these patients do not have a bone tumor. Further imaging can be MRI, CT, or nuclear medicine (scintigraphy or NaF-PET), and the choice depends on the clinical situation. However, MRI is probably suitable for most cases because it shows the tumor directly, is very sensitive for bone marrow replacement, can be used for local assessment of the tumor's extension, and has a very high negative predictive value for bone tumors.

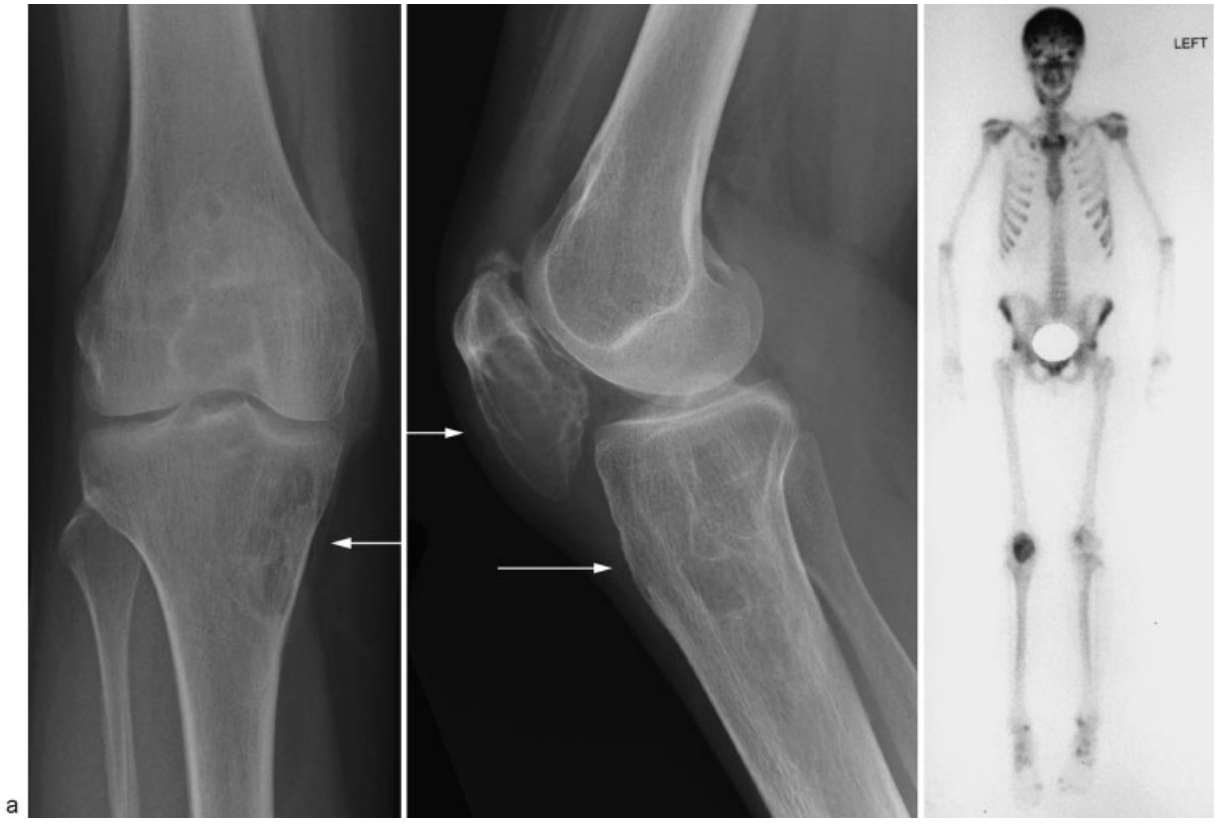

Fig. 6 (**a**) Anteroposterior and (**b**) lateral radiographs of the knee show lytic tumors in the patella and the medial aspect of the proximal tibia (arrows). Biopsy suggested giant cell tumor of bone, but serum calcium was elevated, and there was abnormal uptake in the skull vault on scintigraphy (**c**). The final diagnosis was brown tumors of hyperparathyroidism.

Table 3 Relevance of age to bone tumor diagnosis

Age, y	Nonaggressive	Aggressive
0–10	Simple bone cyst, eosinophilic granuloma, aneurysmal bone cyst	Ewing's sarcoma, eosinophilic granuloma, neuroblastoma, hematologic malignancies affecting bone
10–20	Nonossifying fibroma, fibrous dysplasia, simple bone cyst, aneurysmal bone cyst, osteochondroma, chondroblastoma, chondromyxoid fibroma, adamantinoma	Osteosarcoma, Ewing's sarcoma, adamantinoma, giant cell tumor
20–40	Enchondroma, giant cell tumor	Chondrosarcoma, parosteal osteosarcoma, pleomorphic sarcoma
> 40	Geode or subchondral cyst, intraosseous ganglion	Metastases, multiple myeloma, plasmacytoma, chondrosarcoma, osteosarcoma (Paget's associated), pleomorphic sarcoma, chordoma, lymphoma

Age

Age is a very important consideration in bone tumor diagnosis (►**Table 3**). It is very uncommon to develop benign bone tumors after age 40 (►**Fig. 7**). Preexisting tumors (such as bone islands, healed lesions) may be identified for the first time, however, after age 40, although they have already been present for a long time. A review of previous imaging is useful in these instances. Any new bone tumor seen in patients > 40 years should be considered malignant until proven otherwise. Exceptions would be tumors seen around joints such as subchondral cysts related to osteoarthritis or other joint diseases. After age 40, the most common new bone tumors, especially when there are multiple lesions, include metastases and multiple myeloma. Primary bone tumors including sarcomas and lymphomas can also occur at this age but are less common. If a solitary bone tumor is identified in this age group, a primary sarcoma cannot be excluded, and the patient often needs referral to an RSTC. In a patient < 40 years of age, a bone tumor can be either benign or malignant. Most primary bone tumors (benign and malignant) are diagnosed in the adolescent and young adult age group (range: 13–21 years).

Age of the patient is readily available at the time of image interpretation and useful to establish a reliable differential diagnosis because most bone tumors have a predilection to affect specific age groups. For these purposes, patients can be divided into different age groups, as we do here: age < 20 years, age between 20 and 40 years, and age > 40 years. Although there is considerable overlap between these age groups for the incidence of bone tumors, this separation of patients into different age groups helps achieve a reasonable differential diagnosis.

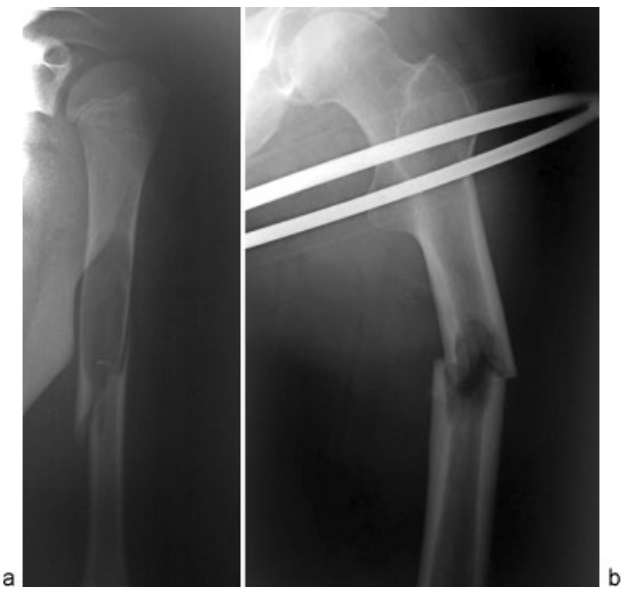

Fig. 7 Importance of age in bone tumor assessment. Pathologic fracture through a lytic tumor in (**a**) an 11-year-old and (**b**) a 60-year-old, respectively. Note that both tumors look similar radiographically with some endosteal scalloping, narrow zone of transition, and absent periosteal reaction. The final diagnosis in (a) was unicameral bone cyst; in (b) the diagnosis was myeloma. Note the "fallen fragment" sign in (a).

