Several options are available for detecting, characterizing, and treating metastases to the bone.

Introduction

Skeletal metastases are the most common malignant bone tumors, occurring in 30% to 70% of all cancer patients.\textsuperscript{1} Breast, prostate, and lung cancers are the major sources of bone metastases, with prostate and lung cancers most common in males and breast cancer in females.\textsuperscript{2} Less frequent sources of bone metastases include bladder cancer in men and uterine malignancies in females.\textsuperscript{2}

Detection of bone metastases is essential for accurate staging and optimal treatment. The goals of imaging are to identify sites of metastasis and to evaluate them...
for the presence of, or potential for, complications such as pathological fractures and spinal cord compression.\textsuperscript{1} Imaging is also used to guide biopsy and assess response to treatment.

**Mechanism**

Bone undergoes constant remodeling, maintaining a dynamic balance between osteoclastic (resorptive) and osteoblastic (bone-forming) activity.\textsuperscript{1,2} As a metastatic lesion in the marrow enlarges, osteoclastic and osteoblastic reactive changes occur simultaneously.\textsuperscript{1} The simultaneous presence of both cell types explains why bone metastases can be lytic, blastic, or mixed.\textsuperscript{1,3} The osteoblastic component of a lytic metastasis represents the reaction of normal bone to the metastatic process.\textsuperscript{1} The radiographic appearance of the lesion can vary, depending on the balance between bone-forming and resorptive processes. Aggressive metastases tend to be lytic, whereas sclerosis indicates a slower, more indolent course.\textsuperscript{1}

Metastases can occur by one of three routes: hematogenous, lymphangitic, and direct extension. Bone metastases occur most commonly by hematogenous spread.\textsuperscript{1,2,4} Both arterial and venous routes of dissemination are possible, but the venous paravertebral plexus of Batson appears more important in osseous metastases. Batson's paravertebral plexus consists of an intercommunicating system of thin-walled vessels with low intraluminal pressure and without valves, allowing for variability in the direction of flow.\textsuperscript{2} They lie outside the thoracoabdominal cavity and are therefore not subject to direct pressure by the abdominal musculature. These factors allow retrograde dissemination of tumor cells through the vessels.\textsuperscript{4} The veins of the plexus also have extensive communication with veins in the spinal canal, explaining the tendency of osseous metastasis to involve the spine.

**Distribution**

The distribution of osseous metastases is influenced by the specific type of primary malignancy; however, there is predominant involvement of the axial skeleton, an area rich in red bone marrow.\textsuperscript{2,4} Red marrow is mostly found in the axial skeleton, while fatty marrow is mostly found in the appendicular bones (eg, long bones). The vertebral column, sacrum, pelvis, and proximal femora are the most common locations for metastatic disease. Within the spine, the lumbar segment is most frequently involved, followed by the thoracic and cervical segments. Infrequent sites of disease include the mandible, patella, and bones of the extremities below the knee and elbow.\textsuperscript{2} In most cases, metastases in the peripheral bones are due to bronchogenic lung carcinoma and occur most often in the phalanges of the hand and scaphoid and lunate bones of the wrist.\textsuperscript{2}

Metastatic lesions can present with any appearance (lytic, blastic, or mixed), regardless of tumor type, but there are some features typical of different tumors. Metastases of lung, kidney, and thyroid cancers are invariably lytic. Blastic lesions are usually seen in prostate (Fig 1A-C) and breast cancers. Mixed lesions are frequently seen in breast carcinoma.\textsuperscript{1}

**Diagnostic Imaging Modalities**

Skeletal metastases can be evaluated by four clinical imaging modalities: plain film radiography, computed tomography (CT), magnetic resonance imaging (MRI), and skeletal scintigraphy.

