



Comparative Effectiveness Review Disposition of Comments Report

Title: *Radiation Therapy for Metastatic Bone Disease: Effectiveness and Harms*

Draft report available for public comment from February 23, 2023, to March 26, 2023.

Citation: Skelly AC, Chang E, Bordley J, Brodt ED, Selph S, Fu R, Yu Y, Holmes R, Dana T, Stabler-Morris S, Riopelle D, Chou R. Radiation Therapy for Metastatic Bone Disease: Effectiveness and Harms. Comparative Effectiveness Review No. 265. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.) AHRQ Publication No. 23-EHC026. Rockville, MD: Agency for Healthcare Research and Quality; August 2023.
doi: <https://doi.org/10.23970/AHROEPCER265>. [Posted final reports](#) are located on the Effective Health Care Program search page.

Comments to Draft Report

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each draft report is posted to the EHC Program website or the Agency for Healthcare Research and Quality (AHRQ) website for public comment for a 3- to 4-week period. Comments can be submitted via the website, mail, or email. At the conclusion of the public comment period, authors use the commentators' comments to revise the draft report.

Comments on draft reports and the authors' responses to the comments are posted for public viewing on the website approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ.

Peer Reviewer, Technical Expert, and Public Comments and Author Response

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General Comments	As agreed, I have reviewed the sections the report that are relevant to consideration of surgery on the spine only. This is within my area of expertise a spine surgeon who evaluates and treats patients with metastatic cancer. I have not reviewed the other sections of the report. The descriptions of the evidence comparing surgery with radiation versus radiation alone are appropriate. The conclusions are appropriate. Methods are sound. The presentation of the results is very good. The discussion is appropriate. The conclusions are appropriate.	Thank you for your comments.
Peer Reviewer #2	General Comments	This is an important report that summarizes the existing literature in an unbiased manner. The target population/audience is explicitly defined and the key questions are appropriate and explicitly stated.	Thank you for your comments.
TEP #1	General Comments	Yes, clinically meaningful and the populations are explicitly defined (PICOTS table page 7). Key questions stated (and diagramed) pages 4-6.	Thank you.
TEP #2	General comments	It is very good overall. Cost analysis and perhaps an introductory figure to compare treatment methods would be useful.	Thank you. Thank you for your suggestions. We agree that costs matter. The introduction necessarily focuses on setting the stage for the key questions for the review. AHRQ reviews do not directly address issues of cost or cost effectiveness; the contextual questions provide limited information on the potential financial impact. In the future we will consider how figures or other visual aids may help present information more clearly in the introduction.
TEP #2	General comments	A summary table that is small, understandable and at 30k feet might be worth doing for abstract use and for what will be quoted by the field.	Thank you. The tables in the Executive Summary are meant to fulfill that purpose.

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TEP #2	General comments	Yes – this report described both the problem and the evidence in a way that I could understand.	Thank you.
TEP #2	General comments	Yes – I could find and understand the results and conclusions.	Thank you.
TEP #2	General Comments/References	Would single column them (I prefer one column only) and make sure DOI's and/or PMID's are present for all of them if possible. Many lack these links - ideally make the links "work".	AHRQ formatting requirements stipulate two columns for reference lists. We will double check the references for DOIs and PMIDs.
TEP #2	General comments/ abbreviations and acronyms	There are a lot....but it is unavoidable. The table at the end was appropriate. If you could limit them even a little it would help.	Thank you.
TEP #2	Executive Summary	Excellent summary and highly useful. This will be what 90% of readers read, plus the figures (good figure use).	Thank you.
TEP #2	Executive Summary	Optional to make an A- an A: Table is busy...a graphical image in addition to the table could be of use perhaps.	Thank you for your suggestions. In the future, we will consider the use of graphical images in our reports to assist with readability.
Peer Reviewer #1	Introduction	See above [<i>Ref: As agreed, I have reviewed the sections the report that are relevant to consideration of surgery on the spine only. This is within my area of expertise a spine surgeon who evaluates and treats patients with metastatic cancer. I have not reviewed the other sections of the report. The descriptions of the evidence comparing surgery with radiation versus radiation alone are appropriate. The conclusions are appropriate. Methods are sound. The presentation of the results is very good. The discussion is appropriate. The conclusions are appropriate.</i>]	Thank you.
Peer Reviewer #2	Introduction	The introduction is well-written but it does not sufficiently address the fact that clinical practice (especially in fee-for-service models) does not reflect published professional statements/guidelines regarding appropriate use of single or hypo-fractionated radiation for bone metastases. This is stated on page 73 (key point 1), 74, and 91 but I think it should be included more explicitly in the introduction.	Thank you for your comments. Page 2 of the introduction introduces the concern that "...there is substantial variation in how palliative radiotherapy is delivered." We've added the following sentence: Despite guidelines and general consensus that single fraction radiation treatment (SFRT) may confer similar benefits and reduce patient burden versus multiple fractions, single fraction regimens may be underutilized."

