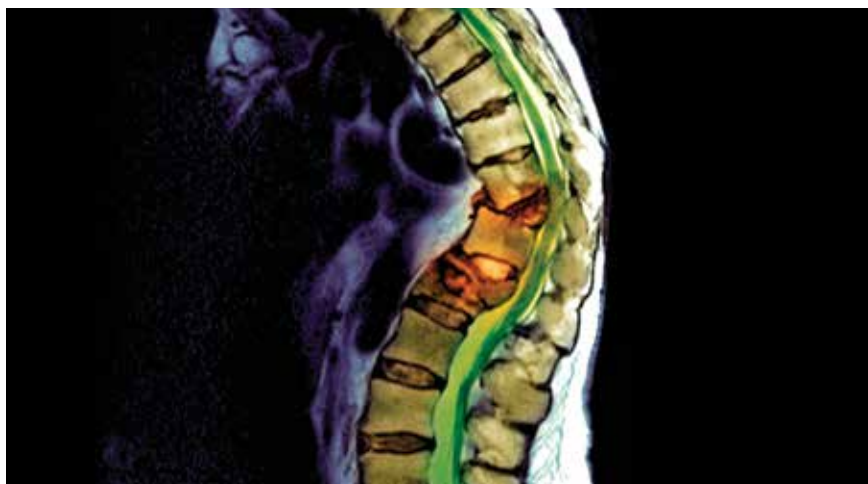


RADIATION & YOUR PATIENT



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Colored MRI scan showing metastasis to the bone (yellow) in the spine of a 70-year-old woman with primary cancer of the breast.

Using palliative radiotherapy to relieve bone metastasis pain

Bryant Furlow

With increasing survival times among cancer patients, the management of metastatic bone tumors and their recurrence is an increasingly common challenge. Recent studies and evidence-based reviews support single-dose palliative radiotherapy, which reduces the physical burdens of multifraction regimens followed, upon recurrence, with re-irradiation or tumor ablation using emerging treatment modalities such as image-guided ultrasound.

Bone is the third most frequent site for metastatic tumors, after the lungs

and the liver.¹ Bone metastases represent the single most frequent cause of pain among cancer patients; often excruciating and debilitating, it commonly leads to a profound decrease in quality of life during cancer patients' final months and weeks of life.^{2,3} Prognosis among patients with bone metastases can vary markedly. Median lung cancer survival times are shorter than 6 months, whereas median prostate cancer survival times are as long as 40 months.⁴

Bone metastases can be osteolytic (bone-destroying), osteoblastic, or mixed.² When spinal compression or pathogenic fractures result, metastases are said to be *complicated*. Common complications include pathogenic bone fractures, hypercalcemia, and spinal cord compression.³ Treatment includes bisphosphonates for osteoblastic or mixed bone tumors, and corticosteroids and surgery for pathogenic fractures.^{2,4} Denosumab (Prolia, Xgeva) is approved for prevention of fractures in patients with bone metastases.⁴ Bone-seeking radiopharmaceuticals such as Sr-89, Sm-153, and Re-186 also show

promise as a palliative modality for painful bone metastases.^{5,6}

But external-beam radiotherapy (EBRT) remains the gold standard for metastatic bone tumor palliation, particularly for uncomplicated tumors, among patients who are experiencing bone pain.³ However, justification of palliative EBRT for asymptomatic bone metastases is controversial.⁷ EBRT can improve function and reduce the need for analgesics (which are not always effective for bone tumor pain). Not surprisingly, patients whose pain is relieved by radiotherapy enjoy better quality of life.⁸

SINGLE VS MULTIPLE DOSE FRACTIONS

Numerous studies have shown single-fraction radiotherapy is as effective as multifraction treatments, but doses and fractionation schedules continue to vary among treatment facilities.^{1,3,9} In 2009, researchers in Canada and the United States reported that most radiation oncologists prescribed multiple radiation dose fractions for palliation of metastatic bone pain.⁹ Whether multiple-dose treatments are justified in most cases of uncompli-