**Plain Film Radiography**

Plain film radiographs are commonly used to evaluate symptomatic areas and to confirm findings seen with other imaging modalities. Because of its poor sensitivity...
(ie, 44% to 50% less sensitive than scintigraphy in detecting breast cancer metastases), it is generally not used as a screening method. \(^3\) \(^5\) Considerable bone destruction must be present before a bone metastasis is evident radiographically. An estimated 30% to 75% reduction in bone density is required for a lesion to be visualized on radiographs. \(^1\) Moreover, the radiographic bone survey remains useful in the event of a “skeletal emergency,” such as an impending pathological fracture, particularly of weight-bearing bones (Fig 2A). Radiography is invaluable for assessing the extent of cortical compromise and the risk of pathological fracture in tubular bones. \(^6\) For example, lytic lesions that destroy 50% or more of the diaphyseal cortex can result in a 60% to 90% reduction in bone strength, significantly increasing the risk of fracture. \(^6\) Radiographs are recommended for patients with symptoms of pain or tenderness that might be related to a weight-bearing bone (eg, femur or tibia). \(^6\) The radiographic bone survey, however, remains important in staging of multiple myeloma due to poor sensitivity of scintigraphy in this condition. \(^4\) \(^6\)

Bone lesions can appear as areas of faint or absent density (osteolytic), as disrupted or absent trabecular structure, or as sclerotic lesions or rims (osteoblastic). \(^3\) The limited contrast in trabecular bone makes radiographic detection of lesions more difficult than that in cortical bone. \(^3\)

### Computed Tomography

CT demonstrates superior bony detail and distinguishes between different densities, allowing detection of metastases within the bone marrow before destruction occurs. \(^3\) The sensitivity of CT for the diagnosis of bone metastases ranges from 71% to 100%. \(^2\) CT is also superior to radiography and skeletal scintigraphy for identifying lesions in the spine and calvarium and for detecting radiographically occult pathological fractures (Fig 2B). The main limitation of CT is that only limited areas can be scanned at a time and thus cannot be used for whole-body screening.

CT can be useful for the assessment of bone tumor response to treatment and is better than radiography for delineating changes in attenuation and size of lesions. Image-guided biopsy is easily performed with CT. This technique can also be used to identify the unknown primary tumor in patients who first present with skeletal metastasis.

### Magnetic Resonance Imaging

MRI can provide detailed imaging of the bone and bone marrow. It is highly sensitive (with a sensitivity ranging from 82% to 100%) for the detection of metastasis because of its ability to demonstrate marrow abnormalities. Normal bone marrow contains a high percentage of fat and demonstrates high signal intensity on T1-weighted sequences. Metastatic lesions typically appear as areas of decreased signal on T1-weighted sequences, reflecting the replacement of normal marrow fat cells by tumor. On T2-weighted images, metastases usually have a higher signal than normal bone marrow due to high water content \(^4\) \(^6\) and demonstrate gadolinium enhancement (Fig 3A-C).

MRI is less sensitive than CT for the detection of cortical bone destruction because cortical bone demonstrates a dark signal on both T1- and T2-weighted sequences. \(^1\) \(^4\) \(^5\) On the other hand, this technique is more effective than CT for elucidating spinal cord compression in patients presenting with spinal symptoms. Due to superior soft-tissue contrast seen with MRI, it can better distinguish benign from malignant vertebral compression fractures. \(^1\) \(^2\)

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**Fig 2A-B.** — (A) Anteroposterior radiograph of the right femur in a patient with lung carcinoma. A lytic lesion in the proximal femur (arrow) is compatible with a metastasis. There is no obvious fracture. (B) Noncontrast axial CT image from the same patient. CT confirms the presence of a slightly expansile, lytic lesion involving nearly the entire cross-sectional area of the proximal right femur. Furthermore, not seen on the radiographs, CT demonstrates significant cortical thinning with a focal cortical break (arrow) compatible with pathological fracture.
Skeletal Scintigraphy

Skeletal scintigraphy, generally referred to as bone scan, is the most widely used method of detecting bone metastasis because it provides visualization of the entire skeleton within a reasonable amount of time and at a reasonable cost. $^{99m}$Tc-methylene diphosphonate ($^{99m}$Tc-MDP) is the most commonly used tracer. It accumulates in areas of increased osteoblastic activity and increased blood flow, and it is reliable for detecting osteoblastic metastases seen in breast and prostate cancers. The method is less sensitive for detecting tumors that have little or no osteoblastic reaction (such as those in multiple myeloma) or aggressive lesions with rapid bone destruction. Lytic lesions can appear as “cold” defects but are frequently overlooked.

