Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Radiation Therapy for Brain Metastases

Draft report available for public comment from July 14, 2020 to September 14, 2020.

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Comments to Draft Report

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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 the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
TEP #1	Quality	Fair	Noted.
TEP #2	Quality	Superior	Noted.
TEP #3	Quality	Good	Noted.
TEP #4	Quality	Good	Noted.
TEP #5	Quality	Superior	Noted.
TEP #6	Quality	Good	Noted.
Peer Reviewer #1	Quality	Superior	Noted.
Peer Reviewer #2	Quality	Good	Noted.
TEP #1	General	Please see below	Noted.
TEP #2	General	This report is comprehensive in its review, clear in its reporting of findings and provides information truly relevant to support shared decision making between patients and providers. The perspectives of patient and family caregiver priorities are captured as priorities for future research, and the findings here indicate that very few studies have included sufficient emphasis on quality of life, functional and cognitive impairment - all key factors to patient decisions among treatment options. These points are included as a clarion call to action on page 50 (regarding strength of current evidence) and 53 (featuring importance of redoubled palliative care research investment).	Noted.

Commentator & Affiliation	Section	Comment	Response
TEP #3	General	The draft report summarizes a large body of research and is clearly and succinctly written. I have a few major comments for the authors to consider. They are relevant to all four key questions unless otherwise stated. Please see attached file.	Comments of the reviewer have been inserted into this document.
TEP #3	General	The draft report summarizes a large body of research and is clearly and succinctly written. I have a few major comments for the authors to consider. They are relevant to all four key questions unless otherwise stated.	Noted.
TEP #4	General	This review selected an important topic that desire to be updated on professional guidelines. Authors raised critical and well defined research questions for guiding this review.	Noted.

Commentator & Affiliation	Section	Comment	Response
TEP #5	General	Questions: The lack of nuance in the key questions leads to lack of nuance and value in the recommendations and conclusions. E.g,, the SRS questions can be boiled down to: Is SRS good or bad. It is not that simple and essentially all radiation oncologists and neurosurgeons actively involved in it operate on a higher level of knowledge than implied by the question. Questions that don't take into account number and volume of lesions, location of lesions, and performance status are not useful.	It is certainly true that clinicians use a nuanced framework incorporating a number of factors such as those mentioned to guide clinical decision making and research. The key questions were created with input from a panel of key informants (including a radiation oncologist), public commentary, and a stakeholder discussion conducted by PCORI. The questions were designed to be broad enough in scope to allow for a review of many patient-related and treatment-related factors. Patient-level data was not available, so some factors such as location of lesions could not be analyzed. For factors such as number of lesions and volume of lesions, this information was abstracted when available, however these were inconsistently reported and when reported lacked sufficient detail (mean and standard deviation) for pooled analysis. This limited our ability to analyze these findings for this systematic review

Commentator & Affiliation	Section	Comment	Response
TEP #5	General	The manuscript is clearly written and organized well. The questions posited are clinically meaningful. The target populations and audience are explicitly defined.	Noted.
Peer Reviewer #1	General	This is a clinically meaningful report. The target population and audience are explicitly defined. The key questions are appropriate and explicitly stated.	Noted.
Peer Reviewer #1	General	One general comment is that citations are missing for some sections. The authors should put the citations on.	We have re-reviewed the report and added missing citations where appropriate.
TEP #6	General	It reads very staccato….not smoothly. It is hard to really get breadth or insight from it.	We have expanded the implication section of the discussion section to address this comment.
TEP #6	General	Bias of KPS is missing in action….a patient in bad shape or with 16 mets is not the same as one in good shape….that should be absent in trials…but trials are selected patients for this reason….those not being selected…get WBRT perhaps a lot more….as SRS may not help them, etc.	We have added this important point to the discussion section.
TEP #6	General	Cost analysis – SRS can generate huge bills. Something to note.	This is an important factor but a cost analysis is not within the scope of this comparative effectiveness review.
TEP #7	General	Use of terminology likely “concrete” effect estimate seems to lack scientific rigor and specificity.	We have deleted or revised the word as appropriate.
TEP #7	General	Statements like “data are lacking for immunotherapy” could be changed to “high quality data are lacking”.	Thank you, we have made this clarification in the report.

Commentator & Affiliation	Section	Comment	Response
TEP #7	General	Seizure analysis did not appear to use a validated system such as the Engel classification.	The method of grading and reporting seizure varied across studies. We have added this point to the results and discussion sections.
TEP #7	General	Overall, it is disappointing that there was not sufficient high quality evidence to definitively answer many KQ's. Is there any value to recommending that higher quality studies should be considered for government and agency funding?	We have added this point to the future research section in the discussion.
TEP #7	General	Regarding the existing data being available through journal publications or data repositories, this is a nice idea but has a cost and sometimes logistical hurdles associated with it. Should we recommend that federal funding be used and policies be developed to more easily facilitate data repositories? Finally, what is the role of patient registries to obtain data for analyses like this in the future?	Thank you, we have added these points to the discussion.
TEP #7	General	The work overall seems well done. Again, this is a very important effort. Thank you for allowing me to review it.	Noted.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1, Kirsten Aquino AANS/CNS	General	1- The authors need to clarify better what is the "Effect Estimate" they calculated that for each question.	We have added a reference to effect estimates to the method section of the Executive Summary to clarify that we used hazard ratios, relative risks, and standardized mean differences. We also added the specific estimate to the key points in the Executive Summary, expanded the Methods section in the report and the appendix.
Public Reviewer #1, Kirsten Aquino AANS/CNS	General	2- The authors mention that Radiation Therapy does not have any effect after Surgery. There are scores of studies that show an overall benefit of radiation after surgery versus surgery alone for brain metastases. The authors even state that the majority of the studies showed this benefit, however when they plotted the results in their model they did not find any significant benefit. I would encourage the authors to reconsider their methodology because it may be difficult to pool data from different studies together and then get unexpected results. While the majority of the studies have shown a benefit, I cannot convince myself to why their computational analysis did not find a benefit.	The analysis in KQ3 showed that none of the individual studies or pooled results across studies demonstrated a statistically significant overall survival advantage with the addition of WBRT or SRS after surgery. Regarding intracranial progression, measures to assess the effects varied, and studies evaluated unique interventions and comparisons, so no two studies could be combined in pooled analysis.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1, Kirsten Aquino AANS/CNS	General	3- WBRT with memantine has shown a delayed risk of cognitive decline. The authors should acknowledge that in their recommendation even though the analysis they did using their computational methods did not show a significant difference. The authors should reconsider their statements regarding memantine.	The results of RTOG 0614 showed delayed risk of cognitive decline. The key findings from this trial were added to the results section and included in the discussion to inform readers. As noted in the discussion, we are unable to provide definitive effect estimates for this outcome because these findings have not been replicated. This is not a critique of the study, but a statement reflecting the strength of evidence.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	General	We thank the authors of the ARHQ Review of Radiation Therapy for Brain Metastases. We greatly appreciate the high degree of effort expended to review and assess the published literature and summarize findings in this report. Please see the coordinate comments below sent on behalf of the ASTRO Brain Metastases guideline task force.	Noted.

Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	General	1) We are concerned that a considerable number of clinically relevant randomized clinical trials have been discarded due to AHRQ methodology, and as a result, the clinically relevant trial questions are not answered in this Review. In contrast, findings where AHRQ methodology can be applied (e.g., use of radiation sensitizers) are disproportionately emphasized relative to their utility in modern clinical practice.	Re 1) We reviewed 9,265 citations, 1,520 as full text, and contacted all known authors who have published relevant RCTs - we are not aware of additional relevant RCTs. We did exclude studies with pre-1990 data per the recommendation from the technical expert panel as the technology does not reflect current clinical practice. The results section of the report summarizes results across studies and focuses on effect estimates that are based on more that one study, consistent with the aims and objectives of the systematic review. However, based these comments, outcomes from individual studies were also added to the text and the summary of findings tables. All included studies are documented in detail in the appendix of the report and findings are fully accessible to the reader. The detailed evidence table shows all 97 included studies. The result chapter did report effect estimates and the strength of evidence for summary estimates and positive findings were highlighted in the report. Some of these findings may not

Commentator & Affiliation	Section	Comment	Response
			be as clinically relevant in current practice as others. There are important outcomes that we found had low or insufficient strength of evidence based on AHRQ EPC program strength of evidence assessment categories, for a number of reasons detailed in the report. It is important for providers, patients, researchers and policy makers to be aware of these limitations of the current evidence base. Of course, current recommendations and decisions must be made based on the best available evidence.
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	General	2) The document mentions in several sections that survival outcomes from multiple studies cannot be combined and analyzed, but the document is not clear as to rationale why this combined analysis cannot be done.	Re 2) The most common reason is that studies did not report the outcomes in sufficient detail (i.e. hazard ratios). Time to event data has to be analyzed as a hazard ratio and although some studies reported the mean survival for the intervention groups, the means alone are not sufficient for further analysis. We have added more detail to the method section to clarify this point.

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Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	General	3) Several modern trials have reported neurocognitive function and patient-reported outcomes as primary or secondary endpoints. In general, these trials have utilized the same neurocognitive testing battery to permit standardization. In addition, several of these trials have significant influenced clinical practice in the brain metastasis population, where these endpoints are deemed clinically significant. The document does not discuss these findings in sufficient detail.	Re 3) The most common reason was that studies did not report the outcomes in sufficient detail (e.g., studies did not report the mean together with a standard deviation, did not report numerical results for the intervention and the control group, or reported findings in other formats such as the number of patients reaching a threshold.
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	General	4) One of the challenges of the brain metastasis population are the myriad tumor histologies and thereby prognoses that influence outcomes. Literature regarding prognostic indices is considered “out of scope” but is quite crucial to interpreting trial results. For example, the WBRT+/- surgery findings could be influenced by differences in entrance criteria between the 3 studies with subgroup analyses by others showing better outcomes for better prognosis patients.	Re 4) Tumor histology and prognosis are certainly important factors. The discussion section was revised to emphasize the importance of prognostic indices for patient care, research and policy makers. The discussion will also be edited to clarify that the studies that developed prognostic indices were not necessarily "out of scope", but to note that these studies were not directly part of this review, based on inclusion/exclusion criteria. With respect to subgroup analyses of studies, patient level data was not available. Subgroup analysis comparisons across studies were not possible when studies did not report the same analysis and outcome in sufficient detail.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	General	5) We would recommend including sample sizes in the source data tables to help the reader gauge the relative importance of the particular study.	Re 5) We were puzzled by this comment as the evidence and the summary of findings table includes the sample size.
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	General	6) As readers, we found the document to be difficult to read. For instance, reviewing the document frequently required flipping back and forth between the reference list and the text. At the end of each section, we would recommend including requisite additional information, such as all of the references reviewed and/or the relevant sections of the tables listed in that section. In conclusion, while the AHRQ Review of Radiation Therapy for Brain Metastases provides some utility in terms of well-researched literature tables, we have concerns with several of its analyses and its clinical relevance in modern clinical practice. Thus, in our development of Task Force Guidelines for the Management of Brain Metastases from the American Society for Radiation Oncology, we do not plan on incorporating the findings of this study.	Re 6) Thank you for the feedback. We have consequently added all relevant studies to the summary of findings table for KQ1-3, including findings that were based on a single study only. It is understood that the guideline will be based on additional considerations outside of the evidence synthesis. We hope that we have addressed your concerns and that the material assembled for you is useful for the guideline development process.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Evidence Summary	With regard to Evidence Summary, can the Main Points be more explicit with regard to which treatments or combinations of treatments would be more beneficial to patients? I found the text under “Implications and Conclusions” more useful.	We have added more detail but acknowledge that we found little robust evidence for comparative benefit.
Peer Reviewer #2	Evidence Summary	Very interesting superficially but looking at the summary section alone the reader cannot tell what is compared to what, i.e., are we comparing intracranial disease control, systemic control, progression free survival, or overall survival or a combination? Are we looking at WBRT compared to SRS or no treatment or some other parameter?	We have reviewed the summary statements and added the comparator where it was not stated and ensured that the outcome is not ambiguous.
Peer Reviewer #2	Evidence Summary	There is no mention of targeted therapy in the summary section. Later on it becomes clear that targeted therapy is combined with cytotoxic chemotherapy. That should be made clear in the summary.	Thank you. We clarified that systemic therapy refers to chemotherapy, targeted therapy or immunotherapy. As you noted, the use of the term 'chemotherapy' when referring to analyses that include cytotoxic chemotherapy and targeted therapies may be misleading, so we changed to using the term systemic therapy through the manuscript.

