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## Review Article

## A review of recently published radiotherapy treatment guidelines for bone metastases: Contrasts or convergence?

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## ABSTRACT

Bone metastases are a common manifestation of malignancy, and external beam radiotherapy (EBRT) effectively and safely palliates the pain caused by this clinical circumstance. The myriad of EBRT dosing schemes and complexities involved with coordinating radiotherapy with other interventions necessitated the need for bone metastases treatment guidelines. Here we compare and contrast the bone metastases radiotherapy treatment guidelines recently published by the American Society for Radiation Oncology (ASTRO) and the American College of Radiology (ACR). These evaluations acknowledge current controversies in treatment approaches, they evaluate the nuances of ASTRO and ACR task force decision-making regarding standard approaches to care, and they project the upcoming research results that may clarify approaches to palliative radiotherapy for bone metastases. The results of these two dedicated radiotherapy guidelines are compared to the brief mentions of radiotherapy for bone metastases in the National Comprehensive Cancer Network (NCCN) guidelines. Finally, the paper describes how treatment guidelines may influence patterns of care and reimbursement by their use as quality measures by groups such as the National Quality Forum (NQF).

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## 1. Bone metastases as a clinical problem

Many cancers metastasize to bone, with the most common sites of origin of primary disease being breast, lung, thyroid, kidney, prostate, and malignant melanoma of the skin. The presence of tumor in the bone can lead to local symptoms such as pain, spinal cord compression, and pathologic fracture, as well as systemic effects caused by hypercalcemia. The work-up and treatment of bone metastases requires input and interventions from many medical disciplines, including radiologists, orthopedic surgeons or neurosurgeons, radiation oncologists, medical oncologists, pain medicine specialists, physical medicine and rehabilitation physicians, and palliative care professionals. The delivery of radiation therapy to these patients requires communication and coordination of scheduling with these other specialists. Furthermore, the aggressiveness of treatment must take into account patient factors such as performance status and co-morbidities, tumor factors such as stage and histology, and treatment factors such as sequencing and risks of concurrent therapy [1–3].

## 2. Radiotherapy for bone metastases

As a palliative intervention, radiotherapy is effective and efficient at treating painful bone metastases, and the side effects associated with its use are manageable and usually self-limiting in nature. Between 50% and 80% of patients gain at least partial relief of their pain following external beam radiotherapy (EBRT), and complete relief may be seen in up to one-third [4]. External beam radiotherapy may be delivered to the same anatomic site of affected bone in the case of recurrent pain. Technological advances have created interest in the possibility that highly conformal therapies may improve either the rates of pain relief or the duration of the results of treatment, especially in cases of tumors located in bones of the spine. These treatments are termed stereotactic body radiation therapy (SBRT), or stereotactic ablative body radiotherapy (SABR), and are given by machines that deliver intensity modulated radiation therapy (IMRT), Cyberknife therapy, Tomotherapy, or proton therapy. Patients with spinal cord compression may receive EBRT primarily or as an adjuvant treatment after surgical decompression. Kyphoplasty or vertebroplasty may be used in cases where there is no spinal cord compression, but where spinal instability is noted and contributes to metastatic bone pain. Furthermore, injectable radiopharmaceuticals such as Strontium 89, Samarium 153, and Radium 223 may be delivered to patients with widespread tumors whose histologies are osteoblastic and therefore easily visualized on

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a Technetium 99 bone scan. Finally, the addition of osteoclast inhibiting agents may be considered concurrently or sequentially with EBRT.

### 3. Emergence of radiotherapy guidelines

The driving forces behind the emergence of radiotherapy guidelines include a desire to maximize pain relief and functional capabilities of an individual patient while minimizing the risks of treatment toxicity. The treatment guidelines are also meant to serve as a means by which to guarantee a minimum standard of care across geographic locales and different practice settings. And, given some areas of incomplete data regarding the proper choice for treatment, one goal of the guidelines is to acknowledge and address the controversies that arise due to that lack of complete data. From a societal standpoint, the guidelines provide a means to assess the best practice patterns as developed countries face an increased number of cancer patients with resource constraints and many developing countries struggle with throughput limitations on antiquated machinery.

