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Special Report

# ACR Appropriateness Criteria® Non-Spine Bone Metastases

Expert Panel on Radiation Oncology–Bone Metastases: Stephen T. Lutz, M.D., M.S.,[1] Simon Shek-Man Lo, M.B., Ch.B.,[2] Eric L. Chang, M.D.,[3] Nicholas Galanopoulos, M.D.,[4] David D. Howell, M.D.,[5] Edward Y. Kim, M.D.,[6] Andre A. Konski, M.D.,[7] Neeta D. Pandit-Taskar, M.D.,[8] Samuel Ryu, M.D.,[9] Larry N. Silverman, M.D.,[10] Catherine Van Poznak, M.D.,[11] and Kristy L. Weber, M.D.[12]

**Abstract**

Bone is one of the most common sites of metastatic spread of malignancy, with possible deleterious effects including pain, hypercalcemia, and pathologic fracture. External beam radiotherapy (EBRT) remains the mainstay for treatment of painful bone metastases. EBRT may be combined with other local therapies like surgery or with systemic treatments like chemotherapy, hormonal therapy, osteoclast inhibitors, or radiopharmaceuticals. EBRT is not commonly recommended for patients with asymptomatic bone metastases unless they are associated with a risk of pathologic fracture. For those who do receive EBRT, appropriate fractionation schemes include 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or a single 8 Gy fraction. Single fraction treatment maximizes convenience, while fractionated treatment courses are associated with a lower incidence of retreatment. The appropriate postoperative dose fractionation following surgical stabilization is uncertain. Reirradiation with EBRT may be safe and provide pain relief, though retreatment might create side effect risks which warrant its use as part of a clinical trial. All patients with bone metastases should be considered for concurrent management by a palliative care team, with patients whose life expectancy is less than six months appropriate for hospice evaluation. The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every two years by a multidisciplinary expert panel. The guideline 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.

## Summary of Literature Review

### Introduction

Bone is one of the most common sites of metastatic spread of malignancy, and the presence of tumor in the bone can lead to pain, hypercalcemia, and pathologic fracture. The treatment of bone metastases is multidimensional and depends on many factors, including sites of metastases and extent of disease. Both osteocytes and osteoplastic lesions may be associated with pain and risk of fracture. Decisions on management frequently involve interdisciplinary care among several types of specialists, including radiologists, radiation

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oncologists, medical oncologists, orthopedic surgeons or neurosurgeons, pain medicine specialists, physiatrists, and palliative care professionals. When considering treatment options, one should weigh the risks and benefits profile of radiation therapy for any particular patient's circumstance, including performance status, comorbidities, and life expectancy. Similar to the approaches used with curative therapies combining chemotherapy and radiation, studies are needed that evaluate the combination, or sequencing, of localized therapies such as surgery and external beam radiotherapy (EBRT) with systemic therapies including chemotherapy, hormonal therapy (HT), osteoclast inhibitors (OI), and radiopharmaceuticals.[1–3]

Under current practice, systemic chemotherapy and/or HT and OI are frequently administered when asymptomatic bone metastases are first diagnosed. EBRT is usually delayed until the metastatic disease progresses and causes significant pain or creates a risk for pathological fracture or spinal cord compression. The use of radiopharmaceuticals is generally considered in a small fraction of patients with persistent multifocal sites of pain or recurrence of pain in a previously irradiated site.[4]

### Variant 1 Discussion

This patient has a good performance status, a life expectancy that may be estimated in years, and a single site of asymptomatic bone metastasis that does not pose an immediate risk for pathologic fracture. The most useful means of predicting the risk for pathologic fracture includes evaluation by a published scoring system.[5]

The optimal management of oligometastases is an active area of research. Investigations comparing site-specific localized therapy to 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") may be treated with curative intent, though the data to confirm that stance are still to be accrued.[6]

Outside of a clinical trial, there is no frank indication to treat this femoral neck lesion with EBRT, as it is not causing symptoms and there is no impending fracture. The use of an OI is considered a standard approach in this setting, though the optimal timing of treatment initiation has not been investigated. 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 (see Variant 1).

### Variant 2 Discussion

This patient has a good performance status but has a symptomatic lesion in a weight-bearing bone. Aside from the importance of optimizing pain control in the palliative setting, the pain associated with the right femoral neck lesion is a feature associated with an increased risk of fracture.[5,7] This patient (as all patients) should receive appropriate analgesic therapy as first line of treatment to provide expeditious relief. An assessment should be performed for risk of pathologic fracture and consideration for surgery, with some surgeons employing grading systems for impending fractures that measure variables such as age, pain score, location of the lesion, radiographic characteristics, and biochemical markers of bone metabolism.[7,8] If the patient does not require surgery and will be treated only with EBRT, she should undergo simulation and treatment planning, with radiation delivery through parallel opposed anterior and posterior fields. As large a strip of skin and soft tissue possible should be spared to reduce the risk of long-term lower-extremity lymphedema, which can be associated with full circumference extremity radiation.