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Peer Reviewer #2	Evidence Summary	The blanket statements on findings across lung cancer, breast cancer, or melanoma is frankly naïve and limits the value of the evidence summary. Physicians and patients are simply not that poorly versed in this topic so as to think they are the same, though it would probably be useful to nonmedical policy makers not interested in meaningful details.	This is a valid point. However, the vast majority of studies included a mixed population of tumor types, and the analyses and outcomes reflect this fact. While individual studies may have performed subgroup analyses based on tumor type or other factors, we do not have the patient-level data required to analyze this across studies.
Peer Reviewer #2	Evidence Summary	The comments on lack of effect of CNS therapies on overall survival is very well known and this summary confirms this knowledge.	Noted
Peer Reviewer #2	Evidence Summary	Please clarify the difference between postoperative radiation therapy and postoperative WBRT. Even looking into the body of the report this is not pointed out clearly when the two terminologies are first used together.	Postoperative radiation refers to any radiation after surgery (WBRT or SRS). This was clarified in the report.
Peer Reviewer #2	Evidence Summary	Clarify in the summary: "Postoperative radiation therapy may decrease the risk of dying from brain metastases, but the pooled effect was not statistically significant": compared to what?	Compared to surgery alone. We made this clarification in the report.
Peer Reviewer #2	Evidence Summary	The attempt to assess quality of life and cognition is excellent and has the same results as essentially all other forays into this topic.	Noted.
Peer Reviewer #2	Evidence Summary	"There was insufficient evidence to determine the effects of WBRT plus surgery, WBRT plus memantine, and hippocampal avoidance WBRT": again, clarify in the summary what the comparator is.	Compared to WBRT alone. We made this clarification in the report.

Public Reviewer #3, Jerome Graber, M.D., M.P.H. University of Washington	Evidence Summary	Should include more mention on the possible influence of brain metastases number and total volume as well as status of systemic disease and histologic and molecular subtypes on prognosis and outcomes. Should also mention that from the 1990s to 2019, the systemic treatments for lung, breast and melanoma cancers have change substantially, so there could be a time effect of this on the studies pooled for this analysis. The term “cancer site” is used, and this is vague and confusing (do they mean cancer primary site? or site/location within the brain?)	For factors such as number of lesions and volume of lesions, this information was abstracted when available, however these were inconsistently reported and when reported lacked sufficient detail (mean and standard deviation) for pooled analysis. Regarding cancer type this was explored. As explained in the results for KQ1b and KQ2b, there were very few studies that included only patients with brain metastases from a single type of cancer. The majority of studies had mixed samples of tumor types which could not contribute to an analysis. In KQ1b, only one study evaluated breast cancer brain metastases only. While there did appear to be a difference in deaths due to brain metastases, this breast cancer subgroup consisted of a single study, so we noted that this finding should be regarded with caution. For KQ2b, only one RCT enrolled only patients with brain metastases from lung cancer, and only one cohort study included breast cancer patient only. While we found no difference in overall survival based on tumor type, only a few studies contributed to this

Commentator & Affiliation	Section	Comment	Response
			analysis. While the systematic review was limited in the ability to analyze these factors, a number of influential prognostic indices and studies that did not meet inclusion criteria have highlighted the importance of these factors. We have expanded the discussion section discussion of this subject to reflect the importance in current decisional dilemmas. Regarding the change in systemic treatments over time, this is a good point and this will be added to the discussion section. Thank you for the comment regarding the term "cancer site", to clarify this was edited to "primary tumor type" throughout the report.
Public Reviewer #4 Danielle Cunningham, M.D. Mayo Clinic	Evidence Summary	Bullet point 1: Would phrase instead alone and in combination with or without systemic therapy, and for resected or unresected 38:38lesions rather than pre or post surgery to be more inclusive of non-operative trials-Bullet point 8: Would rephrase last sentence to Postoperative SRS may have a greater survival advantage compared to WBRT for clarity	Thank you, the suggested edits have been incorporated.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #5, Francisco Espinoza	Evidence Summary	This section is very concise and summarizes the findings of the use of different therapies to treat brain tumors. The use of whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) seem to demonstrate the best results but the evidence in the literature is not sufficient. It would be interesting to see how the use of these therapies work in combination with other interventions that come from fields such as occupational therapy or psychotherapy to see the effects on cognitive, functional status and quality of life.	Thank you for the comment. Our review did not identify studies that directly assessed occupational therapy or psychotherapy as interventions or cointerventions. In the discussion section we have added the need to investigate these cointerventions for patients with brain metastases.
TEP #1	Introduction	Please see below	Noted.
TEP #2	Introduction	Background for review scope and purpose is well described.	Noted.
TEP #4	Introduction	Well described the study rationale of this systemic review.	Noted.
Peer Reviewer #2	Introduction	No comments	Noted.
TEP #5	Introduction	Establishes the problem clearly.	Noted.
Peer Reviewer #1	Introduction	Page 15 of 280: "although hippocampal-avoidance WBRT is more selective regarding the dose for different areas of the brain" is a misleading phrase, particularly for non-radiation oncologists. It may be rephrased to "hippocampal-avoidance WBRT is performed to avoid conformally the memory-specific neural stem compartment in the hippocampi".	Thank you for the comment, this sentence has been edited as suggested.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3, Jerome Graber, M.D., M.P.H. University of Washington	Introduction	Show in table the histology specific prognostic indices for breast, lung and melanoma	We have added mention of these prognostic indices and included references for the readers.
Public Reviewer #5, Francisco Espinoza	Introduction	The introduction defines the different forms of therapy very well. Brain metastases may complicate the lives of cancer patients which requires treatment to attempt to get rid of the tumors. As technology advances there will be more effective ways to remove brain tumors in cancer patients. It would be great to hear more about these [and] #039;other therapies [and] #039; as cointerventions and their effects on increasing treatment efficacy or reducing toxicity. Overall, it is a good introduction that focuses on the different types of radiation therapies.	We have added a neuroprotection section to the results section to highlight the results from studies incorporating memantine and hippocampal avoidance, and added more discussion of these topics in the discussion section.
TEP #2	Methods	Yes [Were the methods clearly described]	Noted.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Methods	The body of the report focuses on a small number of studies where meta-analysis was possible. This is a sensible approach; however, it would be more informative if the authors could attempt to summarize the remaining studies using alternative synthesis methods (please see Chapter 12 of the Cochrane Handbook https://training.cochrane.org/handbook/current/chapter-12). These methods would be superior to a narrative description (or no description at all). For example, authors could consider summarizing the range and distribution of observed effect and vote counting the direction of effect. Method also exists for combining p-values (not vote counting p-values). Please also consider tabulating and visually displaying results that cannot be meta-analyzed. Chapter 12 provided some examples. Appendix D alone is not very informative for understanding the results for each comparison and outcome.	We appreciate the suggestion and thank the reviewer for pointing out that the extent of the variation in result presentation was not communicated sufficiently. The challenge is the wide variety of result presentation and it was not as simple as reporting the range of effect estimates as often there were no effect estimates at all. To address this comment, we have added all individual studies to the text and the Summary of Findings table. The table now makes it clearer what exactly the challenges were (e.g., combining a sentence such as “there was no significant difference” with a p-value, the number of patients meeting a certain threshold, and a study reporting means without measure of dispersion) and documents all available information on the outcome of interest.

