Modern Palliative Treatments for Metastatic Bone Disease

Awareness of Advantages, Disadvantages, and Guidance

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Background: Metastatic disease is the most common malignancy of the bone. Prostate, breast, lung, kidney, and thyroid cancer account for 80% of skeletal metastases. Bone metastases are associated with significant skeletal morbidity including severe bone pain, pathologic fractures, spinal cord or nerve roots compression, and malignant hypercalcemia. These events compromise greatly the quality of life of the patients. The treatment of cancer patients with bone metastases is mostly aimed at palliation.

Objective: This article aims to present these palliative treatments for the patients with bone metastases, summarize the clinical applications, and review the techniques and results.

Methods: It gives an extensive overview of the possibilities of palliation in patients with metastatic cancer to the bone.

Results and Discussion: Currently, modern treatments are available for the palliative management of patients with metastatic bone disease. These include modern radiation therapy, chemotherapy, embolization, electrochemotherapy, radiofrequency ablation, and high-intensity focused ultrasound. As such it is of interest for all physicians with no experience with these developments to make palliative procedures safer and more reliable.

Key Words: palliation, radiation therapy, embolization, electrochemotherapy, radiofrequency ablation, high-intensity focus ultrasound (Clin J Pain 2016;32:337–350)

Metastatic disease is the most common malignancy of bone. Prostate, breast, lung, kidney, and thyroid cancer account for 80% of skeletal metastases. The most common sites of bone metastases are the spine, pelvis, ribs, skull, and proximal femur. Bone metastases are associated with significant skeletal morbidity including severe bone pain, pathologic fractures, spinal cord or nerve roots compression, and malignant hypercalcemia. These events greatly compromise the quality of life of the patients. Pain from bone metastases can be caused by tumor biology, local chemical release of cytokines by tumor cells causing stimulation of intraosseous nerves, pressure or mass effect of the tumor tissue within the bone, and bone destruction causing mechanical instability and pathologic fractures.

The treatment of cancer patients with bone metastases is multidisciplinary. However, the treatment options in these patients are mostly aimed at palliation. The goals of treatment in these patients are pain control, prevention and treatment of fractures, maintenance of independence, and prevention of tumor progression, and improvement of quality of remaining life. Traditional palliative treatments include surgery, if the metastatic lesion is accessible, and/or external-beam radiation therapy. The main indications for surgery are persistent pain refractory to medical therapy, tumors with poor radioisotope uptake, and spinal instability with or without neural compression.

Bone pain without structural insufficiency is often effectively treated with narcotic analgesics and radiation therapy, and often, hormonal therapy, cytotoxic therapy, and/or bisphosphonates. However, all metastatic lesions are progressive causing bone failure. Tumor cell adhesive molecules bind the tumor cells to marrow stromal cells and bone matrix allowing them to grow and produce angiogenic and bone-resorbing factors.

In addition, most, if not all metastatic lesions are hypervascular. Some lesions such as renal and thyroid metastases are highly hypervascular. This may cause technical difficulties with respect to the extent of surgery and primary stability for pain relief.

Currently, treatments are available for the palliative management of patients with metastatic bone disease. These include radiation therapy, chemotherapy, embolization, electrochemotherapy, radiofrequency ablation (RFA), and high-intensity focus ultrasound (HIFU) (Table 1). This article aims to present the available palliative treatments for the patients with bone metastases, summarize the clinical applications, and review the techniques and results. It gives an extensive overview of the possibilities of palliation in patients with metastatic cancer to bone. As such it is of interest for all physicians with no experience with these developments to make palliative procedures safer and more reliable.

PALLIATIVE RADIATION THERAPY

Palliative radiation therapy is an effective treatment for bone metastases. It can reduce pain in 60% of patients, with about 25% of patients achieving a complete response. Palliative radiation therapy can be administered as conventional external-beam radiation or intravenous bone-seeking radiopharmaceuticals. The goal of palliative radiation therapy is to use a short treatment schedule to minimize the commitment of time for therapy and achieve rapid symptomatic relief. Unlike adjuvant radiation therapy in which high radiation doses are administered over several weeks to eradicate tumors, the dose administered with palliative radiation therapy is usually lower and given over a
TABLE 1. Advantages and Disadvantages of Palliative Radiation Therapy, Chemotherapy, Embolization, Electrochemotherapy, Radiofrequency Ablation, and High-intensity Focused Ultrasound for Patients With Metastatic Bone Disease