There may simply be a threshold dose at which pain relief is achieved.

cated bone tumor pain is questionable, given the efficacy of single-dose treatments and the additional costs and physical burdens of multiple-fraction regimens, particularly for elderly patients.¹⁰

In 2011, the American Society for Radiation Oncology (ASTRO) released evidence-based treatment guidelines for

palliative radiotherapy of metastatic bone tumors.³ The guidelines, based on a systematic review of 25 randomized clinical trials, 20 single-armed prospective studies, and four meta-analyses, conclude that safe and effective EBRT can be delivered in a single 8-Gy dose fraction.³

A subsequent 2013 systematic review of 26 randomized controlled clinical trials—the first published systematic review of data on the relative efficacy of different EBRT doses—concluded that “8 Gy should be the standard dose against which future treatments are compared due to its reproducible pain response rate and its established safe profile.”¹¹ But the authors were quick to note that the research literature does not include enough dose variation for a great enough number of patients to quantify a dose/response relationship between single-fraction radiation dose and efficacy of bone tumor pain relief.¹¹ Although the available research literature illustrates that a single dose of 8 Gy is clearly superior to 4 Gy, the optimal dose for bone pain relief is yet to be established.¹¹ Indeed, a dose/response relationship might not exist, the authors note; there may simply be a threshold dose between 4 Gy and 8 Gy at which pain relief is achieved but higher doses offer no additional improvement.¹¹

International guidelines for palliative radiotherapy clinical trials have also been promulgated, which might help answer open questions about dosing. If widely adopted, the guidelines will promote consistent methodologies and endpoints, and facilitate future evidence-based reviews and interpretations of the clinical trial literature.¹²

RE-IRRADIATION

Particularly with improving survival times for cancer patients, re-irradiation is an increasingly important consideration. Eight percent to 42% of patients will undergo re-irradiation following palliative bone radiotherapy.¹³ No

prospective clinical studies of re-irradiation outcomes have been published, but perhaps not surprisingly, single-dose palliative radiotherapy appears to require re-irradiation more frequently due to nonresponsive or recurring metastatic bone tumors than does multi-fraction radiotherapy regimens.¹³

A systematic review of 10 published studies, found that overall, 20% of clinical trial participants undergo re-irradiation, and that pain alleviation was achieved in only 58% of those

Two new treatments are microwave tumor ablation and MRIGFUS.

patients.¹³ Forty percent of patients represented in the review did not benefit from re-irradiation.¹³ Additional studies are clearly needed, but based on the three reviewed studies that included adverse events data, re-irradiation-associated toxicities include mostly mild (grade 1 or 2) nausea, vomiting, and diarrhea and severe fatigue.¹³

When bone metastases or their recurrence are widespread throughout the skeleton, systematic administration of bone-seeking radionuclides, bisphosphonates, or denosumab are appropriate.¹³ But for localized, nonresponding or recurrent metastatic bone pain, the authors find a focal approach seems more suitable.¹³ “Options include more focused radiotherapy, such as stereotactic body radiotherapy (SBRT) for spinal metastases, as well as image-guided therapies,” said the authors.

OTHER EMERGING MODALITIES

Radioresistant tumor recurrence frequently precludes effective

re-irradiation, highlighting the need for alternative modalities for bone tumor palliation. Newer treatment modalities that might help patients for whom radiotherapy is no longer viable are entering the clinic.

Two relatively new treatments are microwave tumor ablation and magnetic resonance imaging (MRI)-guided focused ultrasound ablation (MRIGFUS), a form of high-intensity focused ultrasound (HIFU).¹⁴ In 2012, the FDA approved MRIGFUS for bone metastasis palliation in patients whose tumors do not respond to or who are not candidates for external-beam radiotherapeutic palliation.¹⁴ ■

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