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.[9,10] 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), or proton therapy would improve the outcome for this patient.

EBRT would be expected to palliate pain in this patient at a rate of 50%-80%, and the data suggest a rate of complete pain relief in about one-third of patients.[11] While 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.[2,12] Single-fraction treatment optimizes patient convenience and reduces acute side effects but is associated with about a 20% rate of retreatment to the same site compared to an 8% retreatment rate with the more prolonged courses.[11-13] For patients with femoral metastases not suitable for prophylactic fixation, a multiple-

Table 1. Variant 1. Prostate Cancer

62-year-old man with prostate cancer. Two years after surgical resection of prostate and adjuvant HT, rising PSA level found in routine follow-up. Asymptomatic bone metastasis in right femoral neck; lesion 1.5 cm in size; minimal invasion of bone cortex. Low fracture risk per orthopedic consult. KPS 90. No other metastatic disease. No previous HT, chemotherapy, or OI have been given.

| *Treatment* | *Rating* | *Comments* |
|---|---|---|
| HT alone | 7 | |
| OI | 6 | While the individual ratings spanned the two categories, the final rating reflects the panel's consensus. |
| EBRT and HT | 2 | |
| EBRT alone | 2 | |
| Chemotherapy alone | 2 | |
| Observation | 2 | |
| Radiopharmaceuticals | 2 | |
| Surgical intervention | 2 | |
| Hospice after treatment of the femur | 2 | |
| Direct hospice placement | 1 | |

**Rating scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

EBRT, external beam radiotherapy; HT, hormonal therapy; KPS, Karnofsky performance status; OI, osteoclast inhibitors; PSA, prostate-specific antigen.

fraction regimen would be more appropriate than a single 8 Gy fraction to reduce the risk of pathological facture.[14]

Due to the presence of multifocal disease, systemic chemotherapy options should be explored, and current practice patterns also would 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 has 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) and to decrease pain from bone metastases and improve quality of life in patients with certain disease histologies. OI therapy is an adjunctive therapy to radiation and an analgesic for metastatic bone pain and is routinely administered indefinitely.[15] Inhibiting osteoclast activity does not appear to impart a survival advantage. Recognized effects of the toxicities of potent OIs include renal dysfunction (with intravenous bisphosphonates), hypocalcemia, and osteonecrosis of the jaw (see Variant 2).

### Variant 3 Discussion

This patient presented with lytic disease in a weight-bearing bone, which led to pathologic fracture and necessitated surgical stabilization. He has minimal residual pain following surgery, but should receive postoperative EBRT with the dual goals of pain relief and local tumor control to limit the risk of future fracture. While there are no definitive data to suggest the most appropriate radiotherapy dose, 30 Gy in 10 fractions seems to be a reasonable option with the goal of eradicating microscopic residual disease. No reports exist regarding the use of single-fraction palliative EBRT in the postoperative setting. Treatment should be planned with initial simulation with radiation delivered through anterior and posterior fields with as large as possible skin and soft tissue strip spared to minimize the risk of long-term lower-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, or proton therapy would improve the outcome for this patient. The presence of systemic disease coupled with his reasonably good performance status suggests that systemic treatment should be considered (see Variant 3).

### Variant 4 Discussion

This patient has recurrent pain at a site that previously received palliative radiotherapy with good initial pain relief following treatment. The available data from several smaller, retrospective studies suggest that retreatment with EBRT may provide a reasonable chance for pain relief of 33%-84%, though the most appropriate dose fractionation scheme has not been determined.[16-21] Available studies reviewed provide little information about toxicity following reirradiation, so care should be taken to avoid combined doses greater than the normal tissue tolerances of structures within the retreated volumes. The tolerance of the brachial plexus must be taken into account in treating this patient. The recurrence of pain in any long bone necessitates a reassessment of pathologic fracture risk before delivering reirradiation. Treatment should be planned with initial simulation, with radiation delivered through anterior and posterior fields with as large as possible skin and soft tissue strip spared to minimize the risk of 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, 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 his tolerance of further dosing, though the presence of brain metastases and progressive lung metastases make palliative