<table>
<thead>
<tr>
<th>Palliative Treatments</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Radiation therapy</td>
<td>Effective pain relief</td>
<td>“Pain flare” (temporary increase in bone pain immediately after radiation therapy)</td>
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<tr>
<td></td>
<td>Can be repeated (up to the maximum radiation dose of the dose-limiting organ)</td>
<td>Higher retreatment rate (single-fraction treatment)</td>
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<td></td>
<td>Target radiation therapy (bone-seeking radiopharmaceuticals)</td>
<td>Risk for radiation-induced side effects (wound healing complications, osteoradionecrosis, fractures, radiation-induced sarcomas)</td>
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<td></td>
<td>Noninvasive</td>
<td>Bone marrow limits the dose of β-emitters bone-seeking radiopharmaceuticals</td>
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<tr>
<td>Chemotherapy</td>
<td>Significant pain relief</td>
<td>Risk of chemotherapy-induced side effects (wound healing complications, alterations of bone metabolism, fractures, nervous system, and hepatic complications)</td>
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<td></td>
<td>Control of tumor progression (anticancer agents)</td>
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<tr>
<td></td>
<td>Prevention of skeletal complications (bisphosphonates, denosumab)</td>
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<td>Normalization of bone turnover (bisphosphonates, denosumab)</td>
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<td></td>
<td>Possible effect on survival</td>
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<tr>
<td></td>
<td>Noninvasive</td>
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<tr>
<td>Embolization</td>
<td>Effective pain relief</td>
<td>Invasive (minimally)</td>
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<tr>
<td></td>
<td>Control of tumor progression</td>
<td>Complications (postembolization syndrome, embolization of nontarget vessels)</td>
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<td></td>
<td>Tumor volume reduction</td>
<td>Life expectancy and survival are not influenced</td>
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<tr>
<td></td>
<td>Can be repeated (no dose limit)</td>
<td>Invasive (minimally)</td>
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<tr>
<td>Electrochemotherapy</td>
<td>Combined effect of physical (electric pulses) and chemical (bleomycin) agents</td>
<td>Cannot be used for metastatic spinal lesions</td>
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<td></td>
<td>Effective pain relief and tumor control when radiation therapy was no more effective</td>
<td>Small experience (few published studies, early results)</td>
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<tr>
<td>Radiofrequency ablation</td>
<td>Effective pain relief</td>
<td>Invasive (minimally)</td>
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<tr>
<td></td>
<td>Control of tumor volume and progression</td>
<td>Connective tissue and vascular degeneration</td>
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<td></td>
<td>Can be used for metastatic spinal lesions</td>
<td>Risk of fracture (trabecular structure becomes brittle and not mechanically competent)</td>
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<td></td>
<td>Can be repeated (no dose limit)</td>
<td>Limited by the proximity of the metastases to neurological structures, and large lesions of weight-bearing bones</td>
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<td>High-intensity focused ultrasound</td>
<td>Effective pain relief</td>
<td>Ultrasound frequency depends on tumor depth, ultrasound absorption of bone marrow, and bone diameter</td>
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<td></td>
<td>Combined thermal (heat) and mechanical (pulses) effect</td>
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<td></td>
<td>Controlled lesions</td>
<td>Small experience (few published studies, early results)</td>
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<td></td>
<td>Potential to stop bleeding</td>
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<td>Potentially prevents hematogenous dissemination of tumor cells (possible effect on survival)</td>
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<td>Can be repeated (no dose limit)</td>
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<td>Low cost</td>
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<td>Noninvasive</td>
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shorter timeframe. Commonly used palliative radiation therapy schemes include 8 Gy in a single fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions.14

No significant difference in pain relief has been reported between single and multiple fractions radiation therapy.16 The overall response rate to radiation therapy is 60% and the complete response rate is 25%. However, the retreatment rate is higher following a single-fraction treatment (20% vs. 8% for multiple fractions radiation therapy). While this rate is higher, recurrent symptoms following a single-fraction treatment can be effectively managed with retreatration. A single fraction of 8 Gy is therefore the treatment of choice to palliate painful uncomplicated bone metastases.

**External-Beam Radiation Therapy**

Palliative external-beam radiation therapy is comprised of high-energy x-rays or γ-rays that damage the DNA of cells within the treatment field. Although the exact mechanism of external-beam radiation therapy is unknown, it is believed that tumor regression and cell kill are important components.14 Repeat radiation therapy of previously treated sites may be considered for patients with repeat symptoms after their initial palliative radiation therapy.17 Patients who receive single-fraction radiation therapy as opposed to multiple fractions are more likely to require repeat radiation therapy.18,19 In general, repeat radiation therapy should be considered for painful sites of metastatic bone disease after initial radiation therapy, particularly when this follows an initial period of response. In this setting, there is also evidence that a proportion of initial nonresponders will respond.20

Palliative radiation therapy is typically associated with few treatment-related side effects including a temporary increase in bone pain immediately after radiation therapy, termed “pain flare” ranging from 2% to 44%.14 Pain flare may have an important impact on the quality of life of the patients.21,22 The prophylaxis of pain flare includes analgesics intake and dexamethasone.21,22
Bone-seeking Radiopharmaceuticals

Intravenous bone-seeking radiopharmaceuticals can be considered for the palliative management of patients with multiple painful bone metastases. Bone-seeking radiopharmaceuticals selectively deliver ionizing radiation to targeted areas of amplified osteoblastic activity. The target is a Ca-OH apatite that is abundant in sclerotic metastases particularly from prostate cancer, and in mixed sclerotic/lytic metastases from breast. Current commercially available formulations of radioisotopes in use are β-emitters, including Strontium-89 dichloride (⁸⁹Sr) and samarium-153 lexidronam (¹⁵³Sm-EDTMP).