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Peer Reviewer #2	Introduction	There is also a need to more explicitly emphasize the balance of optimal clinical outcomes (for example, having complete pain control but spending 10 of the last 30 days of life going to/from radiation treatments vs. having nearly complete pain control but having only 1 radiation treatment in that last month of life).	A sentence has been added to convey that decision making should seek to balance the impact of treatment frequency in the remaining months of life with potential for optimizing clinical outcomes.
TEP #1	Introduction	Clear concise statement of the scope of the clinical issue at hand and presentation of the key issues to consider within that larger clinical problem.	Thank you.
TEP #2	Introduction	No issues. A lot of uninterrupted text/a little text heavy...some clear indication of the controversies in a table/graphic would be useful.	Thank you for your suggestions. This is challenging given the page limits.
TEP #2	Introduction	The billing costs of ebrt/imrt/3dcrt/sfirt should be front and center....as costs matter.	Thank you for your suggestions. We agree that costs matter. The introduction necessarily focuses on setting the stage for the key questions for the review. AHRQ reviews do not directly address issues of cost or cost effectiveness or billing Information in the contextual questions provides limited information on the potential financial impact.
TEP #2	Introduction	A treatment plan with dose wash could be of interest maybe...maybe not....	Thank you for your suggestion. This doesn't seem to be within the scope of the introduction or review, particularly given the heterogeneity in populations, etc.
Peer Reviewer #1	Methods	See above [Ref: As agreed, I have reviewed the sections the report that are relevant to consideration of surgery on the spine only. This is within my area of expertise a spine surgeon who evaluates and treats patients with metastatic cancer. I have not reviewed the other sections of the report. The descriptions of the evidence comparing surgery with radiation versus radiation alone are appropriate. The conclusions are appropriate. Methods are sound. The presentation of the results is very good. The discussion is appropriate. The conclusions are appropriate.]	Thank you.
Peer Reviewer #2	Methods	The inclusion and exclusion criteria are clear and the search strategies are explicitly stated and logical.	Thank you for your comments.

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Peer Reviewer #2	Methods	Page 7: The wording for KQ3 in the intervention row in Table 1 is confusing-- what are b) and c) referring to?	<p>Thank you.</p> <p>Key question # is stated in the text above the table and the b and c in the table correspond to the comparisons made:</p> <p>This is in the text:</p> <p>Key Question 3. What is the effectiveness and what are the harms of EBRT in the palliative treatment of bone metastases in symptomatic adults for the following:</p> <ul style="list-style-type: none">a. EBRT compared with another single MBD treatment modality (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/ vertebroplasty)b. EBRT combined with another treatment modality (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/ vertebroplasty) compared with EBRT alone?c. EBRT combined with another treatment modality (e.g., surgery, radionuclide therapy, bisphosphonate therapy, ablation kyphoplasty/ vertebroplasty) compared with the other (same) treatment modality alone?