Radiographic Assessment: Tumor Detection

The bone tumor itself is not visible on radiographs in most instances unless it is mineralized. It is the nature and extent of bone destruction caused by the tumor that is seen on radiographs. The detection and diagnosis of the tumor actually depends on the effect of the tumor on the host bone (►**Fig. 1**). As described earlier, although radiographs are reasonably specific for the differential diagnosis of bone tumors, they are not particularly sensitive for purely medullary lesions in the early stages, for which there has to be destruction of at least 50% of the trabecular bone architecture before a tumor becomes visible on radiograph (►**Fig. 8**).[17] Small tumors are also easily missed on radiographs (►**Fig. 9**). Cortical and surface tumors become obvious earlier than medullary tumors. Trabecular bone density is higher in the epiphyses and metaphysis when compared with diaphysis and tumors in the epiphyses, and metaphysis are therefore easier to detect than those in the diaphyseal medulla because of the contrast provided by the adjacent normal trabeculae. MRI is more sensitive for marrow replacement and soft issue involvement. Furthermore, bone tumor diagnosis on radiography is also delayed when located in flat bones, axial skeleton, and the ribs because the host bone changes are difficult to appreciate due to the superimposition of other structures in areas with a more complex anatomy (►**Fig. 10**).[18] Another reason for

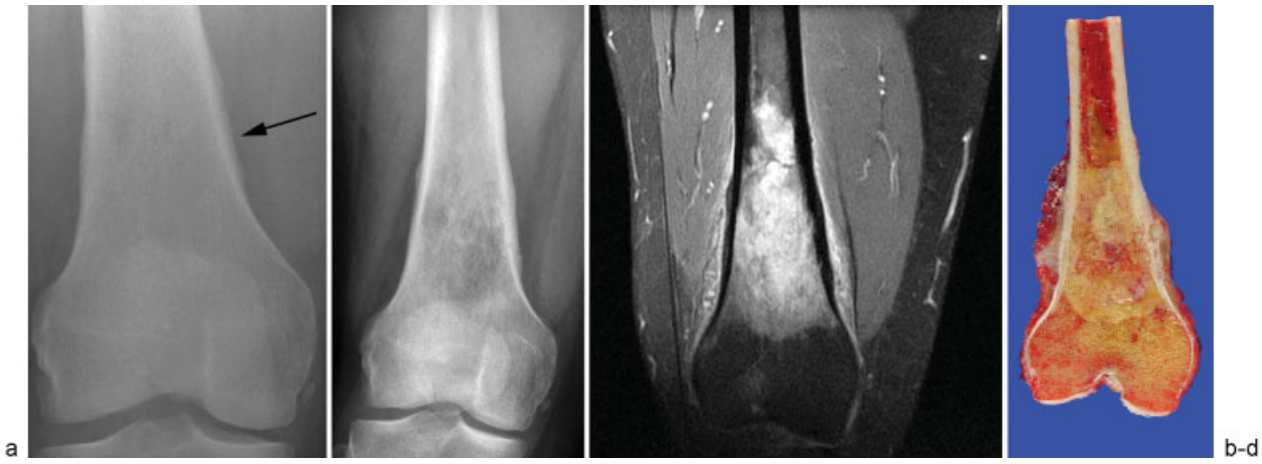

Fig. 8 (**a, b**) Anteroposterior radiograph of the same femur 2 months apart. The permeative infiltrative aggressive tumor is obvious in (**b**) but is difficult to visualize on the earlier radiograph (a) apart from the subtle periosteal reaction (arrow). (**c**) Coronal short tau inversion recovery MR image and (**d**) resected specimen show the true extent of this histopathologically proven bone lymphoma.

misdiagnosis in bone tumors, like tumors elsewhere in the body, may be the so-called satisfaction-of-search effect and not identifying the tumor usually at the periphery of the radiograph. This would then be an observational error.

Radiographic Assessment: Analysis and Interpretation

Aggressive versus Nonaggressive Bone Tumors

Based on radiographs, bone tumors can be differentiated into aggressive and nonaggressive tumors accurately in most instances (►**Table 4**). This distinction refers to their rate of growth. These are the main features that differentiate an aggressive from a nonaggressive bone tumor:[12]

1. Pattern of bone destruction: geographic versus nongeographic
2. Zone of transition
3. Cortical destruction
4. Nature of periosteal reaction
5. Soft tissue and/or joint involvement

All these features are based on the rate of growth of the tumor and the response of the host bone to the nature of the tumor. However, even malignant tumors in the early stages may not show aggressive radiographic features (►**Fig. 2**). Follow-up radiography or further imaging needs to be performed in cases where the diagnosis is not clear. The patient should not be discharged from clinical care without a firm diagnosis.

Pattern of Bone Destruction

Nonaggressive tumors produce a geographic pattern of bone destruction, where the shape of the tumor is evident on the radiograph with well-delineated margins (►**Fig. 11**). The shapes of these nonaggressive tumors can vary, however, from simple shapes such as spheres and ovals to complex shapes. Aggressive tumors, in contrast, can produce nongeographic shapes because the tumor often has one or more rapidly advancing edges. Aggressive tumors can also produce permeative and moth-eaten patterns of bone destruction, when the tumor is advancing partly through the marrow

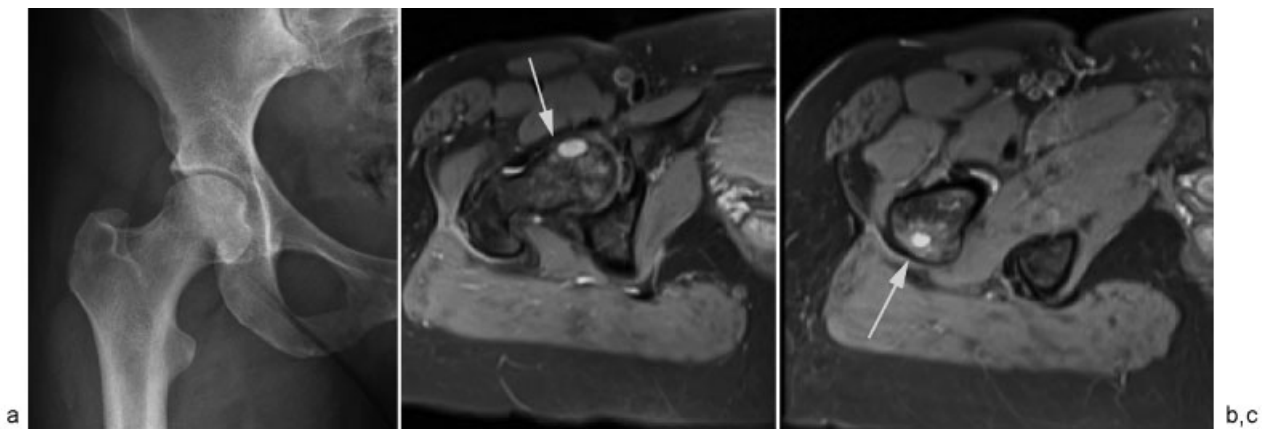

Fig. 9 (**a**) Anteroposterior radiograph, (**b, c**) axial fat-saturated proton-density-weighted MR images of the right hip. Two tiny myxoid liposarcoma metastases (arrows) are seen on MR images. They are very difficult to appreciate on the radiograph due to their small size.

