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Special Report

ACR Appropriateness Criteria® Non-Spine Bone Metastases

Edward Y. Kim, MD,[1] Tobias R. Chapman, MD,[1] Samuel Ryu, MD,[2] Eric L. Chang, MD,[3] Nicholas Galanopoulos, MD,[4] Joshua Jones, MD,[5] Charlotte D. Kubicky, MD, PhD,[6] Charles P. Lee, MD,[7] Bin S. Teh, MD,[8] Bryan J. Traughber, MD,[9] Catherine Van Poznak, MD,[10] Andrew D. Vassil, MD,[11] Kristy Weber, MD,[12] and Simon Shek-Man Lo, MB, ChB[9]; Expert Panel on Radiation Oncology–Bone Metastases

Abstract

Bone metastases are a common clinical problem, affecting many types of cancer patients. The presence of tumor in bone can cause significant morbidity including pain, neurological dysfunction, hypercalcemia, and pathological fracture leading to functional loss. The optimal treatment of a patient with bone metastases depends on many factors, including evaluation of the patient's goals of care, performance status, mechanical stability of the affected bone, life expectancy, and overall extent of disease. Treatment options may include radiotherapy, systemic therapies, surgical stabilization, medical pain management, and radiopharmaceuticals. Ideal management of bone metastases requires a coordinated multidisciplinary approach among diagnostic radiologists, radiation oncologists, medical oncologists, orthopedic surgeons, pain specialists, physiatrists, and palliative care specialists. The American College of Radiology Appropriateness Criteria® are evidence-based guidelines for specific clinical conditions that are reviewed every 3 years by a multidisciplinary expert panel. The guidelines development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances where evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.

Introduction

Bone is a common site of metastasis, affecting patients with a wide variety of malignancies including breast, prostate, lung, colorectal, bladder, endometrial, thyroid, kidney, myeloma, and melanoma. The presence of tumor in bone can cause significant morbidity including pain, neurological dysfunction, hypercalcemia, and pathological fracture leading to significant functional loss. The optimal treatment of a patient with bone metastases depends on many factors, including evaluation of the patient's goals of care, performance status, mechanical stability of the affected bone, life expectancy, and overall extent of disease. Both osteolytic and osteoblastic lesions may be associated with pain and risk of fracture. Management decisions frequently involve collaboration among several types of specialists, including diagnostic radiologists, radiation oncologists, medical oncologists, surgeons, pain medicine specialists, physiatrists, and palliative care professionals. Similar to the approaches used for patients treated with curative intent, optimal management of patients with bone metastases requires multidisciplinary consideration of localized therapies such as surgery and external beam radiation therapy (EBRT) with systemic therapies including pain medications, chemotherapy, hormonal therapy (HT), osteoclast inhibitors (OI), and radiopharmaceuticals.[1–5]

[1]University of Washington, Seattle, Washington.
[2]Stony Brook University School of Medicine, Stony Brook, New York.
[3]University of Southern California-Keck School of Medicine, Los Angeles, California.
[4]University Hospitals of Cleveland, Cleveland, Ohio.
[5]University of Pennsylvania Perelman Center, Philadelphia, Pennsylvania.
[6]Oregon Health & Science University, Portland Oregon.
[7]Texas Oncology, Flower Mound and Carrollton, Texas.
[8]The Methodist Hospital, Houston, Texas.
[9]University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, Ohio.
[10]University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan.
[11]Cleveland Clinic, Strongsville, Ohio.
[12]Department of Orthopedic Surgery, University of Pennsylvania, Philadelphia, Pennsylvania.
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Oftentimes, patients who present with multifocal bone metastases are treated first with medical therapies including narcotics, chemotherapy, HT, bisphosphonates, radiopharmaceuticals, and RANK ligand inhibitors. EBRT is usually reserved for when a specific metastatic lesion causes significant local symptoms such as pain or creates a risk for pathological fracture or neurological injury. Surgical stabilization can treat or prevent the morbidity of a pathological fracture, particularly in weight-bearing bones. In addition, the alpha-emitting radiopharmaceutical therapy, radium 223 dichloride, has a place in the management of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease.[6,7]

Variant 1 Discussion

This patient has newly diagnosed metastatic disease at a single site (femur), an excellent performance status, and has not previously received systemic therapy. Systemic therapy (including biologic agents, chemotherapy, and OI) will be critical for systemic disease control. However, he is at elevated risk of developing pathological fracture in the near future and would benefit from immediate attention to the femoral lesion.

