Ten commandments for the diagnosis of bone tumors

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Ten Commandments for the Diagnosis of Bone Tumors

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Abstract

The diagnosis of tumors and tumorlike lesions of bone is a routine part of both general and specialist radiologic practices. The spectrum of disorders ranges from the small incidental lesion to the potentially life-limiting malignancies whether primary or secondary. In this review, authored by experts from several European orthopaedic oncology centers, we present a collection of pieces of advice in the form of 10 commandments. Adherence in daily practice to this guidance should help minimize adverse patient experiences and outcomes.

Keywords
- diagnosis
- bone
- tumor
- radiograph
- biopsy

In the Old Testament,the prophet Moses gave the people of Israel instructions, known as the Ten Commandments, to govern their daily life. Obeying these simple rules would ensure the individual eternal salvation in the afterlife. Working in specialist orthopaedic oncology centers, we provide 10 analogous commandments for radiologists presented with an undiagnosed bone tumor. Attention to the rules listed here will minimize avoidable mistakes and, although no guarantee of eternal salvation, will help reduce adverse events that could impact patient management and prognosis.

Lesion detection clearly has to be achieved before the exercise of diagnosis can be undertaken. It is not the goal of this article to discuss the issues that can cause delays in bone tumor detection. Suffice to say that the initial radiographic signs may be limited to subtle bone lysis alone before other typical manifestations develop. It has long been recognized that 30 to 50% of cancellous bone must be destroyed before a bone tumor may be visible.[1,2] Bone tumors are susceptible to the same perceptual and cognitive dysfunctions as imaging of other pathologies.[3] Issues with biopsy and staging are also not covered in this review.

Commandment 1: Recognize the Importance of the Patient's Age

The patient's age is critical because it frequently influences the differential diagnosis of a bone tumor. The author of an old respected textbook, the late Jack Edeiken, claimed that 80% of bone tumors could be correctly diagnosed on the basis of age alone.[4] He may have been overstating the case, but many tumors exhibit a peak incidence in a particular age range (►**Fig. 1**).

For example, most primary sarcomas of bone, with the exception of chondrosarcoma, occur in adolescents and young adults and tend to be rare after 40 years of age. Many benign tumors of bone, such as chondroblastoma and osteoid osteoma, are most frequently seen in the second and third decades (►**Fig. 1**). Conversely, metastases and myeloma tend to arise over and be uncommon in those <40 years of age. Certain tumors may be indistinguishable on imaging features alone, but it is the age of the patient that offers the clue to the correct diagnosis (►**Fig. 2**). It is surprising how often a radiologist will provide a perfectly competent description of the radiographic features of a bone tumor but then appears to pluck a diagnosis

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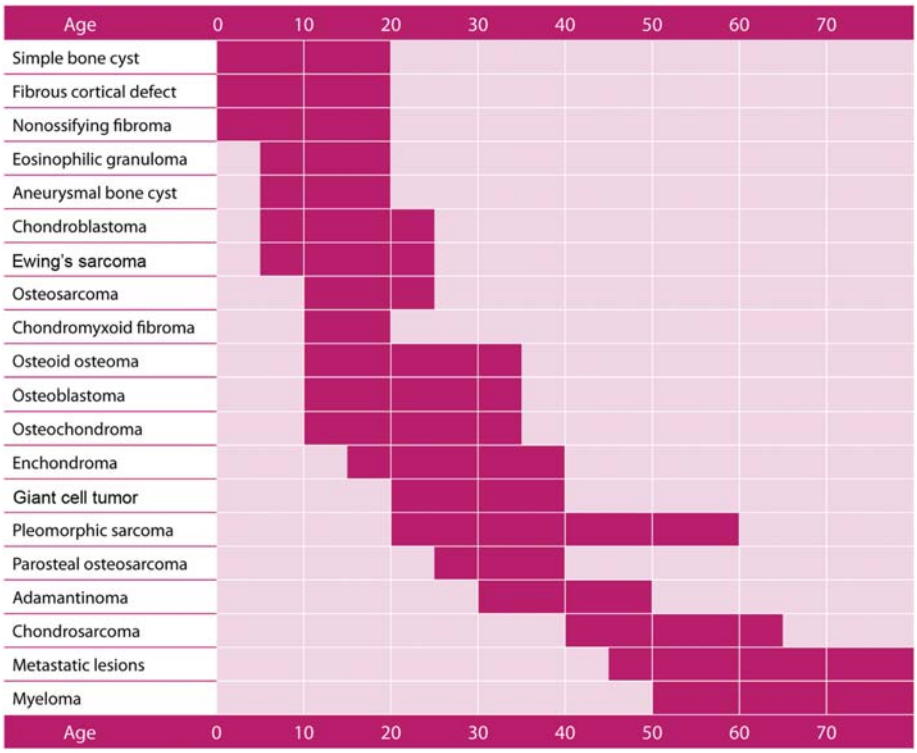

Fig. 1 Age ranges of bone tumors.

