

BMJ Open Optimal dose-fractionation schedule of palliative radiotherapy for patients with bone metastases: a protocol for systematic review and network meta-analysis

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ABSTRACT

Introduction The optimal dose-fractionation schedule of palliative radiotherapy has been debated in patients with bone metastases. Our objective is to comprehensively compare multiple fraction schedules with single fraction radiotherapy in terms of efficacy and toxicities by performing a systematic review and network meta-analysis.

Methods and analysis Electronic searches of titles/abstracts of palliative radiotherapy for bone metastases will be performed, using PubMed, Cochrane Library, Embase, clinical trials, American Society for Therapeutic Radiology and Oncology and European Society of Radiotherapy and Oncology. The primary outcome of interest is the incidence of skeletal-related event following palliative radiotherapy for bone metastases in prospective studies. The risk of bias and quality of evidence will be evaluated based on Cochrane Collaboration's tool and Grades of Recommendation, Assessment, Development and Evaluation in the network meta-analysis. We will conduct subgroup analysis and sensitivity analysis regardless of heterogeneity estimates.

Ethics and dissemination This study will synthesise the evidence regarding dose-fractionation schedule of palliative radiotherapy in patients with bone metastases. We hope the findings from this study will help clinicians and patients select optimum palliative radiotherapy by identifying the optimal dose-fractionation schedule of palliative radiotherapy with the most value in terms of patient-important outcomes. The evidence obtained from network meta-analysis will help to guide head-to-head research in the future. The results will be disseminated through international conference reports and peer-reviewed manuscripts. Ethics review board is not required for this network meta-analysis.

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INTRODUCTION

Bone is the most frequent localisation where some tumours frequently develop secondary growth, with the incidence of over 85% patients with lung, breast or prostate

Strengths and limitations of this study

- Our objective is to comprehensively evaluate the evidence for palliative radiotherapy in patients with bone metastases and compare all multiple fraction schedules with single fraction radiotherapy in terms of efficacy and toxicities.
- We hope the findings from this study will help clinicians and patients select optimum palliative radiotherapy with the most value in terms of patient-important outcomes in future.
- We will conduct a methodological and clinical heterogeneity study of a prespecified subgroup and also a sensitivity analysis to evaluate stability of the results in our network meta-analysis.
- The limitations of this network meta-analysis may be related to risk bias and quality of evidence, as the study includes not only randomised controlled trials (RCTs) but also non-RCTs.

cancers.^{1–3} Generally, bone metastases are asymptomatic in some cases, but it has been confirmed that at least 75% of patients with cancer presenting symptomatic bone metastases.⁴ Bone metastases induced skeletal-related events, for instance, pathological fractures, spinal cord compression and hypercalcaemia, impair quality of life and require multidisciplinary treatments.^{3,5}

Palliative radiotherapy could have considerable impact on patients with asymptomatic and symptomatic bone metastases.^{6,7} Palliative radiotherapy induced ossification is the key to successfully relief cancer pain and kills tumour cells.⁸ In routine practice, five dose-fractionation schedules of radiotherapy, including 40 Gy (2 Gy/fraction), 37.5 Gy (2.5 Gy/fraction), 30 Gy (3 Gy/fraction), 20 Gy (4 Gy/fraction) and 8 Gy (single fraction), are indicated for the treatment

of asymptomatic and symptomatic bone metastases; however, the optimal dose-fractionation scheme is a long-lasting controversy with the paucity of evidence to make the best choice for each patient.⁹

Ratanatharathorn *et al* found that higher dose fractionated radiotherapy produced better outcomes in pain control, in terms of frequency, duration and magnitude, than low-dose regimens.¹⁰ However, the majority of meta-analyses produced the opposite results suggesting that the differences between single fraction and multiple fraction radiation treatment regimens were small and non-significant.^{11–16}

There is little incentive for researchers to conduct active comparison trials for dose-fractionation schedule of palliative radiotherapy, due in part to the cost of clinical trials. Therefore, it is useful to synthesise evidence available from existing trials in dose-fractionation schedule of available palliative radiotherapy to compare the direct (based on previous trial comparisons) and indirect effects (palliative radiotherapy which are not previously identified in head-to-head comparisons).^{17–19} Our objective is to evaluate the evidence of the role of palliative radiotherapy for patients with bone metastases and, using a network meta-analysis, comprehensively compare all multiple fraction schedules with single fraction radiotherapy in terms of efficacy and toxicities.

METHODS AND DESIGN

The protocol of network meta-analysis will be prepared according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA).²⁰ We will report this system review and network meta-analysis according to the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions.²¹

Search strategy

Electronic searches by titles/abstracts of palliative radiotherapy for bone metastases will be performed, using PubMed, Cochrane Library, Embase (Ovid interface) and clinical trials (www.clinicaltrials.gov/). Titles and abstracts referring to palliative radiotherapy for bone metastases will be searched in the electronic American Society for Therapeutic Radiology and Oncology and European Society of Radiotherapy and Oncology. A time frame from conception to 18 April 2019 will be applied for the database search. Two authors who are experienced in the information retrieval will conduct separate search strategies independently. We will manually search references of included related systematic reviews/meta-analyses and other relevant publications to identify additional potential studies. We will record the reason for excluding the full text and generate a PRISMA flow diagram for the network meta-analysis.²²

The search terms will include the following domains of Medical Subject Heading (MeSH) terms: ‘bone

and bones’, ‘neoplasm metastasis’ and ‘radiotherapy’, according to Population Intervention Comparison Outcomes Study Design statement. MeSH and subheadings will be combined with ‘AND’ or ‘OR’. A sample PubMed search strategy is described in details in (see online supplementary appendix).