The most useful means of predicting the risk for pathological fracture includes evaluation by a published scoring system based on anatomical site, degree of pain, type of lesion (blastic, mixed, lytic), and tumor size.[8] Another simplified method of predicting pathological fracture in the femur describes an elevated risk in lesions with >3 cm cortical involvement.[9]

This patient should be evaluated by an orthopedic surgeon for consideration of surgical stabilization of the femur. If he undergoes surgical stabilization, postoperative radiotherapy should be considered. If he does not undergo surgical stabilization, then immediate radiotherapy is indicated. The goals of therapy would be to control pain as well as preserve ambulatory function.

Radiation can be delivered to this site most efficiently through parallel opposed anterior and posterior fields. A strip of skin and soft tissue, as large as possible, should be spared to reduce the risk of long-term lower-extremity lymphedema, which can be associated with full-circumference extremity radiation.

This patient also has oligometastatic disease. The optimal management of oligometastases is an active area of research. Investigations comparing site-specific localized therapy with a more systemic approach with or without localized therapy are ongoing. Some have argued that patients with minimal sites of bone-only metastatic disease (deemed ''oligometastatic'') from certain disease may be treated with curative intent, although the data to confirm that stance are still to be accrued.[10]

Single-fraction radiotherapy (8 Gy $\times$ 1), when compared with higher-dose multifraction regimens, has been associated with a higher risk of postradiation pathological fracture in femoral metastases. If this patient does not undergo surgical stabilization, then a higher-dose multifraction regimen would be reasonable.[9] Local therapy should be followed by systemic therapy including consideration of OI. In light of the slight risk of jaw osteonecrosis associated with OI administration, a pretreatment dental evaluation to assess dentition and potential risk prior to OI use might be warranted (Table 1).

Variant 2 Discussion

This patient has a good performance status and multiple sites of metastatic disease, but has a symptomatic lesion in a non–weight-bearing bone. This patient has a life expectancy that may be measured in years. This patient (as all patients) should receive appropriate analgesic therapy as a first-line treatment to provide rapid relief.

In general, the setup and prescription points for treatment should follow those outlined by the international consensus on palliative radiotherapy endpoints for future clinical trials, which were updated recently.[11] Fluoroscopic simulation, computed tomography (CT) simulation, and clinical simulation are all acceptable methods for planning radiation fields. There are no data to suggest that highly conformal therapy with intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), proton therapy, or brachytherapy would improve the outcome for this patient.

EBRT provides at least partial pain relief in 50% to 80% of patients, and most series suggest a rate of complete pain relief in about one-third of patients.[12] Although a recent international survey showed 101 different dose schedules in common use for treating painful bone metastases with EBRT, the rates of pain relief are equivalent for fractionation schemes including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction.[2,13] Single-fraction treatment optimizes patient convenience and reduces acute side effects but is associated with an approximate 20% rate of retreatment to the same site compared with an 8% retreatment rate with the more prolonged courses.[12–14]

Due to the presence of multifocal disease, systemic therapy options should be explored, and current practice patterns also should include consideration of the use of OI. If both palliative radiotherapy and palliative systemic chemotherapy are to be delivered to this patient, they should be given sequentially rather than concurrently. OI have the ability to decrease the risk of skeletal-related events (fracture, need for surgery or radiation to bone, spinal cord compression, and hypercalcemia of malignancy) as well as the ability to decrease pain from bone metastases and improve quality of life in patients with certain disease histologies.[15] OI therapy is an adjunctive therapy to radiation. In addition, it may alleviate metastatic bone pain, and it is routinely administered indefinitely.[16] Inhibiting osteoclast activity does not appear to impart a survival advantage. Recognized effects of the toxicities of potent OI include renal dysfunction (with intravenous bisphosphonates), hypocalcemia, and osteonecrosis of the jaw (Table 2).

