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Perspective Chapter: Bone Tumors – How to Make a Diagnosis?
Jairo Garcia

Abstract

The diagnosis of bone tumors begins with suspicion due to some clinical symptoms or due to image findings. From this point onwards, it should be understood the need for new imaging exams, usually based on whether the lesion is most likely benign or malignant. Some benign lesions have diagnosis defined by simple radiography; others need more detailed investigation. Malignant lesions always need a detailed location and systemic assessment. Malignant primary tumors occur generally in patients under 20 years, while secondary malignant lesions are usually related to patients over 40 years. Biopsy of a bone injury, when indicated, is always the last exam to be performed, generating a histological diagnosis and defining treatment.

Keywords: bone, cancer, biopsy, tumor, metastasis, diagnostic

1. Introduction

Bone tumor represents a variable entity of neoplasms, mostly benign, about 35–40% [1], or malignant, in this case, can be primary, that osteosarcoma is the only malignant primary tumor producing bone [2], or secondary due to bone metastases, and about 5% of all cancers have bone metastases to the initial diagnosis [3], most commonly from breast and prostate cancers [4]. Bone corresponds to the third most common site of metastases, after lung and liver [5–7], and the spine is the most common site of bone metastasis in the skeleton [8].

Due to the rarity of these lesions and the wide variety of possible diagnoses, the existence of a multi-professional team with orthopedists, radiologists, radiotherapists, oncologists, and pathologist is necessary for both the correct diagnosis and the proper treatment of the patient [9].

2. Clinical evaluation

History and physical examination are the initial approaches for any patient suspected of having a bone neoplasm (Table 1). Data, such as age (isolated corresponds to the most important data [10]), time of complaint, presence of pain, location of the lesion, and personal and family history of cancer, may provide important information for
clinical reasoning and diagnostic management [10–13]; although the physical examination is generally nonspecific [14]. Often the suspicion of a bone neoplasm occurs only due to an accidental finding of some imaging test [1].

About only malignant primary bone neoplasms, these are more common between 0 and 20 years of age (for patients under 5 years old, the diagnosis of metastases of neuroblastoma is more common). Osteosarcoma and Ewing’s sarcoma are more common between 5 and 20 years of age. In patients over 40 years of age, secondary malignancies (metastases) and multiple myeloma are the most common diagnosis [15].

3. Imaging

3.1 Radiography

Every patient with suspected bone neoplasia should be initially evaluated by orthogonal radiography examination and, although the radiologist’s report is of great value, the orthopedist must have the basic knowledge to recognize the information that the bone lesion can provide on radiography [10]. The correct diagnostic approach to a bone neoplasm cannot be adequately achieved without radiographic evaluation [14, 16, 17].

The radiographic findings provide important information about the nature of the bone lesion. We can observe if it is bone-forming (osteoblastic), if it promotes bone destruction (osteolytic) or if the lesion has areas of bone formation as well as areas of bone destruction (mixed). Second, the radiography will provide the lesion location (epiphysis, diaphysis, metaphysis, or surface), presence of periosteal reaction (spiculate, sunlight, onion skin, and Codman’s triangle), presence of halo of sclerosis, presence of pathological fracture, extension to soft tissues (extra compartmental lesion), among other characteristics specific to each type of bone neoplasm that can even define the diagnosis (Table 2) [10, 11, 14, 18].

3.2 CT scan

Computed tomography can better delineate the information obtained on radiography, especially in lesions of bone sites with more complex anatomy, such as the pelvis.
### Table 2.
Differential diagnosis by lesion location.

<table>
<thead>
<tr>
<th>Epiphyseal</th>
<th>Diaphyseal</th>
<th>Metaphyseal</th>
<th>Spine</th>
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<tbody>
<tr>
<td>• Chondroblastoma</td>
<td>• Ewing sarcoma</td>
<td>• Chondrosarcoma</td>
<td>• Metastasis</td>
</tr>
<tr>
<td>• Giant cell tumor</td>
<td>• Lymphoma</td>
<td>• Osteosarcoma</td>
<td>• Multiple myeloma</td>
</tr>
<tr>
<td>• Clear cell chondrosarcoma</td>
<td>• Fibrous displasia</td>
<td>• Metastasis</td>
<td>• Chordoma (sacrum)</td>
</tr>
<tr>
<td>• Dysplasia epiphysealis hemimelica</td>
<td>• Histiocytosis</td>
<td>• Infection</td>
<td>• Histiocytosis</td>
</tr>
<tr>
<td>• Admantinoma</td>
<td>• Enchondroma</td>
<td>• Osteochondroma</td>
<td>• Osteoma osteoid</td>
</tr>
<tr>
<td>• Osteofibrous dysplasia</td>
<td>• Simple bone cyst</td>
<td>• Aneurysmal bone cyst</td>
<td>• Aneurysmal bone cyst</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Non-ossifying fibroma</td>
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</tbody>
</table>
3.3 MRI

