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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.

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]	• Painful bone metastases • Cytological or histological evidence of malignancy	• 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]	• Metastatic bone pain • Life expectancy of at least 3 months	• Spinal cord or peripheral nerve compression syndrome • Actual or threatened pathological fracture • Previous radiotherapy
Kagei [7]	• Painful bone metastases	• Treated with chemotherapy on same day as radiotherapy • Fracture which was not vertebral compression fracture caused by bone metastases
Gaze [8]	• 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 cm^2 was allowed where spinal cord or bowel was included in the field, or 200 cm^2 for more peripheral sites	• 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

Table 1 (*continued*)

Study	Inclusion criteria	Exclusion criteria
Nielsen [9]	• Painful bone metastases localized to a single region that previous radiotherapy to the region concerned could be encompassed within a single radiation field • Histopathologically or cytologically confirmed malignancy and metastases were radiologically verified • Able to complete a pain evaluation form • Life expectancy more than 6 weeks	• Pathological fractures except compression fractures of the vertebral spinal column • Spinal cord compression
Foro [10]	• Painful bony metastases • Any primary tumor	• Pathological fractures • Risk of fractures • Medulla compression • Requiring hemi-body irradiation
Koswig [11]	• Histologically proven breast, lung, prostate and kidney carcinoma • Radiologically solitary osteolysis with or without fracture risk and with pain • Osteolytic lesion had to be suitable for bone density measurements via CT	• Prior irradiation • New systematic therapies in the last two weeks
BPTWP [12]	• Histological or cytological diagnosis of cancer • Age over 18 years • pain • Willingness to complete pain questionnaires for 12 months	• Pathological fracture of a long bone • Previous radiotherapy • Earlier entry into the same trial
Kirkbride [13]	• Painful bone metastases from any primary tumour site and the estimated survival was >4 months	Not available
Ozsaran [14]	• Solitary or multiple bone metastases • Cytological or histological evidence of malignancy • Karnofsky performance status greater or equal to 50 • Allowed to re-enter the trial if they previously untreated painful bone metastases	• Previous radiotherapy • Prior surgical treatment for pathologic fracture or cord compression
Sarkar [15]	• Patient able to determine subjectively the amount of pain. • Cytologically or histologically proven malignant disease with painful bone metastases	• previous radiotherapy • concurrent chemotherapy or hormone therapy • chemotherapy within the last 4 weeks or hormone therapy within the last 8 weeks • Pathological fracture
Altundag [16]	• Histological or pathological malignancy • Painful bone metastases • pain can be assessed/quantified	• prior radiation therapy • surgical intervention • Symptoms of spinal cord compression • Pathological breaks
Badzio [17]	• Cytological or histopathological evidence of cancer • Confirmed by X-ray	• Pathological fracture or previous irradiation to the metastatic sites
van der Linden [18]	• Painful bone metastases • solid tumors • Pain score minimum 2 on 11-point scale (0=no pain to 10=worst imaginable pain) • Metastases treatable in one radiotherapy target volume	• Pathologic fracture or impending fracture needing surgical fixation • Spinal cord compression • Renal cell carcinoma or melanoma • cervical spine • Previous radiotherapy
Roos [19]	• Pathologically confirmed malignancy • Plain X-ray or bone scan evidence of bone metastasis • Pain or dysaesthesia predominantly of a neuropathic nature • Life expectancy at least six weeks. • Able to complete the pain assessments	• Metastasis within the distribution of the neuropathic pain (e.g. shaft of femur metastasis with L2 neuropathic pain) • Prior radiotherapy to the index site • Clinical or radiological evidence of compression of the spinal cord or cauda equina • Pathological fracture of long bone(s) at index site • Change in systemic therapy within 6 weeks before, or anticipated within 4 weeks after commencing radiotherapy • Neuropathic pain due primarily to extra-skeletal tumor
Hartsell [20]	• Age of 18 years or older • Histologically proven malignancy of breast and prostate • Radiographic evidence of bone metastasis • Painful bone metastasis • A Karnofsky performance status of at least 40 • Life expectancy of at least 3 months • Pain assessed with the Worst Pain Score from the Brief Pain	• Pathologic fracture or impending fracture of the treatment site • Planned surgical fixation of the bone • Clinical or radiographic evidence of spinal cord or cauda equina compression and/or effacement

Table 1 (*continued*)