Variant 3 Discussion

This patient has pain at a site that has been previously irradiated. She had initial pain relief with treatment. Available data from multiple smaller, retrospective studies suggest that retreatment with EBRT may provide a reasonable chance of pain relief in 33% to 84% of patients.[17,18] A recent meta-analysis of 10 studies, including data from 2694 patients, estimated pain response in 58% of patients who received reirradiation for painful bone metastases.[19] A recently completed international randomized prospective Phase III trial

Table 1. Clinical Condition: Non-Spine Bone Metastases, Variant 1

52-year-old man with a history of a T1N0M0 non–small-cell lung cancer. Two years after lobectomy, he is found to have a painful metastasis in the right femoral neck. The lesion is 3.5 cm in size with >50% erosion of the medial bone cortex. Karnofsky Performance Status (KPS) 90. No other metastatic disease is found. He has had no previous therapy other than lobectomy.

Treatment	*Rating*	*Comments*
Surgical intervention followed by EBRT, then systemic therapy	9	
Surgical intervention followed by systemic therapy alone	5	
EBRT alone	3	This treatment is associated with a high risk of pathological fracture without prophylactic internal fixation, as evaluated by certain criteria.[8]
EBRT followed by systemic therapy	3	This treatment is associated with a high risk of pathological fracture without prophylactic internal fixation, as evaluated by certain criteria.[8]
Surgical intervention alone	3	
Hospice after treatment of the femur	2	
Systemic therapy alone (may include biologic agents, bisphosphonates, and/or chemotherapy)	2	
Observation	1	
Direct hospice placement	1	
Radiation therapy dose		
8 Gy/1 fraction	4	
20 Gy/5 fractions	5	
24 Gy/6 fractions	6	A high biologically effective dose of radiation may be beneficial for this patient with an excellent KPS and oligometastatic disease.
30 Gy/10 fractions	8	
35 Gy/14 fractions	4	
40 Gy/20 fractions	4	
Treatment technique		
Clinical simulation	5	
Fluoroscopic simulation or 2-D RT	7	
CT simulation	8	
AP/PA	8	
3-D CRT	8	
IMRT	3	
SBRT	2	
Proton therapy to the bone metastasis	2	

Rating Scale: 1,2,3 usually not appropriate; 4,5,6 may be appropriate; 7,8,9 usually appropriate.
AP/PA, anteroposterior/posteroanterior; CRT, conformal radiation therapy; CT, computed tomography; EBRT, external beam radiation therapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

compared a single-fraction (8 Gy x 1) reirradiation schedule with a multiple-fraction regimen (20 Gy in 5 to 8 fractions) in 850 patients with previously irradiated bone metastases. The majority of patients had prostate, breast, or lung cancer. The single-fraction regimen was not inferior to the multiple-fraction regimen with respect to pain control assessment at 2 months. Acute toxicities were worse in the multiple-fraction arm.[20,21]

As in any case of reirradiation, care should be taken to avoid combined doses greater than the normal tissue tolerances of structures within the retreated volumes. The recurrence of pain in any long bone necessitates a reassessment of pathological fracture risk before delivering reirradiation. Treatment should be planned to spare a skin and soft-tissue strip to minimize the risk of developing late chronic upper extremity lymphedema. Fluoroscopic simulation, CT simulation, and clinical simulation are all acceptable methods for planning radiation fields. There are no data to suggest that highly conformal therapy with IMRT, SBRT, brachytherapy, or proton therapy would improve the outcome for this patient.

