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Chapter 86. Radiotherapy of Skeletal Metastases

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INTRODUCTION

Bone is the most common site of symptomatic cancer metastasis. Two thirds to three quarters of patients with advanced disease from breast and prostate carcinomas have skeletal metastases, and lung, thyroid, and renal carcinoma metastasize to bone in ~30–40% of cases.[1] Pain is the most common symptom.[1,2] Additionally, clinical implications of skeletal metastases include pathological fracture, nerve entrapment/spinal cord compression (SCC), bone marrow insufficiency, and hypercalcemia. Hence, bone metastases have a devastating impact on a patient's quality of life.[1,3,4] SCC is of particular concern to cancer patients with a long expected survival[1] (e.g., those with the diagnosis of skeletal metastasis as the first and sole metastatic event).

Optimal management combines medical treatment, radiation therapy, surgery, bone-targeted radiopharmaceuticals, and bisphosphonates depending on the biology of the disease, extent of the skeletal involvement, and the life expectancy of the patient.

EXTERNAL BEAM RADIOTHERAPY

Skeletal metastases are the single most frequent indication for palliative radiotherapy. External beam radiotherapy (EBRT) effectively relieves pain from localized sites of skeletal metastases.[5] However, the lack of tumor-only selectivity limits its clinical use. Furthermore, because skeletal metastases usually are multiple and distributed throughout the axial skeleton,[2,4] larger or multiple fields of irradiation are often necessary. Table 1 outlines factors to be considered when prescribing palliative radiotherapy for bone metastases.

Pain Palliation

Solid empirical evidence has clearly documented that single-fraction (SF) EBRT provides equivalent pain relief compared with multi-fraction (MF) EBRT for uncomplicated bone metastases documented by >25 randomized clinical trials (RCTs) and 3 recent meta-analyses.[6–8]

One of the first RCTs was conducted by the Radiation Therapy Oncology Group.[9] Ninety percent of patients experienced some degree of pain relief, and 54% achieved complete pain palliation. The trial initially concluded that the low-dose, short-course schedules were as effective as the high-dose protracted programs. However, this study was criticized for using physician-based pain assessment. A reanalysis of the same set of data grouped solitary and multiple bone metastases and used the endpoint of pain relief, taking analgesia intake into account, as well as the need for retreatment. The authors concluded that the number of radiation fractions was significantly related to complete combined relief (absence of pain and use of narcotics) and that protracted dose-fractionation schedules were the most effective.[10] This was contrary to the initial report and highlights that the choice of endpoints will influence the outcome.[11]

More recently, results from several large-scale prospective RCTs have been published. The UK Bone Pain Trial Working Party randomized 765 patients with bone metastases to either an SF or MF regimen.[12] There were no significant differences in the time to first improvement in pain, time to complete pain relief, and time to first increase in pain at any time up to 12 mo after randomization, and no differences in the incidence of nausea, vomiting, SCC, or pathological fracture between the two groups. Retreatment was, however, twice as common after SF than after MF radiotherapy. The study concluded that an SF of 8 Gy is as safe and effective for the palliation of metastatic bone pain for at least 12 mo with greater convenience and lower cost than MF treatment.

TABLE 1. FACTORS TO BE CONSIDERED WHEN PRESCRIBING PALLIATIVE RADIOTHERAPY FOR BONE METASTASES

EBRT Single-fraction	*EBRT Multi-fraction*
Indication: pain relief	Indication: local tumor control
Short life expectancy	Expected long-term survival
Concomitant visceral metastases	Predominantly bone or bone only metastasis
Poor performance status	Good performance status
Inflammatory pain	Neuropathic pain
Aspects of cost and inconvenience	Spinal cord compression
	Postoperative EBRT after an orthopedic procedure in selected cases
	Impending fractures where surgery is not indicated

Dr. Bruland serves as Chairman of the Scientific Advisory Board for Algeta, ASA, Oslo, Norway, and is co-founder and minor stockholder in Algeta, ASA, Oslo, Norway, holding the patents of Alpharadin Radium-223. This bone-seeking Radiopharm is currently in phase II/III clinical trials. All other authors state that they have no conflicts of interest.

The large Dutch Bone Metastases Study included 1171 patients and confirmed the results mentioned above.[13] In this trial, the retreatment rates were 25% in the single 8-Gy arm, 7% in the MF arm, and more pathological fractures were observed in the SF group, but the absolute percentage was low. In a cost-utility analysis of this RCT, there was no difference in life expectancy or quality-adjusted life expectancy. The estimated cost of radiotherapy, including retreatments and nonmedical costs, was significantly lower for the SF than for the MF schedule.[14]

A Scandinavian RCT planned to recruit 1000 patients with painful bone metastases randomized to single 8 Gy or 30 Gy (3 Gy in 10 fractions).[15] The data monitoring committee recommended closure of the study after 376 patients had been recruited because interim analyses indicated that the treatment groups had similar outcomes. Equivalent pain relief within the first 4 mo was experienced, and no differences were found for fatigue, global quality of life, and survival between the groups.[15]