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TEP #3	Methods	The Methods section starting on Page 4 could benefit from a bit more details. For example, please describe how the overall risk of bias was formed so that readers can understand Figure 3. Risk of Bias summary (I believe this was not described in Appendix for Methods either). Furthermore, the description of domains of RoB assessment on page 6 is inconsistent with domains displayed in Figure 3. Please add when and how meta-regression and indirect comparison was conducted. Please explain the rationale for limiting the search to 1990 and onwards. Please be accurate about including cohort studies (I was confused whether cohort studies were only considered for safety outcomes or both safety and efficacy outcomes).	To address this point, we have expanded some sections and refer more often to the detailed methods appendix.
TEP #4	Methods	Key research questions and analytic framework for RT treating brain mets (Fig 1) were well defined that including patient populations (with 3 highly selected disease cohorts), interventions. The selection of multiple outcome domains (survival, functional status, health/QoL and AEs on PROs or professional assessments) are well covered the known knowledge in this area. Appendix A provided detailed Methods used. Search strategy is sufficient. Inclusion and exclusion, grading the risk of bias, data synthesis and analysis methods were well defined. It was clear the reason of not included meta-analysis.	Noted.

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Peer Reviewer #2	Methods	It appears chemotherapy combines targeted therapy and cytotoxic chemotherapy [Page 14: "Temozolomide, a drug shown to be effective in cancers that originate in the brain, was the systemic therapy most often assessed. Other studies evaluated veliparib, topotecan, enzastaurin, vandetanib, endostatin, thalidomide, erlotinib, fotemustine, gefitinib, and the combination of bevacizumab and gefitinib"]. This is not appropriate given their very different mechanisms of action. Ideally the data will be recalculated separately: one set for cytotoxic chemotherapeutics and one for targeted or "molecular" therapies.	The broader question was the effect of chemotherapy as compared to no chemotherapy and that is displayed on page 14. However, we stratified the chemotherapy agents into the suggested categories and present the subgroup analyses as well.
Peer Reviewer #2	Methods	The policy for use of only Randomized Controlled Trials (RCT's) substantially limits the value of this analysis. These studies in patients are hugely biased toward individuals with excellent performance status, mobility, access to advanced care and willingness to cooperate. It rules out the use of nuanced modifications in therapy and difficult to monitor therapy as these treatments do not generalize easily across multiple institutions, which are often needed to reach numbers that provide statistical power. The policy used in the document to rule out studies using meaningful historical comparators misses useful, often surprising data, and heavily biases this write up toward the minimally significant (see the forest plots with nearly all data hanging about a midline axis)and marginally useful findings providing provided.	Nonrandomized studies have evaluated questions, including nuanced outcomes based on patient, cancer, or treatment related factors. On the other hand, findings from nonrandomized studies are also subject to significant limitations. The decision to limit inclusion to RCTs for KQ1-3 was based on input from multiple stakeholders, including the Key Informants and Technical Expert Panel. However, all available data on effectiveness outcomes from the included observational studies were also abstracted and are included in the evidence table.

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TEP #5	Methods	I appreciated the links to the AHRQ EPC program methods. IC/EC clearly identified and appropriate. The 1990's date for IC may appear concerning, but in light of the goals of the review was appropriate. Statistical methods were appropriate for the project goals.	Noted.
Peer Reviewer #1	Methods	Page 21 of 280, Figure 2- Please explain what "Background" in the box mean?	This is stated right before the figure.
Public Reviewer #3, Jerome Graber, M.D., M.P.H. University of Washington	Methods	Could adverse events of intracranial hemorrhage/stroke be assessed?	The adverse events that were abstracted and reported were based on input from the Technical Expert Panel. Hemorrhage or stroke were not one of the adverse events selected for analysis.
Public Reviewer #5, Francisco Espinoza	Methods	The methods section clearly states the methods used to conduct the review. In addition, the key questions listed demonstrate the main points discussed in the entire report.	Noted.
TEP #3	Results	Meta-analysis figures should be properly labeled with (1) sample size from each study; (2) relative weight from each study; (3) label under X-axis indicating which treatment is favored on each side of null; (4) more meaningful x-axis tick values.	Because the intervention and comparator is critical for the figures, we were already short of space and could not add more detail to the rows. However, we have revised the x-axis for a more meaningful scale.

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TEP #3	Results	All summary of findings table can benefit from reporting at least the range of effect when meta-analysis was not possible.	The problem was not that studies could not be included in a meta-analysis, rather we could not compute the effect size. We have however, now added a description of the results for individual studies where possible.
TEP #3	Results	Please remove funnel plot and Egger's test for publication bias because there were too few studies and because there was a search date restriction.	We have added the point to the discussion section.
TEP #3	Results	Other minor comments: Page 9, first bullet under "Key Points". Could you help the readers to understand why WBRT plus radiosensitizers improved overall survival compared with WBRT alone but likely does not affect deaths due to brain metastases? Page 10, last paragraph. Two few studies for testing for publication bias. Page 13, paragraphs under KQ1a. Unclear when meta-regression or indirect comparison was conducted. Page 24, first paragraph. What is the reference group for the three p-values reported here? Page 18, last paragraph. "hence effects may have been masked by other" – change masked to confounded.	Re page 9: This point refers to a result that is no longer relevant (both outcomes do not show an statistically significant effect in the updated dataset) Re page 10: Removed Re page 13: We have added a sentence to methods section Re page 24: We believe this comment refers to page 14 and we have revised the sentence for clarity. Re page 18: We respectfully disagree as the sentence refers to the detection of effects.

Commentator & Affiliation	Section	Comment	Response
TEP #1	Results	Page 11 WBRT plus SRS versus WBRT alone: When both the trial from National Cancer Institute, Cairo University, Cairo, Egypt and RTOG 9508 report survival, survival curves, and median OS why can't the results be combined for analysis? This occurs repeatedly throughout the document where for example survival outcomes from different trials are not combined and analyzed. Likely there is a good reason but it does not make sense to me. It would be helpful if reasons are provided throughout and including this example.	Neither study reported survival hazard ratios to allow for studies to be combined.
TEP #1	Results	Page 11 WBRT plus SRS versus WBRT alone: I believe Kondziolka (1999)155 should be included in this analysis as is comparing WBRT plus SRS vs WBRT alone.	Thank you, we have added the author reported data as the effect estimate could not be determined.
TEP #1	Results	Page 13 KQ1a. How does effectiveness vary by dose fractionation schedule and technique: This goes to my earlier question, why are some trials such as Chatani excluded from the OS analysis as median OS times were reported. It does make sense that this trial was not analyzed in the group (250. Zhu J, Dong Q, Wang W, et al. SIB-IMRT in Symptomatic Brain Metastases for NSCLC: A Randomized Controlled Study of WBRT Comparing 25Gy and 30Gy. Journal of Thoracic Oncology) because it incorporates SIB of 50 Gy and is quite different from the other 4 trials.	The Chatani trial reported the median overall survival, rather than a hazard ratio that can be meta-analyzed. Zhu et al. report comparative effectiveness; we have now added the results to the summary of findings table together with the other individual studies.

