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Research paper

A definition of “uncomplicated bone metastases” based on previous bone metastases radiation trials comparing single-fraction and multi-fraction radiation therapy



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ABSTRACT

The most recent systematic review of randomized trials in patients with bone metastases has shown equal efficacy of single fraction (SF) and multiple fraction (MF) palliative radiation therapy in pain relief. It is important to determine the patient population to which the evidence applies. This study aims to examine the eligibility criteria of the studies included in the systematic review to define characteristics of “uncomplicated” bone metastases.

Inclusion and exclusion criteria of 21 studies included in the systematic review were compared. Common eligibility criteria were documented in hopes of defining the specific features of a common patient population representative of those in the studies.

More than half of the studies included patients with cytological or histological evidence of malignancy. Patients with impending and/or existing pathological fracture, spinal cord compression or cauda equina compression were excluded in most studies. Most studies also excluded patients receiving retreatment to the same site.

“Uncomplicated” bone metastases can be defined as: presence of painful bone metastases unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression. Therefore, MF and SF have equal efficacy in patients with such bone metastases.

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1. Introduction

Bone metastases are a common manifestation of cancer [1]. Most patients present with pain and impaired mobility, while others can develop complications such as pathological fractures and compression of the spinal cord or cauda equina [2]. Many randomized studies have been conducted to determine if a dose response exists for pain relief from palliative radiation therapy in patients with painful bone metastases. The most recent systematic review of these trials conclude the equivalency of single fraction (SF) and multiple fraction (MF) treatments for pain relief from “uncomplicated” bone metastases, though the meaning of the term is not explicitly stated in most of the examined studies [3].

The United States national guidelines published by the American Society of Radiation Oncology and the American College of Radiology suggest that there are no differences between SF and MF dosing in palliative treatment for bone metastases [2,4], although definitions distinguishing between complicated and uncomplicated bone metastases were not consistently provided. In practice, most radiation oncologists consider bone metastases causing pathologic fractures or compression of the spinal cord and cauda equina to be complicated. Some also consider those with associated soft tissue components or those within weight bearing bones at high risk of fracture to be complicated as well, but operational definitions vary among practice settings.

A clearer definition of “uncomplicated bone metastases” is required to determine the patient population in which the results of the prospective randomized trials apply. Whereas a workgroup or committee could be established to explore this issue, the translation of existing data to practice patterns necessitates a comprehensive evaluation of the completed trials. So, the purpose of the current study was to examine the inclusion and exclusion

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criteria of the randomized studies as described in the recent systematic review [5–29], thereby clearly defining the characteristics of the patient population in which a SF is equivalent to MF for the palliation of “uncomplicated” bone metastases.

2. Materials and methods

Only fully published trials from the systematic review were included in the analysis, and therefore abstract by Kirkbride et al. [13] was omitted. Study by Amouzegar-Hashemi et al. [24] and abstract by Haddad et al. [29] used the same trial, and therefore the former was used in the analysis. Study by Steenland et al. [26] and follow-up by van der Linden et al. [18] used the same trial, and therefore the former was used in the analysis. Study by Kaasa et al. [28] and its follow-up by Sande et al. [27] also used the same trial, and therefore the former was used in the analysis.

The methods sections of 21 studies comparing SF to MF course of radiation therapy for painful bone metastases out of 25 studies included in the most recent systematic review of bone metastases treatment were examined by PMC, EW and NT for their patient inclusion and exclusion criteria [5–29].

3. Results

The inclusion and exclusion criteria of the 21 studies are listed in Table 1. All 21 studies included patients with bone metastases, whereas all but one study specified painful bone metastases. Thirteen of the 21 studies required cytological or histological evidence of malignancy as part of the inclusion criteria, and 9 of these studies required radiographic evidence of bone metastases. Five of such studies did not specify the method of imaging, 1 specified X-ray, 2 specified X-ray or bone scan, and 1 specified X-ray, bone scan, CT or MRI. Only 2 studies limited accrual to patients with a previously specified primary tumor location, and only 2 studies included patients with pain deemed to have resulted from neuropathic pain.

Of the included 21 studies, 18 excluded patients with pathological fracture, of which 12 studies excluded patients with existing pathological fracture, and 6 studies excluded patients with either existing

(“need of bone surgery” was interpreted as existing pathological fracture) or impending pathological fracture. Three of the studies excluded patients with pathological fracture specified the location of fracture in the long bone, and 1 study followed Mirel’s criteria for measurement of impending fracture. Nine studies excluded patients presenting with spinal cord compression, and 3 studies excluded patients with either spinal cord or cauda equina compression. A total of 18 studies excluded patients who received previous radiation therapy, consisting of 17 studies which excluded patients who received radiation to the same treatment site, and 1 study which excluded patients who received any radiotherapy 10 weeks prior to the study.

4. Discussion

A systematic review showed that SF radiotherapy resulted in equivalent pain relief to MF courses of radiation therapy for patients with uncomplicated painful bone metastases [3]. However, in order to apply the findings of this paper to the appropriate patient population, a description for the term “uncomplicated bone metastases” is preferred. Based upon an analysis of inclusion/exclusion criteria for 21 prospective randomized studies, we suggest the following working definition: uncomplicated bone metastases are those unassociated with impending or existing pathologic fracture or existing spinal cord compression or cauda equina compression.

The strengths of this definition are its simplicity and its usefulness in translating existing data into daily practice. The shortcomings of this definition include the lack of uniform criteria to suggest an impending fracture as well as the variable definitions of spinal cord compression or cauda equina compression. Although 9 studies excluded patients with spinal cord compression alone, and 3 studies excluded patients with spinal cord compression or cauda equina compression, none provided a definition or associated symptoms of such conditions. Furthermore, only 4 studies by Roos et al. [19], Hartsell et al. [20], Safwat et al. [23], and Foro Arnalot et al. [25] required clinical or radiological evidence of compression. Still, in spite of these nuances, the case can be made for conformity of treatment in patients whose clinical circumstances reside within the confines of this definition.

Table 1
Eligibility criteria for randomized controlled studies.

Study	Inclusion criteria	Exclusion criteria
Price [5]	<ul style="list-style-type: none"> • Painful bone metastases • Cytological or histological evidence of malignancy 	<ul style="list-style-type: none"> • Prognosis less than 6 weeks • incapable of completing the pain chart • Pathological fracture of long bone • Previous radiotherapy • Change in systemic therapy within 6 weeks
Cole [6]	<ul style="list-style-type: none"> • Metastatic bone pain • Life expectancy of at least 3 months 	<ul style="list-style-type: none"> • Spinal cord or peripheral nerve compression syndrome • Actual or threatened pathological fracture • Previous radiotherapy
Kagei [7]	<ul style="list-style-type: none"> • Painful bone metastases 	<ul style="list-style-type: none"> • Treated with chemotherapy on same day as radiotherapy • Fracture which was not vertebral compression fracture caused by bone metastases
Gaze [8]	<ul style="list-style-type: none"> • Histologically or cytologically proven cancer, and demonstrated by plain radiography or skeletal scintigraphy • Could be re-entered into the trial if separate, previously untreated, painful areas • Maximum field size of 150 cm² was allowed where spinal cord or bowel was included in the field, or 200 cm² for more peripheral sites 	<ul style="list-style-type: none"> • Prior irradiation • New concurrent systemic treatment • Serious inter-current illness or life expectancy of < 4 weeks • Spinal cord compression, vertebral collapse above the level of L2, impending or established pathological fracture, or prior surgical fixation • Widespread disease requiring large-field or hemi-body irradiation

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