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Systematic review

# Re-irradiation for painful bone metastases – A systematic review

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ABSTRACT

The purpose of this review was to determine the efficacy of re-irradiation in patients with bone metastases. A literature search was conducted in Ovid Medline, OldMedline, Embase, Embase Classic, and Cochrane Central Register of Controlled Trials using relevant subject headings and keywords such as bone metastases, radiotherapy and palliative care. The resulting articles were sorted for inclusion for palliative external beam radiation retreatment response rate data. The literature search produced 2164 references and 15 articles were included in the final selection. Complete, partial and overall response rates were calculated to be 20%, 50% and 68%, respectively. Information on treatment toxicities was scarce. The efficacy of re-irradiation is comparable to initial radiation treatment. However, aspects of re-irradiation treatment including dose fractionation, related adverse events and toxicities require further corroboration.



Bone metastases occur in 50% of advanced cancer patients with the most prevalent symptom being bone pain [1,2]. Radiotherapy is a widely accepted and effective way to palliate pain caused by bone metastases with few side effects [3]. However, the mechanism by which radiation palliates bone pain is unknown. Current hypotheses include tumor cell destruction, modulation of pain mediators, host bone activity, and disruption of neurons involved in the transmission of pain [4]. Despite this limited understanding, the effectiveness of radiotherapy has been demonstrated through numerous randomized controlled trials [5].

As reported in an updated meta-analysis, first time radiation of bone metastases is moderately effective with 60–70% of patients experiencing pain relief [5]. However 30–40% of patients receive no benefit from first time irradiation [5]. With the improving prognosis of patients with bone metastases, those who experience initial pain relief may outlive the duration of the therapeutic response [6]. Many of these patients are eligible for re-irradiation, which is indicated in the following three scenarios [7]:

(1) no pain relief after first time radiation;
(2) partial response to first time radiation and those in whom a better response is desired;
(3) pain relapse after either partial or complete response to the first time radiation.

Although first time radiation is generally accepted in the palliation of pain from bone metastases, there continues to be a general reluctance from radiation oncologists to prescribe re-irradiation due to the lack of concrete safety and efficacy literature. As such, the purpose of this review was to update a systematic review [8] on conventional external beam palliative re-irradiation with recently published literature in order to bridge the gap between scientific evidence and general practice.

## Methods

### *Search strategy*

A literature search was conducted in Ovid Medline and OldMedline from 1946 to May Week 3 2013, Embase Classic and Embase from 1947 to 2013 Week 20, and Cochrane Central Register of Controlled Trials up until April 2013. Relevant subject headings and keywords such as bone metastases, radiotherapy and palliative care were used in the search. Terms such as re-irradiation or permutations of the word were not included in the search to increase conservatism (Fig. 1). Titles and abstracts were screened independently by three authors (EW, GB, MP) to determine relevant references to include for full-text review.

### *Selection criteria for full-text article review*

Articles were selected for full-text review if the main focus of the trial was the use of palliative radiotherapy for bone metastases. Articles that did not mention re-irradiation or retreatment in the

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title or abstract were not excluded in order to be as conservative as possible. Studies involving hemi-body radiation, stereotactic body radiotherapy, or radiopharmaceuticals, either as an initial treatment or secondary treatment were not included for full-text article review. Studies in which the patient population included complications of bone metastases at the site of treatment such as pathological fracture, impending pathological fracture, or spinal cord compression caused by bone metastases before re-irradiation were excluded. Full-text articles selected for further sorting were independently reviewed by three authors (EW, GB, MP) for inclusion in the final review (Fig. 2).

### *Data extraction*

The primary outcome of interest was complete, partial and overall pain response rates of palliative re-irradiation. Due to the heterogeneity of the response rate definitions, these were collected as reported and defined by the respective studies. Due to large difference between the response definitions in the study by Hernanz et al. [9] and the response definitions of the other trials, response rates were re-defined as overall response to maintain the most conservative statistics.

Secondary information including: individual trial primary outcome of interest (either initial radiotherapy or re-irradiation), type of study, eligibility criteria, reasons for re-irradiation, re-irradiation dose, duration of remission, information on third time radiation, and toxicity of treatment were also collected (Tables 1 and 2).