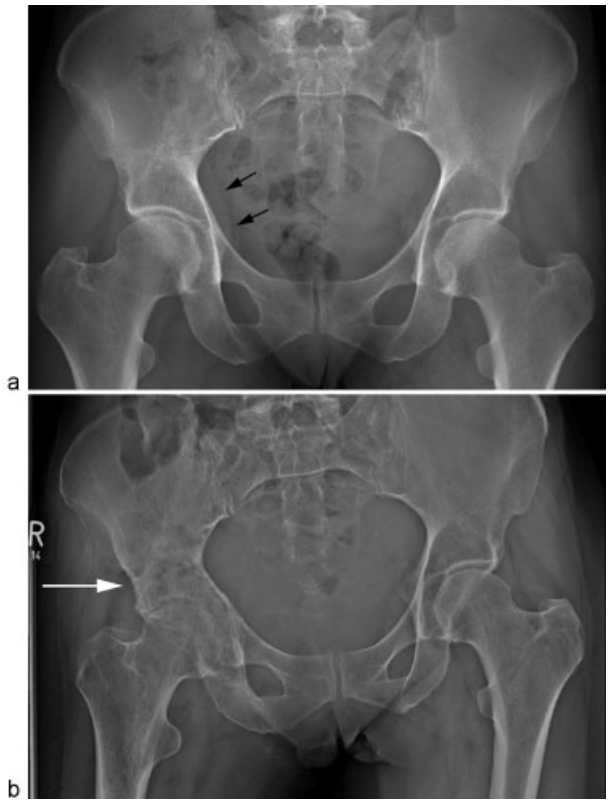

Fig. 10 (**a, b**) Radiographs of the pelvis 2 years apart in a patient with right hip pain. The later radiograph (b) shows the extensive destructive partly mineralized grade 2 chondrosarcoma in the right acetabulum (white arrow). The radiograph 2 years earlier (a) was reported as normal apart from minor osteoarthritis. There is subtle increased density of the right acetabulum with some soft tissue swelling (black arrow) when compared with the left.

spaces with some intervening trabecular preservation (►**Fig. 11**). This permeation can take place along the Haversian canals and may not be obvious on radiographs until late in the disease. Various forms of bone destruction and zones of transition were described by Lodwick in 1965[19] to assess the rate of tumor growth and are still used today with various modifications (►**Figs. 11** and **12**).[17,20]

Zone of Transition

The zone of transition refers to the margin of the tumor and the transition between normal bone and tumoral tissue as seen on radiographs. If a clear sharp line with a pencil can be drawn all around the tumor to demarcate the junction between "tumor" and native bone, this is defined as a narrow zone of transition. In nonaggressive tumors, due to their slow growth, there is a narrow zone of transition between tumor and native bone. The narrow zone of transition, which is also the margin of the nonaggressive tumor, is seen as a thin line of demarcation and can be sclerotic (as in nonossifying fibroma or chondromyxoid fibroma) (►**Figs. 11** and **12**). Some locally aggressive tumors such as giant cell tumor can have a narrow zone of transition, but it is usually nonsclerotic.[21] However, aggressive tumors grow rapidly and do not allow for a sharp margin to form around the tumor, defined as a wide zone of transition (►**Figs. 11c** and **12**). This zone of transition should only be assessed on radiographs or CT. MRI, in contrast, often demonstrates a narrow zone of transition between tumor and native bone and can be misinterpreted as nonaggressive (►**Fig. 12**).

Cortical Destruction

The presence of cortical destruction is a sign of an aggressive bone tumor (►**Fig. 12**). Cortical destruction may be encountered with a neocortex (contained) or without a neocortex (no containment). This means, in effect, that the host bone did not have enough time to produce periosteal new bone (neocortex) around a tumor that is growing rapidly. Even though nonaggressive tumors also grow, they allow the host bone to respond in a timely fashion by forming enough periosteal new bone to envelop the tumor because they grow at a slower rate than aggressive tumors. Nonaggressive tumors such as an aneurysmal bone cyst may, however, cause significant cortical erosion/endosteal scalloping (►**Fig. 13b**), sometimes resulting in areas of cortical discontinuity.

Nature of Periosteal Reaction

The periosteal new bone formation is continuous and smooth in the case of nonaggressive bone tumors because the periosteum has enough time to lay down a continuous layer of new bone (►**Figs. 13** and **14**).[22] Locally aggressive tumors such as aneurysmal bone cysts and giant cell tumors can cause bony expansion, leaving only a shell of periosteal new bone at the periphery of the lesion. Tumors characterized by alternating periods of rapid and slower growth, such as eosinophilic granuloma and Ewing's sarcoma, can result in a lamellated interrupted periosteal reaction (►**Figs. 4** and **14**). Some tumors, in particular surface tumors, can produce a buttressing type of periosteal reaction (►**Figs. 3**

Table 4 Radiographic assessment of aggressive versus nonaggressive tumors

	Nonaggressive	Aggressive
Pattern of bone destruction	Geographic	Nongeographic (moth eaten/permeative)
Zone of transition	Narrow	Wide
Periosteal reaction	Smooth, solid	Irregular, interrupted, complex (Codman's triangle/Sunray speculation)
Cortical destruction	Absent	May be present
Soft tissue/Joint involvement	Absent	May be present

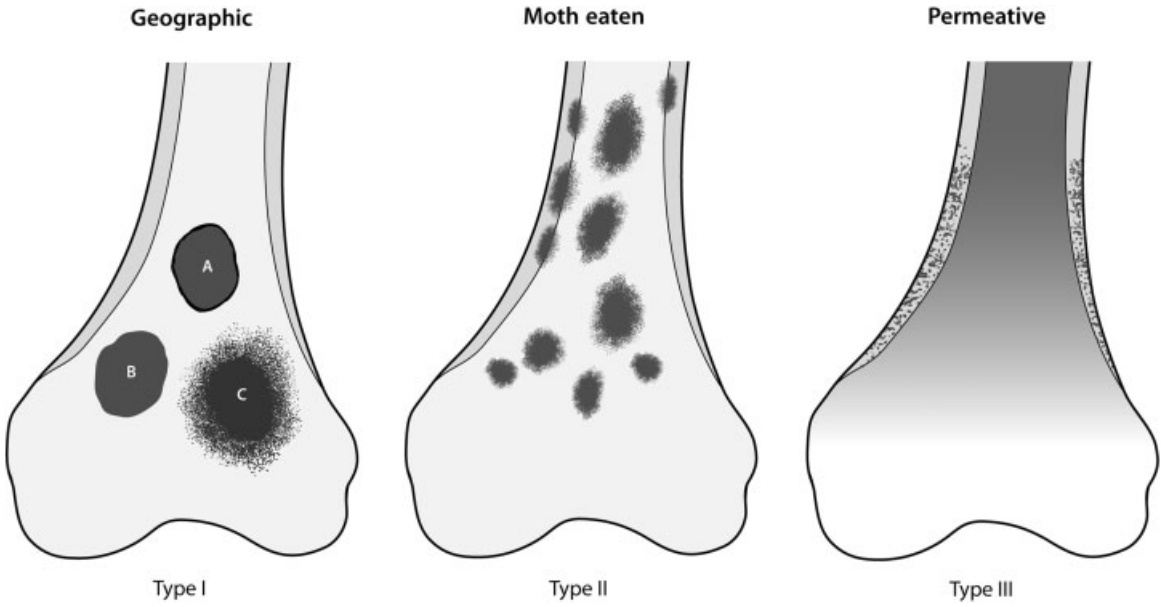

Fig. 11 Schematic drawing of patterns of bone destruction and zones of transition. Geographic bone destruction includes type IA, narrow zone of transition with sclerotic margin; type IB, narrow zone of transition with nonsclerotic margin; and type IC, wide zone of transition. Moth-eaten (type II) and permeative (type III) lesions by definition have a wide zone of transition.