Bone marrow is the dose-limiting organ following intravenous injection of β-emitters bone-seeking radiopharmaceuticals. Furthermore, disease-associated bone marrow suppression already present in these patients often results in delayed and unpredictable recovery. This severely limits the usefulness of β-emitters bone-seeking radiopharmaceuticals, particularly when dosages are increased to deliver potential antitumor radiation levels and/or repeat treatments are attempted. Because of short particle track-length and potent cell killing, an α-particle-emitting bone-seeking radiopharmaceuticals could be a novel alternative agent. In contrast to the β-emitters, α-emitters bone-seeking radiopharmaceuticals deliver a much more energetic and localized radiation that produce densely ionizing tracks and predominantly nonreparable double DNA-strand breaks.

PALLIATIVE CHEMOTHERAPY

Cancer metastasis remains poorly understood in terms of clinical outcome, pathology, and tissue specificity of different tumor types. The predilection of some cancers to target and proliferate in bone is also unclear. Less than 1% of cancer cells entering the blood circulation successfully generate metastatic foci. Consequently, there are few successful treatments that directly target metastatic cancer; identifying effective therapeutic targets for this stage of cancer and prognostic factors to identify those patients prone to develop local and distant progressive disease is challenging.

Genetic profiling of tumors has revealed important regulators of the metastatic process and suggested novel targets for cancer therapeutics. Gene expression “signatures” that correlate with overall tumor metastatic efficiency, and can predict metastasis to a particular organ have been described. However, targeting the tumor cell alone may not be sufficient. Multimodality therapy against tumor cells, their growth factors, and the essential accessory cells with which cancer cells interact is imperative.

The treatment of bone metastases itself uses tumor-specific (chemotherapy, hormone, and target therapy) radiation therapy, and surgery. Medical therapy is mainly used to control tumor progression by anticancer agents and to prevent of skeletal complications using bisphosphonates. Pain control and bone turnover are related; patients with normalized bone turnover experience significant improvement of pain. Possibly, medical treatment may also lead to increased survival of cancer patients with metastatic bone disease. Modern medical palliative treatments for bone metastases include bisphosphonates and denosumab.

Bisphosphonates

Bisphosphonates are synthetic analogs of pyrophosphate characterized by a phosphorus-carbon-phosphorus backbone that renders them resistant to hydrolysis. The R1 and R2 carbon side chains determine the pharmacologic properties of bisphosphonates. Most bisphosphonates contain a hydroxyl group at the R1 position that confers high-affinity binding to calcium phosphate. The R2 side chain is the critical determinant of antiresorptive potency. Zoledronic acid is the most potent tested bisphosphonate.

Bisphosphonates are an important advance in supportive care of patients with bone metastases. They inhibit normal and pathologic osteoclast-mediated bone resorption by direct inhibition of osteoclast activity by cellular mechanisms that affect osteoclast attachment, differentiation, and survival. In addition, they reduce osteoclast activity indirectly through effects on osteoblasts. In 1995, intravenous pamidronate was approved to treat patients with multiple myeloma or metastatic breast cancer based on evidence from randomized controlled trials that pamidronate decreases the risk of skeletal complications. In 2002, intravenous zoledronic acid was approved to treat patients with multiple myeloma and bone metastases from any solid tumor including prostate cancer. This approval was based on the results of three randomized controlled trials involving >3000 patients. These trials evaluated the efficacy of bisphosphonates for men with androgen-independent prostate cancer and bone metastases. Their results indicate that zoledronic acid, but not other bisphosphonates, decrease the risk of skeletal complications in men with androgen-independent prostate cancer and bone metastases.

Denosumab

Denosumab is a human monoclonal antibody for the treatment of osteoporosis, induced bone loss, bone metastases, rheumatoid arthritis, multiple myeloma, and giant cell tumor of bone. It is designed to target RANKL (RANK ligand), a protein that acts as the primary signal to promote bone loss. In many bone loss conditions, RANKL overwhelms the body’s natural defense against bone destruction. Denosumab was approved by US Food and Drug Administration (FDA) for use in postmenopausal women with risk of osteoporosis in June 2010 (Prolia), and for the prevention of skeletal-related events in patients with bone metastases from solid tumors in November 2010 (Xgeva) making it the first RANKL inhibitor to be approved by the FDA. Denosumab inhibits the maturation of osteoclasts by binding to RANKL, protecting the bone from degradation. The drug therefore mimics the endogenous effects of osteoprotegerin, another protein produced by osteoblasts which acts as an alternate receptor for RANKL, modulating the RANK/RANKL-induced osteoclast activity. Denosumab has been shown to be at least as efficacious as zoledronic acid in preventing skeletal-related events.

