Imaging of Bone Sarcomas

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Abstract
Identification, staging, and treatment of bone sarcomas rely on both clinical and imaging evaluations. Although conventional radiography remains the primary imaging modality for characterizing bone tumors, bone scintigraphy, computed tomography, magnetic resonance imaging, and positron emission tomography can each add information for staging and treatment planning. (JNCCN 2007;5:438–447)

Although much less prevalent than other forms of cancer, bone sarcomas pose a dilemma in both diagnosis and treatment. Fortunately, over the past several decades, the advancement and refinement of modalities aimed at treating bone sarcomas, such as adjuvant chemotherapy and limb-sparing surgical techniques, have resulted in better outcomes for many patients.1–13 Appropriate care of patients with bone sarcomas is heavily dependent on a prompt and thorough initial evaluation, and a working knowledge of the various imaging techniques to evaluate bone tumors is paramount for any physician who may encounter one of these patients early in the disease course.

Various imaging studies are used in diagnosing, staging, and monitoring bone sarcomas. Conventional radiography, bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) each have strengths and limitations. This article describes how these modalities are applied to the evaluation and treatment of suspected bone sarcomas.

Diagnostic Evaluation
Patient evaluation begins with a thorough history and physical examination. Most commonly, patients present with pain at the affected site. The pain usually does not improve and may progress to become independent of activity. Ultimately, the patient may experience pain at rest or at night.

Although some tumors show a sex predilection (female predominance with giant cell tumor and parosteal osteosarcoma), this rarely is useful for diagnosis. Similarly, race is of little diagnostic benefit except with Ewing's sarcoma, which is extremely rare in people of African descent. In contrast, the patient's age is very helpful in directing the differential diagnosis of a suspected bone tumor.14,15 Examples include primary osteosarcoma, which usually occurs between the ages of 10 and 25 years; Paget's osteosarcoma, between 55 and 80 years; Ewing's sarcoma, between 5 and 25 years; primary chondrosarcoma, between 30 and 60 years; unicameral and aneurysmal bone cysts, younger than 20 years; chondroblastoma, younger than 20 years; giant cell tumor, between 20 and 40 years; and metastasis and multiple myeloma, older than 40 years.16

Physical examination should include evaluation of the patient's general health in addition to the affected part. Constitutional symptoms, fever, weight loss, and night pain should be documented. Any mass should be measured and inspected for consistency, mobility, pain, temperature, fluctuance, and skin changes. A thorough neurovascular examination is recorded and potential sites of lymph node metastasis are palpated. Imaging studies are then used to formulate a working diagnosis and appropriately stage the lesion. If these studies, along with the clinical information, suggest a malignant bone tumor, the patient should be referred to a musculoskeletal oncology center without additional tests or biopsy. For several reasons, bone tumors must be completely evaluated before proceeding with a biopsy. A thorough evaluation helps narrow the differential diagnosis and leads to a more...
accurate pathologic diagnosis. The type of biopsy performed and placement of the biopsy incision are determined by the extent and potential resectability of the lesion. Additionally, the accuracy of imaging studies such as CT, MRI, or bone scan may be adversely affected by postoperative changes from a premature biopsy.\(^{15-22}\) Biopsy should be performed by a surgeon familiar with musculoskeletal oncology techniques, preferably by one who will perform any definitive procedures. Similarly, if a radiologist is to perform the biopsy, the treating surgeon should be consulted.

**Conventional Radiography**

Since the discovery of the x-ray in 1895 by Wilhem Conrad Roentgen, continuous innovations have occurred in the application of radiographic imaging to study human disease.\(^{23,24}\) Today, it remains the most widely used imaging modality in medicine and continues to be the gold standard for creating an accurate differential diagnosis of suspected bone lesions.\(^{25-27}\) The appearance of a plain radiograph is a function of x-ray beam attenuation as it passes through anatomic structures. The extent of beam attenuation is a function of the energy of the x-ray beam and the tissue’s density. Tissues with high attenuation, such as bone, appear relatively white, whereas fat or lung tissue allows most of the beam to pass through to the film, producing relatively dark areas.\(^{26,27}\)