Table 2. Variant 2. Non-Spine Bone Metastases

42-year-old woman with ER negative/PR negative breast cancer which overexpresses Her-2-neu. Patient developed a symptomatic lytic bone metastasis in right femoral neck; the metastasis was 1.5 cm in size; minimal invasion of bone cortex. Low fracture risk per orthopedic consult. KPS 90. Diffuse asymptomatic bone metastases noted on bone scan with rising CEA. No previous HT, chemotherapy, or OI have been given.

| *Treatment* | *Rating* | *Comments* |
|---|---|---|
| EBRT followed by chemotherapy | 8 | |
| EBRT followed by chemotherapy and OI | 8 | |
| Surgical intervention | 4 | |
| Chemotherapy alone | 3 | |
| EBRT alone | 3 | |
| Radiopharmaceuticals | 3 | |
| EBRT followed by chemotherapy and HT | 2 | |
| EBRT followed by chemotherapy and HT and OI | 2 | |
| HT alone | 2 | |
| Direct hospice placement | 2 | |
| Hospice after treatment of the femur | 2 | |
| **Radiation therapy dose** | | |
| 8 Gy/1 fraction | 5 | |
| 20 Gy/5 fractions | 8 | |
| 24 Gy/6 fractions | 8 | |
| 30 Gy/10 fractions | 8 | |
| 35 Gy/14 fractions | 5 | Shorter courses are preferred to prevent delay of systemic therapy. |
| 40 Gy/20 fractions | 2 | |
| **Treatment planning** | | |
| CT simulation | 8 | |
| Fluoroscopic simulation | 7 | |
| Clinical simulation | 5 | |
| Posterior field only | 2 | |
| Anterior-posterior fields | 8 | |
| SBRT | 2 | |
| IMRT | 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**

CEA, carcinoembryonic antigen; CT, computed tomography; EBRT, external beam radiotherapy; ER, estrogen receptor; HT, hormonal therapy; IMRT, intensity-modulated radiation therapy; OI, osteoclast inhibitors; PR, progesterone receptor; SBRT, stereotactic body radiation therapy.

Table 3. Variant 3. Non-Spine Bone Metastases
54-year-old man with multiple myeloma. He suffers a pathologic fracture of the diaphysis of the right femur and is now status post a surgical pinning procedure with minimal residual pain and good progress in physical rehabilitation. KPS 70. Skeletal survey reveals several other sites of asymptomatic lytic metastases. Has received Bortezomib, dexamethasone, and OI for the 18 months since diagnosis.

| *Treatment* | *Rating* | *Comments* |
|---|---|---|
| EBRT followed by chemotherapy | 8 | |
| OI as a component of treatment plan | 8 | |
| Chemotherapy alone | 5 | |
| EBRT alone | 3 | |
| Observation | 2 | |
| Radiopharmaceuticals | 2 | |
| Direct hospice placement | 2 | |
| Hospice after treatment of the femur | 2 | |
| **Radiation therapy dose** | | |
| 8 Gy/1 fraction | 8 | The relative lack of data in this circumstance led the panel to consider each of the first four fractionation schemes equally appropriate. |
| 20 Gy/5 fractions | 8 | |
| 24 Gy/6 fractions | 8 | |
| 30 Gy/10 fractions | 8 | |
| 35 Gy/14 fractions | 7 | |
| 40 Gy/20 fractions | 5 | Shorter courses are preferred to prevent delay of systemic therapy. |
| **Treatment planning** | | |
| CT simulation | 8 | |
| Fluoroscopic simulation | 7 | |
| Clinical simulation | 7 | |
| Posterior field only | 2 | |
| Anterior-posterior fields | 8 | |
| SBRT | 2 | |
| IMRT | 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**

CT, computed tomography; EBRT, external beam radiotherapy; KPS, Karnofsky performance status; OI, osteoclast inhibitors; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

Table 4. Variant 4. Non-Spine Bone Metastases
66-year-old man with metastatic non-small-cell lung cancer. Seven months status postpalliative radiotherapy to the proximal right humerus to 30 Gy in 10 fractions with good pain relief until the past two weeks. Now has recurrent pain at the previously treated site, though the humerus is not considered to be at risk for pathologic fracture. KPS 60. Stable brain metastases and progressive lung metastases. Has received carboplatin and paclitaxel for the past six months.