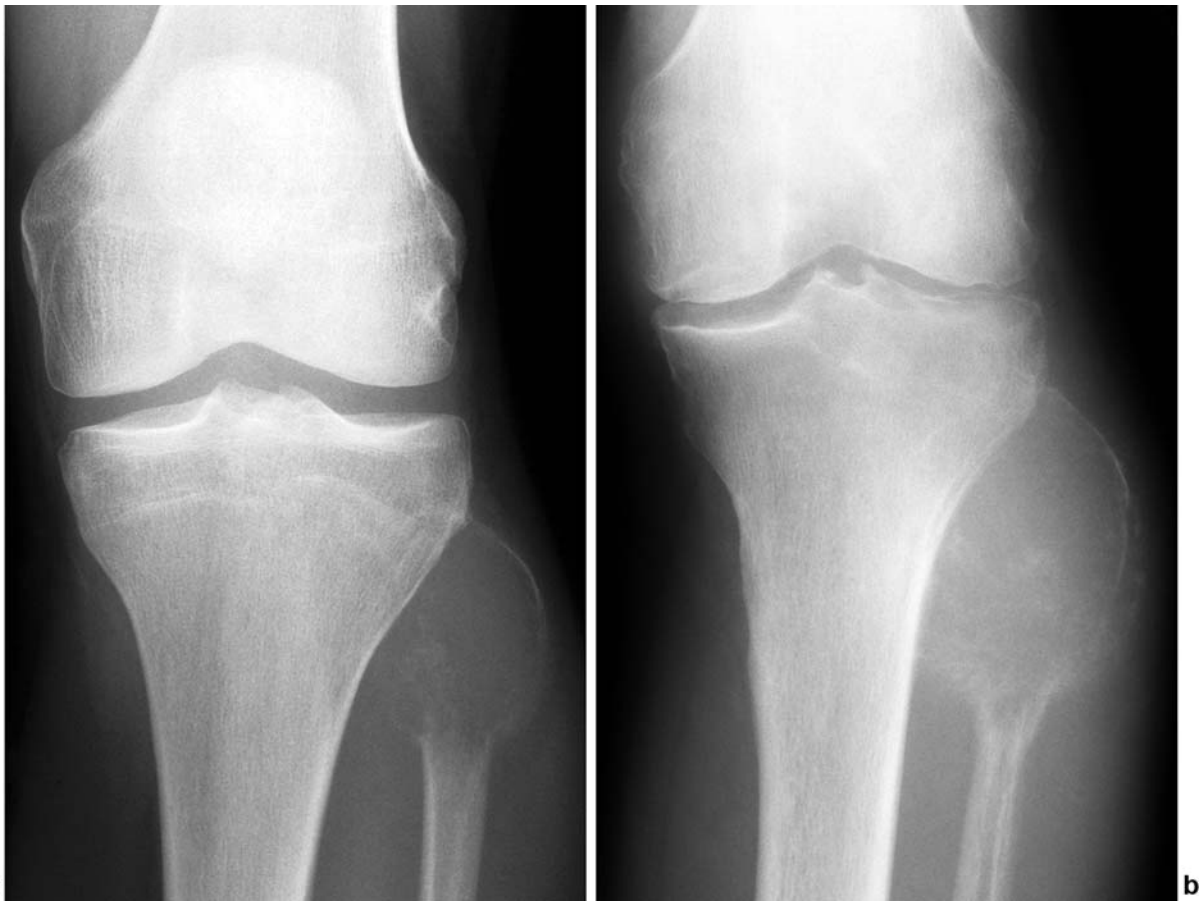

Fig. 2 Anteroposterior radiographs of the knee in (**a**) a 35-year-old and (**b**) a 65-year-old showing similar lytic expansile lesions arising in the head of the fibula. The diagnosis in (a) was a giant cell tumor of bone and in (b) was a renal metastasis.

almost at random with no note taken whatsoever of the age of the patient.

Commandment 2: Remember the Radiograph Is Key to the Differential Diagnosis

When referring to radiographs, we tend to use the epithet "plain," so more recently trained radiologists frequently underestimate their value. Despite all the new technological advances in imaging, the "conventional" (preferred rather than plain) radiograph remains to this day the most useful single investigation to determine the differential diagnosis of a bone lesion.[5,6] It allows analysis of the pattern of bone destruction,[7] nature of any periosteal reaction,[8] and characterization of matrix mineralization.[9]

Textbooks can inadvertently be confusing because they tend, as a cost-saving exercise, to use illustrative cases that show all the typical features in a single figure, thereby ensuring maximum educational impact for minimum page space. Whereas in reality it is not uncommon for a bone tumor to exhibit a single diagnostic feature (►**Figs. 3** and **S1**).[10] Radiologists should therefore be wary of relying on so-called pattern recognition alone for the diagnosis of bone tumors. This approach, commonly referred to in the United States as the "Aunt Minnie" technique,[11] can fail if the tumor has atypical features, arises at an unusual site, or is mimicked by a differing pathology (►**Fig. 4**). The preferred approach combines pattern recognition together with analysis that relies on the meticulous assessment of the differing radiographic features before venturing a differential diagnosis.[12]

Radiologists should resist the temptation to ask for cross-sectional imaging until the radiographic contribution has been fully assessed. Cross-sectional imaging, essential for surgical staging, can be complementary in terms of diagnosis and on occasion contributory (e.g., presence or absence of fluid-fluid levels, perilesional inflammatory response, and gadolinium-enhanced patterns on magnetic resonance imaging [MRI]) and thereby impact the radiographic differential diagnosis. Not infrequently, the opposite may be the case

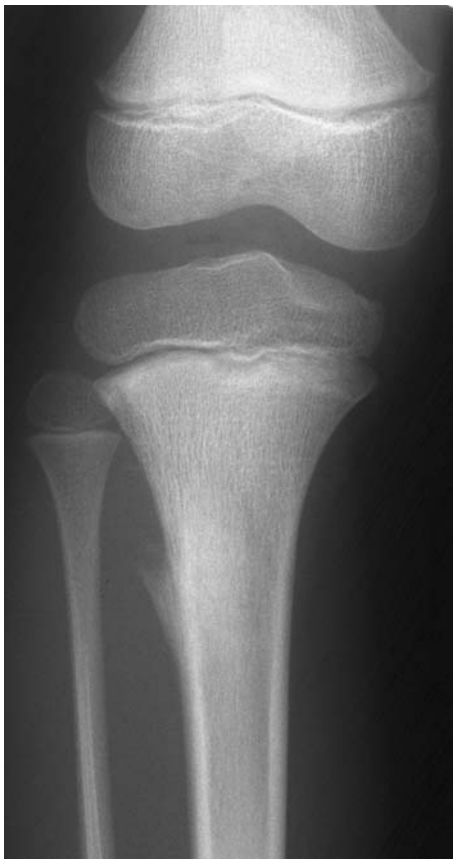

Fig. 4 Anteroposteriorradiograph of the knee in a child with an osteosarcoma of the proximal tibia. The only diagnostic feature in this study is the Codman's angle.

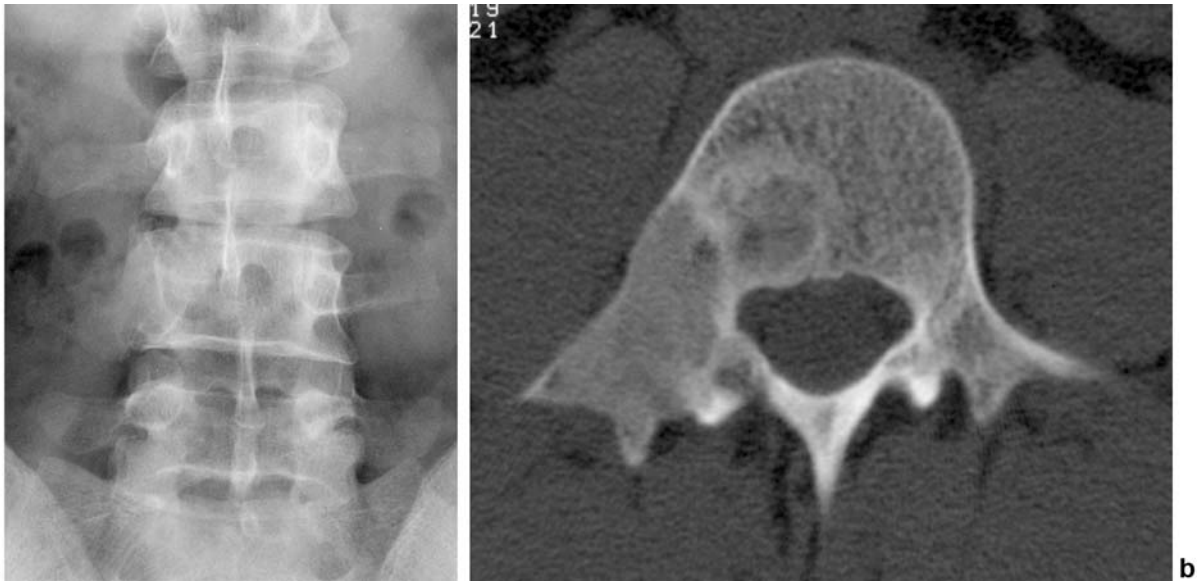

Fig. 3 (**a**) Anteroposterior radiograph and (**b**) transverse computed tomography of the lumbar spine showing an expansile lesion with a ground-glass matrix arising in the right pedicle and transverse process of L4. The imaging is typical but the site atypical for fibrous dysplasia.