PALLIATIVE EMBOLIZATION

Embolization is a useful adjunctive procedure for the treatment of metastatic bone disease. As all metastatic bone lesions are hypervascular, all patients may be indicated for embolization. Indication for embolization of bone metastases is palliation including control of hemorrhage, facilitation of subsequent surgery, inhibition of tumor growth, and relief of pain secondary to decrease in tumor volume and pressure on the richly innervated periosteum and adjacent structures; indications for repeat
embolization are pain and/or imaging evidence of progressive disease. Preoperative or serial embolization techniques using gelfoam, polyvinyl alcohol particles, alcohol emulsions, coils, tissue adhesives, ethanol, and microfibrillar collagen can be used as primary or adjuvant treatment to surgery or radiation therapy. Serial embolization provides for devascularization, size reduction, calcification of margins, and pain relief.

Technique

Diagnostic digital subtraction angiography is performed before the embolization to identify the feeding vessels. In patients with metastases in the pelvis or lower extremities, the contralateral transfemoral access is used (Fig. 1). Then, panoramic aortography is performed followed by selective and superselective arteriography. In patients with extremity lesions (Fig. 2), aortography is not performed. In our practice, N-2-butyl cyano-acrylate (NBCA, Glubran 2; GEM, Viareggio, Italy) was the preferred embolic agent because we consider the most appropriate embolic agent for controlled and permanent occlusion of the target vessels and tumor devascularization. Embolization is considered technically complete when there is stasis of intravascular contrast feeding arteries to the lesion with the most appropriate embolic agent, embolization can be expected to be successful in up to 90% of cases; multiple procedures are frequently necessary.

FIGURE 1. A, Axial computed tomography (CT) scan of the pelvis of a 67-year-old woman with thyroid cancer shows a large posterior pelvic mass. She presented with back pain. Complete staging showed metastases of the spine (T12 vertebra), the pelvis, and the left humeral diaphysis; biopsy of the pelvic lesion showed metastatic thyroid cancer. She was treated with radiation therapy of the spinal and pelvic lesion, prophylactic closed intramedullary nailing and postoperative radiation therapy of the humeral lesion, and chemotherapy. She experienced complete pain relief of the spinal and humeral lesion. Because of persistent pain of the pelvic lesion, selective embolization was decided. Digital subtraction angiography shows (B) hypervascularization of the pelvic metastasis and (C) occlusion of the feeding vessels with N-2-butyl cyano-acrylate. Postembolization, she experienced complete pain relief at her pelvis. Axial CT scans at (D) 6 months and (E) 12 months show tumor volume reduction and ossification.
material and either complete elimination of the tumor’s hypervascular staining, or 80% or greater elimination of the tumor pathologic vasculature compared with the initial diagnostic angiogram. If occlusion is not complete or more feeding vessels were observed, the procedure can be repeated in the same method.

Results

Life expectancy is not influenced by embolization therapy and embolization therapy does not appear to improve survival. However, embolization has an important impact on palliation and quality of life. Previous studies reported embolization has an effective treatment for bone metastases, associated with rapid reduction in pain and tumor volume lasting from 1 to 9 months. It has an immediate palliative effect on pain in 97% of the procedures; imaging shows evidence of tumor necrosis and variable ossification in most cases. However, this palliative effect is transient; symptoms recurred after 8.1 months.

Embolization has been associated with a low complications rate. The postembolization syndrome with symptoms such as fever, pain, and malaise is a complication reported in 18% to 86% of cases. Embolization of adjacent or distant nontargeted vessels can result in normal tissue loss and may be associated with nerve palsy, skin breakdown, and subcutaneous or muscle necrosis and infection. The risk of complications is higher in certain anatomic regions. In the spine, a connection between the artery of Adamkiewicz that originates between the T5 and L2 vertebra and the tumor-feeding vessels must be recognized on preembolization angiography. During pelvic embolizations through the iliac artery and its branches, ischemic neuropathies of the sciatic and femoral nerves may occur if neural vessels were occluded. To prevent these complications, the posterior branch of the internal iliac artery and the inferior gluteal artery must be spared at embolization. Complications related to the embolic agents have also been reported. Gel-foam, polyvinyl alcohol particles, liquid (absolute alcohol), coils, tissue adhesives, ethanol, microfibrillar collagen, and autologous blood clot have been used as embolic agents.