In contrast to plain films, as little as 5% to 10% change in the ratio of lesion to normal bone is required to detect an abnormality on bone scan, and it is estimated that bone scan can detect malignant bone lesions 2 to 18 months earlier than radiographs can. Therefore, skeletal scintigraphy is the preferred initial imaging modality in cancer patients at high risk of bone metastases. Bone scan has published sensitivity rates between 62% and 100%, with a specificity of 78% to 100%. However, tracer accumulation can occur in any area of high bone turnover related to trauma, infection, or arthropathy. To overcome lack of specificity, correlative imaging with radiographs, CT, or MRI is recommended, especially in the context of equivocal findings (single “hot spot” or few lesions). The presence of multiple lesions in patients with a known malignancy is more suggestive of metastatic disease, although other nonneoplastic conditions can also have multifocal areas of uptake.

Monitoring Treatment Response

Response of skeletal lesions to treatment may result in reactive bone formation, or sclerosis. Sclerosis tends to progress from the periphery toward the center. Progressive sclerosis can make areas subtly more visible, giving a false impression of disease progression. Sclerosis of a lytic component usually suggests a positive response to treatment, while advanced or new lysis within a sclerotic or mixed area, or an increase in the size of a blastic lesion, may reflect actual disease progression. Determining response can be difficult as it is not always possible to differentiate residual tumor from the repair process. No consensus has been reached on the type of study to be used or the criteria to be applied for assessing response to treatment. Newer techniques are targeted at improving the distinction between viable tumor and necrotic tissue and the effects of treatment.

Adjunct Imaging Modalities

Positron Emission Tomography

Positron emission tomography (PET) has been found to be superior to bone scan in detecting bone involvement in various malignancies. Two radiopharmaceuticals can be used, $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) or $^{18}$F-fluoride. $^{18}$F-fluoride is administered intravenously as Na (sodium) $^{18}$F.

FDG is a glucose analog that is taken up by tumor cells and phosphorylated and becomes trapped within the cells. Cells with high glucose consumption, such as tumors, are FDG-avid and therefore uptake is an indicator of metabolic activity. Since uptake is not restricted to skeletal metastases, FDG-PET is a mainstay of staging in many malignancies.

Although $^{18}$F FDG-PET has been reported to detect lytic, blastic, and mixed lesions, the data suggest that it is more sensitive for detecting lytic metastases (Fig 4A-B). In particular, $^{18}$F FDG-PET is more sensitive in
detection of skeletal metastases than conventional bone scintigraphy with \(^{99m}\text{Tc-MDP}\) in tumors such as renal cell carcinoma and plasmacytoma/myeloma, which tend to be predominantly osteolytic with little or no local osteoblastic reaction.\(^7\) A recent meta-analysis by Chang et al\(^8\) demonstrated increased sensitivity of 93% and specificity of 95% with FDG-PET in the detection of bone metastasis from lung cancer compared with conventional bone scintigraphy, which demonstrated sensitivity and specificity of 87% and 82%, respectively.

The mechanism of \(^{18}\text{F-fluoride}\) is similar to \(^{99m}\text{Tc-MDP}\), with its accumulation similarly dependent on bone deposition and blood flow. Fluoride deposition accompanies the osteoblastic mineralization of new bony matrix by depositing fluorapatite in place of the common bone mineral hydroxyapatite.\(^9\) Similar to \(^{99m}\text{Tc-MDP}\) bone scintigraphy, \(^{18}\text{F-fluoride PET}\) demonstrates uptake in areas of osteoblastic activity. However, \(^{18}\text{F-fluoride PET}\) achieves good skeletal-to-background ratio as quickly as 1 hour after injection compared with 2 to 4 hours with conventional bone scan.\(^7,10,11\) \(^{18}\text{F-fluoride PET images also produce higher spatial resolution compared to conventional bone scan (Fig 5A-B).}^{11}\) Several studies have shown better metastatic lesion detection with \(^{18}\text{F-fluoride PET}\) than with a \(^{99m}\text{Tc-MDP bone scan.}\)

Although only a few studies comparing \(^{18}\text{F-fluoride PET/CT and bone scan with }^{99m}\text{Tc-MDP}\) exist, \(^{18}\text{F-fluoride PET}\) seems to be more sensitive for evaluation and characterization of bone metastases.\(^11\) \(^{18}\text{F-fluoride PET}\) was more sensitive in detecting skeletal metastases than was planar \(^{99m}\text{Tc-MDP\) scintigraphy either alone or in combination with \(^{99m}\text{Tc-MDP SPECT.}\) In one study, \(^{18}\text{F-fluoride PET detected skeletal metastases in all patients, whereas }^{99m}\text{Tc-MDP bone scan detected lesions in 18 of 23 patients.}^{11}\) Anatomic correlation with CT also increases the specificity of \(^{18}\text{F-fluoride PET.}^{12}\) \(^{18}\text{F-fluoride PET offers the additional advantages of faster adaption and more distant metastases.}\)