The radiograph produced by the contrasting density of human tissues produces a wealth of information when analyzed carefully. Plain radiographs should always be the initial imaging modality for evaluating patients with a suspected bone lesion.\(^{26,27}\) Frequently, the patient’s age combined with findings on plain radiographs provide enough information to yield an accurate diagnosis.\(^{15,26,29}\) Physicians should consider the presence of bone destruction, tumor matrix, periosteal or endosteal reaction, lesion margins, associated soft-tissue changes, and lesion location.\(^{26}\) The appearance of the tumor matrix can suggest a particular diagnosis; infarcts produce a “smoke in the chimney” appearance, fibrous dysplasia yields a “ground glass” appearance in bone,\(^{15,10}\) chondroid lesions often show calcified “rings and arcs,”\(^{11}\) and osteosarcoma and osteoblastoma frequently show matrix ossification. Periosteal reactions have been termed solid, spiculated, Codman triangle, or unorganized.\(^{15,24}\) In general, thick continuous periosteal reaction (Figure 1) is associated with benign entities such as stress fracture, histiocytosis, and infection, whereas thin, discontinuous periosteal reaction is frequently associated with malignant diagnoses such as osteosarcoma and Ewing’s sarcoma (Figures 2 and 3).

The appearance of a tumor’s margin is extremely important. In general, most benign bone lesions have well-defined margins with a rim of reactive bone surrounding the tumor (Figure 4). Malignant bone lesions, on the other hand, have poorly defined margins with a wide zone of transition to normal bone and show patchy cortical destruction with early soft-tissue extension (Figure 5).\(^{31}\)

Additionally, lesion location must be considered. Chondroblastoma (younger patients), giant cell tumor (adults), and clear cell chondrosarcoma show a predilection for the epiphyses of bones. In contrast, Ewing’s sarcoma, histiocytosis, and adamantinoma are found more commonly in the diaphyses of long bones.\(^{15,22}\) In the spine, lesions are considered based on their location within the vertebral body or the posterior elements. Adults with a lesion of the vertebral body usually have metastasis, myeloma, or a hemangioma. A vertebral body lesion in a young patient typically represents histiocytosis, whereas lesions in the posterior elements in younger patients most commonly are osteoid osteoma, osteoblastoma, or aneurysmal bone cyst.\(^{16}\) Collectively, this information...
should allow an accurate differential diagnosis that can help direct further workup and treatment. Bone Scintigraphy

Bone scans detect areas of increased bone metabolism. A radionuclide, most commonly technetium (Tc)-99m–labeled diphosphonate, is administered intravenously and allowed to accumulate in bone. As the radiotracer decays, gamma radiation is emitted and detected with a camera scanning the patient. Increased uptake is shown in areas of increased vascularity or bone metabolism. Whole-body bone scans can detect the presence of skip metastases, or distant sites of bone involvement important for staging. They also are used for postoperative evaluation to rule out local recurrence or late bone metastasis.  

Because plain radiography requires up to a 50% loss of mineralization for detecting a bone lesion, bone scintigraphy sometimes can identify the presence of an osseous abnormality before it is visible on plain films (Figure 6). Unfortunately, radionuclide bone scanning has very limited potential to differentiate benign from malignant osseous or chondroid lesions, because many benign bone tumors show increased radiotracer uptake. A positive bone scan, therefore, indicates the presence of a lesion that requires further evaluation. A negative bone scan, however, is very reassuring unless the lesion is purely lytic, such as multiple myeloma or possible renal cell metastasis, which can produce false-negative studies.

CT

The development of the CT scanner is credited to Godfrey N. Hounsfield in 1973. An advancement of routine radiography, the image produced is still a function of the differential absorption of x-ray beams as they pass through human tissue. With CT, the x-ray beam is collimated into a narrow beam that passes through the patient in thin slices from multiple angles. The beam is absorbed by highly sensitive detectors (single or multiple) capable of identifying subtle differences in tissue density. The scanner computes a tomographic (single slice in 3 dimensions) image that can be reformatted for visualization in different planes (sagittal or coronal). Images can be enhanced by administering contrast (oral or intravenous), giving the CT excellent spatial and contrast resolution that makes it particularly helpful for evaluating lesions in the axial skeleton, such as the pelvis or spine, where complex anatomy and overlap of anatomic structures can make 2-dimensional analysis difficult (Figure 7). Cross-sectional and reformatted 3-dimensional images provide valuable characterizations of bone abnormalities and disease...
processes. CT is used to show the type or presence of cortical bone destruction and presence of matrix mineralization. A sclerotic rim on CT imaging often suggests a benign process, and the presence of fluid levels characterizes cystic structures. Finally, CT imaging may confirm the presence of a pathologic fracture or the characteristic nidus of an osteoid osteoma.

