

Systematic review

Efficacy of multiple fraction conventional radiation therapy for painful uncomplicated bone metastases: A systematic review



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ABSTRACT

Background: Radiation therapy is effective for painful uncomplicated bone metastases, with multiple fraction radiation therapy (MFRT) administered frequently. The optimal dose for MFRT to yield maximum pain relief remains unclear. The aim of this systematic review was to determine pain response across MFRT doses. **Methods:** A literature search was conducted in Ovid MEDLINE(R) <1946 to July Week 3 2016>, Embase Classic & Embase <1947 to 2016 Week 30> and Cochrane Central Register of Controlled Trials <June 2016>. Pain response rates and the side effects for MFRT doses were extracted. **Results:** From the 3719 articles identified from the search, 17 were included for quantitative synthesis. 22.5 Gy/5 had the highest overall response (OR) rate, 30 Gy/15 had better complete response (CR) rate and 20 Gy/2 had better partial response (PR) rate. Only 4 of the 17 included studies directly compared MFRT doses with each other – one reported marginally-better OR for 24 Gy/6 over 20 Gy/2; another found 20 Gy/10 to be slightly more efficacious than 30 Gy/15 and 22.5 Gy/5 for OR. Two randomized trials compared 20 Gy/5 and 30 Gy/10 – one favored 20 Gy/5 while the other concluded 30 Gy/10 to be the better option. The overall rate of GI toxicities, nausea, and vomiting did not differ greatly between MFRT doses. **Conclusion:** No major difference exists between the schedules and toxic events studied in these trials. This is consistent with the wealth of randomized data which show no dose response for pain relief after radiotherapy for metastatic bone pain.

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Radiation therapy (RT) is effective for painful uncomplicated bone metastases [1]. Many studies have examined the efficacy of single fraction (SF) and multiple fraction (MF) regimens, with the majority of them suggesting that SFRT was as effective as MFRT for pain relief [2–10]. The guidelines from Choosing Wisely Canada, the national Choosing Wisely campaign and the American Society for Therapeutic Radiology and Oncology recommend SFRT for uncomplicated bone metastases [11–13]. However, the use of SFRT is not widely practiced globally [14] and MFRT continues to be administered frequently.

The conventional external beam MFRT dose for maximum pain relief remains unknown. Research over the past few decades has focused on comparing MFRT to SFRT in the clinical trial setting [2–4,14]. Conversely, clinical trial studies designed to compare two MFRT doses against each other date back several decades

ago [15,16]. The aim of this systematic review was to determine pain response across MFRT doses.

Methods

Search strategy

A literature search was conducted in Ovid MEDLINE(R) <1946 to July Week 3 2016>, Embase Classic & Embase <1947 to 2016 Week 30> and Cochrane Central Register of Controlled Trials <June 2016>. Keywords and subject headings such as “bone metastasis”, “radiotherapy” and “multiple fraction” were employed, and the search was limited to English-language publications [Fig. 1]. Titles and abstracts of search results were screened to determine eligibility for full-text article review.

Eligibility for full-text articles review

References were included if they reported outcomes of MFRT conventional external beam radiotherapy in the setting of a randomized controlled trial. Articles not clearly identifying patient populations, study designs or dose fractions were also included