### 4. International Consensus Conference Bone Metastases treatment recommendations

The prelude to many of the questions posed and answers offered by the existing bone metastases treatment guidelines was contained in previous International Consensus Conference Bone Metastases treatment recommendation publications. The First International Consensus Workshop on radiation in the treatment of metastatic and locally advanced cancer convened in the United States in 1990 [5]. A group of 116 experts evaluated the available palliative radiotherapy data and generated consensus statements for the treatment of bone metastases, amongst other clinical circumstances. Those statements included treatment pathway recommendations, an assessment of international variations in treatment approach, the effects of successful treatment on quality of life, and the role of economic factors in the management of this patient group. The Second Workshop on Palliative Radiotherapy and Symptom Control convened in London in 2000 and confirmed the efficacy of EBRT in controlling pain caused by metastatic bone disease [6]. That group reviewed the efficacy of a single 8 Gy fraction, they better defined the proper use of radiopharmaceuticals for patients with widespread painful disease, and they recommended the standardization of response measurement that led to the development of the International Consensus on Palliative Radiotherapy Endpoints document. Finally, the Third International Consensus Conference Workshop was held in conjunction with the ASTRO meeting with representatives from ASTRO, European Society for Therapeutic Radiology and Oncology (ESTRO), Trans-Tasman Radiation Oncology Group (TROG) and Canadian Association of Radiation Oncology (CARO) in San Diego, California, in 2010 and called for both formal treatment guidelines and a means by which to enhance palliative radiotherapy efforts in developing countries around the world.

### 5. Formal radiotherapy bone metastases treatment guidelines

The American College of Radiology (ACR) Appropriateness Criteria format employs common clinical circumstances, or “variants”, which serve as a means for an expert panel to vote upon the most appropriate interventions for that scenario (Table 1). The panel members collectively base their assessments upon the results of published literature, though the clinical experience of those experts may influence their decision-making, especially

in situations where the available data set is incomplete. The bone metastases treatment panel consists of representatives from radiation oncology, nuclear medicine, orthopedic surgery, and medical oncology. The clinical case scenarios allow for recommendations about the best combination of interventions as well as an assessment of the proper radiotherapy treatment set-ups and fractionation schemes. While previous ACR publications have included all types of bone metastases situations in a single manuscript, the increasing complexity of treatment of spine metastases and spinal cord compression led to the division of “spine” and “non-spine” topics. The most recent update of the non-spine topic has just been published, while the spine topic update is still being formulated [7].

The first variant in the non-spine topic describes a patient with an excellent performance status, a favorable life expectancy, and an asymptomatic femur lesion which does not pose an obvious risk for pathologic fracture. While the authors acknowledge that research has begun to determine whether patients with bone-only metastatic disease and otherwise favorable findings may be treated aggressively, they stop short of endorsing curative-intent therapy for patients with “oligometastases” because the available data do not yet prove the usefulness of such an approach [8]. Their recommendations therefore call for an osteoclast inhibitor and a hormone blocking agent, with radiotherapy reserved for an oligometastatic treatment trial. The results of ongoing research may well come to indicate that patients in this most favorable clinical circumstance of metastatic disease should be treated more aggressively than others with less favorable prognostic indicators.

The second variant describes a patient with a good performance status who has a painful lesion in a weight-bearing bone. The task force defined the need for quickly establishing a pain medicine regimen while concurrently consulting an orthopedic surgeon to assess the need for surgical pinning to prevent pathologic fracture [9–11]. Given a low risk of fracture determined by the surgeon, the team recommended external beam radiotherapy (EBRT) based upon CT, fluoroscopic, or clinical simulation, with radiation delivery through anterior and posterior fields sparing a skin strip to minimize the risk of long term lymphedema of the extremity. While the panel detailed the pain relief equivalency between a single 8 Gy fraction and multi-fraction schedules, they pointed out the data which suggests that the use of fractionated regimens might minimize the risk of subsequent pathologic fracture in this setting [12]. The group essentially declared that pain relief equivalency has been conclusively determined for either single fraction or multi-fraction regimens, obviating the need for further research to examine that question. Finally, the existence of a fairly significant tumor burden in that patient led to recommendations for considering systemic chemotherapy and osteoclast inhibitors.

In the third variant, the patient has suffered a pathologic fracture from a lytic metastasis in a weight-bearing bone that required surgical stabilization. The panel recommended post-operative radiotherapy with 30 Gy in 10 fractions planned by CT, fluoroscopic or clinical simulation, with anterior and posterior opposed fields and a skin strip spared to once again minimize the risk of long term lymphedema. The vignette is valuable in its ability to highlight the need for orthopedic consultation to assess and provide surgical stabilization as well as the need for communication for the patient to receive the necessary post-operative adjuvant radiotherapy. Given a good performance status and significant tumor burden, recommendations were made for considerations of systemic chemotherapy, hormonal ablation treatment, and an osteoclast inhibitor.

The patient in variant number 4 has previously received palliative radiotherapy for a site of painful bony disease with

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