Washington State Health Care Authority

Health Technology Assessment

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

Appendix J. Peer Review Comments and Disposition

October 10, 2012

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Peer Review Comments and Disposition

Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy

October 8, 2012

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PEER REVIEWERS

The Center for Evidence-based Policy is an independent vendor contracted to produce evidence assessment reports for the WA HTA program. For transparency, all comments received during the peer review process are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.

This document responds to comments from the following peer reviewers:

- Lia M. Halasz, MD
- Jing Zeng, MD

Specific responses pertaining to each comment are included in the public comment tables below.

LIA HALASZ, MD

REVIEWER INFORMATION:

Name: Lia M. Halasz MD

Title: Assistant Professor

Organization/University: University of Washington

QUALITY OF THE REPORT

Please rate the quality of the report by selecting the appropriate boxes. Unlimited text can be inserted into the comments field.

I. Scope		Comments	CEbP Response
Is the target population explicitly defined and relevant?	☒ Y ☐ N ☐ NA		
Were any interventions, comparators or outcomes omitted that should be included?	☒ Y ☐ N ☐ NA	I am concerned that the key questions that define the scope of the report do not address the true comparators for use of SRS and SBRT. The treatment choice for many patients with benign meningiomas, acoustic schwannomas, glomus jugulare tumors, single brain metastases, recurrent glioma, colorectal cancer, single liver metastasis, and operable stage I NSCLC would include surgical resection or SRS/SBRT. Often SRS or SBRT may have less	Thank you for your comment. The objective of the report was to evaluate the evidence base for external beam radiation compared to newer radiation techniques. The report objective was not intended to evaluate all treatments for a particular tumor. The report is a systematic review of studies published that met the specified inclusion criteria and therefore; all studies that met inclusion criteria are summarized regardless of the standard of care. We added additional background context and statements to make it clear that for a certain tumor, surgery is the standard of care not external beam radiation. We agree these outcomes are important.

	morbidity than surgical resection. In addition, though survival rate and harms are emphasized as outcomes, quality of life, neurocognition, symptom control, need for hospitalization, and time away from work are also important endpoints in considering EBRT versus SBRT/SRS.	However, few studies reported results related to quality of life including neurocognition, symptom control, need for hospitalization, and time away from work. We included these results in the tables of evidence in the few instances where they were available. Because of the paucity of findings for these outcomes, they were not summarized in the text except for brain metasteses where there were comparative results for these outcomes.
II. Executive Summary		
Is it clear and concise? ☒ Y ☐ N ☐ NA		
Does it accurately reflect the methods and results of the report? ☐ Y ☒ N ☐ NA	One of the inclusion criteria outlined is "treatments delivered in 10 or fewer fractions." However, SRT reports for radiation courses greater than 10 fractions were included for gliomas (e.g. Marcus 2005) and pituitary adenomas (e.g. Colin 2005).	Thank you for your comment. We added the qualifier "generally" to the criteria.
III. WA Utilization Section		
☐ Y ☐ N ☐ NA	This section was straight forward and informative. May be interesting to look at utilization rates in other states.	Thank you for your comments.
☐ Y ☐ N ☐ NA		
☐ Y ☐ N ☐ NA		
☐ Y ☐ N ☐ NA		
III. Introduction		
Background: Is the background adequately described? ☒ Y ☐ N ☐ NA	Yes. Minor comment: in Figure 2, other linear accelerators belong under the heading of IMRT as IMRT	Thank you for your comment. We deleted figure 2 from the report based on this comment and some of the public comments.