Systemic chemotherapy can be considered depending on the patient's previous exposure to chemotherapy and her tolerance of further therapy. This patient's disease has progressed on bisphosphonates, and RANK ligand inhibitors may be of use. If cytotoxic therapy is considered, it should be delivered sequentially with palliative radiotherapy rather than concurrently. Duration of radiation therapy should be weighed against the urgency of initiating a new line of systemic therapy. A shorter course of palliative reirradiation would potentially delay chemotherapy less than a longer treatment course.

The American Society of Clinical Oncology guidelines for the use of bone modifying agents in metastatic breast cancer recommend the use of OI, bisphosphonate or denosumab, be continued until there is evidence of substantial decline in the patient's clinical status.[16] These drugs may reduce the risk of

Table 2. Clinical Condition: Non-Spine Bone Metastases, Variant 2

62-year-old woman with estrogen-receptor positive/progesterone-receptor positive breast cancer, Her-2/neu non-amplified. She develops a painful lytic bone metastasis in the right humerus after 4 years of a single line of adjuvant hormonal therapy. There is minimal invasion of bone cortex, and the lesion is thought to have a low fracture risk per orthopedic surgery consult. Karnofsky Performance Status (KPS) is 90. Bone scan demonstrates a few other asymptomatic bone metastases.

Treatment	*Rating*	*Comments*
EBRT followed by systemic therapy	8	
Systemic therapy alone (hormonal therapy and bisphosphonates or RANK ligand inhibitor)	4	
EBRT alone	3	
Radiopharmaceuticals	2	
Surgical intervention	2	
Direct hospice placement	1	
Hospice after treatment of the humerus	1	
Radiation therapy dose		
8 Gy/1 fraction	8	
20 Gy/5 fractions	8	
24 Gy/6 fractions	8	
30 Gy/10 fractions	8	
35 Gy/14 fractions	5	
40 Gy/20 fractions	3	
Treatment technique		
Clinical simulation	5	
Fluoroscopic simulation or 2-D RT	7	
CT simulation	8	
AP/PA	8	
3-D CRT	8	
IMRT	2	
SBRT	2	
Proton therapy to the bone metastasis	2	

Rating Scale: 1,2,3 usually not appropriate; 4,5,6 may be appropriate; 7,8,9 usually appropriate.

AP/PA, anteroposterior/posteroanterior; CRT, conformal radiation therapy; CT, computed tomography; EBRT, external beam radiation therapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

Table 3. Clinical Condition: Non-Spine Bone Metastases, Variant 3

65-year-old woman with metastatic hormone-receptor positive breast cancer currently on hormonal and bisphosphonate therapy for skeletal-dominant metastatic disease. She received palliative radiation (30 Gy/10 fractions) to a painful lesion in the right humerus 3 years ago with good pain relief but now has recurrent pain at this site. Radiographs show a lytic lesion with no radiographic evidence of impending fracture. She has several other asymptomatic skeletal lesions and a new 1.5-cm lung metastasis.

Treatment	*Rating*	*Comments*
EBRT reirradiation to symptomatic lesion	8	
Consider changes to systemic therapy only	5	
Radiopharmaceuticals	3	
Surgical intervention	3	
Direct hospice placement	2	
Hospice after treatment of the humerus	2	
Radiation therapy dose		
8 Gy/1 fraction	8	
20 Gy/5 fractions	8	
24 Gy/6 fractions	8	
30 Gy/10 fractions	7	
35 Gy/14 fractions	5	
40 Gy/20 fractions	3	
Treatment technique		
Clinical simulation	5	
3-D CRT	8	
Fluoroscopic simulation or 2-D RT	8	
CT simulation	9	
AP/PA	8	
IMRT	2	
SBRT	2	
Proton therapy to the bone metastasis	2	

Rating Scale: 1,2,3 usually not appropriate; 4,5,6 may be appropriate; 7,8,9 usually appropriate.