Commentator & Affiliation	Section	Comment	Response
TEP #1	Results	Page 14 KQ1c. How does effectiveness differ by the addition of systemic therapies: There is reference in the text to figure 5, should this be referencing figure 6?	Thank you, this has been corrected in the report
TEP #1	Results	Page 14 KQ1c. How does effectiveness differ by the addition of systemic therapies: Why was Sperduto ref 226 not included in this analysis?	The study is reported under KQ2 because it combines WBRT plus SRS.
TEP #1	Results	Page 19 SRS plus WBRT versus SRS alone: There is reference to Kondziolka (1999)155 when should instead reference Kocher (2011) 153 SRS vs. SRS + WBRT. Was the analysis conducted with incorrectly assigned trials?	Thank you, yes, Kondziolka should not have been cited in the sentence, we have corrected the typo. The study by Kocher is described under KQ3.
TEP #1	Results	Page 19 SRS plus WBRT versus SRS alone: Again goes to my earlier points, these 4 trials report survival, survival curves, and median OS why can't the results be combined for analysis?	The studies cannot be combined if they did not report the outcomes in sufficient detail (i.e. hazard ratios).
TEP #1	Results	Page 21 it states: Four studies reported on cognitive function.82, 88, 95, 161 Studies reported insufficient details to compute effect sizes and reported results varied by intervention, comparator, and measures used to assess effects (Appendix D). It would be helpful if cognitive endpoints were analyzed. Trials 82 and 161 should be excluded as they used screening measures (e.g. MMSE). Trials reference 88 and 95 used similar measures of cognitive function (most of the measures were the same) so would be good if these 2 trials could be analyzed together.	Ref 88 (Chang et al.) reported percent of patients with significant neurocognitive decline (deterioration in HVLT-R of at least 5 points) at 4 months, ref 161 (Brown et al.) reported percent of patients with cognitive deterioration with several tests (including HVLT-R) at multiple time points, and mean and SD per group were not reported. But as outlined earlier, we have added the author reported results to the summary of findings table.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Results	Detail of report sections is appropriate and adequate. In particular, highlighting the shortage of studies and evidence available to guide treatments that minimize adverse effects, including quality of life concerns, physical and cognitive impairments, and other priorities for patients and their families.	Noted.
TEP #3	Results	The language used to describe the results does not reflect the certainty of evidence. For example, when the certainty of evidence is low, instead of saying treatment A improves survival, it's more accurate to say A may improve survival. When the certainty of evidence is moderate, one could say A probably improves survival. This is a suggestion for the authors to consider.	We have critically reviewed the language when communicating uncertainty.
TEP #4	Results	Fig 2 layout the included studies. A nice summery of risk of bias on Fig 3. By each key questions, the key points and comparative results per intervention were well reported. Under Appendix C, detailed results were presented for included studies, the effect size if studies allowing to compute. Appendix D with the strength of evidence presented per study. On Results session page 27, author stated the difficulty to summery of functioning status or cognitive functional comparison, both were included in the Framework.	Noted.
TEP #4	Results	Page 30-33, while the strength of the evidence presented, the name of specific SAEs missing except death.	We have added examples of the specific serious adverse events reported in the treatment arms.

Commentator & Affiliation	Section	Comment	Response
TEP #4	Results	Page 34-35, what's the method to quantitatively assess radiation necrosis standard and consistent across studies?	Methods of assessing and grading radiation necrosis varied across studies, including CTCAE, RTOG late radiation morbidity scoring criteria, LENT SOMA and a unique assessment. This point was added to this section of the report.
TEP #4	Results	Page 35-42, would be nice to see the range of AEs been reported from these studies, either patient-reported outcomes (PROs) or professionally assessed. And, it'd be great to provide the reason for current selected items (headache, fatigue, vomiting, seizure), the tool/scale involved (CRC-AEs, PRO-CTCAEs, PRO tools). For example, if any study from 91 reports measured sleeping disturbance, drowsiness, poor appetite or distress from treatment, if there is multiple symptom assessment tool or HRQoL tool with these PRO items been used? These are regarding systemic symptoms that might presenting the tolerability that FDA highly interested, and impact on HRQoL from patient's perspective.	We have added the reported serious adverse events to the section as outlined above, which also addresses this comment. The documented adverse events were prespecified outcomes selected with the help of the technical expert panel; we have added this information when in the radiation necrosis section, i.e., the first specific adverse event documented in KQ4, and refer to Appendix A for more information. Thank you for raising the issue of tolerability and quality of life; we have expanded on the Implications for Clinical Practice, Education, Research, or Health Policy section.
Peer Reviewer #2	Results	Easily understandable Study Flow Diagram.	Noted.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Results	The results are presented in a detailed format. Key attributes of studies were described. No studies were overlooked to the knowledge of this reviewer; nor were any studies included that should not have been. The tables, figures, and appendices were clear and intuitive.	Noted.
Peer Reviewer #1	Results	Page 24 of 280 WBRT plus radiosensitizers- It is mentioned there are 5 studies but only 4 is shown in Figure 4.	Five studies were identified and cited, but two of the studies could not be included in the overall survival analysis presented in Figure 4. To clarify this point, the text was revised to explain this point in the text above Figure 4.
Peer Reviewer #1	Results	Page 25 of 280 WBRT plus SRS versus WBRT alone- It is important to specify that this comparison pertains to patients with limited brain metastases (1-3 lesions).	Thank you, this information has been added to the report.
Peer Reviewer #1	Results	Page 32 of 280 "We also did not detect a systematic of the patient prognosis'- Please rephrase.	Corrected in the report.
Peer Reviewer #1	Results	Page 36 of 280 KQ2b- It appears that reference number 150 is not correctly cited as this is not an SRS specific) and not an RCT. The RT modality is cranial RT. Please clarify.	Thank you, this observation is correct. The citation was removed.
Peer Reviewer #1	Results	Page 40 of 280, SRS after Surgery "The findings favored the observation after surgery arm"- Please specific the endpoints.	The endpoints were specified later in the sentence, but this sentence was clarified to make the endpoints clear.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	Page 48 of 280 Figure 16- El Gantery study should have 3 arms (WBRT + SRS, WBRT, SRS)	The figures can only show pairwise comparisons. However, we have added the results to the alternative comparator to the text.
Peer Reviewer #1	Results	Page 49 of 280 Figure 17- El Gantery study should have 3 arms (WBRT + SRS, WBRT, SRS)	The figures can only show pairwise comparisons. However, we have added the results to the alternative comparator to the text.
Peer Reviewer #1	Results	Page 51 of 280 Fatigue- "The study did not find a statistically significant difference in the incidence of headaches between treatment arms" Are the author referring to fatigue instead of headaches? Please clarify.	Correct, this was fixed in the report.
Peer Reviewer #1	Results	Page 52 of 280 Figure 20- El Gantery study should have 3 arms (WBRT + SRS, WBRT, SRS)	The figures can only show pairwise comparisons. However, we have added the alternative comparator to the text.
Peer Reviewer #1	Results	Page 54 of 280 Figure 22- El Gantery study should have 3 arms (WBRT + SRS, WBRT, SRS)	The figures can only show pairwise comparisons. However, we have added the alternative comparator to the text.
Peer Reviewer #1	Results	Page 56-57 of 280 Serious adverse events- Please include citations for the studies discussed	Thanks, added.
Peer Reviewer #1	Results	Page 57 of 280 No. of adverse events and Radiation necrosis- Please include citations for the studies discussed	Thanks, added.
Peer Reviewer #1	Results	Page 57-58 of 280 Headaches- Please include citations for the studies discussed	Thanks, added.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	Page 58 of 280 Figure 25- The figure legend does not match the figure	We have revised the title to address this comment.
Peer Reviewer #1	Results	Page 59 of 280 Fatigue, Seizure, Vomiting- Please include citations for the studies discussed	Thanks, added.
Public Reviewer #3, Jerome Graber, M.D., M.P.H. University of Washington	Results	grammatical [and] quot;...key points, synthesizes [sic] the data... [and] quot; page 7the distinction between radiosensitizers and chemotherapy is somewhat arbitrary. Consider pooling these analysis (but do include the separate analysis as well)grammatical page 18 [and] quot;did not detect a systematic [sic] of the.... [and] quot;page 22 KQ2b: this would be a good place to include more data on the different histologic and molecular subtypes, as well as tumor number and volume possible effectsgrammatical page 27 [and] quot;details were insufficient details [and] quot;grammatical page 37 [and] quot;some the WBRT arm [,] and across [and] quot;	Thank you, the grammatical errors were corrected and the final report will be copyedited. Outcomes for the factors mentioned (histologic subtype, tumor number and tumor volume) were abstracted, however the ability to analyze outcomes was limited for several reasons. Patient-level data was not available. Most studies had a mixture of histologies, which could not be separated out, and there were few studies looking at specific tumor histologies. Where possible, outcomes for tumor type were reported. For tumor size and volume, reporting was inconsistent and often lacked sufficient detail (mean and standard deviation), limiting the ability to analyze these findings for this systematic review