## Results

The literature search produced 2164 references. Of these, 70 full-text articles were selected for further review based upon inclusion criteria. Fifteen articles had relevant data, with 8 articles primarily on initial radiotherapy for bone metastases and 7 with the primary intervention being re-irradiation. Three articles were published prior to 1990 [4,10,11], five articles were published from 1990 to 2000 [1,12–15], and the remaining seven articles were published from 2000 to 2013 [9,16–21]. Seven additional articles mentioned re-irradiation rates; however, they were not included due to lack of retreatment pain response data.

Of the fifteen studies, complete and partial responses were available for 6 of the studies [13–17,21], and was not captured in the remaining 9 studies [1,4,9–12,18–20]. Due to the retrospective nature of select articles included in this review, intent-to-treat patient analysis was not appropriate. Therefore, the evaluable population of 645 patients was used [1,4,9–21].

### *Efficacy*

In this review, the definition of a complete response was based on the definitions in the original studies. The complete response rate after re-irradiation was determined to be 20%, with 70 of 355 evaluable patients experiencing a complete response. The partial response rate was 50% (177/355 evaluable patients) and the overall response rate was 68% (438/645 evaluable patients) (Table 3).

### *Toxicity*

Toxicities were not consistently reported in the included studies (Table 4). Only seven of the fifteen studies mentioned toxicity related observations [9,14,16–19,21]. Jeremic et al. found that spinal cord compression occurred in 2.2% of patients after retreatment. Of the patients retreated in their study, 18.5% experienced grade 1 or 2 nausea and vomiting and 11.9% of patients experienced grade 1 or 2 diarrhea. No grade 3 or 4 toxicity was reported [14].

The remaining 6 studies did not report any spinal cord compression or toxicity exceeding grade 3 [9,16–19,21]. Hayashi et al. reported only rare occurrence of grade 1 or 2 hematological or gastrointestinal toxicity, and no occurrence of radiation myelopathy [16]. Similarly, van der Linden et al. reported that most patients who underwent re-irradiation experienced no or mild nausea and vomiting (Table 4). Severe nausea occurred in 3 patients and one patient experienced a severely painful skin reaction [18].

Roszkowski et al. reported the occurrence of nausea, vomiting, erythema of the skin, diarrhea, fever, fatigue, granulocytopenia, erythocytopenia, and L'hermitte's sign as 15.8%, 3.5%, 40.4%, 1.8%, 7.0%, 24.6%, 8.8%, 10.5%, and 1.8%, respectively. They also reported no serious complications [19]. Sayed et al. also reported no acute or late toxicity [21]. Hernanz et al. reported mild grade 1–2 rectal toxicity; however, this may include patients who were not retreated for bone metastases but for pelvic lymph nodes [9].

### *Pathological fractures*

The rate of pathological fractures after re-irradiation was not commonly reported (Table 4). Jeremic et al. found pathological fractures to occur in 2.2% of patients after retreatment [14]. The remaining studies did not report any pathological fractures [1,4,9–13,15–21].

### *Pattern of pain response*

Mithal et al. found that patients who previously had a complete response were more likely to achieve pain response upon retreatment. They also found that response durations were dependent on response categorization. Patients who had initial partial response were noticed to have shorter pain relief duration after retreatment [13]. Similarly, Jeremic et al. found that patients with previous complete response were more likely to achieve a complete response than those who had an initial partial response [14]. Duration of remission was also longer in previous complete responders than partial responders and there was no significant difference in the rate of pain relapse after retreatment between responders and non-responders to initial treatment [14,16]. On the other hand, van der Linden et al. found that initial response status did not influence the response to retreatment with similar response rates between previous non-responders and responders [18].

### *Non-responders*

In the Dutch Bone Metastasis Study, patients who did not respond to initial radiation treatment were retreated. Of the initial 53 non-responders treated with either a single fraction of 8 Gy or 24 Gy in 6 fractions, 33 (62%) responded to subsequent retreatment [18]. Jeremic et al. reported that 12 of the 26 (46%) initial non-responders responded to the retreatment and Mithal et al. found that 6 of the 8 previous non-responders responded to re-irradiation [13]. However, the two non-responders in the Hayashi et al. trial did not respond to subsequent re-irradiation [16]. Price et al. similarly found that retreatment was ineffective for seven patients who were previous non-responders [4].

### *Single fraction or multiple fractions retreatment*

In a prospective study by Sayed et al., no significant differences were found in pain response between patients treated with a single fraction of 8 Gy compared to a multiple fraction schedule of up to 20 Gy over 5–8 fractions [21]. Response rate stratified by retreat-