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Fig 4A-B. — (A) Axial PET image from the patient with breast carcinoma illustrated in Fig 3. There is a focal area of increased activity (arrow) in the subtrochanteric right femur. This lesion was radio-graphically occult (radiograph B). (B) Anteroposterior radiograph of the right femur in the same patient with breast carcinoma. A subtle lucency can be seen, but no definite lesion is identified.

Fig 5A-B. — (A) Whole-body methylene diphosphonate (MDP) bone scan and (B) \(^{18}\text{F-Na PET scan done 1 year later in a 61-year-old man with prostate cancer.}^{18}\text{F-Na PET demonstrates better spatial resolution compared to conventional bone scan as well as multiple new areas of increased uptake in the lumbar spine, which were proven metastases.}^{11}\) Uptake in the cervical spine and left shoulder were degenerative in nature. Fig 5A-B images courtesy of Jaime L. Montilla-Soler, MD.
study times, improved workflow, and increased convenience to the patient and referring physician. However, widespread use of $^{18}$F-NaF as a bone-imaging agent has been limited by familiarity with $^{99m}$Tc-MDP scintigraphy and by issues related to insurance reimbursement for $^{18}$F-fluoride PET.\textsuperscript{11}

**Single Photon Emission Computed Tomography**

Single photon emission computed tomography (SPECT) uses the same radionuclide as conventional bone scan, but images are acquired in a cross-sectional rather than planar method, thus providing better anatomic localization of lesions.\textsuperscript{5} SPECT and bone scan may not detect purely lytic lesions, but this limitation is minimized by combining SPECT with CT.\textsuperscript{15} Due to its limited availability, SPECT/CT is not typically used for first detection of metastatic disease, but it can be used to evaluate indeterminate findings on whole-body bone scans.\textsuperscript{5} Currently, the main drawback of SPECT is that the data are obtained for only a limited skeletal region. In busy routine practice, it is not possible to perform several SPECT acquisitions to tomographically assess the entire skeleton.

**Novel/Evolving Imaging Modalities**

**Whole-Body MRI**

Whole-body MRI uses fast pulse sequences over multiple anatomic regions to achieve a survey of the entire body.\textsuperscript{6} It is currently being used as an adjunct or alternative to established multimodality approaches for tumor staging or for screening for recurrence after curative therapy.\textsuperscript{13} For MRI bone screening, the combination of unenhanced T1-weighted spin echo and turbo-short tau inversion recovery (STIR) sequences proved to be highly sensitive in discriminating benign from malignant marrow disorders.\textsuperscript{13} Promising results have been reported for detection of metastases in bone, liver, and brain; whole-body MRI has also been proposed as an application for integrated assessment of multiple myeloma.\textsuperscript{15}

In addition, whole-body diffusion-weighted imaging (WB-DWI) is an evolving application. While WB-DWI is being used for detection of lymphadenopathy as well as tumors in the abdomen and peritoneum,\textsuperscript{14} it has potential skeletal applications as well.

**Diffusion-Weighted Imaging**

Diffusion-weighted MRI (DWI) is being added to standard musculoskeletal MRI sequences at many institutions. DWI is based on the motion of water molecules. Water molecules outside the body demonstrate random Brownian motion.\textsuperscript{14} Extracellular water has more freedom, or is less impeded in its motion, in comparison to intracellular water molecules, which are limited in their motion by intracellular organelles, macromolecules, and cell membranes.\textsuperscript{15} The degree of restriction to water diffusion in biological tissue is inversely correlated to cellularity and the integrity of cell membranes.\textsuperscript{14} The water molecules are more restricted in tissues with a high cellular density associated with numerous intact cell membranes (eg, tumor tissue). In contrast, in areas of low cellularity or where the cellular membrane has been breached (eg, necrosis), the motion of water molecules is less restricted.\textsuperscript{14,15} Based on the DWI sequences, the apparent diffusion coefficient (ADC) is calculated. The ADC is independent of the magnetic field strength and can overcome a pitfall of DWI known as “T2 shine-through.”\textsuperscript{14} Areas of restricted diffusion in highly cellular areas show low ADC values compared with less cellular areas that demonstrate higher ADC values.\textsuperscript{14}