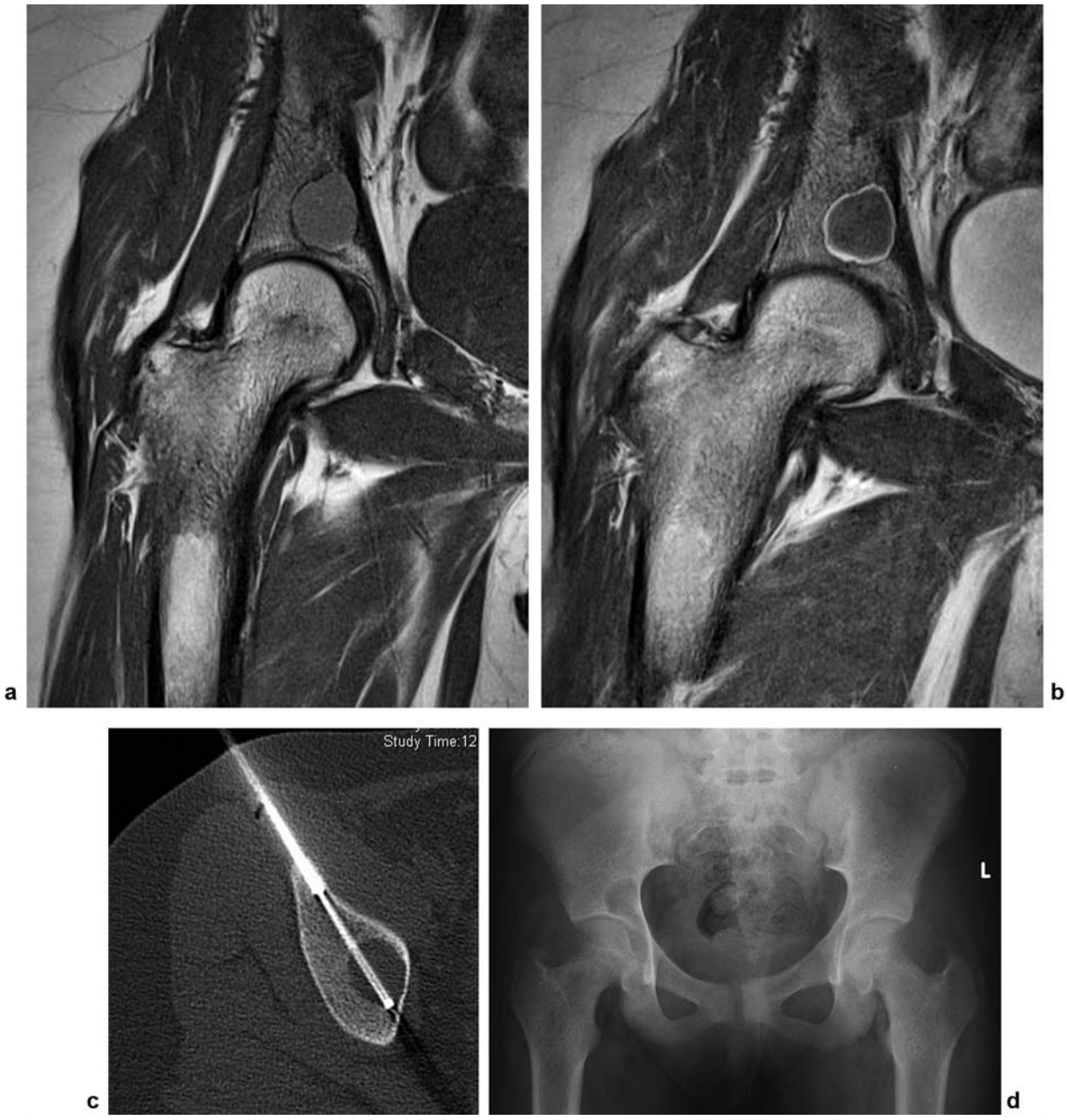

Fig. 5 (**a**) Coronal T1-weighted pre-gadolinium and (**b**) post-gadolinium images showing a cystic lesion in the roof of the acetabulum. (**c**) Computed tomography–guided biopsy for the presumed cyst. Histology confirmed the presence of a hemorrhagic cyst, but it was (**d**) the pelvic radiograph that revealed the true nature of the patient's condition: rickets! The acetabular cyst was therefore a brown tumor of secondary hyperparathyroidism. Serum calcium in this case would be expected to be low.

where the appearances on cross-sectional imaging are nonspecific and it is the radiographs that clinch the diagnosis (►**Fig. 5**). An important role for further imaging is to confirm or exclude multiple lesions.

Commandment 3: Correlate Current Imaging with Previous Studies

Imaging only gives a snapshotintime of what a bone lesion looks like on the date and time it was obtained. It may be possible to infer the behavior of a lesion from a single radiographic study, but there is no substitute to being able to review previous imaging, where available. This may require some detective work on behalf of the radiologist who must remember in the first instance that the patient is the initial port of call if regrettably not always a reliable source of information.