		does not just consist of arc therapy or tomo therapy.	
		Also, in the background on cost information, may want to have information on SRS for brain tumors, since SRS makes up the majority of cases rather than SBRT. I realize that this data may not be available, but should perhaps even mention that.	Thank you for your comment. There was little cost data identified. This study comes from an Agency for Healthcare Research and Quality report. We deleted this study out of the Executive Summary and Background of the report.
		Minor comment: Sentence that reads : "When used outside the CNS, it is referred to as SBRT and is usually delivered in ten fractions" is incorrect. Should it read "three to ten fractions"?	Thank you for this correction. The sentence should have read "ten or fewer fractions." We will use your numbers in the final report since they have greater specificity.
Clinical Overview: Is there an adequate and/or accurate clinical overview of the question?	☒ Y ☐ N ☐ NA	Perhaps more explanation of the decision to compare SBRT/SRS with EBRT only and not surgery or chemotherapy needs to be explained.	Thank you for your comment. The objective of the report was to evaluate the evidence base for external beam radiation compared to newer radiation techniques. The report objective was not intended to evaluate all treatments for a particular tumor. The report is a systematic review of studies published that met the specified inclusion criteria;therefore, all studies that met inclusion criteria are summarized regardless of the standard of care. We added additional background context and statements to make it clear that for certain tumors,surgery is the standard of care not external beam radiation.
		Also, I think it is important to	Figures 1 and 2 and the background section on

				emphasize that SRS and SBRT utilize the same radiation therapy as EBRT but are techniques to further spare normal tissues. It is not akin to testing the efficacy of a different medication.	pages 33 and 34 are meant to address this issue. To further emphasize the point, we have added several sentences to the background section.
Policy Context: Is the policy context clear?	☒ Y	☐ N	☐ NA	Yes.	
IV. Methods					
Are the methods for identifying relevant studies clearly described?	☒ Y	☐ N	☐ NA		
Are the criteria for the inclusion and exclusion of studies clearly described?	☒ Y	☐ N	☐ NA	Yes, but one of the inclusion criteria outlined is “treatments delivered in 10 or fewer fractions.” However, SRT reports for radiation courses greater than 10 fractions were included for gliomas (e.g. Marcus 2005) and pituitary adenomas (e.g. Colin 2005)	Thank you for your comment. We added the qualifier “generally” to the criteria.
Are the methods for grading studies and guidelines clearly described?	☒ Y	☐ N	☐ NA		
Was something excluded that should have been included?	☒ Y	☐ N	☐ NA	Kocher 2011 (EORTC 22952-26001) was excluded given that it had a surgical arm, however, it is a multi-institutional RCT and speaks to the argument for or against SRS for brain metastasis instead of whole brain RT. This decision is often based on the concept of the advantages of SRS being sparing	Kocher 2011 is discussed at background in the report but not included in the findings section due to the fact that the authors did not stratify the results by those who had SRS versus surgery. In addition, the authors made the assumption that surgery and SRS are equivalent in terms of outcomes.

				side effects of whole brain RT versus the advantage of whole brain RT decreasing in brain failure for brain metastases. I think it is important to use the RCT we have especially given how few there are.	
Was something included that should have been excluded?	☒ Y	☐ N	☐ NA	The category of "glioma" separate from glioblastoma multiforme is confusing. Clinically, high grade and low grade gliomas have different treatment strategies and indications for SRS.	We agree that having a category for glioma, which can be high grade (i.e. glioblastoma multiforme and anaplastic astrocytomas) or low grade and a separate category for glioblastoma multiforme may be confusing. However, we could not categorize study patients based on the descriptions provided in the articles. We elected to use the descriptor as reported by the author.
				It would be good to verify articles on SRT as these often pertain to fractionated courses with more than 10 treatments.	Thank you for your comment. We have verified the studies and added the qualifier "generally".
V. Results					
Is the presentation of the results well-structured and organized?	☒ Y	☐ N	☐ NA		
Has the evidence been accurately synthesized?	☐ Y	☒ N	☐ NA	For glioblastoma multiforme, the RCT (Souhami 2004) pertains to use of SRS as upfront treatment of GBM, but the conclusions state the evidence is for recurrent GBM. These are two different indications that should be made clear as SRS for recurrent GBM and high risk GBM may still have a role even if not indicated for upfront cases.	Thank you for noting that we should separate studies involving newly diagnosed from those involving patients with recurrent glioblastoma. We now emphasize this distinction in the description of the studies and in the overall summary. This change does not alter the conclusions appreciably since the strength of evidence is low for newly diagnosed glioblastoma and very low for recurrent glioblastoma.