Study	Inclusion criteria	Exclusion criteria
	Inventory, requiring a score of at least 5 on a scale of 10 (or a score of less than 5 but taking narcotic medications with a daily oral morphine equivalent dose of at least 60 mg) • Patient with up to 3 separate sites of painful metastases • Patient receiving biphosphonates or systemic therapy (hormonal therapy, chemotherapy, immunotherapy, or systemic radioisotope therapy) as long as no introduction of any systemic therapy within the 30 days before entry into the study	
El-Shenshawy [21]	• Painful bone metastases from a solid tumor • Radiologically verified bony metastases • Histopathologically or cytologically confirmed malignancy	• Previous radiotherapy • Pathological fractures except compression fractures of the vertebral spinal column and suspicion of spinal cord compression • Chemotherapy and/or hormonal treatment was allowed but not during radiotherapy, and all changes related to such treatment were carefully registered • New concurrent treatment
Hamouda [22]	• Localized bone metastases • Histological or cytological evidence of malignancy • Radiographic evidence of bone metastasis • No change in chemotherapy or hormonal therapy within 30 days	• Pathological fractures • Previous radiotherapy
Safwat [23]	• 18 years or older • Known malignancy metastatic to bone causing neuropathic pain • Life expectancy of at least 3 months	• Clinical or radiological evidence of cord or cauda equina compression • irradiation or hormonal treatment, biphosphonates or chemotherapy within 10 weeks prior to the study
Amouzegar-Hashemi [24]	• Adult with painful uncomplicated bone metastases	• Cord compression or existing or impending pathologic fracture
Foro Arnalot [25]	• Age of 18 years or older • Estimated life expectancy of at least 1 month	• Reported pain due to a pathological fracture or • impending fracture following Mirels' criteria; patients with a score of 9 were referred for prophylactic surgical fixation • Clinical or radiographic evidence of spinal cord compression • Pain at more than one site • Prior radiotherapy • Pain could not be assessed either because of an overall poor state of health or due to difficulties in applying the ordinal pain scale (OS)
Steenland [26]	• Painful bone metastases from solid tumor • Pain score of at least 2 on 11-point scale at time of admission • Bone metastases treatable in one target volume • Karnofsky index of 60% or more	• previously irradiated • Pathological fracture needing surgical fixation • Spinal cord compression • Melanoma or renal cell carcinoma • Cervical spine
Sande [27]	• Biopsy- or cytology-proven malignancy and bone metastasis verified either by bone X-ray, bone scan, CT or MRI • Karnofsky performance status above 40 • Painful bone metastases	• Previous irradiation • Spinal cord compression • Need of bone surgery • unable to complete the QOL assessment tools • Life expectancy less than 6 weeks
Kaasa [28]	• Painful bone metastases • Biopsy-or cytology-proven malignancy, bone metastasis verified by bone X-ray, bone scan, CT or MRI • Karnofsky performance status above 40	• Previous irradiation • spinal cord compression • Need of bone surgery • Unable to complete the QOL assessment tools • Life expectancy less than 6 weeks
Haddad [29]	• Adult with painful uncomplicated bone metastases	• Cord compression or existing or impending pathologic fracture

In contrast, the use of SF and MF radiation therapy treatments vary in patients with complicated bone metastases. A randomized controlled trial by Patchell et al. evaluating the efficacy of direct decompressive surgery showed that decompressive surgical resection and post-operative MF radiation therapy (30 Gy in 10 fractions) combined is superior to radiation therapy alone for patients with cord compression by metastatic cancer restricted to a single area and fair to good motor function below the injury level [30]. Furthermore, MF (median dose 30 Gy) in postoperative radiation therapy following stabilization of impending pathological fracture was associated with increased functional status, decreased failure of the prosthesis, and perhaps improved overall survival [31]. In another randomized trial by Maranzano et al., 8 Gy SF radiation therapy was shown to be effective in achieving palliation in patients with metastatic spinal cord compression by bone metastases and poor performance status. However, this may be

attributed to the short life expectancy (6 months or less) of included patients, who would benefit from minimal toxicity and convenience of SF [32]. Moreover, a study by Roos et al. comparing SF and MF in patients with bone metastases presenting with neuropathic pain suggested SF was not as effective as MF in treating neuropathic pain, although it was not statistically significantly worse [19].

It is important to recognize that our definition of uncomplicated bone metastases may be incomplete. Only 2 of the 21 studies in the updated review excluded patients presenting with neuropathic pain, a common complication of bone metastases. Therefore, we could not incorporate the absence of neuropathic pain into our definition. Furthermore, bone metastases with soft tissue mass were not excluded in any of the studies examined. As such, the absence of a soft tissue mass cannot be considered a characteristic of uncomplicated bone metastases. Only 1 study verified bone metastases through 3D imaging such as CT or MRI, and 12 studies did not require any radiographic evidence. Therefore, interpreting results of older studies should consider the lack of reliable radiographic evidence. Future trials may benefit from examining the bone metastases with soft tissue masses for a dose response phenomenon.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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