and **14**). However, aggressive tumors, due to their rapid growth, generate a disorganized, discontinuous complex periosteal response that may manifest as sunray spiculation or Codman's triangle (►**Figs. 13** and **14**).[22] These descriptions are often associated with an osteosarcoma diagnosis, but this periosteal response is not specific to osteosarcoma and can occur with any aggressive bone tumor or metastasis (►**Fig. 13c**). However, benign and malignant bone tumors can exist without eliciting any cortical destruction or periosteal response, especially in the case of early intramedullary tumors. There may be a noncalcified periosteal reaction as well, best depicted by MRI.

Soft Tissue and/or Joint Involvement

The presence of a soft tissue mass or joint destruction associated with a bone tumor strongly favors an aggressive tumor (►**Fig. 12d**). The tissue fat planes around bone surfaces and joints should therefore be carefully assessed in the presence of a bone tumor. It is, however, common to have a joint effusion associated with a periarticular bone tumor, even when the joint is not involved. Therefore the presence of joint effusion as evidence of joint involvement by tumor should not be misinterpreted. Because local staging is crucial for proper treatment planning, the affected compartments, infiltration, or encasement of nerves and vessels and infiltration of the joint capsule should be reported, but this needs MR cross-sectional imaging.[23]

It is important to consider the reason for classifying bone tumors into "aggressive/nonaggressive" and not "benign/malignant."[13,24] Although most aggressive tumors are malignant and most nonaggressive tumors are benign, this is not always the case. Malignant tumors such as myeloma can often present as nonaggressive tumors on imaging, and often innocuous tumors, such as eosinophilic granuloma, can present as aggressive tumors. In addition, several intermediate but locally aggressive tumors such as giant cell tumors, chondroblastomas, and others can cause severe bone destruction. Nevertheless, the characterization of tumors as aggressive versus nonaggressive is clinically useful because all do-not-touch tumors are in the nonaggressive category. Similarly, aggressive-looking benign tumors such as eosinophilic granuloma cannot always be differentiated from Ewing's sarcoma before a biopsy and therefore need referral to an RSTC. Of note, the differentiation of aggressive from nonaggressive bone tumor is the most important part of imaging assessment of a bone tumor. When a tumor is judged aggressive, the patient should be referred to the appropriate RSTC for further assessment including a biopsy.

As mentioned previously, all bone tumors in patients $>$ 40 years of age should be considered aggressive until proven otherwise, and metastases and multiple myeloma are more common than primary bone sarcomas. However, after further investigation such as a bone scan, PET/CT scan, or whole-body MRI scan, if the bone tumor is solitary, a primary bone sarcoma remains a possibility, and the patient needs to be referred to the RSTC for further management including biopsy. Infection should be considered in the differential diagnosis of bone tumors. Depending on the type of infection, both aggressive and nonaggressive tumors can occur. This is particularly the case in children and young adults with epiphyseal and metaphyseal tumors.

Some other criteria in bone tumor assessment should be addressed in the radiologic report.[25]

1. Location of the bone tumor: epiphyseal/metaphyseal/diaphyseal or medullary (central, eccentric), cortical, surface
2. Matrix