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TEP #1	Methods	Yes, in reviewing Appendix Table A-1, inclusion and exclusion criteria and well-defined and logical. The outcomes measures are well defined (and the manuscript takes time and attention to where there is variation in outcomes definition). Statistical methods are appropriate.	Thank you.
TEP #2	Methods	Well done, no changes. I liked it and the use of the appendix to put things into a place where people can take a deep dive.	Thank you.
Lisa Bradfield, ASTRO Guideline Taskforce	Methods	Was there an expressed query for trials of RT vs. no RT that was performed? We think the answer is no but want to have this confirmed.	No. There was not a specific search done targeting trials of RT vs. no RT. Our searches were very broad and should have been sufficient to capture these. We did do a revised search for reirradiation because we found so few originally (wanted to do our due diligence), but that is the only “expressed query” performed.
Peer Reviewer #1	Results	<i>See above [Ref: As agreed, I have reviewed the sections the report that are relevant to consideration of surgery on the spine only. This is within my area of expertise a spine surgeon who evaluates and treats patients with metastatic cancer. I have not reviewed the other sections of the report. The descriptions of the evidence comparing surgery with radiation versus radiation alone are appropriate. The conclusions are appropriate. Methods are sound. The presentation of the results is very good. The discussion is appropriate. The conclusions are appropriate.]</i>	Thank you.
Peer Reviewer #2	Results	The authors state that SF EBRT is associated with a small decrease in overall pain response at up to 4 weeks post-treatment compared to MF EBRT. This is likely to be misinterpreted by the readership and I do not think is the main take away that should be emphasized as this data is based on the inclusion of two poor quality studies (which, when removed from analysis, leads to no difference found between SF and MF at 4 weeks).	Thank you for your comments. The review team, which did include clinical as well as systematic review methodology experts felt that it was important to report this for transparency together with the associated sensitivity analyses so that readers could consider their own conclusions. The Appendix also contains analyses based on last follow-up.

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Peer Reviewer #2	Results	It is also unclear to what extent the pain response is deemed clinically significant and this is worth mentioning.	<p>Consistent with other reports from our EPC, clinical significance thresholds for magnitude of effect are provided in Appendix J.</p> <p>The magnitude of effect is represented in the ES tables as well as the tables in the discussion section.</p>
Peer Reviewer #2	Results	I think it is worth looking at the overall pain response between MF EBRT and SF EBRT for studies that have data for the 4 week post-treatment time point. Using the range of post-treatment to up to 4 weeks creates notable variety in the time frames at which pain is assessed (for example in one study data was included that was only at 2 weeks post treatment).	<p>Thank you for your suggestion.</p> <p>For meta-analyses looking at post-RT up to 4 weeks, if studies reported earlier time frames, we used the data closest to the 4 weeks for pooled data represented in figure 3 comparing SF and MF EBRT. Given the substantial consistency across studies showing no difference between SF and MF EBRT, additional analyses excluding studies at <4 weeks would not change conclusions.</p> <p>Upon review of our data in the meta-analysis, 2 studies reported data for less than 4 weeks: Foro Arnalot 2008 at 3 weeks and the RR was 0.87 (95% CI 0.75 to 1.02). Again, removing this trial would not change the conclusions.</p>
Peer Reviewer #2	Results	The figures and tables were descriptive and clear. The layout of results was organized well. It was helpful to have it clearly stated which combination of therapies had insufficient data. (page 58).	Thank you for your comments.
Peer Reviewer #2	Results	The contextual factors are extremely well written and capture the context of this report very well.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
TEP #1	Results	Results are reported in adequate (and great) detail for our purposes. One thing I wish was done more adequately throughout was the speaking to this issue of patient prognosis and timeframe of risk. For example, the Hoskin et al. JAMA 2019 RCT of single vs. mutlifraction for cord compression is in a short prognosis patient population (Median OS 3 months). It matters what population we are studying, as this population doesn't necessarily apply to a patient with longer OS. Many studies have the median OS of patients (in general) so might help to have added this info more up front to know what general condition this patient population is in. A cord compression study in patients with median survival of 9-12 months says something very different from a study with a population surviving a median of 3 months. Tables don't parse that out.	We understand that prognosis may impact outcomes. Although this information was not included in results tables, where OS is reported, it is described in the appendices for secondary outcomes. Detailed data abstraction includes information on OS, attrition (including death), tumor/other factors that were reported that my impact prognosis and the extent to which studies reported information on prognosis. Not all studies provide information on survival. Only one study formally stratified by prognosis; see Appendix Table B 34.
TEP #2	Results	I like figure 3 [ref: <i>Single versus multiple fraction EBRT: Overall pain response by timeframe</i>]. Good overall. Hard to make this part simple and short, so no changes. I think the figures are well done.	Thank you.
TEP #2	Results	No changes - good and broken into sections in what is clearly a compromise demanded by the complex, varied data.	Thank you.
Lisa Bradfield, ASTRO Guideline Taskforce	Results	Did RCTs restrict interventions between baseline and assessment that could influence the primary endpoint? For example, receipt of systemic therapy could influence pain response after delivery of RT. Did trial inclusion criteria or baseline characteristics parse out the timing of interventions like analgesics/steroids/chemo between those which were present at baseline vs. those that were not present at baseline (ie. interventions given concurrently)?	Information on concurrent treatments can be found in the detailed Evidence Tables in Appendix E, specifically column H. Additionally, study inclusion and exclusion criteria (column E) provide information regarding prior/current/concomitant treatments allowed or disallowed.