Two meta-analyses published in 2003 each showed no significant difference in complete and overall pain relief between SF and MF EBRT for bone metastases.[6,7] Results were remarkably similar, with the paper of Wu et al.[7] reporting a complete response rate (absence of pain) of 33% and 32% after SF and MF EBRT, respectively, compared with 34% and 32% for Sze et al.[6] Overall response rates from the two meta-analyses were 62% and 59%, compared with 60% and 59%,[6] for SF and MF, respectively. When restricted to evaluable patients, overall response rates became 73% for each arm.[7] Most patients experienced pain relief in the first 2–4 wk after EBRT.[7] Side effects were similar and generally consisted of nausea and vomiting.

An updated meta-analysis reviewed 16 RCTs that compared SF and MF schedules[8] involving a total of 2513 randomizations to SF arms and 2487 to MF arms. The overall response rate to SF EBRT was 58%, and complete response rate was 23%, which was not significantly different from the 59% and 24% experienced by patients randomized to MF EBRT. No differences in acute toxicity, pathological fracture (3.2% of patients fractured after SF versus 2.8% after MF), or SCC incidence were found, thus confirming the conclusions of the 2003 systematic reviews.

Neuropathic Pain and Spinal Cord Compression

There is some evidence that certain groups of patients would benefit from a protracted schedule. In a comparison of a single 8 Gy versus 20 Gy (4 Gy in five fractions) for 272 patients with a neuropathic pain component,[16] it was found that SF was not as effective as MF; however, it was also not significantly worse. The authors recommended MF as standard radiotherapy for patients with neuropathic pain. However, in patients with short survival or poor performance status, as well as when cost/inconvenience of MF is relevant, SF could be used instead.[16]

In the treatment of neoplastic SCC, the most appropriate radiation therapy schedule is still undefined. Patients with pending or complete SCC have been excluded and/or not addressed in the eligibility criteria in most RCTs. Only one RCT has studied the outcome in patients with SCC and an estimated outcome of 6 mo or less with no indication for primary surgery.[17] However, two EBRT schedules not commonly used were compared; 16 Gy in two fractions over 1 wk or a split course of 15 Gy in three fractions, followed by 4 days rest, and the additional 15 Gy in five fractions. No significant differences were reported between the two arms.[17]

Until the results from a recently published RCT comparing surgery and postoperative EBRT and EBRT alone[18] were presented in favor of primary surgery, the common view was that the outcome did not differ between EBRT and surgery for patients with vertebral metastases and SCC.[19]

Impending Fracture and Risk Prediction

An impending fracture has a significant likelihood of fracture under normal physiological stresses. Although some physicians believe that all patients with proximally located femoral metastases should undergo preventive surgery, this would result in a large number of unnecessary surgical procedures.[20] Furthermore, a proportion of patients will not be candidates for an operative procedure or will refuse surgical intervention. Often a minimum life expectancy (6–12 wk), a reasonable performance status, manageable co-morbidities, and adequate remaining bone to support the implanted hardware are required to justify the morbidity and mortality risk.[21]

If an orthopedic intervention is not appropriate, patients may receive EBRT alone. Although EBRT can provide pain relief and tumor control, it does not restore bone stability, and remineralization will take weeks to months.[22] Patients should be warned of the increased risk of fracture in the peri-radiation period because of an induced hyperemic response at the periphery of the tumor that temporarily weakens the adjacent bone. Pain relief may allow the patient to be more mobile and, hence, at greater risk for fracture. As such, measures to reduce anatomic forces across the lesion (crutches, a sling, or a walker) are routinely introduced during this time.

Although there is no consensus on appropriate dose fractionation, most authors recommend a MF course of EBRT in a patient with an impending or established fracture.[20] One retrospective series analyzed 27 pathologic fractures in various sites treated with doses of 40–50 Gy over 4–5 wk. Healing with remineralization was seen in 33%, with pain relief in 67%.[23] In practice, 20–40 Gy for established pathologic fracture is generally given over 1–3 wk. In patients with an apparently solitary, histologically confirmed metastasis, especially after a long disease-free interval, some clinicians may wish to give even a higher dose, 40–50 Gy, under the assumption that this will provide long-term control.

Reirradiation

Subsets of patients with metastatic disease have longer life expectancies than in the past because of advances in systemic therapy and may therefore outlive the duration of benefit provided by their initial palliative EBRT. This may require consideration of reirradiation of previously treated sites at a later date.[24]

The clinical indications, optimal dose and fractionation, and techniques for retreatment are controversial[25] because of lack of precise quantitative data on the time course, magnitude, and tissue specificity of long-term occult radiation injury recovery.[26]

Retreatment rates after SF EBRT varied from 18% to 25% compared with 7% to 9% after MF EBRT.[12,13,15,27] The Dutch Bone Metastases Study Group recently reanalyzed their data to specifically report the efficacy of reirradiation.[28] Of patients not responding to initial radiation, 66% who initially received a single 8 Gy responded to retreatment compared with 33% of patients who initially received a MF course. Retreatment in patients after pain progression was successful in 70% of those who received SF initially compared with 57% of those who received more than one fraction. Overall, reirradiation was effective in 63% of all such treated patients.