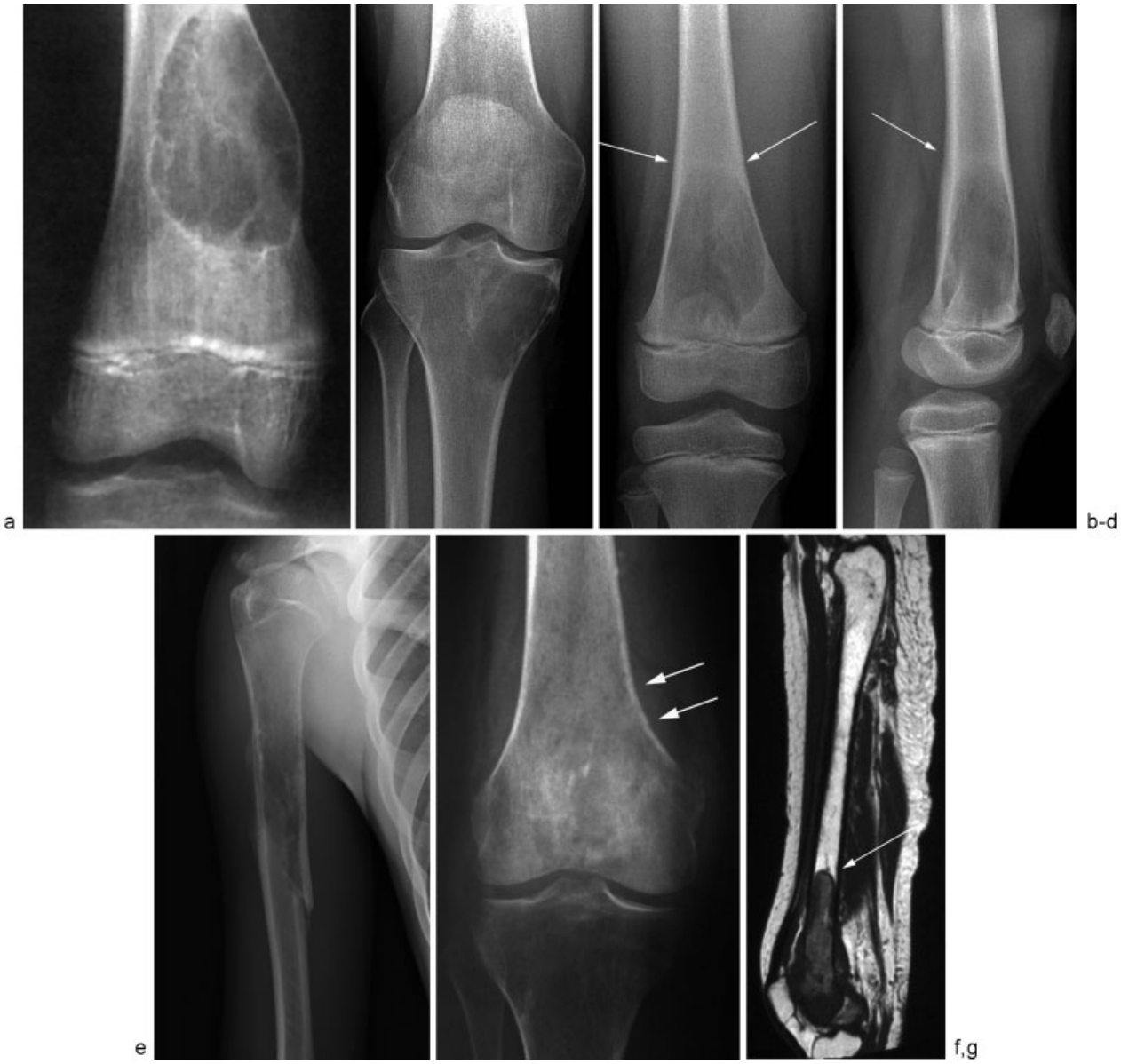

Fig. 12 Images demonstrating patterns of bone destruction and zones of transition. (**a**) Anteroposterior (AP) radiograph of the femur in an adolescent shows a large geographic eccentric metaphyseal lesion with a sclerotic margin (corresponding to type IA in ►**Fig. 11**). The final diagnosis was a nonossifying fibroma. (**b**) AP radiograph of the knee shows a geographic eccentric lesion in the proximal tibia with a narrow nonsclerotic zone of transition (corresponding to type IB in ►**Fig. 11**). The final diagnosis was a giant cell tumor. (**c**) AP and (**d**) lateral radiographs of the knee in a 9-year-old child show a geographic lesion with a wide zone of transition most evident in the proximal margin of the lesion (corresponding to type IC in ►**Fig. 11**). The final diagnosis was an osteosarcoma. Also note the subtle displacement of the soft tissues on the anterior aspect of the femur in (d). (**e**) AP radiograph of the proximal humerus in an 18-year-old boy shows a nongeographic moth-eaten appearance of a diaphyseal osteosarcoma with cortical destruction and aggressive interrupted periosteal reaction (corresponding to type II in ►**Fig. 11**). Also note the pathologic fracture. (**f**) AP radiograph of the knee in a 67-year-old with permeative destruction of the distal femur and a wide zone of transition in myeloma (corresponding to type III in ►**Fig. 11**). (**g**) Sagittal T1-weighted MR image in the same patient as (f) shows a very sharp proximal transition with normal marrow. MRI shows the margin better because it directly visualizes the tumor; the radiograph mainly shows the host response. Radiographic criteria of margin/zone of transition obviously cannot be used on MRI.

3. Part of the body involved: for example, hands and feet, tibia, posterior aspect of distal femur, and posterior elements of spine (►**Fig. 1**)
4. Single or multiple tumors

The location of the bone tumor within a particular bone is one of the most important features and helpful in the differential diagnosis. Various bone tumors have a predilection to affect various sites in a particular bone. ►**Fig. 15** lists various differential diagnoses to consider based on the age of the patient and the location of the bone tumor within a particular bone. However, there is considerable overlap in these lists of differential diagnoses. For example, although Ewing's sarcoma and eosinophilic granuloma are most

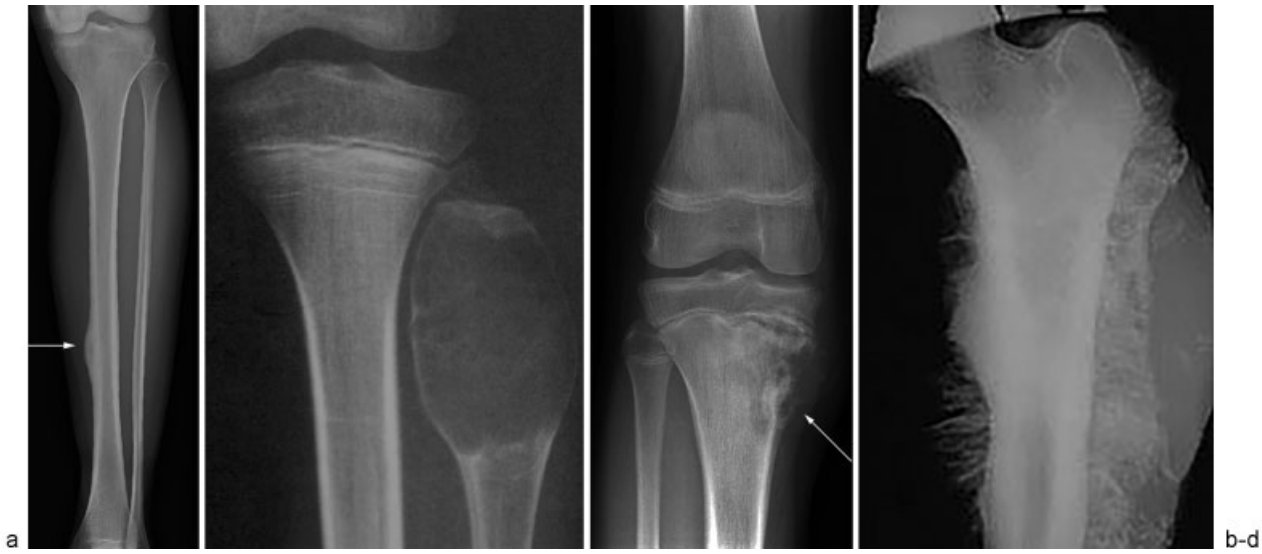

Fig. 13 Periosteal reaction. (**a**) Solid periosteal new bone formation secondary to an osteoid osteoma (arrow). (**b**) Significant cortical erosion/thinning, endosteal scalloping, and bony expansion caused by a proximal fibular aneurysmal bone cyst. (**c**) Interrupted periosteal reaction with Codman triangle (arrow), severe cortical destruction in osteosarcoma. (**d**) "Sunray spiculation" seen in a prostate metastasis.

commonly seen centrally in the diaphysis, they can be seen in other locations of the bone such as metaphyses and even epiphyses/apophyses. Greater cell turnover occurs in the metaphyseal region that results in an increased likelihood of genetic mutations in the cells in this region resulting in bone tumors arising more commonly in the metaphyseal region. Individual bone tumors have a predilection to affect the medullary space, in the cortex or on the surface of a bone. Osteoid osteoma and adamantinoma have a propensity to arise in the cortex. Giant cell tumors and aneurysmal bone cyst are usually located eccentrically in the medullary space, and simple bone cyst and enchondroma typically affect the central medullary space.

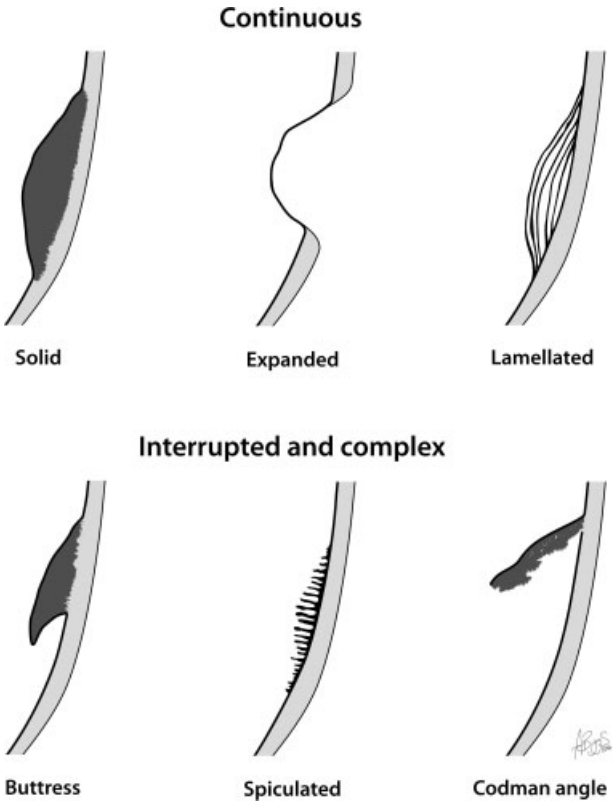

Fig. 14 Schematic drawing of types of periosteal reaction. Of note, in case of aggressive tumors the cortex is not an intact structure.