Although MRI has replaced CT for local staging of bone tumors in most cases, CT scanning remains a vital part of this process because it is the preferred test for evaluating the presence of pulmonary metastasis in patients with a known or suspected bone sarcoma.

MRI
The development of MRI over the past 2 decades has had tremendous impact on musculoskeletal imaging. The contrast resolution of MRI is nearly 50 times that of conventional radiography and roughly 10 times that of CT, while sparing the patient from exposure to radiation. Additionally, the images can be manipulated by varying signal parameters that allow the characterization of tissue types. This key feature enables the anatomic, high-resolution evaluation of neoplasms and contributes tremendously to tumor staging and the planning of limb salvage surgery.

MRI uses the magnetic properties of atomic nuclei (protons) to generate and detect signals that can be converted into a grayscale image. The most abundant of these atoms within human tissue is hydrogen-1, which is primarily responsible for the nuclear magnetic resonance (NMR) signal used to generate a traditional MRI. Some nuclei, such as sodium-23, phosphorous-31, and fluorine-19, are capable of generating an NMR signal but are several orders of magnitude less abundant within living tissue. By applying a nonionizing magnetic field, a fraction of spinning hydrogen ions within a given tissue (primarily in water and lipid molecules) align themselves along the line of magnetic field. When stimulated with a radiofrequency (RF) pulse, these ions change alignment and tilt. The amount of tilt or flip is determined by the strength and duration of the radiofrequency pulse. On returning to equilibrium, the ions generate radio waves that are detected by a receiver coil. The strength of this signal is a function of the amount of hydrogen nuclei within the tissue. The frequency of the signal is proportional to the size of the applied magnetic field. Protons in different chemical environments experience different magnetic fields because of interference from local electrons. The
frequency shift attributable to these fields is termed chemical shift and helps explain the differing NMR signal of hydrogen-1 in fat and water. On detection by the receiver coil, the signal is amplified and processed into the pixel grayscale level of the image.27,39

A key advantage of MRI is the number of available mechanisms used to create contrast within an image. Among the different pulse sequences used in generating images, spin echo sequences are used most often.

Images are obtained by applying a series of RF pulses. A receiving coil follows at a specified time, detecting the energy released from the realigning (relaxing) protons.39 Two key relaxation parameters are used: T1 and T2. T1 is the exponential time constant for a proton to return to equilibrium after receiving an RF pulse so that it can generate a full signal on subsequent pulses (the interval between pulses is termed the TR time). Rapid RF pulses give weaker signals from the protons with a long T1 time.39 T1-weighted images are generated with a short TR time (400–600 ms) and are best for evaluating the extent of a tumor within bone marrow.41 T2 is the exponential time constant for a proton’s NMR signal to decay after it is generated. Protons with a short T2 can be differentiated from those with a long T2 by delaying the detection of the NMR signal after the RF pulse. This detection delay is referred to as the TE time.27 Images created using a long TE time (>70 ms) are referred to as T2-weighted images and are most useful in determining cortical bone or soft-tissue involvement. Proton density images have long TR and short TE times. An important distinction between T1 and T2 images is the relative brightness of fluid on T2 images and darkness of fluid on T1 images (Figure 8).27 Most musculoskeletal tumors are very cellular and tend to behave like water. On T1-weighted images, tumors are often low to intermediate in signal intensity and can easily be identified against or within fat (including fatty marrow) but tend to blend with muscle. On T2-weighted images, many tumors are bright and easily identified.44

Additional pulse sequences are also used to generate images. Gradient echo imaging uses a series of smaller superimposed magnetic fields to generate the NMR signal with shorter imaging times. Inversion recovery images use RF pulses applied in a particular...
order, effectively cancelling all signal normally produced by fat.31

Exogenous sources of contrast can be applied to alter the NMR signal. The most widely used contrast agents are the gadolinium (Gd) chelates, which are 1000 times more visible than iodine x-ray contrast agents. Gd metal asserts its effect by shortening the T1 relaxation of water. Hence, protons near a Gd atom will continue to yield a high signal on T1-weighted images.27 Gd-contrasted images may be useful in determining whether a lesion is solid or cystic and defining areas of viable tumor to help guide biopsy decisions.