		For the harms of SRS in the treatment of brain metastases, the manuscript Chang 2009b was labeled as a good quality trial, but the endpoint result of decreased performance of Hopkins Verbal Learning Test at 4 months was not included.	Thank you for the comment. We have added this information to the report and note that it is based on a subgroup (53%) of patients enrolled in the study and use of Bayesian statistics to obtain the projected difference between patients receiving SRS+WBRT and those receiving WBRT alone.
		For the harms of SRS in the treatment of gliomas, I completely disagree with the statement that SRS "potentially stimulates recurrence and progression to a more aggressive tumor type." The indication for treating low grade gliomas with SRS is often when they have transformed to a higher grade tumor and there is no evidence that radiation contributes to that transformation.	Thank you for your comment. We have removed this statement from the overall summary. The reviewer is correct in noting that without well-done randomized controlled trials and long-term follow-up, a cause and effect relationship can not be assumed as suggested.
Does the report adequately address effectiveness?	☐ Y ☐ N ☐ NA	The report does summarize the available literature, and I agree that level I evidence does not exist for most SRS and SBRT uses. SRS and SBRT often allow treatment for patients who are not candidates for EBRT or surgery given anatomical location or previous radiation therapy. I agree with excluding dosimetric comparisons from the report, however the ability of SRS and SBRT to improve technique and spare normal tissue may need to be	Thank you for your comments.

				considered in policies and it could be explained in the background section that SRS and SBRT are not different types of RT but technical advances using the same type of RT as EBRT. It is not akin to a new chemotherapy drug. Many indications for SBRT and SRS are rare enough that randomized controlled trials are not practical (as supported by the low number of cases performed annually in the WA utilization section) but I do agree that we have a continued need for further outcomes data.	
Does the report adequately address harms?	☒ Y	☐ N	☐ NA	Yes, I think that the available literature is summarized in the report, though the lack of good quality studies does point to a continued need for outcomes data on these treatments.	Thank you for your comments.
VI. Guidelines					
Are the guidelines adequately summarized?	☒ Y	☐ N	☐ NA	Note: I think there was a typo in the first section mentioning guidelines where it states that ACR guidelines do not recommend SBRT for stage I NSCLC. I think it should read "operable stage I NSCLC"?	The report was edited to read *operable* stage I NSCLC.
Is the quality of the guidelines clearly described?	☒ Y	☐ N	☐ NA		
Is there an adequate comparison of the guidelines to the evidence in the report?	☒ Y	☐ N	☐ NA		

VII. General Conclusions					
Do they summarize the effectiveness of the intervention?	☐ Y	☒ N	☐ NA	Though reports on SBRT for nonoperable NSCLC may not include a comparative arm, previous review (Sibley GS 1998) of medically inoperable T1-2N0 patients treated with RT alone 60-66Gy (standard EBRT) resulted in a 5y OS of about 15% with 30% of patients dying after local failure. Thus, 3-year OS rate of 50% to 60% and local control rates of 80% to 100% are large improvements over what was previously offered to patients. This is likely the reason that most case series did not use comparators in their methods. Please see additional comments above, question: "Has the evidence been accurately synthesized?"	Thank you for your comment. We added a brief background section to the evidence summary for lung cancer, so readers can easily make the comparison of estimates of survival with no treatment compared to SBRT, even though these estimate come from different studies done during different times. We agree that the differences are large.
Do they balance the effectiveness with the potential harms?	☐ Y	☒ N	☐ NA	In order to do this adequately, effectiveness and harms would need to be compared with the alternative treatment, which is often surgery.	Thank you for your comment. The objective of the report was to evaluate the evidence base for external beam radiation compared to newer radiation techniques. The report objective was not intended to evaluate all treatments for a particular tumor. The report is a systematic review of studies published that met the specified inclusion criteria and therefore; all studies that met inclusion criteria are summarized regardless of the standard of care. We added additional background context and statements to make it clear that for certain tumors,surgery is the standard of care not