Certain tumors show a predilection to affect certain bones. Parosteal osteosarcoma, for example, often affects the posterior aspect of the distal femur. A lucent bone tumor in the hand or foot is likely to be an enchondroma, and the tibia is a common site for adamantinoma and osteofibrous dysplasia in a young child. A well-circumscribed lesion in the calcaneum is an unicameral cyst, lipoma (which may show regressive changes), or an intraosseous ganglion. Most lesions arising in the sternum are malignant, whereas most tumors in the patella are benign. Metastases are most often seen in areas containing red bone marrow, especially the axial skeleton.

Although the matrix of a tumor is often not useful in differentiating between the various bone tumors, a cartilaginous or osseous matrix can help identify chondromatous or osseous bone tumors. Also, a ground-glass matrix in radiographs or CT images may also suggest fibrous dysplasia. The matrix patterns demonstrated in radiographs of bone tumors may yield important clues about the true nature of a lesion, especially when only limited biopsy material is available from extraosseous or nonrepresentative areas. Therefore, in the evaluation of bone tumors and tumorlike conditions, the histologic findings must be correlated with the radiographic examination, and the location where the biopsy material was obtained must be specified.[26]

Multiple tumors seen in patients $>$ 40 years of age usually suggest metastases or myeloma. However, several benign tumors and tumorlike conditions like brown tumors of

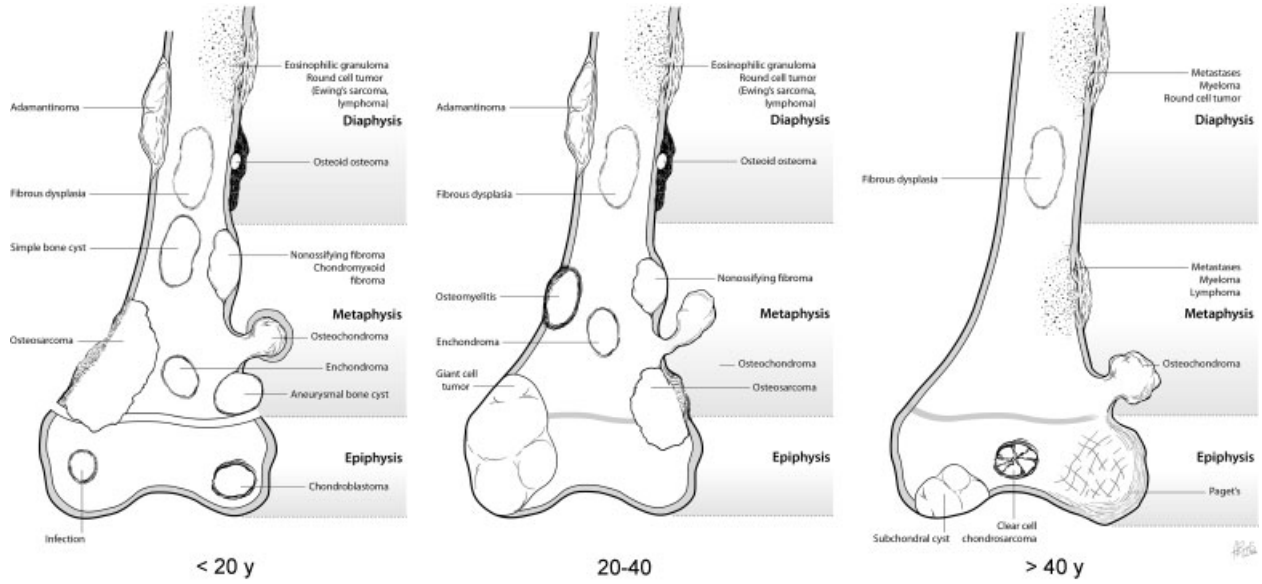

Fig. 15 Differential diagnosis of bone tumors based on age and location.

hyperparathyroidism can cause multiple bone lesions (►**Fig. 6**).

Osteolytic versus Sclerotic Tumors

Most bone tumors are osteolytic, although sclerotic and mixed tumors can also occur. The matrix itself is not a true indicator of whether a tumor is benign or malignant. However, several osteolytic benign tumors such as a simple bone cyst or a nonossifying fibroma can heal spontaneously and during this process become sclerotic (►**Fig. 16**). Similarly, tumors may become sclerotic after treatment (►**Fig. 16**). Reactive sclerosis can also occur around bone tumors such as Ewing's sarcoma and lymphoma, and a bone lymphoma may present as a diffusely sclerotic tumor. The sclerotic (ivory vertebra) and mixed patterns are more common in Hodgkin's lymphoma although not pathognomonic.[18] Mineralized primary bone tumors such as osteosarcoma and chondrosarcoma can appear sclerotic (►**Fig. 5**), but they are less common than sclerotic metastases in adults (►**Fig. 16**).

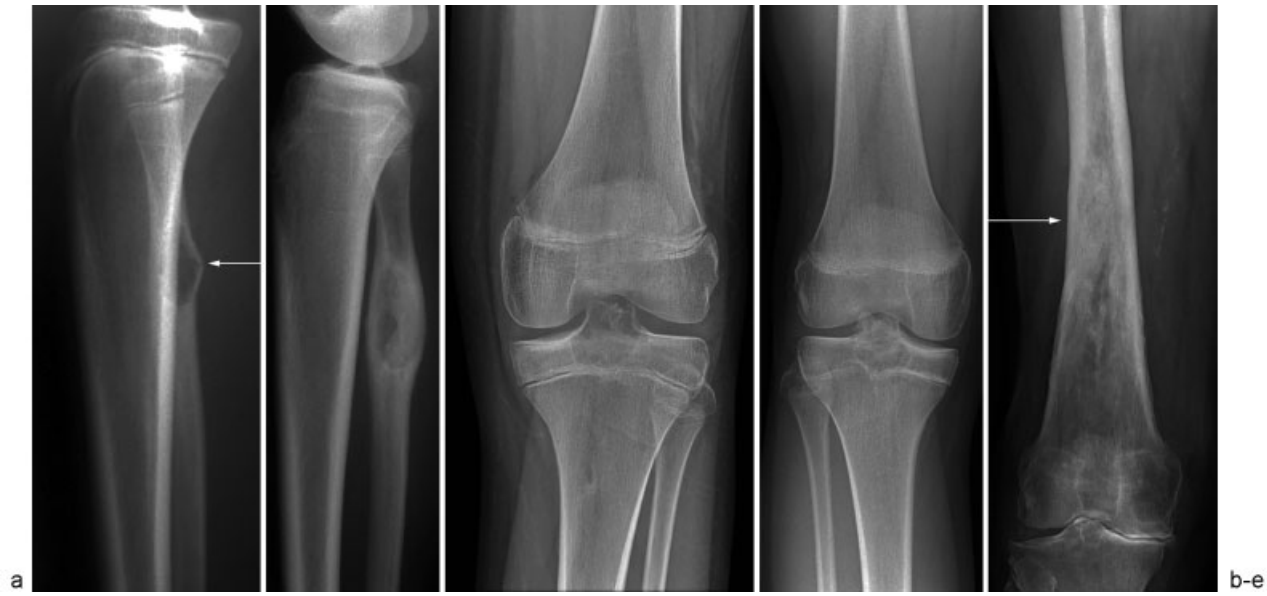

Fig. 16 Sclerotic lesions. (**a**) Lateral radiograph shows a lytic nonossifying fibroma in the proximal fibular diaphysis with a subtle cortical fracture line (arrow) that healed and turned sclerotic 3 years later (**b**). (**c**) Anteroposterior radiograph of the knee in a 12-year-old girl shows a chondroblastoma in the proximal tibial epiphysis that was treated by radiofrequency thermoablation. (**d**) Radiograph of the same knee as in (c) 2 years later shows healing response seen as sclerosis. (**e**) Radiograph of the distal femur in chronic osteomyelitis shows diffuse sclerosis in the distal femur with slight bone expansion and cortical thinning (arrow).