AP/PA, anteroposterior/posteroanterior; CRT, conformal radiation therapy; CT, computed tomography; EBRT, external beam radiation therapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

subsequent skeletal-related events and may aid in controlling bone pain. It is of note that in the pooled analysis of the Phase III studies of denosumab versus zoledronic acid, denosumab demonstrated superiority in delaying the time to subsequent skeletal-related events with a relative risk of 0.82 (95% confidence interval [CI], 0.75 to 0.90), $p < 0.001$ (Table 3).[22]

Variant 4 Discussion

This patient has been heavily pretreated for metastatic prostate cancer and now has hormone-refractory disease. The patient may consider additional systemic therapy. As his bone metastases appear relatively symptomatic, sipuleucel-T is not a likely next step. Abiraterone/prednisone and enzalutamide may be considered options if not used already.[23–25] Note that enzalutamide is FDA approved for disease progression after docetaxel therapy. In addition, a clinical trial, cabozantinib, or mitoxantrone may be options for this individual depending on his goals of care, marrow reserve, and performance status.[25,26]

Although it may be technically possible to deliver EBRT to multiple symptomatic lesions, the patient's burden of disease suggests he may be a favorable candidate for radiopharmaceutical therapy. Multiple series have reported pain response rates ranging from 45% to 80% with samarium-153 or strontium-89.[27–29] An international prospective randomized trial of radium-223 versus placebo showed improvements in quality of life scores, decreased skeletal events, and improved overall survival with administration of radium-223.[7]

Table 4. Clinical Condition: Non-Spine Bone Metastases, Variant 4

66-year-old man with metastatic hormone-refractory prostate cancer. He has widespread osteoblastic skeletal disease with increasingly painful lesions in the lumbar spine, hips, and extremities. Prior therapy has included hormonal therapy, bisphosphonates, docetaxel chemotherapy, and EBRT to one of his painful hip lesions.

Treatment	*Rating*	*Comments*
Radiopharmaceuticals and EBRT to symptomatic lesions	8	
Radiopharmaceuticals	8	
EBRT to most symptomatic lesions	7	EBRT is an effective modality for pain relief of selected lesions, but the amount of bone marrow treated should be minimized to prevent compromising the patient's remaining systemic therapy options.
Direct hospice placement	5	
Changes to systemic therapy only	4	
Medical pain management only	4	
Radiation therapy dose (if EBRT used)		
8 Gy/1 fraction	8	
20 Gy/5 fractions	7	
24 Gy/6 fractions	7	
30 Gy/10 fractions	7	
35 Gy/14 fractions	4	
40 Gy/20 fractions	3	
Treatment technique (if EBRT used)		
Clinical simulation	5	
Fluoroscopic simulation or 2-D RT	7	
CT simulation	8	
3-D CRT	8	
IMRT	2	
SBRT	2	
Proton therapy to the bone metastasis	2	

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate.
CRT, conformal radiation therapy; CT, computed tomography; EBRT, external beam radiation therapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

The use of radiopharmaceuticals does not preclude the delivery of palliative EBRT. If this patient were to receive focused EBRT to painful lesions, it would be prudent to consider the volume of bone marrow within the treatment field given the potential for diffuse bone marrow suppression that has previously been reported with radiopharmaceuticals[29] (Table 4).

Variant 5 Discussion

This patient has severe pain from a single site of bone metastases with a functional performance status. This patient (as with all patients) should receive appropriate analgesic therapy as first-line treatment to provide rapid symptom relief. Systemic therapy for melanoma is an evolving field, but overall prognosis remains poor. Melanoma is traditionally considered less sensitive to conventionally fractionated radiotherapy.[30,31] The majority of studies evaluating radiotherapy for skeletal metastases consist of prostate, breast, and lung cancer patients.[20] There are inadequate data available to determine whether tumor histologies traditionally thought of as ''radioresistant'' respond equally well to palliative radiotherapy as other more traditionally ''radiosensitive'' histologies. The ability of melanoma cell lines to repair sublethal DNA damage suggests melanoma may be more sensitive to large doses per fraction or a hypofractionated course of therapy.