DWI has been shown to differentiate between areas of treatment-induced necrosis from highly cellular residual tumor. Additionally, DWI is being applied for monitoring response to chemotherapy and radiation, and appears to have the ability to predict treatment response.\textsuperscript{14}

**PET Radiotracers**

Many recently published reports have emphasized the potential advantages of PET using new radiotracers such as $^{11}$C-acetate, $^{11}$C and $^{18}$F-labeled fluoroethylcholine, and $^{18}$F-fluorocholine (FCH) in assessing skeletal metastases in prostate cancer patients.\textsuperscript{12} Increased cell proliferation in tumors and upregulation of choline kinase in cancer cells are suggested as two possible mechanisms for increased choline uptake, particularly in prostate cancer cells.\textsuperscript{12} Beheshti et al\textsuperscript{16} reported that $^{18}$F-FCH PET/CT showed promising results in early detection of metastatic bone disease and monitoring response to therapy.

**Summary**

Bone scintigraphy remains the most common method for detecting osseous metastasis since it is a whole-body imaging modality. However, the lack of specificity of scintigraphy usually requires additional evaluation with a cross-sectional modality such as MRI or CT. Although those can elucidate only a single or limited area, they allow better lesion characterization. CT offers high bony detail, and it is also used to perform image-guided interventions. MRI has superior soft-tissue contrast and can clarify overall marrow involvement. Plain film radiography is a mainstay in the evaluation of osseous lesions and is important for assessing complications such as pathological fracture.

Monitoring response of osseous metastases can be difficult, and there is no established consensus on the type of study or criteria to be used. PET/CT has become a mainstay in the staging of many malignancies and is also useful in the evaluation of osseous metastasis. $^{18}$F-fluoride PET is being used for evaluation of blastic
metastasis, but widespread use is limited. Newer modalities such as WB-MRI and DWI as well as PET radiotracers show promise but continue to evolve.

Management of Painful Skeletal Metastases

The increasing longevity of the population and the advances in the management of cancer patients have contributed to an increasing number of individuals living with metastatic bone disease. The majority of patients who develop bone metastases will suffer from significant bone pain. In addition to potentially intractable pain, complications of skeletal metastases include fracture, decreased mobility, reduced performance, and poorer quality of life. Beyond proper diagnosis of skeletal metastases, management of bone pain is an important component in the overall management of patients with metastatic bone disease. Current treatment options include analgesic medications, systemic chemotherapy, bisphosphonates, hormonal therapy, radiation therapy, radionuclides, localized ablation techniques (radiofrequency, cryoablation, microwave, and laser), and surgical stabilization.

Targeted pharmacologic therapy for pain control, including chemotherapy, hormonal therapy, and narcotic analgesic medications, have limitations in the treatment of most painful bone metastases. Many medical therapies do not achieve durable pain relief, and most require chronic administration. Chemotherapy may be ineffective, having either no response or toxicity that limits the treatment dose. Bisphosphonate therapy is used for decreasing and delaying the complications of bone metastases and for pain relief. Although there is evidence to support its effectiveness in providing pain relief, it is not recommended as first-line treatment. Chemotherapies often become the default therapeutic choice, even with their potential side effects that may include drowsiness, dizziness, headaches, nausea or vomiting, and development of dependence.

External-Beam Radiation Therapy

External-beam radiation therapy (EBRT), with or without systemic chemotherapy or hormonal therapy, is the standard of care for the alleviation of pain caused by skeletal metastases. Prospective randomized trials comparing single- vs multiple-fraction radiotherapy regimens resulted in overall pain relief in 53% to 86% of patients with uncomplicated bone metastases. Complete response varied from 15% to 58%. A higher response rate was seen for patients with breast cancer and prostate cancer than for those with lung cancer. A higher incidence of re-treatment occurred with the single-fraction treatment (18% to 35%) than with a 10-fraction treatment (8% to 9%). Although re-treatment of nonresponders and those with disease progression can be successful, patients may not be able to receive recurrent treatment because of toxicity or limited tolerance of normal tissue for additional radiation.

Percutaneous Ablation

Percutaneous ablation for the palliation of painful bone metastasis has developed into an effective, minimally invasive alternative to the more established practices of EBRT and systemic therapy.