Advanced Imaging Modalities following Radiography: MRI and CT

After the initial assessment on radiographs, if the tumor is either aggressive or is potentially malignant, additional imaging of the local area is often needed (CT or MRI scan).[27] These additional imaging examinations can occasionally offer further information such as the intralesional matrix, lesional fat, blood products, associated soft tissue involvement, or the presence of fluid-fluid levels. The latter have a prevalence of 2.7% in bone tumors and are most often encountered in aneurysmal bone cysts (►**Fig. 17**); however, fluid-fluid levels remain a nonspecific finding and can occur in a wide range of bone and soft tissue tumors, both benign and malignant.[28]

MRI is particularly helpful in chondroid tumors and in cysts due to the high fluidlike signal on T2-weighted images (►**Fig. 3**). MRI and CT can also be used to demonstrate the presence or absence of cortical destruction and periosteal reaction that will help differentiate benign from malignant tumors when these features are difficult to determine on radiographs.[29] MRI is the best additional imaging modality for local staging because it allows for accurate assessment of the extent of the disease and the effect of the tumor on the surrounding structures including the joint, neurovascular structures, muscle compartments, and skin.[15,30] MRI also gives details of the extent of the compartmental involvement to help complete excision of the tumor.

The sequences that form the mainstay of tumor assessment on MRI are T1-weighted and T2-weighted fast spin-echo images with or without fat suppression. Commonly used MRI protocols for bone tumors include a T1-weighted and a fluid-sensitive sequence of the full length of bone along the long axis to assess the longitudinal extent of the tumor, to diagnose any skip lesions, and to aid the resection level at surgery (►**Fig. 17**). Axial images through the bone should also be performed and typically include axial T1-weighted and T2-weighted images (with or without fat suppression) to

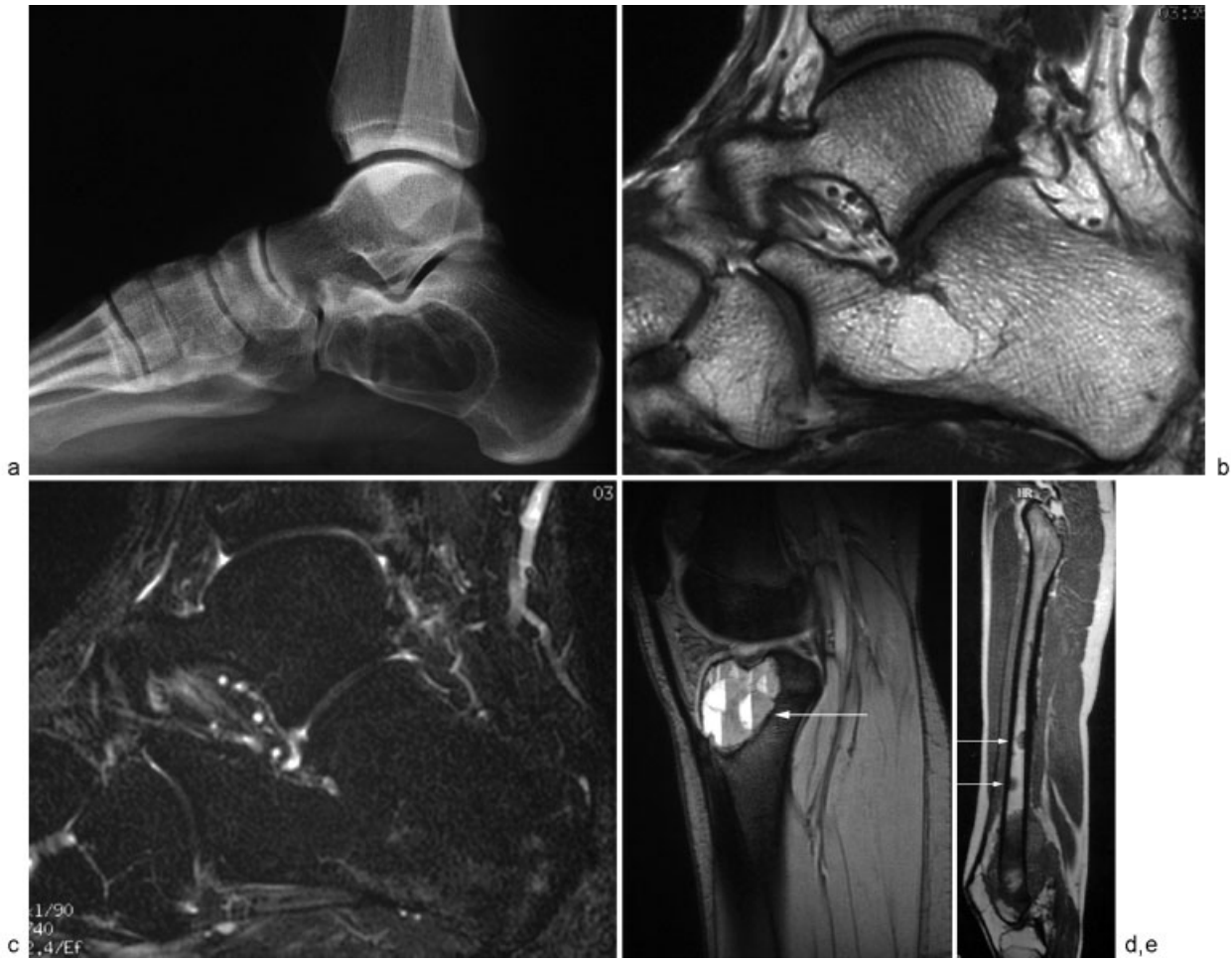

Fig. 17 Value of MRI in primary bone tumor assessment. (**a**) Lateral radiograph of the calcaneum shows a nonaggressive lytic bone lesion that could be either a simple bone cyst or intraosseous lipoma. (**b**) T1-weighted and (**c**) short tau inversion recovery MR sagittal images show signal compatible with fat in the lesion confirming that this lesion is a lipoma. (**d**) Sagittal gradient-echo MR image in a different patient shows fluid-fluid levels in the proximal tibial lesion, in keeping with an aneurysmal bone cyst. (**e**) The sagittal whole femur large field-of-view T1-weighted MR image shows skip lesions more proximal (arrows) to the originally identified osteosarcoma in the distal femur. MRI helps the surgeons identify the tumor extent and thereby the level of resection needed to achieve radical treatment.

assess the involvement of surrounding structures including the neurovascular bundle. The adjacent joint should always be included in the scan. Some sarcoma treatment centers routinely use intravenous gadolinium chelates; other centers only use gadolinium chelate enhancement in selected types of cases. Sarcoma treatment centers may prefer to perform the MRI examination according to their own (often elaborate) protocols. It is useful to liaise with the local sarcoma treatment center for advice before setting up MRI protocols.