Major considerations for choosing an embolic agent are speed and reliability of delivery, duration of occlusive effect, and preservation of normal tissue. Liquid embolic agents have low viscosity that allows for easy injection through small catheters or catheters with many bends through tortuous blood vessels. NBCA or “liquid glue” is a liquid embolic agent that spreads according to its polymerization time and the vascular flow. A distinct advantage of NBCA in lipiodol is its dense radiopacity. Thus, its exact site of occlusion can be observed and documented. Moreover, it can be used in patients with clotting pathologies. Bolus administration of small doses (0.1 to 0.2 mL) of sandwiched NBCA under fluoroscopic control, followed by arteriography provides for the efficacy and safety of the procedure.

ELECTROCHEMOTHERAPY

Electrochemotherapy is the local potentiation, by means of permeabilizing electric pulses locally delivered, of
the antitumor activity of a nonpermeant anticancer drug possessing a high intrinsic cytotoxicity (bleomycin). Cell death is consequent to direct DNA damage because of the formation of DNA adducts or DNA double-strand brakes induced by bleomycin. The combined effects of these physical and chemical agents are completed by induction of local vascular lock and host immune response.

Electrochemotherapy has proven effectiveness in the treatment of metastases from solid tumors (breast, melanoma) located in the skin or subcutaneous tissue. The ESOPE trial demonstrated that electrochemotherapy can obtain 74% complete response and 85% objective response of treated tumor nodules.\textsuperscript{50,51} Since the publication of the Operating Standard Procedures, the electrochemotherapy technology has been disseminated and is already successfully used in > 60 hospitals in the European Union for cutaneous and subcutaneous tumor nodule treatment.

Recent development of the electrochemotherapy technique, brought this method to be used on bone metastatic patients, trying to improve pain relief and local control of the metastases in patients where radiation therapy was no more effective, or in cases where surgery was debatable or difficult to perform (deep lesions and small lesions). Before the clinical application, preclinical studies employing an in vivo animal model of healthy rabbit (femoral distal epiphysis) were investigated in our Institute by histologic and functional analysis after electroporation and the effect of ablation on bone cells by electroporation has been described.\textsuperscript{51} These authors showed that bone osteogenic activity and structural integrity is preserved,
differently from other ablating techniques such as radiotherapy and thermal ablation. Particularly, osteogenic activity in the ablated area had recovered by 30 days and biomechanical testing showed structural integrity of the bone. This is probably one of the major advantages of electrochemotherapy compared with radiation therapy or other ablating techniques such as radiofrequency thermal ablation or cryosurgery. In fact, in radiofrequency thermal ablation the heat dissipation is associated with connective and vascular structure degeneration. Furthermore, when RFA is applied to bone, it leaves the trabecular structure brittle and not mechanically competent. On the other side, cryosurgery is particularly time consuming, requires multiple probes, and has a number of side effects.

### Technique

Electrical pulses are delivered via bone needle electrodes to metastases by an electric pulse generator (Fig. 3). Bleomycin is administrated intravenously with a dosage of 15 mg/m² 8 minutes prior electric pulse supply. Target lesion was surrounded by up to 6 electrodes delivering 8 electrical pulses/100 ms and with an electric field of 1000 V/cm for each couple of needles. The response to electrochemotherapy is evaluated with new staging (MRI/CT) at 4 and 8 weeks. Even if results are still to be confirmed by a longer follow-up and larger cohort of patients, early results are encouraging and continuous improvements of the techniques are ongoing (Fig. 4).

### RFA

RFA is a form of electrosurgery in which an alternating current of high-frequency radio waves (>10 kHz) passes from an electrode tip in human tissue and dissipates its energy as heat. A radiofrequency generator forms an electric current that flows from the generator, through the electrode into the patient, and out through a grounding electrode or pad back to the generator. Resistance of tissue causes local ions to vibrate. This ionic agitation results in friction around the electrode tip as ions attempt to pursue changes in direction of the alternating current and create heat to the point of dessication—hence, the term “thermal ablation.” In contrast to electrocautery, the primary source of heat is the tissue around the radiofrequency electrode.

RFA has emerged as a safe, easy, and predictable technique for thermal ablation in the liver, kidney, heart, prostate, breast, brain, lung, lymph nodes, thyroid and parathyroid glands, nerve ganglia, and bone (Fig. 5). In the past 2 decades, interest in the application of RFA for the treatment of bone primary or metastatic diseases has increased. The new imaging modalities, able to locate and define musculoskeletal lesions using CT has made it possible for RFA to become a viable option for treating malignant lesions particularly in nonresectable and deep-seated metastases such as pelvis and particularly spine.