Magnetic resonance imaging does not have a great diagnostic value in bone neoplasms, but it is the best test for local staging and surgical planning [17]. Evaluating structures adjacent to the lesion, such as the extension to soft tissues (most important sign of bone malignancy [16]) and the involvement of neurovascular structures, as well as the extent of spinal cord involvement and the presence of "skip" metastases (present in 25% of osteosarcomas) [14]. The examination should always include the two joints adjacent to the host bone (Figure 2) [10].

MRI is useful in assessing the response to chemotherapy, radiotherapy, and postoperative follow-up to detect mainly local recurrence [20, 21].
3.4 Scintigraphy

Bone scintigraphy is routinely requested in the evaluation of malignant bone neoplasms, the exam measures changes in bone metabolism (increased turnover and osteoblastic activity), it is quite sensitive, but nonspecific (Figure 3) [16, 22].

Evaluation of bone metastases by scintigraphy is very useful since it can evaluate the skeleton in a complete way. The drug is well tolerated (technetium-99 m methylene diphosphonate [17]) and its analysis is not interfered with by metallic implants.

Osteoblastic lesions are easier to identify, while osteolytic lesions need a certain size to be detected [22]; examples of this are multiple myeloma and renal cell carcinoma metastases, which are usually negative in scintigraphy [23]. Non-neoplastic changes may appear in regions, for example, of degenerative disease in vertebrae and joints [22].

3.5 PET-CT

Corresponding to a procedure that combines the images of a positron emission tomography (PET) and a computed tomography (CT), there is no contraindication to the test, except in pregnant or breastfeeding patients. PET and CT scans are performed at the same time with the same machine using 18F-fluorodeoxyglucose (18F-FDG, surrogate analog in glucose metabolism) as a marker. The SUV (standard uptake value), calculated at the end of the exam, provides semi-quantitative
information on glucose metabolism in the evaluated tissues, with a cut-off between 2.0 and 2.5 for defining benign and malignant lesions. PET-CT is evaluated for staging and monitoring the response to treatment of tumors, including detection of metastases and recurrence. Studies indicate that PET-CT shows sensitivity, specificity, and accuracy superior to scintigraphy to find metastases [24]. However, if it works according to the histological diagnosis, different results are observed. To screen for bone metastases in Ewing’s sarcoma, PET-CT has better sensitivity than scintigraphy, whereas in osteosarcoma they are similar [25], although it has better accuracy than scintigraphy for the detection of approaching the growth plate in osteosarcoma [26]. PET-CT as a predictor of oncological response presents better results in Ewing’s sarcoma than those presented in osteosarcoma [25] (Figure 4). In benign cartilaginous neoplasms, such as enchondromas or osteochondromas, the SUVmax value is generally less than 2, while in chondrosarcomas, most have values above 2, which represents a good tool for diagnostic differentiation [27, 28]. Patients with primary bone lymphoma and multiple myeloma have good applications for PET-CT for staging, follow-up, and prognostic evaluation [29].

3.6 Other modalities

PET-MRI is an examination modality where the metabolic phase of the study is performed using 18F-FDG/PET and the anatomical acquisition is performed by MRI. It has a good indication in tumors, such as lymphomas and sarcomas, but imaging protocols still need to be defined separately for each type of malignancy, both bone and soft tissue [30]. As advantages reduces radiation exposure, can optimize diagnostic accuracy, and is a good predictor of histological response. In addition, better delimitation of the primary tumor (invasion of soft tissues). As a disadvantage, there is still no diagnostic advantage in performing the staging of the patient by PET/ MRI in relation to conventional exams [30, 31], it presents several results similar to PET-CT [32] and still has limitations for the evaluation of nodules. Lungs smaller than 5 mm in size, and chest CT is still superior in this regard [32, 33]. PET-MRI can even be used for radiotherapy planning and detection of tissue damage by chemotherapy.
Regarding specific diagnoses, for example, in osteosarcoma, PET/MRI can better define the anatomical location of the lesion, but the lesion detection rate is similar to PET/CT. In Ewing’s sarcoma, it is superior to PET-CT in the evaluation of an organ with high metabolic activity, such as the brain, probably the PET/MRI will become the exam of choice in these patients [29]. In the investigation of metastases for prostate and breast carcinoma, PET/MRI is presented as a great tool in the evaluation of these patients, but still not statistically superior to conventional methods [34]. However, although PET/MRI proves to be valuable, it cannot replace conventional exams if it is not accessible to most cancer patients [35].

