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Critical Review

Effectiveness of Reirradiation for Painful Bone Metastases: A Systematic Review and Meta-Analysis

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Summary

Although reirradiation of painful bone metastases is often performed, literature on its effectiveness is scarce. This meta-analysis provides for a comprehensive overview and represents the most quantitative estimate of reirradiation effectiveness to date. Out of 707 titles, 10 articles were selected for systematic review and seven for meta-analysis. Of the 2,694 patients initially treated for metastatic bone pain, 527 (20%) patients underwent reirradiation. The pooled overall response rate was 0.58 (95% CI = 0.49−0.67).

Purpose: Reirradiation of painful bone metastases in nonresponders or patients with recurrent pain after initial response is performed in up to 42% of patients initially treated with radiotherapy. Literature on the effect of reirradiation for pain control in those patients is scarce. In this systematic review and meta-analysis, we quantify the effectiveness of reirradiation for achieving pain control in patients with painful bone metastases.

Methods and Materials: A free text search was performed to identify eligible studies using the MEDLINE, EMBASE, and the Cochrane Collaboration library electronic databases. After study selection and quality assessment, a pooled estimate was calculated for overall pain response for reirradiation of metastatic bone pain.

Results: Our literature search identified 707 titles, of which 10 articles were selected for systematic review and seven entered the meta-analysis. Overall study quality was mediocre. Of the 2,694 patients initially treated for metastatic bone pain, 527 (20%) patients underwent reirradiation. Overall, a pain response after reirradiation was achieved in 58% of patients (pooled overall response rate 0.58, 95% confidence interval = 0.49−0.67). There was a substantial between-study heterogeneity ($I^2 = 63.3\%$, $p = 0.01$) because of clinical and methodological differences between studies.

Conclusions: Reirradiation of painful bone metastases is effective in terms of pain relief for a small majority of patients; approximately 40% of patients do not benefit from reirradiation. Although the validity of results is limited, this meta-analysis provides a comprehensive overview and the most quantitative estimate of reirradiation effectiveness to date.

Keywords: Radiotherapy, Reirradiation, Retreatment, Bone metastases, Palliative treatment

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Introduction

Pain is one of the most common symptoms associated with cancer and up to 90% of patients experience some form of pain during the course of their illness (1). Unrelieved pain affects all aspects of quality of life, and influences the patient's ability to endure treatment or to achieve a peaceful death (2). The most common cancer-related pain syndrome requiring treatment is bone pain secondary to bone metastases (3). After the lung and the liver, the skeleton is the most common metastatic site (4). The malignant tumors that frequently metastasize to the skeleton are from common primary sites, in particular breast, prostate, and lung (4). The burden of bone metastases is considerable and effective treatment of metastatic bone pain is important (3). In addition to pain medication, single-fraction (SF) external beam radiotherapy (EBRT) is widely accepted as the standard of care for palliative treatment of uncomplicated metastatic bone pain (5), effective in achieving pain reduction in around 60% to 70% of patients (6). As no dose—response relationship was seen from the more fractionated regimens with higher total doses, single fraction radiotherapy is considered more convenient to the patient and is less costly to the society (7, 8).

Reirradiation can be offered in the following scenarios (9): (*1*) no pain relief or pain progression after initial radiotherapy; (*2*) partial response after initial treatment and hope to achieve further pain reduction with more radiation; and (*3*) pain relapse after initial partial or complete response. The group requiring reirradiation is substantial, as up to 40% of patients do not obtain any pain relief after initial treatment, and only about one-third of responders achieve a complete response (6, 10). Pain relapse is also common; approximately 50% of initial responders show pain relapse within 1 year after treatment (11). Actual proportions of patients who undergo reirradiation range from 8% to 42%, with higher reirradiation rates after SF radiotherapy compared with multi-fraction (MF) radiotherapy (5, 10).

Despite the large number of patients undergoing reirradiation for treatment of painful bone metastases, reported evidence on its effectiveness in this specific population is currently scarce. Most studies on radiotherapy for painful bone metastases have also performed reirradiation for nonresponding or recurrent pain, but no prospective study on reirradiation has been published to date (5, 9, 12). Currently, a large randomized controlled trial (SC20) (13) of dose-fractionation schedules for the reirradiation of painful bone metastases is being performed, but has not yet been published.

Therefore, we conducted a systematic review and meta-analysis of the available literature to quantify the effectiveness of reirradiation for treatment of patients with unresponsive or recurrent metastatic bone pain.

Methods and Materials

Search strategy

A free text search was performed to identify eligible studies using the MEDLINE, EMBASE, and the Cochrane Collaboration library electronic databases (from 1980 to January 10, 2011). No limits were used. Our overall search strategy included search terms and their synonyms for painful bone metastases, radiotherapy and reirradiation (complete search syntax is listed in Appendix E1). Additional articles were retrieved by cross referencing of research papers, editorials, systematic reviews, and textbooks. Searches were not performed for unpublished studies.

Study selection

The primary goal of our study was to assess pain response after reirradiation in patients with painful bone metastases not sufficiently responding to initial radiotherapy (RT) or exhibiting recurrent pain after initial response. We allowed all types of study design. Articles in languages other than English, German, French, and Dutch were not taken into account. Studies that met the following criteria were included: (part of) the participants received reirradiation at the site of initial RT for radiation-refractory metastatic bone pain; both the initial treatment and the retreatment consisted of localized EBRT; reported outcomes included (at least) pain response after reirradiation; and original research data were reported. If eligibility for inclusion could not be decided based on abstract screening or if the abstract was not available, the full text article was reviewed.

To qualify for the meta-analysis, an additional number of inclusion criteria needed to be met: outcomes were available on an individual patient level (allowing per-patient analysis); and the size of the study population was 10 patients or more.

Data extraction and quality assessment

The primary endpoint was the pain response rate. Pain response rate was categorized into partial response (PR) according to the definition used in the original study, complete response (CR) according to the definition used in the original study and overall response (OR) defined as occurrence of either partial or complete response. Secondary endpoints were as follows: toxicity of reirradiation according to the definition used in the original study; time to response defined as time interval (in weeks) between reirradiation and onset of response; and duration of remission defined as time interval (in weeks) between onset of response and pain progression. Extracted data included study population characteristics, treatment characteristics, pain response and toxicity outcomes, and study quality parameters. All data were extracted directly from the text or calculated independently according to the available information. In case of missing data, authors were contacted for additional information.

We assessed quality of publications using those items listed in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement that we considered important and relevant for quality assessment (14). Data extraction and quality assessment was performed independently by two observers (M.H. and J.W.).

Statistical methods

All analyses were performed using the R statistical environment version 2.13.0 (R Development Core Team, 2011) and the Metafor package version 1.6-0 (15). A value of $p < 0.05$ was taken to indicate significance. Funnel plots were generated to visually assess potential publication bias. Overall response rate was used for meta-analysis. These proportions were logit transformed before analysis and pooling. The back-transformed values are presented as overall response rate of evaluable patients with the corresponding 95% confidence interval (CI). The I^2 statistic (*i.e.*,