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Lisa Bradfield, ASTRO Guideline Taskforce	Results	<p>In the key question 3b regarding EBRT/SBRT + surgery vs EBRT/SBRT alone (p58-59). Is there a way to emphasize (or make it painfully obvious) that all the quality literature is spine mets only and not others (ie, there was no literature for upper extremity bone mets or lower extremity or pelvis bone mets)? Would help with clarification of outcomes.</p>	<p>There are already several statements in the description of included studies that the RCT and the NRSI were in patients with spinal metastasis, including the following statement: “In all five studies, spinal metastases were an inclusion criterion.”</p> <p>The overall SOE for the outcomes includes consideration of all studies. Two of the NRSI that were rated as fair did include patients with nonspine metastasis, however the treatment was focused on the spine.</p>
Lisa Bradfield, ASTRO Guideline Taskforce	Results	<p>Along those lines: EBRT + surgery vs surgery alone (p72). Can we be explicit that spine mets was excluded from this study?</p> <p>Rationale: In the surgery world, spine tends to be treated differently than non-spine. Indications for surgery for each also tend to be different, e.g., pathologic fracture in the femur is almost always treated surgically. Pathologic fracture in the spine vertebral body is not always treated surgically, and often it is not.</p>	<p>Spine metastasis is not mentioned in this study specifically. The listed exclusion criterion for this study was: Previous radiation therapy to the fracture site.</p> <p>The inclusion criteria, which is reflected/described in the description of included studies, were: ICD-9 codes for metastases to the bone or pathologic fracture and a surgical procedure code involving a femur, acetabula or humerus; Impending pathologic fracture confirmed by orthopedic surgeon. Author’s Table 1 lists femoral and humeral fracture sites in addition to “other” (7% vs. 3%) which is not further specified; but presumably non-spine as well. While all of this infers that treatment was of nonspine fracture/impending fractures, it’s not explicitly stated</p>