Speed of progression of a lesion is a good indicator of the aggressivity. For example, the rapid advancement (days/weeks), particularly in children, from normal to grossly abnormal radiographs is the hallmark of infection/acute osteomyelitis as opposed to primary sarcoma of bone (weeks/months) (►**Figs. 6** and **S2**). There are also potential medicolegal implications of omitting to review previous imaging even if not immediately available. In that situation the prudent radiologist will note the existence of the

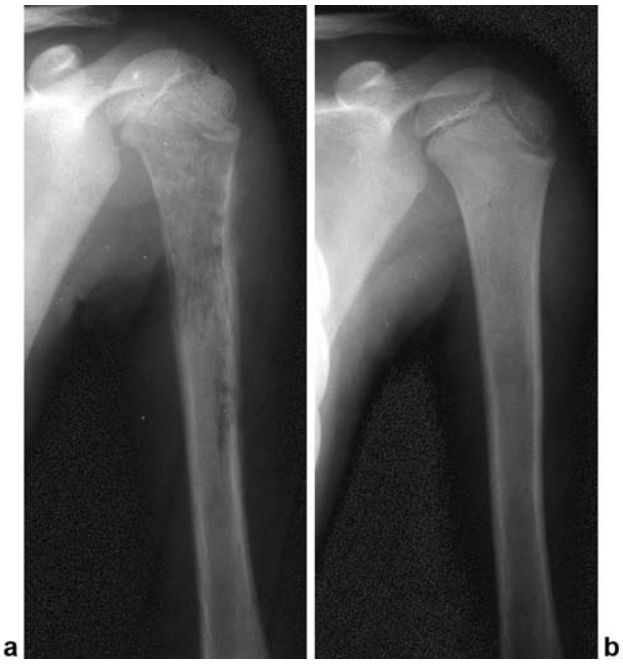

Fig. 6 (**a**) Anteroposterior (AP) radiograph in a child showing an aggressive lesion of the proximal humerus. (**b**) An AP radiograph obtained 2 weeks earlier is entirely normal. Only acute osteomyelitis, and not sarcoma, can progress that quickly.

historical studies and recommend the current imaging is reviewed as, and when, all the earlier imaging becomes available.

Commandment 4: Do Not Ignore the Ancillary Patient Information

Older readers will recognize the need for radiologists in the past to be experts in graphology (the study of handwriting), familiar with being faced with an illegible scribble in the box for clinical information on the original request form. In this age of electronic requesting, the problem is not so much trying to decipher the information but rather the paucity of information provided. Critical information such as age (Commandment 1) is a core component of the patient's record on the radiology management system and therefore universally available. Other information in terms of history and ancillary tests depends on the willingness of the referring clinician to share all the relevant information, such as inflammatory markers, serum calcium, and so on (►**Fig. 5**). In fairness, much of these data may not be available to the clinician at the time of initiating the imaging request.

The opposite situation may occur with information overload. In the United Kingdom, general practitioners (community physicians), coming relatively late to electronic records, can, at the click of a mouse, download virtually the whole patient medical history going back many years. In this set of circumstances,it would so easy to overlook a critical nugget of information within a swathe of irrelevant data (►**Fig. S3**). A default response for many radiologists is a natural tendency to wish to please the referring clinician or pathology colleagues by affirming the suggested diagnosis.

Prudent radiologists should be prepared to question any tentative diagnosis proposed even if they may on occasion appear to be behaving in a less than helpful manner. In addition, radiologists need to develop a strategy with clear advice given within the imaging report on what further tests would be appropriate and how these may impact the differential diagnosis. One solution used in the first author's unit initiated several years ago was the introduction of a daily diagnostic multidisciplinary meeting between radiologists and surgeons to triage the latest referrals to the orthopaedic oncology unit and thereby determine the next steps in the patient pathway (e.g., further imaging, biopsy). However, this solution does have significant cost and resource implications.

Commandment 5: Obtain a Chest Radiograph if the Patient with a Bone Tumor Is Older Than 40 Years

Metastatic disease to bone is $\sim$ 30 times more common than primary bone tumors. It is not unusual for it to have a relatively occult presentation, and it certainly may exhibit atypical imaging appearances (►**Fig. 7**). The cautious radiologist, faced with an undiagnosed bone tumor in the relevant age group ($>$ 40 years of age), will insist on a prompt chest radiograph. Its universal availability, low cost, and modest radiation dose more than justify its use to confirm or exclude primary malignancy or further metastatic disease in the lungs and can later save embarrassment on behalf of the radiologist. The reader might be tempted to question whether it would be more appropriate to proceed directly with a chest computed tomography (CT) because of its increased sensitivity in the

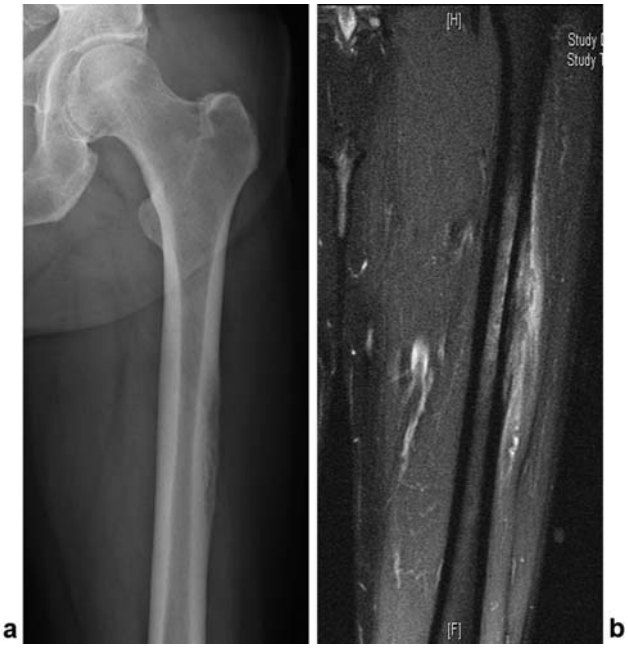

Fig. 7 (**a**) Anteroposterior radiograph showing a surface lesion involving the lateral cortex of the femoral diaphysis. (**b**) The coronal short tau inversion recovery magnetic resonance image suggests a possible inflammatory lesion. Needle biopsy revealed an adenocarcinoma metastasis from a lung primary later confirmed on chest computed tomography.

detection of pulmonary pathology.Because this is a relatively low-yield commandment, it is best that chest CT, because of cost and radiation dose, be reserved only for the more obviously aggressive bone lesion or in some instances not until the diagnosis of malignancy has been established.

Commandment 6: Solitary Bone Lesions, Suspected to Be Malignant, in a Patient with a History of Previous Malignancy, Still Require Biopsy

The ratio of bony metastases to bone sarcomas is likely to increase in the future as improved medical and surgical therapies result in increased survival rates for a wide range of primary malignancies. Understandably, there is a knee-jerk reaction to assume that any solitary bone lesion in a patient with a history of prior malignancy is therefore a metastasis from that original primary. Statistically, this may be correct, but it is not safe to draw that conclusion because it can all too frequently lead to suboptimal management.

Anyone working in the field of bone sarcomas is familiar with the scenario of the pathologic fracture of a long bone in a patient with a prior history of malignancy, assumed incorrectly to be a metastasis, treated with internal fixation such an intramedullary nail. This not only causes a delay in making the correct diagnosis but also results in the dissemination of the tumor throughout the entire length of the bone, rendering subsequent curative limb-salvage surgery problematic or even impossible. In this situation the preferred course of action is to recommend a bone biopsy even if the histologic report can be anticipated in most cases.