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4 Danielle Cunningham, M.D. Mayo Clinic	Results	Would rephrase Risk of bias sentence to Risk of bias varied, and data on treatment toxicities were at higher risk for bias than data on effectiveness of treatment. oIn the WBRT + radiosensitization section, would add that WBRT + radiosensitizer leads to increased toxicity oWould add though several studies demonstrate neurocognitive benefit to section describing WBRT + memantine or hippocampal sparing-Report spends significant time discussing WBRT + radiosensitizer, but this is not commonly employed in practice-Goal of memantine with whole brain RT is not to improve overall survival but rather to mitigate neurocognitive effects.	We have added the increased toxicity of radiosensitizers to the discussion section. Details of the neurocognitive benefits of memantine and hippocampal-avoidance WBRT reported in single RCTs were added to the results (under a new heading of neurocognition) and discussion sections. In the discussion section we clarified that radiosensitizers are not routinely used or recommended in current practice.

Public Reviewer #5, Francisco Espinoza	Results	The results sections effectively shows the comparison of the various interventions and their effectiveness with WBRT or alone. Very detailed evidence of what interventions work together. The addition of research on the effects of other interventions from different disciplines on cognitive effects, quality of life, and functional status would show more promising results in the treatment of cancer patients. With improvements in technology there is an increased chance of survival for patients which means that these three outcomes become more relevant to the overall post-surgery treatment of the patient. Occupational therapy is one field that offers to improve the quality of life of cancer patients through involvement in meaningful activity. In a research involving the effects of occupational therapy on health-related quality of life in women with breast cancer, Petruseviciene et al., (2018) attribute the improvement of QOL of the cancer patients to engagement in meaningful and purposeful activities which in turn affects the patients emotional status, self-esteem, and confidence. In the study, the intervention group completed a 6-week community based occupational therapy program which resulted in a statistically significant improvement in aspects of quality of life such as physical functions, role functions, and fatigue, (Petruseviciene et al., 2018). In another study on patients with brain tumors, CHAN, Xiong [and] amp; Colantonio, (2015) describe the ways in which occupational therapy can be crucial to the recovery of these patients such as assistance with activities of daily	Thank you for the comment. While none of these studies met eligibility criteria for this review, you raise a useful point. In the discussion section we have added the need to investigate these cointerventions for patients with brain metastases.

Commentator & Affiliation	Section	Comment	Response
		living, energy conservation, anxiety management, pain and symptom control, and fatigue reduction. Combining occupational therapy with brain metastases therapy can be an effective cointervention that may significantly improve the quality of life, functional status, and cognitive function of patients with cancer.References:Chan, V., Xiong, C., [and] amp; Colantonio, A. (2015). Patients With Brain Tumors: Who Receives Postacute Occupational Therapy Services? American Journal of Occupational Therapy, 69(2). doi:10.5014/ajot.2015.014639Petruseviciene, D., Surmaitiene, D., Baltaduoniene, D., [and] amp; Lendraitiene, E. (2018). Effect of Community-Based Occupational Therapy on Health-Related Quality of Life and Engagement in Meaningful Activities of Women with Breast Cancer. Occupational Therapy International, 2018, 1-13. doi:10.1155/2018/6798697	
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 1	1) We are concerned that multiple radiation sensitizers are being combined together in the "radiation sensitizer" group and would recommend that each study should stand on its own since biologically these are different radiation sensitizers. In addition, the results of these trials are not influential in modern clinical practice where these radiation sensitizers are rarely utilized, and the endpoint of nausea is not commonly one of clinical concern in this patient population.	Re 1) Only 3 studies could be combined for any of the outcomes, hence we were unable to subdivide them further. We have added a reminder for the reader that the forest plots display the individual study results to address this comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 1	2) For the analysis of WBRT+SRS versus WBRT alone, we are unclear as to why survival results from RTOG 9508 and from El Gantery et al. cannot be combined.	Re 2) They are combined in KQ4, but the studies do not report on the same effectiveness outcome in sufficient detail to combine the studies for KQ1.
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 1	3) We would recommend including Kondziolka et al. (1999) in the analysis comparing WBRT plus SRS versus WBRT alone.	Re 3) Yes, the study is now included in the new narrative synthesis