Radiofrequency Ablation

Radiofrequency (RF) ablation is the most widely adopted method of percutaneous ablation for the treatment of soft-tissue tumors. The first application of its use in bone was described by Rosenthal et al in the treatment of an osteoid osteoma. RF ablation is performed by delivering RF energy with one or more needle electrodes placed directly into the treatment site under sonographic or CT guidance (Fig 6). High-frequency alternating current passes into the tissue, causing frictional heat that extends further into the surrounding tissue as conductive heat, inducing cell death through coagulation necrosis.

Several clinical trials have demonstrated the effectiveness of RF ablation for palliation of pain from bone metastases. In a recent multicenter American College of Radiology Imaging Network trial of 55 patients treated with RF ablation to palliate pain from bone metastases, a decrease in pain severity was seen at 1 month and 3 months following treatment. Based on a 100-point pain scale, the average decrease in pain intensity was 26.9 at 1 month and 14.2 at 3 months. Patients also had a statistically significant improvement in mood. Grade 3 toxicity occurred in 3 patients (5%). In another multicenter trial of 43 patients with painful osteolytic bone metastases, the mean score for worst pain prior to treatment was 7.9 on a 10-point pain scale. This decreased to 4.5, 3.0, and 1.4 at 4, 12, and 24 weeks, respectively.

Fig 6. — Percutaneous radiofrequency ablation of an osteolytic bone metastasis for pain palliation. Axial CT scan of the pelvis demonstrates tines from a radiofrequency needle probe (arrow) extending into the lytic bone tumor.
respectively, following RF ablation. Opioid analgesic usage decreased significantly at 8 and 12 weeks after treatment. Adverse events were seen in 3 patients.

**Cryoablation**

Percutaneous cryoablation is performed in a fashion similar to that of RF ablation. Insulated cryoprobes of 1.2 to 2.4 mm in diameter are utilized. These applicators use high-pressure argon gas that expands within the distal uninsulated segment of the cryoprobe, causing rapid cooling (the Joule-Thomson effect) to temperatures as low as –100°C (Fig 7). Following the freeze cycle, helium is introduced, which generates heat with expansion within the cryoprobe and allows thawing of the ice ball for probe removal. Cryoablation has certain advantages over RF ablation. The ablation margin is readily visible on CT imaging during treatment, due to the low attenuation of the ice ball, allowing for more precise targeting of the treatment field. Patients experience reduced pain during treatment and immediately thereafter. Compared with RF energy, deeper penetration of ice into bone is seen, which may allow more effective treatment of osteoblastic bone lesions. Interim results from single-center prospective clinical trials have been encouraging.27,28 In their study involving 14 patients, Callstrom et al27 reported a decrease in the mean score for worst pain in a 24-hour period, from 6.7 before treatment to 3.8 (P = .003) at 4 weeks after treatment, based on a 10-point pain scale. All 8 patients who were taking narcotic medications prior to treatment reported reduced medication use after cryoablation. Pain control appeared durable, with 4 of 5 patients in the 24-week follow-up interview reporting excellent pain relief. No serious complications were reported.27

**Microwave Ablation**

Microwave ablation utilizes a thin antenna (14.5 gauge) placed, under imaging guidance, in the treatment site. A microwave generator emits an electromagnetic wave through the uninsulated portion of the antenna, causing agitation of water molecules in the surrounding tissue. The agitation produces heat, resulting in cell death via coagulation necrosis.29 Microwaves travel through all types of tissue, including those with high impedance, such as lung or bone. Microwaves also have less susceptibility to the heat sink effect in adjacent larger vessels, thereby reducing possible distortion of the ablation zone. The heat sink effect is more problematic with other thermal ablative techniques, leading to regions of incomplete ablation.30 The benefits of microwave ablation also include higher intratumoral temperature, larger and more uniform ablation volume, and faster ablation time. The use of microwave ablation for treating patients with bone metastases has been limited, but early results are promising.31,32 Other ablative techniques are available, such as laser ablation and a new, nonthermal, ablative modality known as irreversible electroporation (IRE), which uses high-voltage direct current to irreversibly open nanopores of cell membranes to induce cell death. However, little data are available, especially for IRE, regarding treatment of patients with bone metastases. Clinical trials are necessary to determine the efficacy of these procedures for the palliation of pain from metastatic bone lesions.33-35

**Summary**

All of the percutaneous ablative techniques described here have some limitations or disadvantages. Although minimally invasive, they require skilled interventionalists to place needle probes or applicators into the accessible target. Probe placement into osteoblastic metastases with preserved cortical bone may be difficult. The proximity of critical normal structures, including nerves, major blood vessels, bowel, and bladder, must be considered to prevent injury, and this influences patient selection. Treatment also requires regional anesthesia, moderate sedation, or general anesthesia for adequate intraprocedural pain control.