Remember that peculiar to renal cell carcinoma (RCC), ~7% of RCC bone metastases are solitary at presentation.[13] A codicil to this commandment is that not all new tumors arising in relation to a preexisting bone lesion are necessarily related to that underlying condition. Sarcoma of bone related to Paget's has been well recognized ever since its original description almost 20 years before the discovery of X-rays, but other malignancies may arise in pagetic bone including metastases, myeloma, and lymphoma (►**Fig. S4**).[14] Clearly, not all bone lesions in the >40age group are malignant and require biopsy (Commandment 8).

Commandment 7: Not All Multiple Bone Lesions Are Metastases or Myeloma

Just as in Commandment 6, there is a similar temptation to assume that multiple bone lesions in a patient > 40 years of age are likely to be bone metastases or multiple myeloma. This conclusion may well be true, particularly if there is a history of prior malignancy. However, the cautious radiologist should not jump to conclusions without reviewing the evidence.

For example, pelvic insufficiency fractures occur in 5 to14% of patients treated for gynecologic or anal cancers with radiotherapy, and to the uninitiated these can resemble multiple metastases, particularly on bone scintigraphy (►**Fig. 8**).[15,16] In this situation, both CT and MRI can be

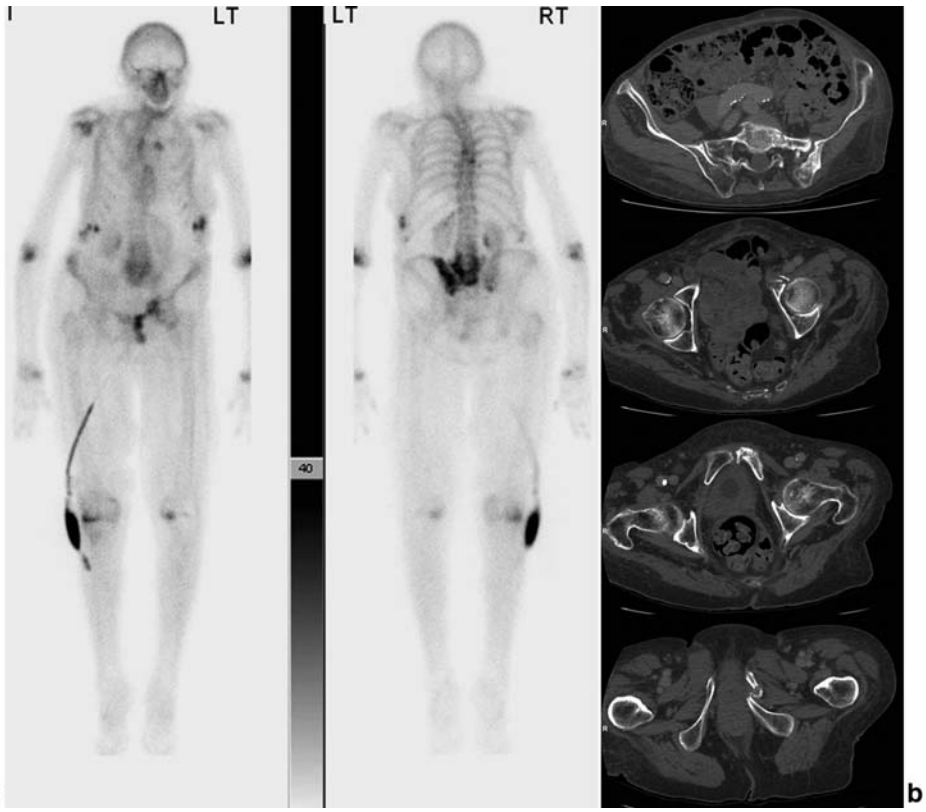

Fig. 8 (**a**) Whole-body bone scintigraphy in an elderly woman showing increased activity over the left sacrum, ilium, acetabulum, pubis, and inferior pubic ramus suspected to be metastases. (**b**) Transverse computed tomography revealed insufficiency fractures at all five sites.

diagnostic showing the fractures in the absence of true bone destruction. Vascular malignancies such as epithelioid hemangioendothelioma and angiosarcoma of bone can be multifocal in up to two thirds of cases simulating metastatic disease. A clue to the diagnosis is that the multifocal distribution frequently involves contiguous bones and will predominantly affect a single, usually lower, limb (i.e., monomelic) (►**Fig. 9**). Inflammatory/rheumatologic processes including CRMO (chronic recurrent multifocal osteomyelitis) and SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome