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 1	4) The analysis of WBRT plus surgery versus WBRT alone cites the Vecht (Ann Neurol. 1993 Jun;33(6):583-9) and Mintz (Cancer. 1996 Oct 1;78(7):1470-6) RCTs but excludes the landmark Patchell et al RCT (New England Journal of Medicine. 1990 Feb 22;322(8):494-500.). We anticipate that omission of the Patchell RCT is due to the criterion that studies had to be reported in the 1990s or later. If the Patchell study had been included, it is possible that survival would have been improved with surgery in the analysis.	Re 4) Correct, eligibility criteria (Table A1) excluded studies based exclusively on pre-1990 data, based on input from the Technical Expert Panel. The Patchell study referenced enrolled patients from 1985 through 1988, and as such was excluded. We considered adding the findings of the trial to the existing studies, but the outcome data cannot be combined. To address this point, we have added the findings of this study to the discussion for the readers.
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 1	5) We would recommend separating WBRT plus memantine text from WBRT plus steroids text since their clinical indication and biology are quite different. Instead, we would recommend combining WBRT plus memantine with WBRT plus hippocampal avoidance (mentioned under “Other results”) in a separate section of neuroprotection. Additionally, given the practice-changing nature of these studies, we would recommend discussion of the results of RTOG 0614 and NRG CC001, as they are unlikely to be repeated.	Re 5) Thank you for the suggestion. WBRT and memantine and hippocampal avoidance WBRT will be placed in separate section for neuroprotection under KQ1. Key findings from these trials are now included in the summary of findings table along with all other individual studies.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 2	1) For the analysis of SRS plus WBRT versus SRS alone, the reference mentions Kondziolka (1999), when it should be referencing Kocher (2011). We would recommend reviewing the analysis to make sure the correct study findings were included.	Re 1) Thank you, the citation has been corrected.
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 2	2) The text states only one RCT reported on overall survival and reported sufficient data to compute the hazard ratio. We were surprised by this statement, since there are at least 4 major RCTs that evaluate SRS +/- WBRT (Aoyama, Jama 295.21 (2006): 2483-2491; Chang, lancet oncology 10.11 (2009): 1037-1044.; Brown, Jama 316.4 (2016): 401-409; Hong, JCO 37.33 (2019): 3132-3141.) and 1 major RCT that reports on local therapy (SRS or surgery) +/- WBRT (Kocher JCO 29.2 (2011): 134). All of these trials report OS and many have been combined in prior meta-analyses (e.g., Tsao MN, Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database of Systematic Reviews. 2018(1).)	Re 2) Thank you for this comment. Brown et al. provided overall survival with hazard ratio and confidence intervals. We have reviewed Chang et al. and Aoyama et al. in the Cochrane review and we were able to compute the hazard ratio using the review as confirmation for our assumptions. The study by Hong et al. is included in KQ3. We combined the studies in a meta-analysis where possible and summarized them narratively.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 2	3) We are surprised that data on neurocognition could not be reported given that 2 studies had used this as a primary endpoint (Chang, lancet oncology 10.11 (2009): 1037-1044.; Brown, Jama 316.4 (2016): 401-409), with both showing improvements with SRS alone.	Re 3) Chang et al. – reported percent of patients with significant neurocognitive decline (deterioration in HVLT-R of at least 5 points) at 4 months, with a p-value. Mean and standard deviation for outcomes were not reported. Brown et al. reported percent of patients with cognitive deterioration with several tests (including HVLT-R) at multiple time points, with a p-value. Mean and standard deviation for outcomes were not reported. The data were reported similarly, but lack of mean and standard deviation prevented combining these studies for these neurocognitive outcomes.
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 2	4) We question the QOL analysis (figure 9) stating that the Brown et al study had no difference in QOL when the manuscript reports that there was a difference in QOL at 3 months in the abstract and at 12 months among long-term survivors. In addition, the QOL analysis from the Kocher et al study (published separately by Soffieti et al Journal of clinical oncology 31.1 (2013): 65-72) was not included.	Re 4) Meta-analyses for randomized trials use means and SDs per group at the latest follow up. However, we have added the information about positive signals for the 3 month follow up to the text.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 2	5) We are unclear as to why intracranial failures could not be analyzed when the 5 trials (Aoyama et al, Chang et al, Kocher et al, Brown et al, Hong et al) included intracranial failure analyses.	Re 5) Brown et al. reports intracranial progression with HR and CI. Chang et al. reports rate of intracranial progression at 1 year and number of patients with failure. Aoyama et al. reports rate of intracranial progression at 1 year and number of patients with failure. Hong et al. reports OR for intracranial failure. Kocher et al. reports number (and %) of patients with intracranial progression. While statistical pooling was not possible, we have summarized the results narratively.
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Key Question 3	1) The comparative effectiveness of postoperative SRS vs WBRT is directly informed by the one phase 3 multicenter trial on the topic (NCCTG N107C, Brown et al, lancet oncology 18.8 (2017): 1049-1060.) which addresses many of the relevant questions of this section (OS, intracranial control, QOL, and cognitive function). This trial reported that SRS (rather than WBRT) was associated with no differences in OS, superior cognitive function, superior QOL, and inferior intracranial control. Is it possible to summarize these findings for the reader? It seems somewhat unlikely that there will be a similar phase 3 trial design (postoperative SARS vs postoperative WBRT) forthcoming to pool together with the N107C data.	Following the comments, we have expanded the KQ3a section and report the study in more detail. In addition, we have also highlighted the key findings in the discussion.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Discussion/ Conclusion	Implications that include clear call for additional research capturing outcomes beyond disease-free or progression-free survival are appropriately discussed and featured throughout the report analysis of studies. Notably, the evidentiary limitations for particular quality of life outcomes concerns are captured clearly and correctly.	Noted.
TEP #3	Discussion/ Conclusion	The report will benefit from adding depth to the implications for research and practice.	We have expanded on the section in responding to peer reviewer comments.
TEP #4	Discussion/ Conclusion	This session provided clear information on study applicability, implications, and limitations. Proposals for future research are reasonable, while it'd be great to point out the challenge and importance of using PRO tools in such late stage cancer to gain better information of patient benefit from the given therapy by patient's perspectives.	Mention of the importance of patient reported outcomes was added to the proposals for future research.
Peer Reviewer #2	Discussion/ Conclusion	A very useful statement on page 49: regarding "..patients with a single brain metastasis in the RTOG 9508 trial. Local control was improved with the addition of SRS in both studies. The previously reported ASTRO guideline found that SRS added to WBRT improves survival for good prognosis patients with single brain metastasis, and it improves local control" is provided. This give useful guidance for patient management but is not in the "main points" summary on page 1 or "key points" on page 9. Please see that information is included in those locations.	This finding has been added to the key points and main points sections.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Discussion/ Conclusion	This reviewer appreciates the author's statements related to the need for future research to include more patient-reported outcomes. The last few statements on p. 50 were especially salient to this topic. This reviewer also appreciates the term, "decisional dilemmas" to address the concept of shared decision making in very challenging clinical situations. The limitations are clearly described. No important literature was omitted.	Noted.
Peer Reviewer #1	Discussion/ Conclusion	The major findings are clearly stated. The limitations of the studies are adequately described. The investigators included all the pertinent literature.	Noted.
TEP #6	Discussion/ Conclusion	See above.	Noted.
Public Reviewer #3, Jerome Graber, M.D., M.P.H. University of Washington	Discussion/ Conclusion	grammatical [and] quot;by the ASTRO [guideline] [and] quot;consider discussing that most trials studied interventions only at one time point. In real clinical practice, it is common for patients to have different treatments sequentially (i.e. multiple rounds of SRS, or SRS after WBRT or vice versa, chemotherapy after WBRT or SRS).	We added this important point to the applicability section of the discussion section.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #5, Francisco Espinoza	Discussion/ Conclusion	The discussion section summarizes the effectiveness of each therapy very well. WBRT seems to show the most promising results for improving the overall survival of patients. The use radiosensitizers in WBRT also shows positive results in improving overall survival. More research is needed to determine the effectiveness of the other interventions, which is still unclear.	Noted.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Discussion/ Conclusion	In conclusion, while the AHRQ Review of Radiation Therapy for Brain Metastases provides some utility in terms of well-researched literature tables, we have concerns with several of its analyses and its clinical relevance in modern clinical practice. Thus, in our development of Task Force Guidelines for the Management of Brain Metastases from the American Society for Radiation Oncology, we do not plan on incorporating the findings of this study.	There are limitations of the systematic review in addressing some of the current questions for guidelines. This review is not able to provide effect estimates for questions that have been investigated by a single study. This review was limited to RCTs for KQ1-3, so findings from nonrandomized studies, which may evaluate questions not addressed by RCTs, were not included. As noted in the report, variability in interventions, comparators, and reported outcomes limited the ability to combine studies. We found that many Key Questions had low or insufficient strength of evidence and provided explanations. While we hope an understanding of the strengths and limitations of this evidence can be useful, the above factors may limit the ability of this systematic review to address some decisional dilemmas important to the American Society for Radiation Oncology.
Public Reviewer #5, Francisco Espinoza	References	Proper references included. Organized and numbered	Noted