RFA creates necrotic tissue in a targeted area via the application of heat that induces tissue coagulation. Alternated current is sent through an electrode into the target tissue causing local ionic agitation, creating friction that, in turn, generates heat; consequent resistive heating produce cell death. The necrotizing effect of heating decreases in proportion to the fourth power of the distance from the tip of the electrode thus limiting the effective size of the lesion generated by the technique. Usually is accepted that temperature >50°C applied for 4 to 8 minutes can produce cell death. However, if temperature exceeds 100°C, boiling and vaporization of the surrounding tissue can increase local impedance to further current limiting the effective zone tissue. In contrast to electrochemotherapy, RFA can be used also for spine metastases, with extreme caution to avoid damaging spinal cord and nerves. Literature review report good results (pain relief) ranging from 75% to 95%. RFA is limited by the proximity of the metastases to neurological structures to avoid major neurological injury, and large lesions of weight-bearing bones to avoid fracture by irreversible ablation of the bone.
The application of ultrasound in clinics is no longer limited to diagnosis. HIFU is being promoted as a safe and the only completely noninvasive and extracorporeal method to treat primary solid tumors and metastatic bone disease. The key of HIFU treatment is to deliver the energy required to raise the tissue temperature to a cytotoxic level sufficiently fast such that the tissue vasculature does not have a significant effect on the extent of cell killing. The first therapeutic trial of high-intensity ultrasound beams was carried out in 1942.

**Technique**

HIFU devices for clinical use fall into 3 main categories: extracorporeal, transrectal, and interstitial. Extracorporeal transducers are used for targeting organs that are...
readily accessible through an acoustic window on the skin, whereas transrectal devices are used for the treatment of the prostate and interstitial probes being developed for the treatment of biliary duct and esophageal tumors.\textsuperscript{65} HIFU relies on the same principles as conventional ultrasound. The time-averaged intensities of typical diagnostic ultrasound (B-mode, pulsed, or continuous Doppler) can be up to 720 mW/cm\textsuperscript{2} according to the US FDA regulations. In contrast, the intensity of HIFU in the focal region is about several orders higher, 100 to 10,000 W/cm\textsuperscript{2}, with peak compression pressures of up to 70 MPa, and peak rarefaction pressures up to 20 MPa.

Two main mechanisms are involved in the HIFU ablation: a thermal effect and a mechanical effect. The thermal effect of HIFU is heat generation due to absorption of the acoustic energy with a rapid elevation of temperature in the local tissue. Tissue temperature elevated to >60°C in 1 second will generally lead to instantaneous and irreversible cell death via coagulation necrosis in most tissues, which is the primary mechanism for tumor cell destruction in HIFU therapy. Ultrasound beam focusing results in high intensities only at a specific location within a small volume (eg, about 1 mm in diameter and about 10 mm in length), which minimizes the potential for thermal damage to tissue outside the focal region. As the thermal mechanism is better understood and its effect is easier to control, it is preferred in tissue ablation.\textsuperscript{66}

**Results**

HIFU has the following advantages that justify research efforts: pain is minimized (Fig. 6); the procedure cost is low as compared with traditional surgery; there are no remaining scars; recovery is faster than with traditional surgical methods; if any hemorrhage occurs, ultrasound has the potential to stop the bleeding; the therapy can be repeated, theoretically, an infinite number of times because there is no dose limit; there is no ionizing radiation from MRI and diagnostic ultrasound, as opposed to other systems that are guided by radiographs; and maintenance of the system is low.\textsuperscript{65} HIFU can target bone tissues and induce necrosis of osteocytes in normal rabbits.\textsuperscript{69} In the targeted region, the destruction of endothelium cells of microvessels and thrombosis was readily detected, suggesting that HIFU could potentially prevent hematogenous dissemination of the tumor cells.\textsuperscript{70} The treatable diameters of bone tumors increase with the absorption ratio of bone marrow to tumor, acoustic window of surface skin, and diameter of bone, but decrease with muscle depth and specific absorption rate ratio of the bone tumor to the surface skin, bone marrow, and bone.\textsuperscript{71}

The optimal driving frequency depends on tumor depth, ultrasound absorption of bone marrow, and bone diameter, but was independent of the acoustic window area and specific absorption rate ratio of the bone.\textsuperscript{71} In a study, 96 patients with bone tumors have been successfully treated with HIFU; there were patients with primary bone tumors and bone metastases.\textsuperscript{72,73} All treated regions after HIFU had no intensification and there was an even, thin intensification rim around the region. In bone scan, disappearance of radioactive uptake was found and a radioactive cold region was produced, suggesting complete inactivation of the tumor foci. After an average follow-up of 23.1 months, no local recurrence was found in any of the cases, which shows that HIFU can be an effective stand-alone therapy to manage malignant bone tumors.\textsuperscript{72,73} Although in its infancy, HIFU appears to be a safe, noninvasive promising treatment approach for cancer patients with bone metastases.