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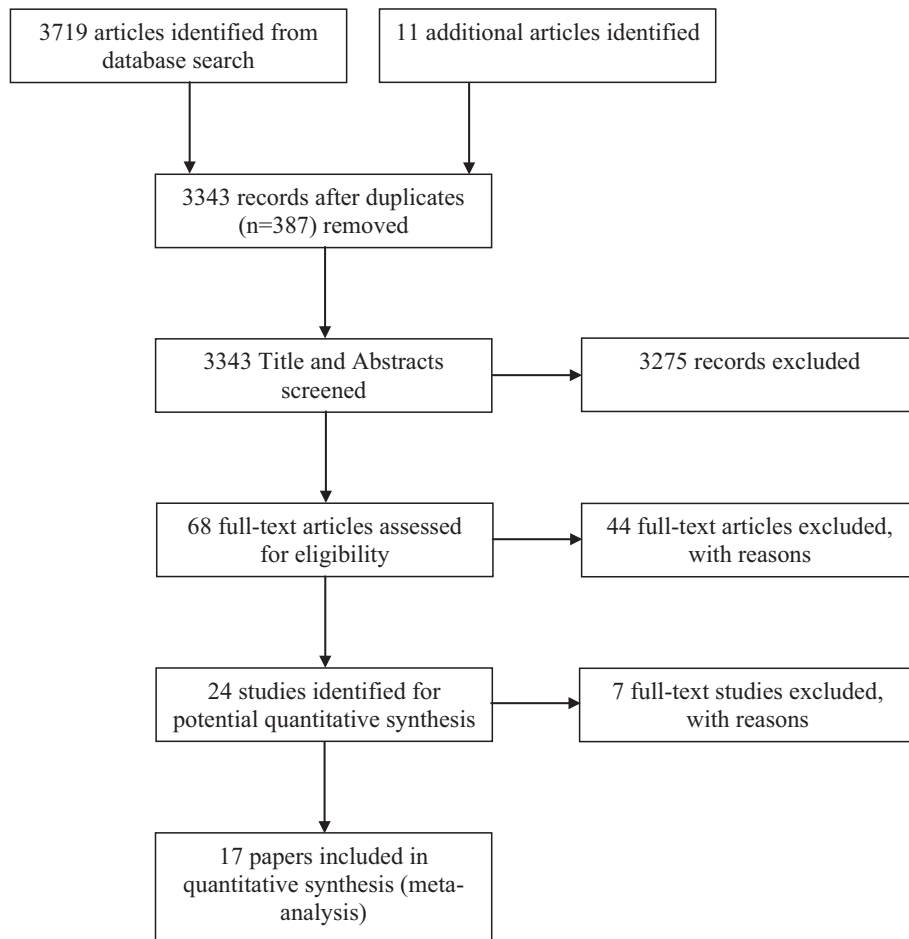


Fig. 1. PRISMA flow diagram.

for review. Studies were excluded if they were duplicates, combined radiotherapy with other concurrent local or systematic treatments, or employed hemi-body-, radiopharmaceutical- or stereotactic radiation therapy. In the case where two or more papers were published from a single trial, the initial study was chosen for inclusion and subsequent studies were excluded.

Articles selected for synthesis

If full-text articles documented pain response, they were identified as candidates for inclusion in this review. Reference lists of articles were also reviewed, and full-text articles of relevant papers obtained and analyzed. Fig. 1 presents a flow diagram describing the study selection process.

Data abstraction

The primary endpoints were pain response. When possible, reported pain response was categorized into partial, complete and overall pain response as reported in each study. Pain response assessments closest to 1–2 months following MFRT were recorded, as this is a common time to evaluate response and also a clinically important time frame for assessment of re-treatment [17,18].

Partial response (PR) rates were recorded as defined by authors in their studies, and complete response (CR) was generally defined as absence of pain following MFRT; defined criteria for CR and PR, were noted when reported. Overall response (OR) was defined as an improvement in pain after radiotherapy, and usually a summation of PR and CR. When studies did not separately document PR

and CR, the response rate was documented as OR. PR, CR and OR were documented under the analyses of both Intention-To-Treat (ITT) and Evaluable Patients (EP). Response rates when reported using percentages were converted to ratios; when multiple ratios yielded the same percentage, the number with lower patient response was used. When a conflicting number of EP was presented, the larger-value of EP was taken into account. Under circumstances where EP was not documented, ITT was recorded as EP.

The secondary endpoints were the rates of re-treatment, spinal cord compression, pathological fracture and acute toxicities such as nausea, vomiting and diarrhea. Additional information extracted from articles included the type of study, key eligibility criteria, dose, pain assessment tool, and time to pain response.

Results

3343 references were identified and screened for title & abstract: 3719 originated from the database search, 11 additional papers were included, and 387 duplicates were removed. 68 full-text articles were assessed for eligibility, with 24 of them identified for potential quantitative synthesis [Fig. 1]. Ultimately, 17 [2–6,10,16,19,14,20–26] papers that reported on pain response were included in this review. Only 4 compared different dosages of MFRT with each other [10,15,16,26], one of which was a three-arm study comparing 2 MFRT doses and 1 SFRT dose [26].

Three studies [16,19,20] documented pain response but not the side effects. Ten [2,4–6,10,21–23,25,26] reported on re-treatment rates, 3 [4,6,25] on spinal cord compressions, 8 [2,4–6,10,21,23,25]

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