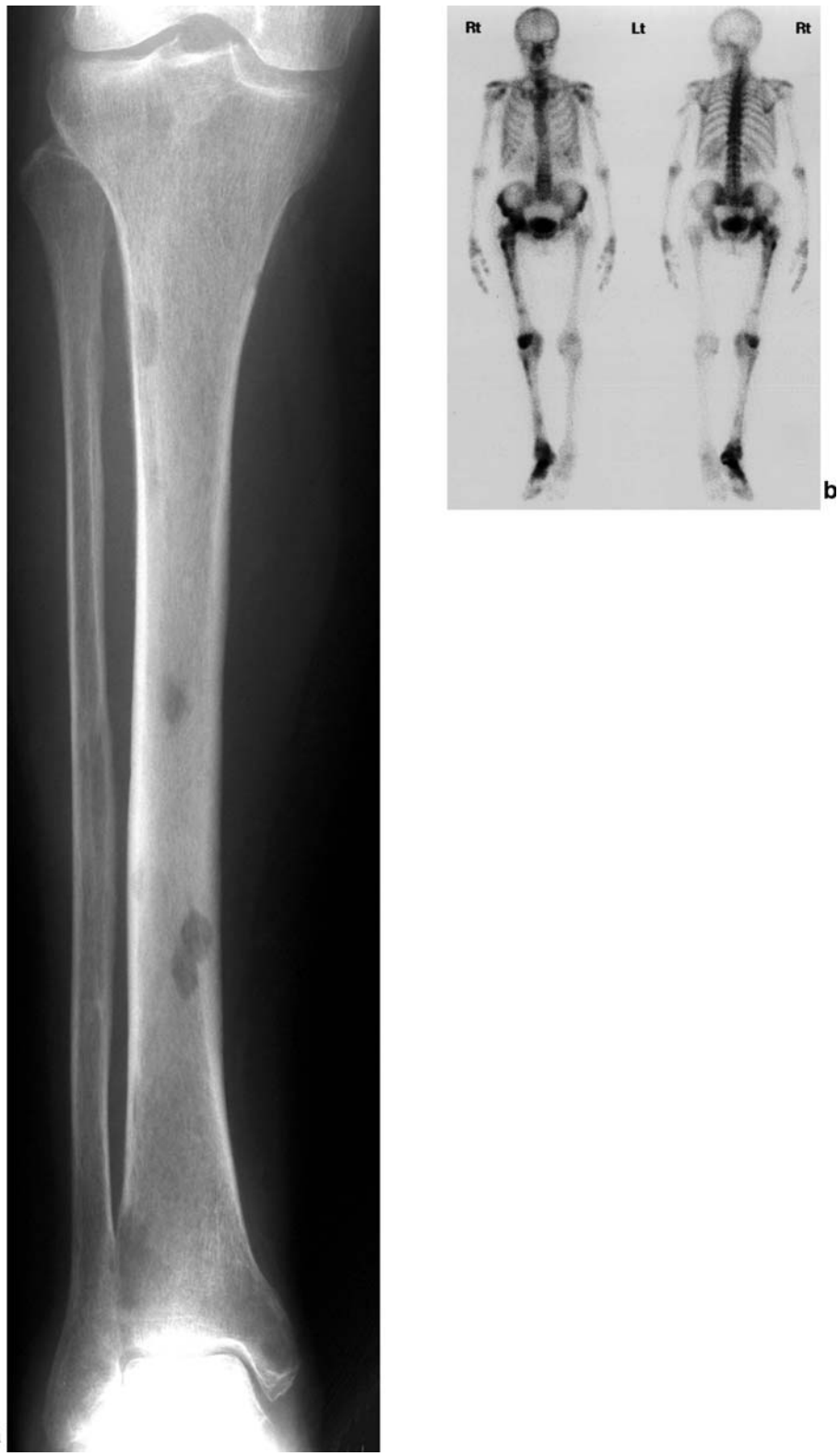

Fig. 9 (**a**) Anteroposterior radiograph of an elderly patient with multiple lytic lesions in the tibia suggestive of metastases or myeloma. (**b**) Whole-body bone scintigraphy confirms multiple lesions all confined to the right lower limb (monomelic). Biopsy revealed multifocal angiosarcoma of bone.

may also, to the uninitiated, be mistaken for multifocal malignancy.

The art of diagnosis is, therefore, a constant struggle between "Occam's razor" *(the desire to seek a single diagnosis rather than diagnosing two or more unrelated conditions)* and "Hickam's dictum" *(multiple signs and symptoms may be due to more than one disease)* (►**Fig. 10**).[17] The latter is increasingly important because the combination of improved health care and an increasingly aging population means that many patients survive and continue to live with diverse medical conditions (►**Fig. S5**).

Commandment 8: Do Not Forget Tumor Mimics

It stands to reason that many non-neoplastic lesions may mimic a bone tumor on imaging. Bone may respond in a finite number of ways in terms of pattern of destruction, periosteal reaction, and matrix production irrespective of the underlying pathology. What constitutes a tumor mimic will depend to a certain extent on the experience of the radiologist confronted with a bone lesion as well as where they are working. All the authors of this article are employed in specialist units in Western Europe and would be unlikely to include hydatid disease of bone in our selected differential diagnosis of a lytic/trabeculated lesion. But the same could not be said for a radiologist working in countries such as Turkey where the *Echinococcus granulosis* parasite is endemic in sheep-rearing communities.[18]

Over the years the concept of the "don't touch" or "leave me alone" lesions has become well entrenched in radiologic practice no more so than when dealing with bone lesions.[19–21] These are conditions where the imaging features, usually radiographic, are sufficiently typical that the diagnosis is in no doubt, and therefore biopsy is not so much unnecessary as contraindicated. These can be broadly classified into five categories.

Artifacts (►**Fig. 11**) and normal variants (e.g., humeral pseudocyst)[22,23]

Posttraumatic lesions (►**Fig. S6**) (e.g., stress fractures and avulsion injuries)[24,25]

Infection (►**Fig. S7**) (e.g., subacute osteomyelitis and tuberculosis)[26,27]

Small benign bone tumors (e.g., fibrous cortical defect, bone island, fibrous dysplasia[►**Fig. 3**], hemangioma, enchondroma)

Miscellaneous (e.g., periosteal/cortical desmoid and Paget's disease)[28]

A variant of the "don't touch" lesion is the "wait-and-see" lesion. In this situation the index of suspicion of clinically significant pathology is extremely low but not entirely excluded. It may then be appropriate to reassure both patient and referring clinician by repeating imaging, often just a radiograph, after an interval of several months. This category includes small incidental/indeterminate bone lesions detected on cross-sectional imaging in the spine and pelvis for other clinical indications that may include a history of visceral malignancy. The delay before reimaging may be reduced in some indeterminate marrow lesions with the application of problem-solving imaging techniques such as chemical shift MR imaging,[29,30] diffusion-weighted MR imaging[31] as well as

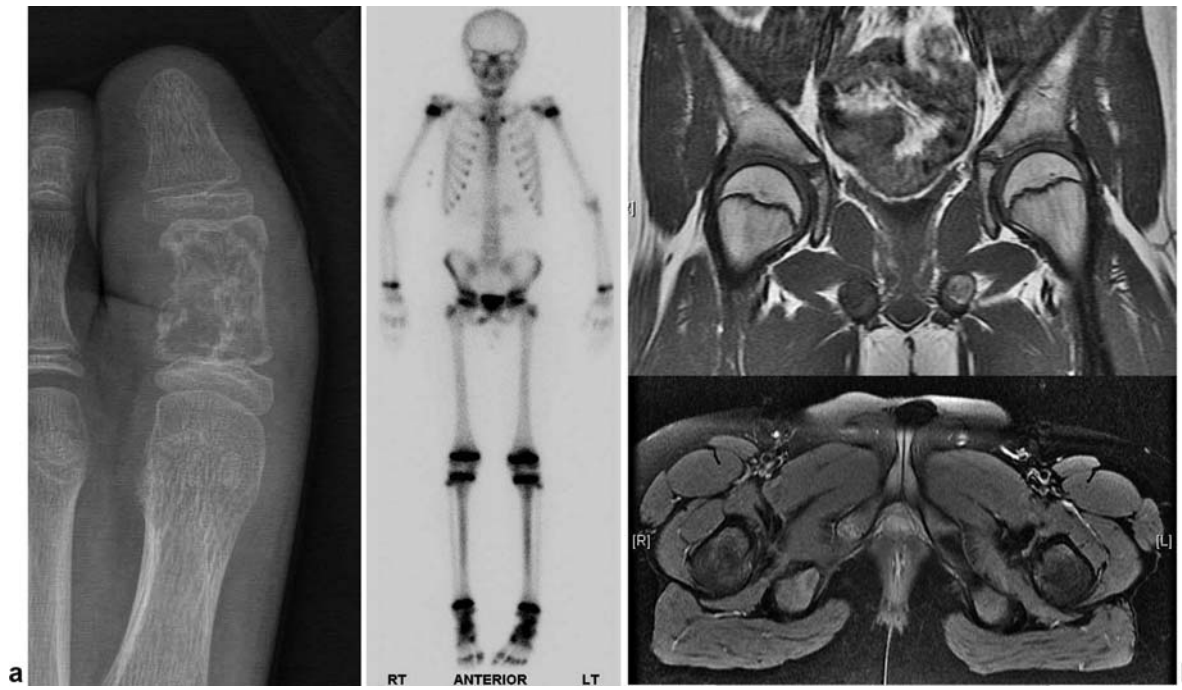

Fig. 10 (**a**) Posteroanterior radiograph of the hallux in an 11-year-old boy with a biopsy-proven Ewing's sarcoma of the proximal phalanx. (**b**) Whole-body bone scintigraphy revealed a focus of increased activity over the right inferior pubic ramus initially interpreted as a metastasis. (**c**) Coronal T1-weighted and axial proton-density fat-suppressed images showed an edema pattern. The final diagnosis was a stress response at the ischiopubic synchondrosis (van Neck's osteochondritis) and not a metastasis.