**PALLIATION BASED ON METASTATIC LOCATION**

The spine is the most common site of bone metastases. Cancer patients with metastatic spine disease often present with a variety of symptoms requiring emergent treatment to preserve function. Common clinical features include pain from spinal instability, pathologic fractures, and neurological symptoms. Approximately 20% of these patients present with metastatic spinal cord compression.\textsuperscript{74} Treatment options in patients with metastatic spine disease are mostly aimed at palliation. Palliative treatment of metastatic bone disease of the spine is diverse. Analgesics, chemotherapy, corticosteroids, bisphosphonates, and denosumab may be used to treat cancer-related pain. Radiation therapy is an established means of achieving analgesia for spinal metastases, and may also reduce radiation-sensitive tumors; it remains the gold standard of palliative treatment for patients with metastatic spine disease, and is often used in combination with adjuvant medical treatments and surgery.\textsuperscript{75} After radiation therapy, approximately 60% of patients have decreased tumor-related spinal pain, whereas 23% to 35% experience complete pain relief. In cases of persistent or recurrent spinal pain, the patients can tolerate retreatment with palliative radiation therapy without any significant risk for increased spinal cord toxicity, but with a significantly higher risk for subsequent pathologic fracture.\textsuperscript{76} Surgery is indicated only if the anticipated improvement in quality of life outweighs the risks. Considerations in decision making for surgical treatment of spinal metastases are life span of the patient, general medical condition, number of spinal levels involved, age, cancer type, and radiation status. Extensive decompression and circumferential fusion have been associated with improved outcome including ambulation and quality of life.\textsuperscript{77,78}

The pelvis is the second most common site of bone metastases after the spine. Pain, bone destruction causing mechanical instability, and pathologic fractures are the most common manifestations.\textsuperscript{79} Treatment is mostly aimed at palliation. Traditional treatments for pelvic metastases include surgery and external-beam radiation therapy.\textsuperscript{80} Novel palliative adjunctive treatments for metastatic bone disease of the pelvis include selective embolization, cementoplasty, RFA, and electrochemotherapy.\textsuperscript{7,81–83} If bone destruction is limited, or the metastatic lesion is small and difficult to access, analgesics, radiation therapy, chemotherapy, bisphosphonates, embolization, RFA, and electrochemotherapy can be considered.\textsuperscript{5,82} In contrast, if there is extensive bone destruction, diffuse involvement of the pelvis, impending or existing pelvic discontinuity, and periacetabular metastases, surgical treatment is necessary.\textsuperscript{80}

The objective of surgery for pelvic metastases is directed at preserving hip function and palliation by cementoplasty or resection and total joint reconstruction when the acetabulum is involved. Lesions of the hemipelvis not directly involving the hip joint, pathologic fractures sustained through an area of the pelvis other than the acetabulum, and avulsion fractures of the anterior superior/inferior iliac spines, iliac crest, and pubic rami seldom require surgical stabilization and reconstruction because pelvic stability is maintained.\textsuperscript{80} In our practice, to avoid reconstruction-related complications, we do not routinely perform complex reconstruction procedures in cancer.
patients with pelvic metastases treated by resection. We believe that reconstruction of the pelvis adds complexity to surgery that inherently has a high associated complication rate. We perform preoperative embolization in all patients with hypervascular tumors to reduce intraoperative blood loss. Electrochemotherapy may be used for metastases of the sacrum and pelvis for pain relief and local tumor control in patients where radiation therapy was no more effective such as after previous treatment or scarce tumors sensitivity, and in cases where surgical treatment is debatable or difficult to perform such as with deep-seated or very small lesions.

The most common site of long bone metastatic disease is the femur followed by the humerus; the proximal parts of the bones are most likely to be affected. Acrometastases that is metastases distal to the elbow and knee are rare. Long bone metastases are a major clinical concern and cause severe pain, fractures, reduced mobility, and significant deterioration of quality of life. Ten percent to 30% of the patients with long bone metastatic disease will experience a pathologic fracture. The overall union rate for these fractures can be as low as 35% of the cases, whereas in lung cancer patients, fracture healing rarely occurs. Even when healing is possible, it is often delayed. In patients

FIGURE 6. Radiograph (A) and axial magnetic resonance (MR) imaging (B) of the pelvis of a 64-year-old man with metastatic renal cancer. C, Axial MR imaging of the pelvis 6 months after high-intensity focused ultrasound. The patient is pain free with limited range of motion of the right hip.
with pathologic fractures in long bone metastases, determining prognosis and expected survival is important to establish treatment. Patients with longer expected survival require a more aggressive treatment. In contrast, those with shorter expected survival may benefit from a less aggressive, less morbid treatment. As most of these patients have limited life expectancy, the goals of treatment should be fracture stabilization, pain relief, early mobilization and restoration of limb function and weight-bearing, minimal surgical morbidity and perioperative complications, and ease of nursing care. Radiation therapy and surgical stabilization is a standard of care for localized pain caused by long bone metastases. Palliative surgical techniques include cementoplasty, RFA, and electrochemotherapy. However, the risk of pathologic fracture is high when percutaneous treatments are solely performed in a long bone without internal fixation. Moreover, RFA of tumor lesions <3 cm in diameter results in considerable necrosis but this phenomenon decreases drastically for diameters >3 cm. Therefore, prediction of impending pathologic fractures in patients with metastatic bone disease and rigid fixation or reconstruction of sustained fractures is important.