We will perform a pilot test to evaluate inter-rater reliability and adjust each screening stage: title and abstract, followed by full-text screening. Independent reviewers will screen the titles/abstracts of related studies based on an inclusion and exclusion criteria. The eligible or potentially eligible trials will be assessed by reading through the full texts when necessary. Moreover, disagreements will be resolved by having a discussion, with the help of the third reviewer.

Eligibility criteria

The eligibility criteria must include the followings: (1) Symptomatic and asymptomatic bone metastases; (2) Interventions and Comparators: any dose-fractionation schedule of palliative radiotherapy, which is defined as alleviating focal symptoms of bone metastases or minimising the occurrence of skeletal related events with low total dose^{23 24}; (3) Randomised controlled trials (RCTs) and prospective studies; (4) Report or provide enough information to calculate ORs; (5) The outcomes are overall response of pain and the incidence of skeletal related event (pathological fracture, spinal cord compression, surgery to bone and hypercalcaemia) and grades 3–4 haematological and non-haematological toxicity; (6) There will be no restriction on language, status and year of publication and (7) The samples are not subject to any restriction, for example, age, gender, performance status, ethnicity or nationality. The excluding criteria are applied as follows: (1) reirradiation, brachytherapy, radiopharmaceuticals, particle irradiation, intraoperative irradiation, half-body irradiation or concurrent irradiation and chemotherapy; (2) Reviews, posters, abstracts, editorials and case reports and (3) cross-sectional, cohort, case-control or retrospective study designs.

Outcomes

The primary outcome of interest is overall response of pain and the incidence of skeletal related event (pathological fracture, spinal cord compression, surgery to bone and hypercalcaemia)^{25 26} following palliative radiotherapy for bone metastases in prospective studies. Overall response of pain is defined as the sum of partial response and complete response. Pain progression is defined as at least a two-point increase in pain scores without a reduction in analgesics, or a $\geq 25\%$ increase in analgesics without a decrease in pain scores. The partial response is defined as at least a two-point reduction in pain scores without an increase in analgesics, or an analgesic intake decreased by more than 25% without an increase in pain scores. The complete response is defined as a pain score of zero (no pain) and no increasing morphine equivalent dose daily. Indeterminate response is defined as response

that could not be classified according to pain progression, partial response or complete response definitions.¹² The secondary outcomes are grades 3–4 haematological and non-haematological toxicity. The haematological toxicity is defined as anaemia, thrombocytopenia, leucopenia and neutropenia. For the response rates which are not reported in some trials, the percentages of responses will be recalculated according to the number of patients in the original studies.

Data extraction and management

The management of literature search records will be carried out in EndNote X7. A spreadsheet will be created in Microsoft Excel 2010 (Microsoft, Redmond, Washington, USA, www.microsoft.com) to collect outcomes of interest, such as the first author, study design, recruitment time frame, characteristics of bone metastases, details of interventions, sample size and endpoints (pain response, odds ratios and grades 3–4 haematological and non-haematological toxicity).

Bias risk

The quality and the risk of bias of RCTs will be estimated according to the following domains outlined in the Cochrane Collaboration's tool,²⁷ which includes seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other bias. RCTs will be independently reviewed by two authors and reported as high risk of bias '-', low risk of bias '+', or unclear risk of bias '?'. All non-RCTs will be assessed by Risk Of Bias In Non-Randomised Studies of Interventions guidelines.²⁸ Any disagreement in assessment will be resolved via having a discussion, with the help of the third reviewer.

Quality of evidence

The quality of evidence in the network meta-analysis will be evaluated based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE), which include the following five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias.²⁹ The staging system categorises GRADE evidence into four stages: (1) high, (2) moderate, (3) low and (4) very low quality. For RCTs, the starting confidence level for each network estimate is high, but will be rated down based on the evaluation of the five domains. For observational studies, the starting confidence level for each network estimate is low, but will be rated up based on the evaluation of the three domains: large effect, plausible confounding and dose–response gradient.³⁰ We will complete the GRADE process with GRADEprofiler software (GRADEpro, V.3.6.1) (available at: www.gradeworkinggroup.org).