Skin and soft-tissue sparing techniques should be utilized. A single treatment would minimize the patient's time commitment, transportation requirements, and discomfort from being transferred on and off the treatment table.[32] Fluoroscopic simulation, CT simulation, and clinical simulation are all acceptable methods for planning radiation fields. Treatment with large fractions might be more likely to cause a temporary pain flare, but anti-inflammatory medications are capable of minimizing this effect.[33] There are no data to suggest that highly conformal therapy with IMRT, SBRT, brachytherapy, or proton therapy would improve the outcome for this patient (Table 5).

Summary

- EBRT successfully provides rapid palliative relief from painful bone metastases in most cases.
- The acute side effects of palliative EBRT are usually minimal and self-limiting, whereas long-term side effects are uncommon and may not be clinically relevant in a patient group with limited life expectancy.
- Radiotherapy is not commonly recommended for asymptomatic bone metastases that are not associated with a risk of pathological fracture as the primary goals of therapy are pain relief and functional preservation.
- Prospective randomized trials have proven equivalent pain relief with varied fractionation schemes, including 8 Gy in 1 fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, or 30 Gy in 10 fractions. Prolonged courses

Table 5. Clinical Condition: Non-Spine Bone Metastases, Variant 5

47-year-old man with a history of malignant melanoma, now with a painful metastatic lesion in the left scapula. Karnofsky Performance Status (KPS) is 70. He has had no prior therapy for metastatic disease. Staging scans show an asymptomatic 3-cm liver metastasis.

Treatment	*Rating*	*Comments*
EBRT and consideration of systemic therapy	8	
Systemic therapy alone	4	This patient may be a candidate for targeted therapies, but radiation offers rapid palliation of pain.
EBRT alone	3	
Hospice after treatment of the scapula metastasis	2	
Direct hospice placement	2	
Radiopharmaceuticals	2	
Radiation therapy dose		
8 Gy/1 fraction	8	
20 Gy/5 fractions	7	
24 Gy/6 fractions	8	
30 Gy/10 fractions	8	
30 Gy/5 fractions	8	
35 Gy/14 fractions	6	
40 Gy/20 fractions	3	
Treatment technique		
Clinical simulation	5	
Fluoroscopic simulation or 2-D RT	7	
CT simulation	8	
3-D CRT	8	
IMRT	2	
SBRT	2	
Proton therapy to the bone metastasis	2	

Rating Scale: 1,2,3 usually not appropriate; 4,5,6 may be appropriate; 7,8,9 usually appropriate.
CRT, conformal radiation therapy; CT, computed tomography; EBRT, external beam radiation therapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

are associated with a lower incidence of retreatment, although shorter courses maximize patient and caregiver convenience by reducing the number of trips to the radiation department.

- Patients who undergo surgical stabilization for impending or completed pathological fracture of a long bone may be treated with postoperative radiotherapy to 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction.
- Reirradiation with EBRT may be feasible and effective, although retreatment to sites including radiation-sensitive critical structures should include careful consideration of the cumulative radiation doses that may exceed normal tissue tolerance. Reirradiation with a single 8 Gy fraction is not inferior to multiple-fraction radiation and has less acute toxicity.
- Management of metastatic bone disease is palliative. A multidisciplinary team of care providers, including the palliative care team, should be available to the patient. Goals of care should be defined with the patient. Hospice referral should be considered if the life expectancy is 6 months or less, but this does not preclude the use of radiation for pain control.

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Address correspondence to:
Edward Y. Kim, MD
University of Washington
Radiation Oncology Department
Box 356043
Seattle, WA 98195-6043

E-mail: edykim@uw.edu
Reprints: publications@acr.org