In the lower extremities, the long bones are weight-bearing and require rigid fixation to maintain ambulation of the patients with bone metastasis. In the upper extremity, closed intramedullary fixation, with or without percutaneous treatments is the treatment of choice for long bone metastatic disease. Conservative therapy may be an alternative in the upper extremities, although nonoperative treatment of pathologic fractures rarely leads to pain relief or return of function. Closed intramedullary fixation, supports the concept of minimal surgical morbidity over open reduction and internal fixation or megaprosthetic reconstruction, as the surgical technique is less aggressive, produces less morbidity, and facilitates rehabilitation. Closed intramedullary nailing is feasible in the presence of minimal bone destruction and intact segments of the long bone proximal and distal to the fracture. Reconstruction nails should be preferred in all cases to prophylactically stabilize the neck of femur and intertrochanteric proximal femoral region. Wide resection is justified for solitary metastasis, “favorable” tumor histotype, good general condition, and long free interval from treatment of primary cancer. In addition, metastatic disease in the proximal or distal femur or the proximal humerus, especially those involving the joint surface, are often best treated with wide resection and arthroplasty. However, in many cases, surgical treatment is intended for palliation. In this setting, minimizing the morbidity associated with an orthopedic procedure is important. In patients with large areas of bone destruction, internal fixation can be combined with palliative treatments such as cementoplasty, RFA, and electrochemotherapy for additional mechanical stability, pain control, and local tumor suppression. External-beam radiation therapy is necessary to prevent progressive bone destruction and loss of fixation following surgical treatment of patients with radiosensitive tumors. However, although local progression may be inhibited by radiation therapy in radiosensitive tumors, the risk of radiation-induced skeletal complications such as stress fractures and nonunions increases. Electrochemotherapy may be used on patients with long bone metastatic disease for pain relief and local tumor control in patients where radiation therapy was no more effective such as after previous treatment or scarce tumors sensitivity, and in cases where surgical treatment is debatable or difficult to perform.

**AUTHORS’ COMMENTARY**

On the basis of our experience from management of tumor patients, we propose a treatment algorithm that would be helpful for decision making and treatment of patients with metastatic bone disease (Fig. 7). Treatment decision in these patients requires complete staging, biopsy,..
and oncolgical principles. The goals of palliative treatment are pain control, prevention and treatment of fractures, maintenance of independence and prevention of tumor progression, and improvement of quality of remaining life. Initial management should include administration or optimization of analgesics dosage. A variety of pain medications are available for pain management of patients with metastatic bone disease, including opioids, nonsteroidal anti-inflammatory drugs, steroids, bisphosphonates, and denosumab. Chemotherapy may be administered depending on the primary tumor’s histology; combined chemotherapy and bisphosphonates is effective for treating some patients, especially those with multiple myeloma or breast cancer. Radiation therapy remains the most common treatment for most bone cancers. We consider most metastatic bone lesions hypervascular; some metastatic lesions such as renal and thyroid metastases are highly hypervascular. Therefore, we perform selective embolization with a permanent embolic agent in almost all our patients with bone metastases. If the patient already has severe symptoms of bone metastases, successful treatment is also less likely. In these patients, we opt for repeat radiation therapy (if applicable) and embolization, or perform RFA and electrochemotherapy.

Orthopedic surgeons should be involved early to treat an impending pathologic fractures to keep a limb functional and the spine stable. We perform surgical treatment in patients with metastatic bone disease of the extremities in cases with persistent pain refractory to medical therapy, tumors with poor radioisotope uptake, spinal instability with or without neural compression. We perform surgical treatment in patients with metastatic bone disease of the spine and epidural spinal cord compression in cases with unknown primary tumor, recurrence after radiation therapy, progression of neurological deficits while on radiation therapy, spinal instability, severe pain unresponsive to medical treatments, and no total paraplegia for >48 hours. Surgical treatment for metastases of the pelvis should be aimed for palliation; there is rarely an indication for wide en bloc resection for solitary bone metastases such as from renal or thyroid cancer without extraskeletal metastases. When periacetabular bone loss is minimal, curettage and cementation may be all that is required to control local disease, relapse pain, and restore function. When the lesion is small but causes destruction of the hip joint, a hip replacement operation should be performed. Initial management for pathologic fractures of the long bones should include cast immobilization or external fixation to avoid tumor-cell dissemination. Primary tumor’s histology, response to chemotherapy and radiation therapy, and fracture union are the most significant predictive factors for overall survival and local disease control. Fracture displacement and type of stabilization do not significantly affect the outcome. By using these management guidelines we aim for improved cancer management, and patients’ survival and quality of life.

REFERENCES


eneous image-guided radiofrequency ablation of painful meta