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<p>Lisa Bradfield, ASTRO Guideline Taskforce</p>	<p>Results</p>	<p>Is it possible to create tables like Appendix B4-6 but for the outcomes of pain and ambulatory status? If so, is it also possible to collapse the endpoints for all RT-- ie, results are listed In Appendix E for pre- vs. post-RT per randomization arm, such as SF vs. MF. Can these data be collapsed such that it is pre- vs. post-any RT (ie, pre- vs. post-RT pain scores for combined SF +MF)? Can meta-analysis of pain response be performed with hazard ratios for pre- vs. post RT (either keeping the randomization arms separate or combined as previously mentioned)?</p>	<p>The report analyses, tables and plots are consistent with the protocol for answering the key questions, discussions with the sponsor and AHRQ guidelines. Detailed data abstraction is available in the appendices.</p> <p>The EPC sought clarification on the requests and discussed them with ASTRO. ASTRO expressed a desire to have additional overall analyses based on combining data across RCT treatment arms (i.e., non-comparative analyses).</p> <p>Several concerns were raised by the EPC:</p> <p>The EPC analysis in the report followed the published protocol which focused on comparative effectiveness evaluations and reflects discussions with ASTRO throughout the project. These additional analyses would be beyond the scope of the protocol and raise methodological concerns.</p>



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Lisa Bradfield, ASTRO Guideline Taskforce (cont'd)	Results (cont'd)	(comment above)	<p>Per the protocol, only comparative studies were selected for inclusion and case series (pre-post studies) were excluded. Any analyses of pre-post data from included studies only would ignore the cases series/pre-post studies that were excluded based on the protocol, and estimates may (or may not) differ importantly from analyses that would include such excluded studies. This approach would not be methodologically sound.</p> <p>The evidence for pain in particular (both dichotomous outcomes related to response and continuous form such as VAS) is contained throughout the report and appendices and detailed data abstraction.</p> <p>The EPC expressed willingness to create additional tables such as those in appendix B from the data abstraction and asked ASTRO to provide a prioritized short list of such outcomes. A follow-up response from ASTRO indicated that, based on further discussion with the sponsor, additional tables would not be needed</p> <p>As we do not have access to individual patient data, time to event, etc., meta-analyses on hazard ratios are not possible.</p>

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Peer Reviewer #1	Discussion/Conclusion	See above [Ref: As agreed, I have reviewed the sections the report that are relevant to consideration of surgery on the spine only. This is within my area of expertise a spine surgeon who evaluates and treats patients with metastatic cancer. I have not reviewed the other sections of the report. The descriptions of the evidence comparing surgery with radiation versus radiation alone are appropriate. The conclusions are appropriate. Methods are sound. The presentation of the results is very good. The discussion is appropriate. The conclusions are appropriate.]	Thank you.
Peer Reviewer #2	Discussion/Conclusion	The implications and findings are clearly stated. I appreciate the authors highlighting the need for high quality studies evaluating functional status and quality of life.	Thank you.
Peer Reviewer #2	Discussion/Conclusion	On page 92 (line 29), I recommend rewording "substantial increased risk" of re-irradiation" to "greater likelihood for re-irradiation" since there is evidence that radiation oncologists are more likely to feel comfortable re-irradiating a site that has only received 1 fraction than a site that has had MF EBRT.	Thank you. This has been reworded.
TEP #1	Discussion/Conclusion	Yes, implications and limitations are adequately stated. It would have helped to characterize studies a bit further by providing greater detail (and discussing further) the prognosis of the population, as noted above.	Thank you for your comments. This was not generally described in the various studies. Where OS is reported, it is described in the appendices for secondary outcomes. Detailed data abstraction includes information on OS, attrition (including death), tumor/other factors that were reported that may impact prognosis and the extent to which studies reported these.
TEP #2	Discussion/Conclusion	Good. No cost analysis is done - on policy it is key to understand that SBRT bills at a higher rate so use of SBRT may be driven by billing...perhaps not for this paper but something to note...single fraction 3d such as 8 x 1 saves money...compared to 30 Gy in 10 fractions...etc.	Formal evaluation of treatments costs or cost-effectiveness was not within the scope of this review and is not done for AHRQ EPC reviews. Contextual Question 3 addresses patient financial distress based on EBRT dose/fraction scheme or technique and provides limited information on the potential financial impact.
TEP #2	Discussion/Conclusion	It is good. Link to the summary figures perhaps.	Thank you.

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