Whole body MRI is an imaging method that uses a core protocol with essential imaging contrasts and it can be completed with sequences to evaluate other specific regions as needed, is a modality under evaluation for its applications and usefulness in bone sarcomas, however, it is observed that is better than scintigraphy to the screening for metastases [36] and is a good screening for cancer in patients with genetic syndromes, such as Li-Fraumeni, especially after the second test (lower false positive value, [37]) (Figure 5). In patients with prostate cancer, multiple myeloma and melanoma, whole body MRI is already introduced in international protocols, while its usefulness in neoplasms, such as breast cancer, ovarian cancer, and lymphoma is on the rise [38, 39]. WB-MRI is an excellent test for detecting bone metastases, especially in the spine region [40].

4. Metastases from unknown site

Patients over 40 years old who present with a painful new bone lesion should be investigated to mainly rule out bone metastasis or multiple myeloma [41].
Bone metastases occur in about 70% of advanced breast, lung, kidney, thyroid, and prostate carcinomas, while in gastrointestinal tumors, only 20% of patients have bone metastases, and among these patients, about half will present complications related to metastases, such as pathological fracture, spinal cord compression, pain requiring radiotherapy or surgery, and hypercalcemia, in about 10% of cases [42].

Breast and prostate cancers are the most common to generate bone metastases, however, when the patient has no diagnosis, the most common lesions to generate bone metastases are lung and kidney cancer [41]. Common sites of bone metastases are the proximal femur, pelvis, spine, ribs, and skull. Acral metastases are rare and they are usually related to lung cancer [42].

When evaluating patients with unknown site metastases, the focus is on finding the primary site of the neoplasm, and in about 85% of cases, a well-executed diagnostic evaluation can be successful to define the primary tumor. In the meantime, the evaluation begins with a comprehensive history and physical examination. Laboratory evaluation should include a complete blood count, erythrocyte sedimentation rate, alkaline phosphatase, liver function, renal function, thyroid function, electrolytes, PSA for men, and protein electrophoresis. Imaging evaluation begins with radiography of the lesion and the entire skeleton, as well as bone scintigraphy and CT scan of the chest, abdomen, and pelvis [41].

5. Staging

Tumors are proliferations of atypical, autonomous, irreversible cell clones with a tendency to lose cell differentiation. Tumors classified as benign are those that do not present cellular atypia, grow pushing the adjacent tissues, demonstrate the histological aspect of low aggressiveness, low tendency to local recurrence, and low tendency to spread (production of metastases). On the other hand, neoplasms considered malignant have a variable degree of cellular atypia, grow infiltrating adjacent tissues, demonstrate a more aggressive histological aspect, a high tendency to local recurrence, and a high tendency to spread.

The Enneking classification [43] (Table 3), for bone tumors has a first structure for the evaluation of benign tumors, a second structure defined for the evaluation of malignant tumors, and both in order to present an evolutionary degree of the lesions according to the increase in the stage in the classification.

The classification of the American Joint Committee on Cancer [44] (Table 4), defines only primary malignant bone neoplasms (except for primary bone lymphoma and multiple myeloma). This classification evaluates factors, such as histological grade, presence of regional metastases (lymph nodes), or distance (pulmonary and non-pulmonary), in addition to the size of the lesion. Related to the tumor size, it is observed that Ewing's sarcomas ≤8 cm have a better prognosis than those >8 cm, as well as in osteosarcoma that lesions ≤8 cm have a better prognosis in relation to osteosarcomas >8 cm greater in size.

Another staging related to primary bone sarcomas is in relation to the histological response to neoadjuvant chemotherapy. The surgical specimen is evaluated to analyze the degree of tumor necrosis and in patients with osteosarcoma and Ewing's sarcoma who present a degree of necrosis ≥90% are classified as good responders and who generally have good survival. This type of analysis was developed by Huvos [45, 46] (Table 5), initially for patients with osteosarcoma, however, it demonstrates to be applicable to Ewing's sarcoma [47].
6. Biopsy

Biopsy of a bone neoplasm is a fundamental and final part of the diagnostic evaluation, with the objective of obtaining sufficient material for the histological diagnosis with minimal morbidity, limiting potential tumor spread, and not harming the surgical treatment [48, 49]. A surgeon experienced in the treatment of bone
neoplasms or in Ref. centers must perform the biopsy in order to minimize the known complications of the method. A study showed that biopsies performed by other surgeons present up to 18% of diagnostic errors; 10% present as poorly planned biopsies or with insufficient material; 9% have some skin, bone, or soft tissue complication; 10% influenced the course of the disease and 3% resulted in unnecessary amputations [50]. Pathological fractures (Figure 6), are not common after biopsy procedures but may occur in about 10–25% of procedures performed in patients with osteosarcoma, 5% in chondrosarcomas, and 8–9% in Ewing's sarcomas (Figure 7) [51].

