Chapter 9
External Beam Radiotherapy and Bone Metastases

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Abstract While the management of bone metastases requires multidisciplinary care, external beam radiotherapy (EBRT) remains an effective and efficient method by which to palliate pain and prevent pathologic fracture. Dose fractionation schemes ranging from 8 Gy in a single fraction to 30 Gy in ten fractions can provide equivalent relief with a minimal risk of side effects. Highly conformal or stereotactic body radiation therapy shows promise in the treatment of these patients, with its most appropriate niches to be determined through continued accrual to ongoing clinical trials. Treatment guidelines and quality measures have been developed to better define the use of EBRT in the setting of painful bone metastases.

Keywords External beam radiotherapy • Bone metastases • Fractionation • Pain • Highly conformal therapy • Stereotactic body radiation therapy

9.1 Introduction

Bone metastases are a common manifestation of malignancy, and they require multidisciplinary collaboration to determine the optimal palliative regimen. Radiation is useful in the treatment of both symptomatic and asymptomatic osseous lesions. Bone metastases often result from primary tumors that have arisen in the breast,
prostate, lung, thyroid, kidney, and bone marrow (in the form of multiple myeloma) [1]. Primary tumors from other sites can metastasize to the bone as well, though less frequently. Symptoms caused by bone metastases commonly present earlier in the clinical course of metastatic neoplasm than do symptoms caused by visceral metastasis. As described elsewhere in this textbook, patients who experience bone metastases may suffer a wide range of clinical symptoms ranging from localized pain or pathologic fracture to functional deficits from compression of the spinal cord, nerve roots or peripheral nerves. The manifestation of these symptoms relates to the anatomic location of the affected bone and the osseous and extraosseous extent of the lesion [2, 3]. A bone is weakened both by the direct effects of tumor invasion as well as by perturbations in the normal remodeling mechanisms mediated by the interplay between osteoblasts and osteoclasts. This may result in the inability to bear a load, therefore leading to microscopic or even larger, macroscopic fractures. Spine bones that suffer decreased integrity can compress, with their decrease in height causing the adjacent muscles to spasm in an effort to augment spinal stability. Alternatively, nerve compression or invasion by tumor can create pain with different characteristics that radiates to another anatomic site. The perception of pain may therefore include descriptions by the patient such as “sharp”, “burning”, “shock-like”, “cramping”, “achy” or “unrelenting”. Systemic effects may include nausea, vomiting, fatigue, anorexia, and psychological changes caused by hypercalcemia. Bone metastases that are asymptomatic may also require treatment if there is impending spinal cord compromise or significant involvement of weight bearing bones. This may especially be true in the management of lesions of the acetabulum, where surgical options are limited.

### 9.2 Radiotherapy for Pain

Estimates suggest that 50–75 % of radiographically evident bone metastases cause discomfort at some point during the patient’s disease course. The treatment of painful bone metastases remains the most common use of palliative radiotherapy, and external beam radiotherapy (EBRT) provides effective and time-efficient pain relief with a low risk of complications. EBRT provides at least partial pain relief in 60–80 % of affected patients, with a complete response in 25–30 % [4]. Though some have suggested that tumors from soft tissue or kidney origin are less responsive to radiotherapy, painful metastases caused by those histologies may still respond quite well to treatment.

Pain relief from bone metastases of any histology may not begin until several days after the initiation of EBRT and may take several weeks to reach its full palliative relief. In the Dutch Bone Metastasis Study, the mean time to the onset of pain relief in both arms was 3 weeks [5]. Thus, pain medicine regimens must be initiated and properly maintained during the time until the effects of radiotherapy are manifested. In addition, patients must be reasonably comfortable lying flat for 15–20 min so that radiation therapy can be delivered. The stepwise approach of pain medicine dosing
described by the World Health Organization should be employed to achieve sufficient pain relief during this interval [6]. Depending upon the intensity or nature of the pain, pain medicine regimens may include non-steroidal anti-inflammatory agents, narcotic analgesics, or adjuvant pain medicines such as corticosteroids, nerve-stabilizing medicines, or anti-depressants.

The duration of pain control or pain response varies, but is typically several months. In the Dutch Bone Metastasis Study, a subgroup analysis was performed on patients surviving more than 52 weeks [7]. The mean duration of response in both arms was approximately 29–30 weeks. Unfortunately, approximately 55% of patients had progression of pain at the treated site at a mean interval of 16–17 weeks. If pain recurs, retreatment can be considered (see Retreatment, Sect. 9.7 below).