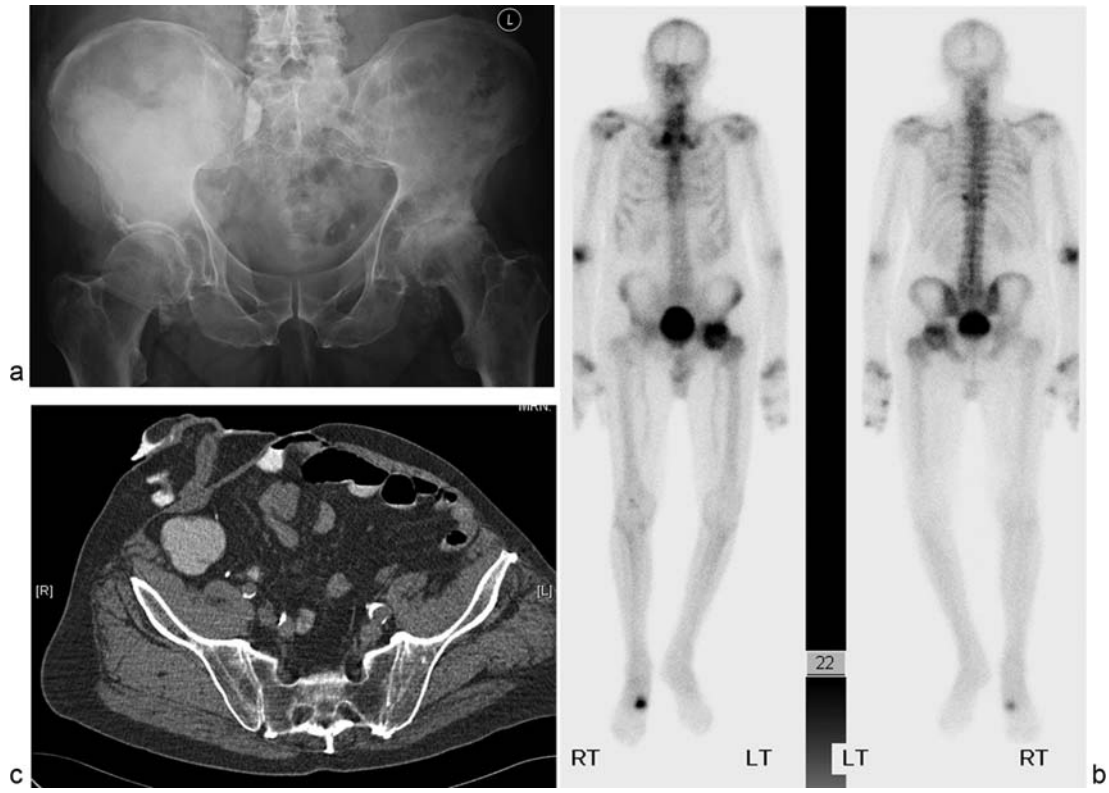

Fig. 11 (**a**) Anteroposterior radiograph of the pelvis of an elderly man referred to an orthopaedic oncology unit for investigation of a sclerotic lesion in the right ilium that did not show increased activity on (**b**) the whole-body bone scintigraphy. (**c**) Axial computed tomography of the pelvis showed the right ilium to be normal and revealed that the apparent sclerosis was artifactual due to an overlying colostomy device. There was no relevant clinical information in this regard at the time of referral.

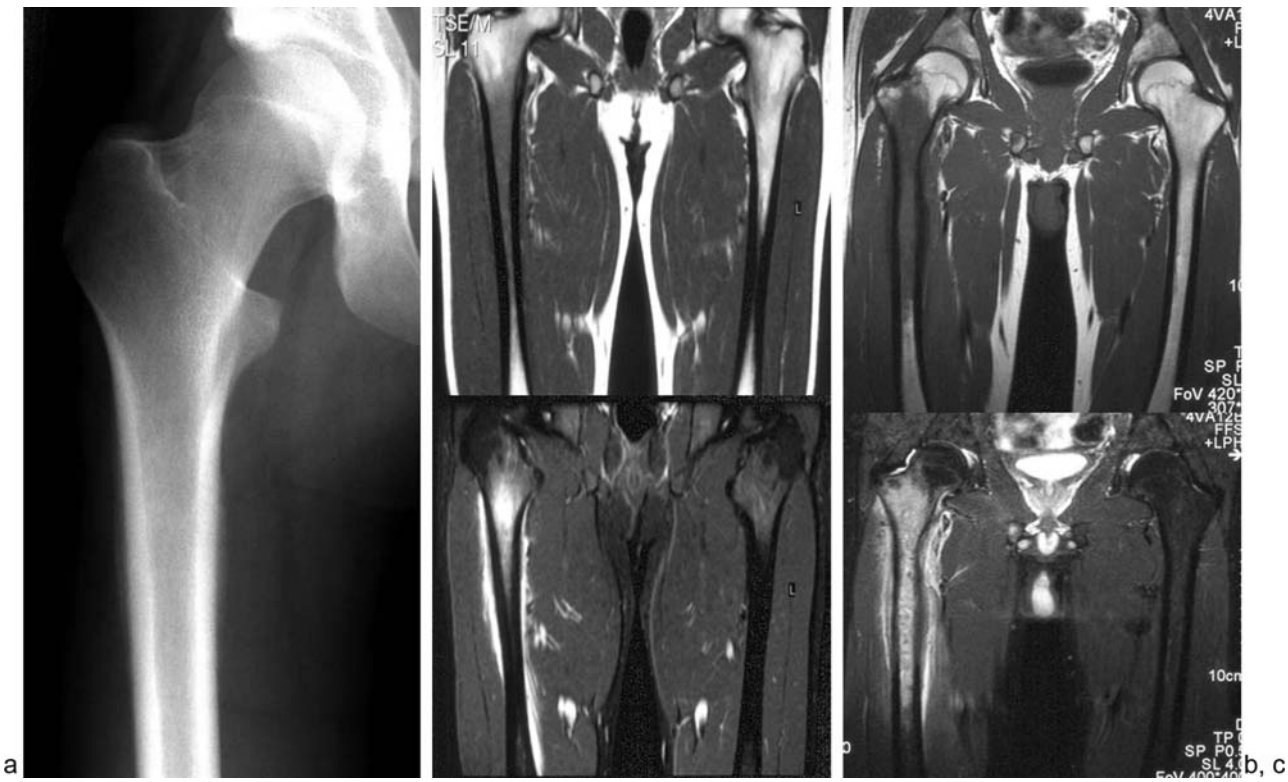

Fig. 12 (**a**) Anteroposterior radiograph of the hip,(**b**) coronal T1-weighted and short tau inversion recovery images, and (**c**) the same at follow-up 2 months later. The lamellar periosteal reaction on the radiograph and predominantly edema pattern on the initial magnetic resonance imaging (MRI) was interpreted as suggestive of a stress fracture of the proximal femur. The patient's symptoms did not resolve on rest, and the lesion had shown significant progression with extraosseous soft tissue on the second MRI. Biopsy confirmed Ewing's sarcoma.