Figure 6. (A) patient with an osteolytic lesion on the left femoral shaft, (B) fluoroscopy image of femur fracture during biopsy procedure, and (C) stabilization with external fixator was performed (patient with liver cancer).

Figure 7. (A) patient with a lytic lesion in the diaphysis of the right femur and an onion skin periosteal reaction, (B) extension femoral lesion with the presence of skip metastasis, (C) evolution to pathological fracture after biopsy procedure, and (D) stabilization with plaster cast.
There are two types of biopsy: open and percutaneous. Although for a long time the incisional (open) biopsy was considered the gold standard, the minimally invasive techniques (percutaneous – fine needle aspiration and core needle biopsy) have presented similar results [48, 49].

6.1 Fine needle biopsy/FNAC

High incidence of false negatives. Even when the result is positive, there is a great limitation in the diagnostic tissue evaluation due to the scarce specimen obtained by the procedure. The advantages of the method are that it is a procedure with minimal morbidity and is relatively inexpensive [48].

6.2 Core needle biopsy

Lower incidence of false-negative results when compared to fine-needle biopsy. The architectural structure of the tissue is preserved, so the tissue sample is suitable for histological evaluation and tumor grade, as well as for immunohistochemistry and molecular analysis. The procedure with minimal morbidity and low cost [48] (Figure 8).

6.3 Open biopsy

Indicated when a large volume of tissue is needed for proper diagnosis or when a percutaneous biopsy cannot be safely performed. Incisional biopsy is performed along the planned path in case of resection of the neoplasm and with the smallest incision compatible with the procedure. Transverse incisions should be avoided because their resection with a contaminated path during the treatment of the neoplasm, in addition to requiring a greater volume of excised tissue, can compromise the preservation of the limb. The formation of bruises and the use of drains that can contaminate the soft tissues should be avoided. The disadvantages of incisional biopsy are the possibility of contamination of soft tissues, complications with the operative wound, and is a more expensive procedure compared to percutaneous procedures [48].

Figure 8. Correct sequence for performing a biopsy procedure. (A) x-ray of the affected limb, (B) local staging (biopsy should be performed after complete systemic staging), and (C) core needle biopsy using fluoroscopy.
7. Biopsy imaging techniques

7.1 Fluoroscopy

Widely available, relatively inexpensive, and easy-to-use method. The lesion is evaluated in orthogonal positions with the needle being introduced perpendicular to the lesion, in the course of surgical planning and in order to contaminate the least amount of tissue possible (Figure 8) [52].

7.2 Ultrasound

Operator-dependent method requires some expertise to use, however, it exempts the patient from exposure to radiation, has a good evaluation of superficial lesions, is low cost, and presents a high image resolution [53–55]. The appropriate probe is chosen for the evaluation of the lesion and adjacent structures, once the probe achieves the right position at the region of choice for material acquisition; the needle is introduced parallel to the probe so that the entire path and tip of the needle can be observed.

7.3 CT

Relatively expensive method, greater exposure to ionizing radiation and in many places requires differentiated logistics, as the device is generally not limited only to biopsy procedures. Very useful in performing biopsies of complex structures, such as the pelvis or regions that require greater precision, from the surgeon, such as the spine. The accuracy of the CT-guided core-needle biopsy procedure is high, around 96%, and with a low complication rate, between 0 and 7.4% [56–59] (Figure 9).

Figure 9.
(A) biopsy of osteoblastic lesion in vertebral body guided by CT scan, (B) bone fragments removed with a core needle, and (C) core needle.
8. Conclusions

The diagnostic evaluation of bone tumors, therefore, must be carried out systematically, starting with the history and physical examination, which will guide the diagnostic hypotheses and necessary complementary tests. A patient referred for specialized evaluation should not be delayed to obtain staging images for investigation, being standard radiography is sufficient for this purpose. A biopsy is the last procedure to be performed. It depends on the initial staging to be planned and should be performed at the service where the patient will start his treatment and preferably by the doctor responsible for the surgical treatment.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

CT                computed tomography
PET              positron emission tomography
MRI              magnet resonance imaging
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