**MR-Guided Focused Ultrasound Surgery**

MR-guided focused ultrasound surgery (MRgFUS) is a noninvasive thermal ablation technique that combines high-intensity focused ultrasound tissue ablation with MRI for imaging guidance. MRI is used for treatment planning as well as for monitoring actual treatment. T2-weighted images are used to evaluate the tumor and surrounding anatomic structures and to define treatment volume and treatment path. MR thermometry is performed with phase map imaging, which relies on subtle changes in resonance frequency of tissue at different temperatures, thus providing real-time temperature feedback during treatment. The focused ultrasound energy increases temperature sufficiently to cause protein denaturation and cell death via coagulation necrosis. Immediately fol-
MRgFUS Procedure

MRgFUS treatment of bone metastasis is performed under conscious sedation and involves a focused ultrasound phased array system integrated with a clinical MRI system. The procedure described is based on a current commercially available MRgFUS system (ExAblate 2000 system; InSightec Ltd, Haifa, Israel).

Pretreatment MRI localizes the painful bone lesion. The targeted lesion is positioned directly above a water bath within the MR table that contains the phased array transducer. Acoustic coupling is accomplished by placing a coupling gel pad with degassed water between the patient and the chamber containing the transducer. The skeletal structure in the treatment region is evaluated to identify any abnormalities that may prevent safe treatment. Adjacent organs such as bowel, lung, or major nerves are evaluated to ensure that they are not in the path of the ultrasound treatment beam. If the bone metastasis is identifiable on the MR images, the contour of the bone cortex in the targeted area is traced, followed by an estimation of the treatment volume. If the bone is not well visualized, CT images can be overlaid on the MR images to better define the cortical margin that is drawn. Based on the treatment volume and the defined cortical margin, the total number of planned sonications and their locations are determined. Pretreatment

Treatment of Bone Metastases With MRgFUS

Treatment of bone metastases with focused ultrasound has advantages over treatment of soft tissue, due to higher absorption of acoustic energy (up to 50 times that of soft-tissue tumors) and lower thermal conductivity of bone tissue, leading to reduced penetration of energy into the bone. The treatment is targeted to heat the cortical margin of the bone lesion. This allows for a wider zone of coverage at the bone surface with each delivery of focused ultrasound energy (termed sonication) and the need for fewer sonications, resulting in faster treatment time. Although the relationship between bone invasion by tumor and bone pain is unclear, it has been postulated that stimulation of nerve endings in the endosteum and stretching of the periosteum by increasing size of the tumor are contributing factors.

Fig 8A-D. — (A) CT scan demonstrating a solitary osteoblastic metastasis located in the right iliac bone adjacent to the sacroiliac junction (arrow). (B) MRgFUS planning image for a sonication. Axial MRI scan shows the targeting of the bone lesion, with the beam bath for acoustic energy seen in light blue. The focal point (cross hairs) is placed deep to the cortical bone. The blue oval is the actual target for heat deposition. The green line represents the contour of the bone cortex. (C) Phase map image of a sonication treatment. The arrow points to the temperature history cursor on a phase map image (temperature map) at the site of sonication. The cursor can be moved within the image to evaluate temperature rise. (D) A temperature history graph demonstrating the measured temperature over time at the specified position of the cursor in image C.
verification of planning accuracy is performed with subtherapeutic sonications. When a mild increase in temperature is observed at the exact intended target (geometric and thermal-dose verification), then the actual treatment is started, using therapeutic energy levels. Sonications are performed on each successive planned sonication site, while temperature rise is monitored with MR phase-map imaging (Fig 8A-D). For each selected treatment location, sonication parameters, including acoustic energy, sonication duration, and acoustic power, are evaluated and adjusted. Acoustic power is adjusted during the entire treatment to not exceed the thermal-dose threshold between 65°C and 85°C, with maximum acoustic energy reaching 2,000 joules. The sonication duration is approximately 30 seconds, with a cool-down duration of 90 seconds between sonications. They are continued until the prescribed target area has been treated. Posttreatment diagnostic MRI is conducted, including T2-weighted sequences and contrast-enhanced T1-weighted images, to evaluate the extent of the ablated area (Fig 9A-B).