Direct comparison and network meta-analyses

We will perform the traditional pairwise meta-analysis between each direct comparison, and generate graphics (network map, contribution plot, comparisons adjusted

funnel plot, pairwise meta-analysis, estimation of inconsistency, local heterogeneity and surface under the cumulative ranking curve (SUCRA) graphs)) for network meta-analysis using Stata V.13.0 (StataCorp). A network plot will be constructed consisting of nodes and edges per outcome, and the weight of each node will be proportional to the number of patients. A contribution plot will be proposed to evaluate the contribution of direct and mixed interventions to the estimation of network meta-analytical summary effects. A comparison-adjusted funnel plot will be conducted to assess the potential publication bias of all included studies (if more than 10 studies are present). To compare all dose-fractionation schedule of palliative radiotherapy, network meta-analysis for all outcomes is planned using GeMTC V.1.4.3, (MRC Biostatistics Unit, Cambridge, UK). Results regarding the pain, skeletal related event, grades 3–4 haematological and non-haematological toxicity are expressed as ORs for dichotomous outcomes with 95% CIs/credible intervals. Both fixed and random-effects models will be run for pain, skeletal-related event, grades 3–4 haematological and non-haematological toxicity.³¹ We, thus, use the deviance information criterion (DIC), of which a difference of more than five points is considered significant, for Bayesian model selection. We will select the model with the lowest value of DIC to explain our results.^{32 33} A rough comparison will be performed between the fit of the inconsistency model with that of the consistency model.^{34 35} Node-splitting analysis and loop-specific approach will be used to assess inconsistency in each comparison into direct and indirect evidence and closed loop in network meta-analysis, respectively.^{36 37} When there is no obvious inconsistency, the consistency model will be used; otherwise, an inconsistent model will be used.³⁶ The group with SUCRA of being the most effective in term of efficacy and safety will be evaluated based on the network meta-analysis results. According to SUCRA, we will rank the best probability of each intervention, followed by the second, the third and so on. We will perform a cluster analysis with SUCRA in terms of efficacy and tolerability. The extent of heterogeneity is assessed with the I^2 statistic. If $I^2 > 50\%$, we estimate statistical heterogeneity as evidence of high; as moderate if $25\% \leq I^2 \leq 50\%$; as low if $I^2 < 25\%$.³⁸ Two-sided $p < 0.05$ is considered significant.

Transitivity, homogeneity and consistency assumption

To achieve valid results, we will perform three key assumptions underlying the network meta-analysis (transitivity, homogeneity and consistency assumption).³⁹ First, we will conduct a thorough comparison of important study and patient characteristics. Second, we will perform a multivariate metaregression analysis to examine possible sources of heterogeneity using the same interventions. Lastly, indirect evidence via a common comparator is not different from direct evidence in the network.^{26 37}



Subgroup and sensitivity analyses

We will conduct prespecified subgroup analyses for our primary outcomes based on symptomatic and asymptomatic bone metastases. Symptomatic bone metastases are loosely defined as the use of palliative radiotherapy or surgical intervention to relieve pain, incident of new symptomatic pathological bone fractures and spinal cord compression,⁴⁰ whereas asymptomatic bone metastases are defined as no bone pain and no evidence of pathological fracture or spinal cord compression.⁴¹ Additional subgroup analyses will be conducted, if possible, based on the cancer type (breast and prostate cancer vs others), site of bone metastases (vertebral metastasis vs limb metastasis) and publication year (before 2002 vs after 2002).⁴²

A series of three sensitivity analyses will be conducted according to the impact of Bayesian model (fixed-effect model vs random-effect model), study design (RCTs vs prospective studies) and overall low risk of bias. Then, additional sensitivity analyses will be conducted by excluding one paper at a time and observing the robustness of the results.⁴³

DISCUSSION

The high prevalence of bone metastases imposes a substantial socioeconomic burden, which attracts the attention of governments, pharmaceutical companies, academic researchers and other healthcare payers. More recent RCTs and non-RCTs have demonstrated the potential benefits of certain dose fractionations of palliative radiotherapy.^{6 11 44–47} However, the results of publications focusing on palliative radiotherapy in patients with bone metastases varied significantly for study designs and varying outcomes of interest, especially for different dose-fractionation schedule. The optimal dose-fractionation schedule of palliative radiotherapy in patients with bone metastases has long been debated, with multiple fraction schedules and single fraction radiotherapy in terms of efficacy, safety and cost-effectiveness. Accordingly, there are substantial practice changes among radiation oncologists treating bone metastases. Single fraction radiation remains frequently used in Europe, Canada and Australia,^{48–50} while multiple fraction radiation is likely advocated in the USA⁵¹ and China.⁵²

To the best of our knowledge, the results of network meta-analysis of prospective trials will fill a crucial knowledge gap of optimal dose-fractionation schedule of palliative radiotherapy in patients with bone metastases. We hope the findings from this study will help clinicians and patients select optimum palliative radiotherapy in the future by identifying the optimal dose-fractionation schedule of palliative radiotherapy with the most value in terms of patient-important outcomes. Additionally, currently under-recognised palliative radiotherapy comparisons may be identified by system reviews and network meta-analysis to guide future research and head-to-head RCTs.

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Contributors QH and DC conceptualised the network meta-analysis. QH and XW codeveloped the search strategy. Both XT and QH were major contributors in writing the manuscript. The protocol was revised by DC, YC, XL and KC. DC was serving as guarantor and corresponding author of this study. All authors approved the final manuscript and agreed to submit the protocol in the journal.

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