Technological advances of MRI have enabled improvements in both delineation of anatomical detail and in functional imaging techniques that interrogate tissues at the cellular level.[31] Additional MRI techniques such as chemical-shift imaging, diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS), and dynamic contrast-enhanced (DCE) MRI are not used routinely for bone tumor assessment. The potential of chemical-shift MRI to allow for discrimination of marrow-infiltrating neoplasms from benign red marrow, of DWI to reveal tumor cellularity, MRS to assess noninvasively metabolic aberrations in a variety of sarcomas, and DCE to assess treatment response in which traditional size-based assessment criteria may underestimate efficacy in clinical trials has been reported.[30,32–34] Nevertheless, in our opinion, the mainstay of MRI remains conventional MRI sequences including T1 and T2 fast spin-echo sequences and the delineation of the bone tumor using at least two perpendicular planes. Imaging in all three planes is even better, if feasible. The entire bone and neighboring joint should be visualized. Advanced MRI techniques are probably best performed at the RSTC.

When MRI is not available or contraindicated, CT can provide similar information about the extent of the tumor. CT is also useful for further characterization of tumors with mineralized matrix and sclerotic tumors. It can provide further characterization of tumors in the cortex and periosteal locations. CT is often necessary in tumors in the ribs, posterior elements of the spine, and other flat bones with a higher cortex to medullary bone ratio. In some bones like the ribs and phalanges, CT may perform better than MRI because of higher spatial resolution and fewer motion artifacts. CT also may perform better than MRI in the small bones of the feet due to the higher resolution. The degree of edema on MRI is not in itself a measure of the malignant potential of a bone tumor. Of note, the more correct term would be bone marrow edema-like signal alterations, which reflects the fact that these signal changes do not only represent edema in many cases.

Several benign bone tumors cause extensive surrounding bone and soft tissue edema,[35] for instance an osteoid osteoma.[27] When a tumor elicits a lot of surrounding reaction including sclerosis and edema, the true extent of the tumor itself can be obscured by the reactive changes on MRI. CT may be superior to MRI in demonstrating the nidus in osteoid osteomas and may be useful to identify the origin of a tumor, particularly in the periosteal and parosteal locations and in assessing the relationship of the tumor to the medulla. But standard CT cannot demonstrate soft tissue or bone marrow edema, which is a useful differentiating feature of certain tumors like osteoid osteomas, chondroblastomas, and infection (of note innovations such as dual-energy CT enable identification of bone marrow edema[36]). Also, in selected cases, osteoid osteomas are juxta-articularly localized, reactive changes (cortical thickening, medullary sclerosis) are lacking, and a predominant synovitis may be present, which is preferentially appreciated using MRI.[37]

The role of FDG- or NaF-PET/CT and PET/MRI in the initial diagnostic work-up of bone tumors is still not established. These investigations can show a number of incidentalomas that have no relevance to the patient's clinical condition. There is an overlap in the maximum standard uptake value (SUV_{max}) between benign and malignant tumors. This is not surprising, given that some benign bone tumors such as osteoid osteomas, chondroblastomas, and aggressive eosinophilic granulomas are very active metabolically. Several nontumorous inflammatory lesions can also result in an abnormally high SUV.

Sodium fluoride (NaF)-PET/CT may show several incidental lesions even when compared with FDG-PET/CT owing to the nature of bone metabolism.[38,39] Therefore, PET/CT does not yet have a role in the initial differentiation of benign from malignant bone tumors but may aid in problem solving in a suspected local recurrence.[40] Similarly, other imaging investigations such as ultrasound and angiography have no role in the routine initial assessment of bone tumors. Once a radiograph and MRI and/or CT have been performed, further imaging should be performed at the RSTC as necessary. Local staging using MRI should be done before biopsy, and a search for distant metastases in the case of malignant bone tumors with CT or PET/CT can be performed after obtaining an histologic diagnosis.

Nonaggressive Tumors

Several nonaggressive tumors do not need any further management and can be treated conservatively. These are referred to as do-not-touch tumors and include nonossifying fibroma or fibrous cortical defect if < 3 cm in diameter, simple bone cysts, small enchondromata, and bone islands. However, certain nonaggressive tumors may still need treatment such as infection, osteoid osteomas, and chondromyxoid fibroma. Occasionally, following initial radiologic assessment when a tumor is deemed nonaggressive, it may still be difficult to determine whether a tumor is a do-not-touch tumor or a tumor needing further diagnostic work-up and/or treatment. In these cases, it is preferable to obtain advice from the multidisciplinary team at the RSTC.

Indeterminate Tumors and Aggressive Tumors

Tumors where the differentiation is deemed difficult between aggressive and nonaggressive diagnosis should be considered indeterminate. Indeterminate and aggressive tumors should be considered a primary bone malignancy (sarcoma/lymphoma) until proven otherwise and referred to an RSTC for further assessment including biopsy. Depending

on the local setting, indeterminate tumors could be referred to an RSTC with or without performing an MRI beforehand. This depends on the local collaboration setting, the communication between the RSTC and the referring physician and the general radiologists, as well as the quality of the MRI. Some RSTCs have the policy that if all indeterminate tumors were referred to a tertiary center without performing an MRI, it would often result in a delay in patient management. On the contrary, other RSTC staff believe that performing an MRI examination in these patients locally would delay referral and management, and thus they prefer that these patients are sent straight to them to complete the diagnostic work-up, because some of these patients after a consultation do not need anything more than a radiograph.

Biopsy

A biopsy for a potential benign or malignant primary bone tumor should always be performed at the RSTC under the guidance of an appropriate multidisciplinary team with expertise not only in the technical issues of the biopsy but also in histopathologic and surgical assessment, which can often be difficult in these rare tumors. The multidisciplinary team at the RSTC should include multiple clinicians specializing in sarcoma including a radiologist, pathologist, oncologic surgeon, and oncologist. Importantly, the biopsy should always be performed after all initial imaging assessment has been completed including MRI and in collaboration with the orthopaedic oncologist who performs the definitive surgery. In the extremities, attention to compartmental anatomy is paramount.[41]

A bone biopsy for these tumors can involve fine-needle aspiration, core needle biopsy, or incisional biopsy, and sometimes also excisional biopsy or shark bite. Controversy regarding the diagnostic yield of these biopsy techniques continues. The current literature has not clarified the optimal biopsy technique for the diagnosis of bone and soft tissue tumors. However, core needle biopsy is usually preferable to incisional biopsy because of the low risk of contamination and the low cost. The use of imaging guidance also increases the diagnostic accuracy of musculoskeletal biopsies and reduces the risk of complications. If the result of a percutaneous biopsy is nondiagnostic, an incisional biopsy should be performed.[42]

CT-guided core needle biopsy is a safe, accurate, and highly effective procedure that obviates the need for open surgical biopsy in a significant number of cases. When combined with fusion imaging, CT guidance is an accurate method of targeting specific regions of interest. In a recent study on 380 bone tumors, accuracy of 80.8% with diagnostic error of 7.1% and nondiagnostic rates of 12.1% were reported.[43] It is recommended that biopsy samples always be sent for both histologic and microbiological assessment because infection should always be considered in the differential diagnosis of all bone tumors. Also, the site of biopsy (usually with CT or fluoroscopy) must be documented because not infrequently the question in the multidisciplinary debate arises as to whether the biopsy was taken from a representative part of the lesion.

Conclusion

All bone tumors should be assessed initially on radiographs to determine whether the tumor is aggressive or nonaggressive. Nonaggressive tumors that fall under the do-not-touch category can be managed at any health care setting. All tumors deemed aggressive and other tumors that are "nonaggressive" but need further management should be referred to the RSTC. Biopsy and surgery of these tumors should only be performed at the RSTC under the care of a dedicated sarcoma multidisciplinary team.

Note

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