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #5, Francisco Espinoza	Abbreviations and Acronyms	Very helpful for those not familiar with the acronyms.	Noted.
Public Reviewer #5, Francisco Espinoza	Appendixes	Very well organized	Noted.
Public Reviewer #5, Francisco Espinoza	Does this report describes both the problem and the evidence in a way that you could understand?	This repost clearly states the problem, which is brain metastases, and the evidence which includes the different forms of therapy and their effectiveness in treating the problem. The report is clear and understandable. The use of charts and flow charts are helpful to see the summary of the findings.	Noted.
Public Reviewer #6, Anonymous	Does this report describes both the problem and the evidence in a way that you could understand?	not really, need to emphasize the local control benefit if radiation therapy (i.e. SRS to the resection cavity and unresected tumors). difficult when only limited to RCTs	The outcomes were selected with the help of a stakeholder expert panel but however we want to mention that intracranial progression was a key outcome and the results are summarized in the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, American Society for Radiation Oncology (ASTRO) Brain Metastases guideline task force	Did you find this report unnecessarily difficult to read?	Yes, see attached letter.	Noted.
Public Reviewer #5, Francisco Espinoza	Did you find this report unnecessarily difficult to read?	The report was not difficult to read	Noted.
Public Reviewer #6, Anonymous	Did you find this report unnecessarily difficult to read?	Yes	We have revised the layout to summarize the findings to make it easier for readers.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #5, Francisco Espinoza	Could you find and understand the results and conclusions?	The results and conclusions were clearly explained with a substantial amount of evidence to support the findings. There are very clear connections made to the interventions that are effective with the research that backs up the evidence.	Noted.
TEP #1	Clarity and Usability	The team did a commendable job pulling and sorting through all these trials and studies. However as a reader it is difficult to flip back and forth between the reference list and what you are reading. It would be helpful at the end of each section there is some additional information. For example the entire references reviewed in that section, for example the WBRT plus SRS versus WBRT alone section on page 11 it would be helpful to have the full references provided. Alternatively the relevant sections of tables such as C.1 could be provided. Regardless of what additional information is provided (to help the reader so they don't have to flip back and forth or use 2 screens) it could still also be summarized at the end of the current document as is currently provided (i.e. reference list, tables).	Thank you for this observation. The result section of the report summarizes almost 100 studies and 188 publications, hence it is difficult to provide detail without making the text hard to read. However, we have added individual results to the summary of findings table in the Result chapter so that the reader has a summary in one place. In addition, all individual studies are reported in the Result appendix.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Clarity and Usability	Expressing gratitude for meaningfully including patient and caregiver perspectives in the process for planning this systematic review, during the review itself, and in in comments opportunity to refine the synthesis of findings. Also applaud recognition of palliative care as an essential adjuvant therapy alongside disease-directed treatment in patients with brain metastases, in accordance with ASCO clinical guidelines and the National Consensus Project for quality palliative care.	Noted.
TEP #5	Clarity and Usability	I appreciate the opportunity to participate in this important review. The issue of brain metastases is an unfortunately common scenario with a clear potential for shared decision making.	Noted.
Peer Reviewer #1	Clarity and Usability	No further comments.	Noted.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Clarity and Usability	Asking about difficulties with reading the report is not a surprising question as it is well down in the weeds with a format that largely serves the writers of the relatively repetitive AHRQ documents. For instance, rather than just providing something as important as the definition of strength of evidence when first mentioned in the methods, the reader is directed to Appendix A, a relatively long document in and of itself. Then the reader has to dig for those facts rather than simply being told a page number in the appendix. I believe this reflects writing by authors and their delegates used to copying and pasting key items into these documents to save them time, rather than make them readable.	This point may have been addressed by adding individual studies to the summary of findings table.