**MRgFUS Treatment Results**

The initial evaluation of safety and effectiveness of MRgFUS in pain palliation was shown in two feasibility studies. In the first study, 12 patients of 13 with a mean follow-up of 59 days received adequate treatment and follow-up. One patient’s treatment was prematurely terminated due to intolerance of pain related to sonication. A total of 10 patients reported prolonged improvement in pain and reduction in analgesic medication usage. No severe adverse events were recorded. In the second single-center study, which included 11 patients, 12 metastatic lesions were treated. In these patients the mean visual analog pain score (VAS), on a 10-point scale, was reduced from 6.0 before treatment to 0.5 at 3 months posttreatment. All patients reported decreased intake of pain medication, including 7 patients who ceased taking all pain medication. No adverse events were reported.

In the most recent multicenter prospective trial, Liberman et al performed 36 treatments on 32 bone lesions in 31 patients. Of the 25 patients with a follow-up of 3 months or longer, 18 (72%) reported significant improvement in pain, and their average VAS rating reduced from 5.9 before treatment to 1.8 at 3 months after treatment. Nine patients had a complete response, 6 had no response, and 1 reported an increase in pain. Of the 9 patients who were prescribed opioid pain medications prior to treatment, 67% reported reduction in usage post-treatment. No severe adverse events were reported. A phase III multicenter randomized prospective trial is in progress to evaluate the efficacy of MRgFUS for the palliation of pain from bone metastases or multiple myeloma in patients who have failed or are not candidates for radiation therapy. This trial is nearing completion of its targeted accrual of 150 patients. The results, which may become available by the time of this publication, should provide more support for the efficacy of this therapy (J.C., unpublished data, 2012). Another multicenter prospective randomized trial has been started in Europe (not in the United States) comparing MRgFUS with EBRT for the palliation of pain from skeletal metastases.

The advantages of MRgFUS treatment for the palliation of bone pain include a noninvasive approach with a short recovery time, and without the need for interventional expertise. Osteoblastic as well as osteolytic lesions can be treated similarly. Unlike conventional multifractionated radiation therapy, treatment is performed in one session, without ionizing radiation and with the possibility of repeat treatment for symptom recurrence or new tumors.

There are limitations to use of the procedure as well. The location of the lesion might prevent treatment since the targeted lesion needs to be coupled to the array transducer without intervening air bubbles or vital structures. This problem may be diminished with the use of a mobile conformal array transducer, which is presently being investigated. The use of MRgFUS for metastases in the skull and the spine, except the posterior elements of the lower lumbar spine, is limited; before applying MRgFUS to lesions in the spine, additional investigation is necessary to determine the safety of the nearby spinal cord and nerve roots during treatment. Patients who cannot undergo MRgFUS are those with metal orthopedic hardware near the treatment field and those with cardiac pacemakers or other contraindications to MRI. Finally, fracture risk assessment in weight-bearing long
bones is necessary prior to treatment, in order to reduce the potential for pathological fractures.

Conclusions
Skeletal scintigraphy remains the most commonly used diagnostic imaging modality for the evaluation of skeletal metastases. More sensitive imaging modalities are available to better define metastatic lesions and possibly alter patient management. Further investigation is needed, based on the primary tumor, disease state, patient symptoms, and available treatment options. Newer imaging modalities such as $^{18}$F-Na PET and whole-body MRI are not routinely available, but they may be more widely used in the future as treatment modalities evolve.

Treatment of painful bone metastases requires a multifaceted approach. Radiotherapy continues to be the mainstay for palliation of bone pain. Image-guided percutaneous ablative treatment of skeletal metastases provides a minimally invasive treatment option that appears to be safe, effective, and durable. Local ablative treatments require appropriate patient selection, and anatomic considerations are critical to successful outcomes. MRgFUS provides a noninvasive alternative to local ablative methods. Preliminary investigations show promise, and further data supporting the efficacy and validity of this treatment are anticipated.

References