Hence, it is important to consider reirradiation of sites of metastatic bone pain after initial EBRT, particularly when this

follows an initial period of response. There is also evidence that a proportion of initial nonresponders will respond. The preferred dose schedule, however, is at present unknown, but a large, prospective, randomized intergroup study using common reirradiation schedules has been launched.[29]

BONE-SEEKING RADIOPHARMACEUTICALS

Treatment with intravenously injected bone-seeking radiopharmaceuticals (BSRs) is an intriguing alternative that selectively delivers ionizing radiation to targeted areas of amplified osteoblastic activity and targets multiple (symptomatic and asymptomatic) metastases simultaneously. The target is Ca-OH-apatite, which is particularly abundant in sclerotic metastases from prostate cancer but is also present, although more heterogeneously distributed, in mixed sclerotic/osteolytic metastases from breast cancer. This is evident from the biodistribution image common to all BSRs—exemplified as "hot-spots" visualized on a routine diagnostic bone scan (by ^{99m}Tc-MDP; a radiolabeled bisphosphonate). BSRs effectively relieve pain and have been thoroughly reviewed.[30–34] In the commercially available formulations, the radioisotopes involved are β-emitters: strontium-89 dichloride (Metastron; GE Healthcare, Chalfont St. Giles, UK) and ^{153}Sm-EDTMP (Quadramet; Schering AG, Berlin, Germany, and Cytogen Co., Princeton, NJ, USA).

Because of the millimeter range of the emitted electrons, the cross-irradiation of the bone marrow represents an ever-present concern. After intravenous injection of a β-emitting BSR, bone marrow is an innocent bystander and the dose-limiting organ. 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-emitting BSRs, especially when dosages are increased to deliver potential antitumor radiation levels and/or repeated treatments are attempted. Few clinical studies to date have reported on the feasibility of combining BSRs and chemotherapy.[35–38]

Because of short particle track-length and potent cell-killing, an α-emitting BSR could be an intriguing alternative.[39] In contrast to the β-emitters, the α-particle emitters deliver a much more energetic and localized radiation that produce densely ionizing tracks and predominantly nonreparable double DNA strand breaks. In a phase 1 study of single-dosage administration of escalating amounts of the natural bone-seeker ^{223}Ra in 25 patients with bone metastases from breast and prostate cancer,[40] dose-limiting hematological toxicity was not observed. Mild and reversible myelosuppression occurred, with only grade one toxicity for thrombocytes at the two highest doses. Results from a phase 2 RCT of external beam radiation plus either saline or ^{223}Ra injections (given four times at 4-wk intervals) have recently been published.[41] Radium-223 treatment resulted in a statistically significant decrease from baseline compared with placebo both in bone alkaline phosphatase and prostate-specific antigen. A favorable adverse event profile was observed, with minimal bone marrow toxicity for patients who received ^{223}Ra. Importantly, survival analyzes from this phase 2 trial showed a significant overall survival benefit for ^{223}Ra.[41]

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Chapter 87. Orthopedic Treatment of Metastatic Bone Disease

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INTRODUCTION

More than 1.4 million people are diagnosed with cancer each year,[1] and ~50% of those will develop bone metastasis. As treatments improve for primary and metastatic disease, patients are living longer with their disease. This often causes them to experience the morbidities of related bone disease. Although the most worrisome clinical problem is progressive disease in the skeleton, patients can also experience treatment-related osteoporosis. Additional physiologic disruptions in patients with bone metastasis include anemia and hypercalcemia. The bone lesions themselves can cause extreme pain and put the patient at risk for pathologic fractures. Patients become less mobile and may function at a lower level. Prolonged immobilization caused by pain or risk of fracture creates potential problems with thromboembolic disease or decubitus ulcers. Lesions in the vertebral region can cause progressive neurologic deficits. Overall quality of life is often markedly diminished.

Comprehensive treatment of bone metastasis is beyond the scope of this chapter, but advances in chemotherapy, targeted biologic therapy, and vaccines have been variably effective. Different forms of radiation are used to target cancer cells within the bone to provide palliative pain relief and potentially abrogate the need for surgical intervention. External beam radiation, cyberknife, and radiopharmaceuticals such as samarium are used depending on the location of disease. This chapter focuses on treatment that affects the neoplastic process and the bone microenvironment. A brief review of the molecular events related to metastatic bone disease will be discussed. The use of bisphosphonate therapy as well as surgical stabilization will be summarized.

BIOLOGY OF METASTATIC BONE LESIONS

Tumor–Bone Interface

The tumor cells interact within the bone microenvironment so that tumor growth is stimulated[2–7] (Fig. 1). The majority of work has been done in the area of breast cancer bone metas-

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