Despite the many advantages of MRI, several limitations remain, such as low specificity.26–32 The appearance of infection, benign tumors, malignant tumors, and trauma may be indistinguishable,26 and the appearance of structures that remain dark on all images (e.g., cortical bone, tendon, air, flowing blood) may be similar. Additionally, implanted metallic devices may be contraindicated for MRI, and care should be taken to document safety of such devices before proceeding. Finally, although MRI is highly accurate in defining the extent of a bone abnormality, CT and conventional radiographs remain superior for visualizing bony detail and matrix mineralization.26,27,31

Nonetheless, MRI affords unparalleled tissue contrast, precise anatomic detail, and excellent sensitivity for imaging bone marrow, making it essential to the staging of known or suspected bone sarcomas. MRI is the best imaging modality for evaluating the extent of a lesion within bone and soft tissues before and after chemotherapy or radiotherapy (Figure 9).31,40,41,53–57 It is also the best test to evaluate the relationship between a tumor and adjacent structures.
For complete evaluation of a suspected bone malignancy, standard spin echo T1-weighted sequences, fast spin echo fat-suppressed T2-weighted or inversion recovery sequences, and post-contrast T1 fat-suppressed images are extremely useful. The entire bone should be included to evaluate for skip metastases, which is a poor prognostic indicator.

PET scanning relies on the detection of 2 positively charged photons (each 511 keV) that result from the interaction of administered positrons (positively charged electrons) and native electrons inside living tissue. These 511-keV gamma rays (photons) are emitted at 180° from each other and are registered by dual detectors encircling the body. By detecting these gamma rays at the same time, their spatial distribution can be reconstructed and corrected for tissue attenuation signal loss. This allows quantification of the distribution of a radiopharmaceutical and its correlation with tissue metabolic activity. Uptake in PET scanning is quantified using standardized uptake values (SUVs). In general, an SUV of more than 3 suggests an aggressive process.

Currently, the most commonly used isotope is 18F-labeled 2-fluoro-2-deoxyglucose (18FDG). Several features of 18FDG have been extremely useful. Intracellular transport does not distinguish it from glucose, uptake increases in cells with high metabolic activity (malignancies generally have higher rates of glycolysis than normal tissue), and low membrane permeability results in intracellular accumulation. Other isotopes, such as fluorine-18, carbon-11, and 15-oxygen, have short half-lives precluding their use in clinical settings.

Recently, dual-modality scanners capable of concurrent CT or MRI and PET scanning have been developed to allow integration of anatomic, functional, and metabolic information gathered from each imaging modality. This information is valuable because the detection of metabolically active tissue can assist with guided biopsy. In general, high-grade sarcomas and aggressive benign lesions show higher uptake than benign lesions. This trend becomes tenuous when considering cartilaginous bone lesions, possibly because of the relatively low metabolic activity of cartilage, which shows primarily anaerobic glycolysis.

Although highly sensitive, FDG PET unfortunately has relatively low specificity. High uptake has been reported in patients with chronic inflammatory conditions such as osteomyelitis or arthritis and in many benign conditions such as acute fracture, fibrous dysplasia, and Paget's disease. Therefore, the role of PET scanning in the initial evaluation and staging of suspected bone malignancy remains investigational.

The usefulness of PET scanning in monitoring for recurrent disease or response to treatment also has been varied in the literature. Some studies have shown high sensitivities (93%–98%) for detecting recurrent or residual disease, whereas others have found both sensitivity and specificity of FDG PET in detecting recurrent tumors to be lower than those for MRI.

Summary

The appropriate application of imaging technology is of paramount importance for physicians evaluating and treating suspected bone malignancy. Each patient's workup begins with a thorough history and physical examination emphasizing the patient's age, history of malignancy, and presence or absence of pain. The lesion is first evaluated with plain radiographs,
which provide information about bone destruction, tumor matrix, periosteal or endosteal reaction, lesion margins, associated soft-tissue changes, and lesion location. Clinical and radiographic findings should allow formulation of a working differential diagnosis to help determine the necessity for further imaging studies. CT is often used to further evaluate matrix mineralization and bony architecture for lesions in axial locations and to evaluate pulmonary metastasis. Whole-body bone scanning can be used to evaluate lesion activity and possible multifocal bone involvement. MRI is used to extend the evaluation of a lesion within the bone and soft tissues and the relationship of the lesion to surrounding anatomic structures. The role of PET scanning remains undefined. It may prove useful in staging (especially for detecting nonpulmonary metastasis), evaluating response to chemotherapy, and detecting recurrent local or metastatic disease during follow-up.

References