| *Treatment* | *Rating* | *Comments* |
|---|---|---|
| Hospice after treatment of the humerus | 8 | |
| EBRT followed by chemotherapy | 6 | |
| EBRT alone | 6 | While the individual ratings spanned the two categories, the final rating reflects the panel's consensus. |
| Direct hospice placement | 5 | |
| Chemotherapy alone | 4 | |
| OI as a component of treatment plan | 4 | |
| Observation | 3 | |
| Radiopharmaceuticals | 2 | |
| **Radiation therapy dose** | | |
| 8 Gy/1 fraction | 8 | |
| 20 Gy/5 fractions | 6 | |
| 24 Gy/6 fractions | 5 | |
| 30 Gy/10 fractions | 3 | |
| 35 Gy/14 fractions | 2 | |
| 40 Gy/20 fractions | 2 | |
| **Treatment planning** | | |
| CT simulation | 8 | |
| Fluoroscopic simulation | 7 | |
| Clinical simulation | 7 | |
| Posterior field only | 2 | |
| Anterior-posterior fields | 8 | |
| SBRT | 2 | |
| IMRT | 2 | |
| Proton therapy to the bone metastasis | 1 | |

**Rating scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

CT, computed tomography; EBRT, external beam radiotherapy; KPS, Karnofsky performance status; OI, osteoclast inhibitors; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

care or hospice admission reasonable options. A clinical trial that investigates reirradiation is available and should be considered to further define the appropriate use of radiotherapy in the setting of recurrent painful metastasis at a previously treated site.[22] (See Variant 4.)

### Variant 5 Discussion

This patient has severe pain from a single site of bone metastases with poor performance status and progressive visceral disease that suggests a very limited prognosis. This patient (as with all patients) should receive appropriate analgesic therapy as first line of treatment to provide expeditious relief. He should be treated with a hypofractionated course of radiotherapy to 8 Gy in a single fraction through anterior and posterior opposed fields. Skin and soft tissue sparing techniques should be considered, though the chance of survival long enough to manifest late toxicity is minimal. The single treatment minimizes his time commitment, transportation requirements, and discomfort from being transferred on and off the treatment table.[23] Fluoroscopic simulation, CT simulation, and clinical simulation are all

Table 5. Variant 5. Non-Spine Bone Metastases
47-year-old man with metastatic malignant melanoma. Unrelenting pain due to a lytic metastasis in the pubic ramus. KPS 30. Marked cachexia with progressive disease in the liver and para-aortic lymph nodes.

| *Treatment* | *Rating* | *Comments* |
|---|---|---|
| Hospice after treatment of the pubic bone | 8 | |
| Direct hospice placement | 7 | |
| EBRT alone | 7 | This choice does not preclude hospice referral. |
| EBRT and chemotherapy | 2 | |
| Chemotherapy alone | 2 | |
| Radiopharmaceuticals | 2 | |
| OI | 2 | |
| **Radiation therapy dose** | | |
| 8 Gy/1 fraction | 9 | |
| 20 Gy/5 fractions | 6 | Shorter courses are preferred to allow for hospice referral. |
| 24 Gy/6 fractions | 4 | |
| 30 Gy/10 fractions | 2 | |
| 35 Gy/14 fractions | 2 | |
| 40 Gy/20 fractions | 2 | |
| **Treatment planning** | | |
| CT simulation | 8 | |
| Fluoroscopic simulation | 8 | |
| Clinical simulation | 8 | |
| Posterior field only | 2 | |
| Anterior-posterior fields | 8 | |
| SBRT | 2 | |
| IMRT | 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**

CT, computed tomography; EBRT, external beam radiotherapy; KPS, Karnofsky performance status; OI, osteoclast inhibitors; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

acceptable methods for planning radiation fields. A single 8 Gy fraction might be more likely to cause a temporary pain flare, but antiinflammatory medications are capable of minimizing this effect.[24] There is no data to suggest that highly conformal therapy with IMRT, SBRT, or proton therapy would improve the outcome for this patient. He would benefit from direct hospice placement as well (see Variant 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, while long-term side effects are uncommon and often irrelevant 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 pathologic fracture.
- Prospective randomized trials have proven equivalent pain relief with varied fractionation schemes, including 8 Gy in one fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, or 30 Gy in 10 fractions. Prolonged courses are associated with a lower incidence of retreatment, while 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 pathologic 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, though retreatment to sites including radiation-sensitive critical structures may prove risky and should be performed only as part of a clinical trial if retreatment would lead to cumulative radiation doses in excess of normal tissue tolerance.
- Management of metastatic bone disease is palliative. A multidisciplinary team of care providers should be available to the patient, including the palliative care team. Goals of care should be defined with the patient. Hospice referral should be considered if the prognosis is six months or less, but this does not preclude the use of radiation for pain control.

For more information, practitioners are encouraged to refer to www.acr.org/ac

## Author Disclosure Statement

No competing financial interests exist.

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