SPECT (single-photon emission computed tomography)-CT and PET (positron emission tomography)-CT.[32]

An exception to the precautionary imaging performed after several months are the central cartilage tumors (CCTs) of bone that can remain static for many years. This remains a controversial subject even among recognized bone tumor experts. As a ruleofthumb, most CCTs arising in flat bones should be considered malignant. It is the CCTs arising in the long bones, particularly at the most common sites in the proximal humerus and around the knee, where diagnostic uncertainty prevails. Large lesions or those with overtly aggressive imaging features need to be promptly referred to a specialist in orthopedic oncologic diagnosis and management. Whereas smaller, often incidental, lesions typically require MRI follow-up whose frequency will be determined by local specialist protocols.[33]

Commandment 9: If Clinical Behavior Is Atypical,Do Not Hesitate to Perform Follow-up Imaging Studies

Although we would recommend a pragmatic approach to a suspected bone tumor, this suggestion should not become unduly dogmatic. If delayed imaging of an indeterminate bone lesion advocated in Commandment 8 does indeed show interval change,the working diagnosis may need to change, and a biopsy may be required to establish the final diagnosis (►**Fig. 12**). Similarly, if the clinical picture changes in terms of symptoms (new and/or increasing), ancillary test results (blood tests), or new relevant clinical history not forthcoming or present at the time of the initial review,the radiologist needs to revisit their first working diagnosis and be prepared to alter it accordingly in light of the new information (►**Fig. S8**). Further follow-up imaging and a biopsy may then be indicated.

Commandment 10: Remember the Importance of the Radiologic-Pathologic Correlation

We tend to assume that histology is automatically the gold standard for diagnosis. This may be the case in some organ systems but frequently does not apply in bone tumor pathology. The World Health Organization classification of bone tumors, which excludes metastases, runs to >150 pages, reflecting the diverse spectrum of neoplastic diseases in bone.[34] For example, todate there are seven variants of osteosarcoma of bone alone. A telangiectatic osteosarcoma may mimic an aneurysmal bone cyst both on microscopy and imaging and vice versa.

It has to be recognized that the pathologists are increasingly utilizing molecular and immunohistochemical studies to refine their diagnostic process. However, the most competent of bone pathologists still find it notoriously difficult to distinguish an enchondroma from a low-grade/grade I chondrosarcoma, also known as atypical cartilage tumor.[35] Giant cells can be identified in a plethora of conditions such that a giant cell tumor of bone and a brown tumor of hyperparathyroidism may appear indistinguishable under the microscope (►**Fig. 5**).

The radiologist also has the added advantage of being able to see the bigger picture as compared with the pathologist who must make a diagnosis based on a few biopsy fragments of the lesion. A prime example would be in a case of an elderly patient where the pathologist correctly diagnoses an osteosarcoma based on biopsy findings but it is the radiologist who is able to identify that the sarcoma is arising in Paget's disease (►**Fig. 13**). The importance of the radiologic-pathologic correlation cannot be overemphasized. In most specialist units, this close collaboration is delivered in the form of regular multidisciplinary team meetings (aka tumor boards in the United States). Such regular formalized meetings are rarely available in nonspecialist centers. In this situation the generalist should consider initially taking the opportunity to discuss the case with a local musculoskeletal trained radiologist. Ample evidence in the literature indicates that this second pair of eyes can help reduce significant discrepancies.[36–38] If this second opinion is not accessible in a timely

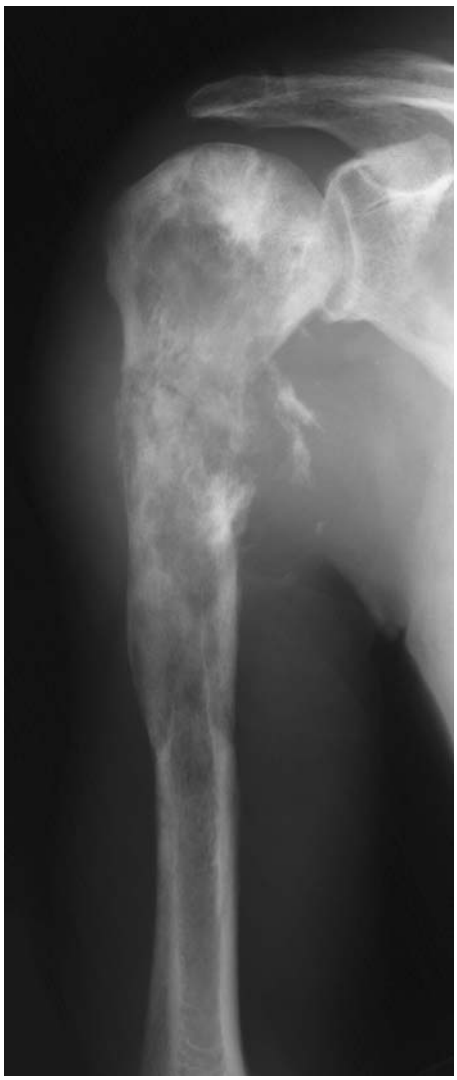

Fig. 13 Anteroposterior radiograph of the humerus in an elderly man. Needle biopsy of the central portion of the lesion correctly confirmed osteosarcoma, but it is the radiographic features both proximal and distal to the destruction that reveals this is due to malignant transformation in Paget's disease.

manner, the threshold for referral of the patient to a specialist unit should be relatively low.

Conclusion

If there is one take-home message here, it is that the conventional radiograph remains the imaging technique by which most bone tumors will be detected due to low cost and availability, and it remains preeminent in the diagnosis of bone tumors. We acknowledge that readers may have other perfectly reasonable suggestions to include in a list of top 10 commandments on this subject. But religious adherence to the rules as listed should minimize day-to-day problems for the radiologist faced with a suspected bone tumor. As Moses might say, were he alive today, "Keep on taking the tablets!"

Conflict of Interest
None declared.

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