The mechanisms of radiotherapy effects on normal and cancerous cells are well known. Linear accelerators create photons that interact with DNA and other molecules, such as water, to create double-stranded DNA breaks. These double stranded DNA breaks are more easily repaired by normal cells than cancer cells and interfere with the replication of cancer cells. Pain relief following EBRT may occur faster than tumor cell death, suggesting a more complex phenomenon which may include a decrease in the tumor cell production of factors, e.g. cytokines, that can lead to stimulation of nocioceptors on adjacent nerves, as outlined in Chap. 3.

### 9.3 Impending or Pathological Fracture

Patients with documented bone metastases should be actively evaluated for radiographic findings that suggest a risk for pathologic fracture. The chances for morbidity and mortality of a completed fracture are much higher than would be true for a properly managed impending fracture. Unfortunately, even a diligent clinician cannot always definitively determine the true risk of pathologic fracture from clinical and radiographic information [8, 9]. Analysis from prospective studies and ongoing research into computer risk models do suggest promising improvements in the prediction of fracture risk. Pathologic fractures most commonly occur in weight-bearing bones that experience torsional forces, though bones which are significantly weakened may fracture even in bed-ridden patients who simply readjust their position in their sleep. Surgical stabilization of weakened bones can prevent pathologic fracture with EBRT of 20–30 Gy given afterwards to promote tumor lysis which can allow for healing and minimize persistent pain [10, 11].

Radiation when given to a bone that is at risk for a pathologic fracture decreases the tumor burden and promotes healing of the normal bone. Bisphosphonates also play a role in preventing pathologic fracture. These modalities are complementary and are often used in combination.

One reason commonly cited against the use of higher dose per fraction radiation regimens is the potential for pathologic fracture. In the analysis of the RTOG 97-14, there was no difference in the long-term risk of pathologic fracture with the single fraction regimen compared to multi-fraction regimen [12].
### 9.4 Dose Fractionation

Many different fractionation schemes have been used to treat metastatic bone pain, with one survey showing that over 100 regimens are in use worldwide [13]. Multiple prospective, randomized trials have been completed to analyze equivalency of specific regimens during the past three decades. Most of those studies have compared single-fraction regimens such as 8 Gy in a single fraction to other multi-fraction regimens. Short-term pain relief, mean time to response, mean duration of response are equivalent with courses of 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction. Table 9.1 compares the four largest randomized trials of fractionation.

The advantages of the single fraction treatment include greater patient and caregiver convenience as well as fewer short-term side effects [12]. Many physicians believe that this technique should be reserved for patients with a short life expectancy; however, an unplanned subgroup analysis of patients surviving >52 weeks in the Dutch Bone Metastasis trial suggests that higher total doses offer no additional benefit over a single fraction [7, 14]. In addition, both in that study and in RTOG 97-14, physicians routinely overestimate patient survival [7, 15]. Another theoretical advantage of the higher dose per fraction is the increase in double stranded DNA breaks seen with increased dose per fraction and the potential to overcome the relative radioresistance of certain tumor histologies, e.g. renal cell carcinoma. There is limited data in this setting as the majority of patients enrolled in these trials have breast, lung or prostate primary tumors.

The circumstances when a higher total dose of 20–30 Gy could be considered include bone metastases with a large extraosseous component or osteolytic lesions with impending pathologic fracture in those who are medically inoperable [16]. The goals of the longer course in these circumstances are to maximize tumor control and remineralization, issues that are more relevant for those who will likely survive for several months. A single trial of patients with neuropathic pain from bone metastases did not show superiority for either 20 Gy in 5 fractions or a single

<table>
<thead>
<tr>
<th>Trial, year [Ref]</th>
<th>Randomization dose/fraction number</th>
<th>Response rate SF (%)</th>
<th>Response rate MF (%)</th>
<th>Retreatment rate SF/MF</th>
<th>Complete response SF (%)</th>
<th>Complete response MF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Pain Trial Working Party 1999 [37]</td>
<td>8 Gy/1 vs. 20 Gy/5</td>
<td>274/351 (78 %)</td>
<td>257/330 (78 %)</td>
<td>23 %/10 %</td>
<td>57 %</td>
<td>58 %</td>
</tr>
<tr>
<td>Dutch Bone Metastasis Study 1999 and 2004 [5, 38]</td>
<td>8 Gy/1 vs. 24 Gy/6</td>
<td>395/556 (71 %)</td>
<td>396/543 (73 %)</td>
<td>24 %/6 %</td>
<td>37 %</td>
<td>33 %</td>
</tr>
<tr>
<td>Hartsell et al. 2005 [12]</td>
<td>8 Gy/1 vs. 30 Gy/10</td>
<td>187/455 (41 %)</td>
<td>188/443 (42 %)</td>
<td>18 %/9 %</td>
<td>15 %</td>
<td>18 %</td>
</tr>
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*SF* Single Fraction, *MF* Multi-fraction
8 Gy fraction, though the proper fractionation for this clinical circumstance remains somewhat controversial [17].

