



## Original Article

## Effectiveness of Repeat Radiotherapy for Painful Bone Metastases in Clinical Practice: A 10 Year Historical Cohort Study



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## Abstract

**Aims:** Repeat radiotherapy for palliation of painful bone metastases is often prescribed to non-responders or those with recurrent pain, although studies on retreatment remain scarce. We assessed the effectiveness of retreatment for painful bone metastases in terms of pain relief in everyday clinical practice and identified factors associated with response.

**Materials and methods:** We carried out a single-institution 10 year retrospective cohort study among 247 patients retreated for painful bone metastases. Response was defined as a decrease in pain between 2 and 12 weeks after retreatment. The overall pain response rate was calculated in an evaluable-patients-only analysis and a worst-case analysis. Multivariate logistic regression analyses were used to identify factors associated with pain response.

**Results:** A follow-up of  $\geq 2$  weeks was available in 162 of 247 patients (65%). The overall pain response was 66% (95% confidence interval 58–73%) in an evaluable-patients-only analysis and 43% (95% confidence interval 37–50%) in a worst-case analysis. Response to first irradiation (odds ratio 2.16,  $P = 0.049$ ) and use of systemic therapy (odds ratio 0.39,  $P = 0.037$ ) were independently associated with the response to retreatment. The median overall survival was 7.1 months.

**Conclusion:** In everyday clinical practice, retreatment for painful bone metastases leads to pain reduction in 66% of evaluable patients and 43% of patients in a worst-case analysis. Patients who responded to initial radiotherapy were more likely to respond again and those on systemic therapy were less likely to respond. Overall, repeat radiotherapy should be considered in patients with persisting bone pain.

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**Key words:** Bone; cohort studies; palliative care; radiotherapy; retreatment; survival

## Introduction

Metastatic bone disease is the most common cause of pain in cancer patients [1,2]. Radiotherapy is a proven effective and widely accepted palliative treatment modality for metastatic bone pain [3,4]. Nonetheless, up to 40% of patients fail to obtain pain relief, only a minority of patients achieve complete remission and recurrent pain is common [4–6]. Overall, life expectancy has increased and more patients with cancer will need additional palliation as they

outlive the temporary effect of radiotherapy [7]. Repeat radiotherapy (retreatment) can be given to patients who failed to obtain pain relief after initial radiotherapy, to patients who desire additional palliation after partial response or to patients who experience pain recurrence after an initial satisfactory response [3,8]. Although many patients with painful bone metastases will probably undergo retreatment in clinical practice, retreatment research in general has only gained attention over the last few years [9] and studies on retreatment are scarce [10]. Recently, the first randomised controlled trial on retreatment was published in which two dose fractionation schedules were compared in patients with painful bone metastases needing repeat radiotherapy [11]. It was concluded that 8 Gy in a single fraction seems to be non-inferior and less toxic than

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20 Gy in multiple fractions, with an overall pain response of 28% versus 31% for 8 Gy in a single fraction and 20 Gy in multiple fractions, respectively [11]. However, results from clinical trials are not always generalisable to daily practice [12]. Therefore, the objective of this historical cohort study was to assess the effectiveness of retreatment for patients with painful bone metastases in everyday clinical practice and to identify possible predictors associated with response.

## Patients and Methods

### *Study Population and Data Collection*

This study was approved by our local institutional review board. We retrospectively identified patients diagnosed with bone metastasis from a solid tumour who received palliative external beam radiotherapy between 1 January 2000 and 31 July 2011 at the University Medical Center Utrecht, The Netherlands (an academic tertiary referral centre). Of the 3949 patients who received radiotherapy for bone metastases, 321 patients (8%) underwent retreatment. Retreatment was defined as repeat radiotherapy of the initial target volume including the metastasis of interest. As at the period of study no formal clinical recommendations on the use of retreatment existed, fractionation schedules were left at the discretion of the treating physician. Patients were excluded if retreatment was administered within 4 weeks after the initial radiotherapy ( $n = 26$ ) [8] and if initial or repeat radiotherapy was given for indications other than pain (e.g. neurological symptoms without pain, consolidation or postoperatively;  $n = 48$ ). In total, 247 patients who received retreatment for painful bone metastases were included.

Hospital records were reviewed by one researcher to collect data on baseline demographics, primary tumour, localisation, number of clinically known bone metastases at retreatment and previous (<1 year) or concomitant use of systemic therapy (chemotherapy, bisphosphonates or hormonal treatment). For the initial treatment and retreatment the following data were recorded; dose fractionation schedule, presence of neurological symptoms, performance status (World Health Organization  $\leq 1$  or  $\geq 2$ ), analgesic intake (phase 1–2: non-opioids/weak opioids; paracetamol, non-steroidal anti-inflammatory drugs, or tramadol, or phase 3–4: strong opioids; e.g. oral or non-oral morphine) and baseline level of pain. As no numerical pain scores were available, information from patient records was used to categorise pain; mild pain in case of intermittent or low-intensity pain, moderate in case of constant pain, and severe when the patient was immobilised/hospitalised due to pain. Additionally, the initial response status based on the treating physician in the patient's history was recorded; no response with initial radiotherapy (i.e. no pain improvement), initial partial response and hope to achieve further pain reduction (i.e. pain improvement did occur but additional palliation was desired) or pain recurrence after initial satisfactory response (i.e. pain improvement followed by

relapse). Survival data were obtained through the population registry until 23 October 2013.

### *Follow-up and Response Assessment*

After treatment completion, patients received standard telephone follow-up by the treating radiation oncologist about 1 month after treatment to evaluate the effect on pain and to monitor acute side-effects such as nausea, diarrhoea or skin toxicity. If this report could not be retrieved or follow-up was carried out by the referring primary treating physician, follow-up data were acquired from visits within any other department. The response to retreatment was defined as a decrease in pain at the retreated site, as reported by the patient at the physician's interview in person or by telephone, between 2 and 12 weeks after retreatment. When changes in opioid administration were taken into account, the response was defined as a decrease in pain without analgesic increase (change from phase 1–2 to phase 3–4) or an analgesic decrease (cessation of phase 3–4 analgesics) without an increase in pain. This broad time period was chosen to gather enough data on follow-up. Patients' records were also analysed for the occurrence of late toxicities or pathological fractures until the date of last contact or death. Acute and late toxicities were retrospectively graded according to the criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer [13].

### *Statistical Analysis*

In an evaluable-patients-only analysis, the overall pain response rate was calculated as the proportion of responders of all patients with at least 2 weeks of follow-up, including response assessment with the corresponding 95% Wilson confidence interval [14]. Also, a worst-case overall response rate was calculated assuming all patients with missing responses were non-responders. Multivariate logistic regression models were fitted to explore predictors of response. Multiple imputation was carried out to impute missing values for performance status ( $n = 14$ ) and the initial response ( $n = 1$ ). The number of events limited the number of possible covariates, therefore only covariates considered most relevant were included [6,11,15,16], i.e. tumour type (breast versus other), localisation (limb versus other), performance status (World Health Organization  $\leq 1$  or  $\geq 2$ ), initial response (recurrence after response versus no/insufficient response) and previous (<1 year) or current use of systemic therapy (yes/no). Predictors were identified using backward stepwise selection and the likelihood-ratio test [17]. Overall survival was defined as the length of time from the first retreatment fraction until death. For all survival analyses the Kaplan–Meier method was used. Analyses were carried out using the R statistical environment version 3.0.2 (R Development Core Team, 2013) [18]. All tests were two-sided, a  $P$  value < 0.05 defined statistical significance.

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