A single fraction course is more commonly associated with re-treatment to the same painful site than fractionated courses, with rates of 20 % versus 8 %, respectively. This may be due in part to reluctance on the part of radiation oncologists to give additional fractionated radiation after a fractionated course. In addition, there has been less reported benefit to retreatment after multi-fraction regimens than after single fraction regimens [5].

9.5 Process of Radiation Therapy Planning and Delivery

Radiation oncologists commonly consult on patients with bone metastases following a definitive diagnosis and evaluation by other oncology physicians. Therefore, the radiation oncologist must gather and interpret all of the relevant clinical data and radiographic studies while optimizing communication with those other healthcare providers. Once EBRT has been determined to be appropriate by the radiation oncologist and has been accepted in an informed fashion by the patient, they are scheduled for a simulation or radiation planning session. One purpose of the simulation is to establish a reproducible patient position that allows treatment of the affected area without giving unnecessary radiation dose to other body parts, e.g. the arms. At simulation, the patient’s body shape and anatomy is captured in the treatment position either by fluoroscopy or a quick CT scan to allow for dose calculation and reproducible set-up for subsequent treatment(s). While simulation may be completed by clinically assessing bony landmarks or using fluoroscopy to visualize bony anatomy, the most common mechanism for simulation involves a 20–30 min appointment which includes obtaining a CT scan of the patient in the same position that treatment will be delivered. The dosimetry, or dose planning, is completed next and involves computerized measurement of the best means by which to deliver dose to the intended target while minimizing treatment to adjacent normal tissues. For patients who do not live near a radiation facility or who suffer pain with transfer to and from CT scanners and treatment tables, it is most efficient to complete the consultation, simulation, and initiation of single fraction therapy during the same day. There are physicist and physician review of the radiation plan to ensure accurate delivery of radiation. Prior to treatment, portal images are obtained to verify that the set-up of the patient is correct and that the correct area is in the treatment field. The delivery of radiotherapy commonly takes only 10–15 min per dose, and it is painless other than discomfort that may be associated with transfer to fraction lying on the treatment table.

9.6 Side Effects of EBRT

Radiation therapy for bone metastases may cause acute side effects that are most often predictable, mild, manageable with conservative measure; and dependent upon the area of the body which is irradiated. Fatigue is the main systemic side
effect associated with treatment, though the fatigue from radiotherapy is usually less significant than that which is caused by the disease or other treatment modalities. Local side effects can include skin irritation, gastrointestinal complaints like nausea or diarrhea, or dysphagia. Factors such as the daily dose and total dose delivered can influence the risk for acute, sub-acute, and long-term toxicity. Previous trials have suggested a slightly higher risk of acute side effects following multiple fractions of radiotherapy when compared to a single, larger fraction for bone metastases [14, 18]. Tumor cell kill can cause a transient increase in bone pain around the time of the first few fractions of radiotherapy in 20–40 % of patients [19]. When it occurs, this pain flare may be minimized by the use of non-steroidal anti-inflammatory drugs or oral dexamethasone.

The late effects of radiotherapy, which by definition occur several months to years after treatment, are relatively rare but can be more serious than acute side effects. While the acute effects of treatment depend mostly upon the total dose of delivered radiotherapy, the late side effects of radiation depend upon both the total dose delivered and the size of dose delivered per treatment. In other words, larger daily doses of radiation correlate with a higher risk of long-term side effects. Patients with bone metastases have historically not lived a sufficiently lengthy time to commonly suffer late side effects. Improvements in systemic treatment have allowed some patients with bone metastases to live longer and potentially put them at risk for long-term toxicity that can be associated with short course, high dose per fraction therapy. To date, this has not been clinically significant given the relatively short survival in metastatic cancer and modest total dose delivered when larger fraction sizes are used. In the Dutch Bone Metastasis, a separate stratification and randomization was performed for patients who were thought to have a better prognosis, after 1 year, only 53 % of those patients were alive [7]. On average, physicians overestimated the survival of patients with metastatic cancer by 3 months. Factors that are associated with improved survival include histology (breast or prostate), absence of visceral metastasis, Karnofsky Performance Status and the Functional Assessment of Cancer Therapy (FACT) [15].

### 9.7 Retreatment with EBRT

Patients who have been previously treated with EBRT receive re-treatment to that same painful site with some frequency. If the first course of palliative radiation was a multi-fraction course, the retreatment rates are about 8 %. For those whose first course was a single fraction of 8 Gy, the retreatment rate is 20 % [4]. Approximately 55 % of patients experience recurrent pain at the treated site. At least one trial demonstrated less benefit from retreatment after initial multi-fraction regimens [5]. The true incidence of recurrent pain is uncertain, given that retreatment in those trials was given at the discretion of the treating physician. In general, both patients and physicians are more likely to accept re-treatment after an initial single fraction versus
a more prolonged radiotherapy course [5]. Recent consensus conference groups have therefore begun to better define the criteria by which re-treatment should be considered. Given that pain sometimes recedes slowly following radiotherapy over a period of days to weeks, the minimum interval before re-treatment should be considered is 4 weeks [20]. There is little prospective data available to predict the risk for combined side effects from initial treatment and re-treatment of painful bone metastases, though retrospective studies suggest that re-treatment can be given with relatively safety and a 50–70 % chance for pain relief [21]. A prospective international study did not demonstrate any non-interiority for a single 8 Gy retreatment versus 20 Gy in 5 fractions. The multifraction re-treatment course was associated with more side-effects [22].

9.8 Highly Conformal Therapy

Several emerging technologies are capable of producing EBRT that is considered highly conformal [23]. The goal of these techniques is to deliver high doses to the target while minimizing damage to adjacent structures. These approaches include intensity modulated radiation therapy (IMRT), which uses an inverse planning process with dose constraints for organs at risk (OAR) in the treated volume. Stereotactic body radiation therapy (SBRT) involves the delivery of large, highly conformal doses with fastidious attention paid to dose planning, patient set-up, and localization. This technique may be especially useful in the re-treatment of an area where the spinal cord has reached tolerance due to their initial definitive course of radiation therapy. Image guided radiation therapy (IGRT) can help to optimize patient positioning [24]. Proton beam therapy takes advantage of spatial qualities of radiation dose delivery to maximize dosing to the intended target [25].

SBRT has been used for painful bone metastases involving the spine, both as a primary treatment and as a method for delivering re-treatment to spine bones that have previously received standard external beam radiotherapy [26]. Treatment regimens studied include 30 Gy in 5 fractions, 27 Gy in 3 fractions, 40 Gy in 5 fractions or 16–24 Gy in a single fraction [27–29]. The results of these early trials are promising with prospective, randomized data likely to further define the best use of this technology [30] SBRT may be used for the primary treatment or retreatment of spine metastases. However, the relative lack of information about the long term effects of very large single doses through innovative delivery systems may create a higher risk of long term side effects than would be true for more established treatment approaches, so care must accompany this approach [31]. Routine use should not be employed until sufficient evidence from clinical trials justifies the substantive increase in cost when compared to standard external beam radiation therapy. Figure 9.1a–c Illustrates treatment of a shoulder metastasis with 8 Gy in a single fraction in the axial, coronal and sagittal planes. Figure 9.2a–d Illustrates SBRT to a vertebral body metastasis with 16 Gy in a single fraction.
Guidelines and Quality Measures

Though the optimal treatment of bone metastases with radiotherapy has been evaluated in multiple prospective randomized trials, there has been a great deal of variability in the dose fractionation regimens employed by radiation oncologists. One survey revealed that 101 different dose fractionation schemes were employed worldwide for this single clinical circumstance [13]. These disparities have led to the formation of treatment guidelines by the American Society for Radiation Oncology (ASTRO) and the American College of Radiology (ACR) [32–34]. These guidelines confirm that the available data reveal four fractionation schemes that are equivalent in the successful management of painful bone metastases: 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction. The guidelines acknowledge a trade-off between increased convenience and a higher re-treatment rate with single fraction therapy. Additionally, the publications differentiate between treatment approaches that have proven to be effective through clinical trials and those approaches that require further investigation before being used in a routine, non-protocol setting. The use of one of the four approved fractionation schemes is considered a measure of quality as determined by the
National Quality Forum (NQF) [35]. The NQF is a non-profit organization that is tasked to assess healthcare priorities in the United States while providing a means to measure and report on the performance of healthcare providers and healthcare facilities. Furthermore, the choice to offer appropriate length fractionation schemes for patients with painful bone metastases is under review in an initiative called “Choosing Wisely” [36], a program started to help physicians become better financial stewards of healthcare use.

9.10 Summary

Bone metastases continue to be a significant clinical problem, with pain being the most common symptom requiring intervention. External beam radiation therapy continues to serve as the main form of treatment for painful bone metastases, with good coordination required between the radiation oncologist and other specialists including medical oncologists, surgeons, palliative medicine specialists, and physiatrists.
Short course treatments effectively provide symptom relief, with many patients best treated by a single fraction. The acute- and long-term side effect rates from EBRT are minimal and usually self-limited. Highly conformal therapy for bone metastases shows great promise, especially in patients with recurrent pain in the spine after previous conventionally fractionated curative therapy. Bone metastases treatment guidelines and quality measures provide data-derived direction to the management of patients with this clinical condition.

References

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36. ABIM (2012) Choosing Wisely