				external beam radiation.
Do they address the strengths and limitations of the evidence adequately?	☒Y	☐ N	☐ NA	Yes, though by just using systematic reviews, which are often poor quality themselves some of the details of the RCTs we do have are left out (please see comments above).	The systematic review conclusions take into account the studies included in the review regardless of the quality. We summarize higher quality individual studies within the reviews that are relevant to the report. In regard to the Kocher 2011 article cited above, the study is discussed in the background of the report but not included in the findings section due to the fact that the authors did not stratify the results by those who had SRS versus those that had surgery as their initial treatment before being randomized to WBRT or observation. The focus of the Kocher 2011 RCT was to assess the impact of WBRT on outcomes.
VIII. Tables				
Are the figures clear and easy to read?	☒Y	☐ N	☐ NA	

I X. OVERALL REPORT RATING [1 = Very Poor, 2=Poor, 3=Average, 4=Good, 5 = Excellent]

Overall quality of the report:	☐ **1**	☒ **2**	☐ **3**	☐ **4**	☐ **5**
Clarity of the report:	☐ **1**	☐ **2**	☐ **3**	☒ **4**	☐ **5**
Presentation (design/formatting):	☐ **1**	☐ **2**	☐ **3**	☒ **4**	☐ **5**
Methods:	☐ **1**	☐ **2**	☒ **3**	☐ **4**	☐ **5**
Grading of the body of evidence:	☐ **1**	☐ **2**	☐ **3**	☒ **4**	☐ **5**
Scientific accuracy:	☐ **1**	☐ **2**	☐ **3**	☒ **4**	☐ **5**
Clinical relevance:	☐ **1**	☒ **2**	☐ **3**	☐ **4**	☐ **5**

X. Other Comments I think the methods and writing of the report are well done. It is clearly written and informative. However, I am concerned about the context the report will be taken in considering that the important comparator for many SRS/SBRT treatments is surgical resection rather than EBRT.

JING ZENG, MD

REVIEWER INFORMATION:

Name: Jing Zeng

Title: Assistant Professor

Organization/University: University of Washington, Department of Radiation Oncology

QUALITY OF THE REPORT

Please rate the quality of the report by selecting the appropriate boxes. Unlimited text can be inserted into the comments field.

I. Scope				**Comments**	**CEbP Response**
Is the target population explicitly defined and relevant?	X Y	☐ N	☐ NA		Thank you.
Were any interventions, comparators or outcomes omitted that should be included?	☐ Y	X N	☐ NA		Thank you.
II. Executive Summary					Thank you.
Is it clear and concise?	X Y	☐ N	☐ NA		Thank you.
Does it accurately reflect the methods and results of the report?	X Y	☐ N	☐ NA		Thank you.
III. WA Utilization Section					Thank you.
	☐ Y	☐ N	☐ NA		Thank you.
	☐ Y	☐ N	☐ NA		Thank you.
	☐ Y	☐ N	☐ NA		Thank you.
	☐ Y	☐ N	☐ NA		Thank you.
III. Introduction					Thank you.
Background: Is the background adequately described?	X Y	☐ N	☐ NA		Thank you.
Clinical Overview: Is there an adequate	X Y	☐ N	☐ NA		Thank you.

and/or accurate clinical overview of the question?				
Policy Context: Is the policy context clear?	X Y	☐ N	☐ NA	Thank you.
IV. Methods				Thank you.
Are the methods for identifying relevant studies clearly described?	X Y	☐ N	☐ NA	Thank you.
Are the criteria for the inclusion and exclusion of studies clearly described?	X Y	☐ N	☐ NA	Thank you.
Are the methods for grading studies and guidelines clearly described?	X Y	☐ N	☐ NA	Thank you.
Was something excluded that should have been included?	☐ Y	X N	☐ NA	Thank you.
Was something included that should have been excluded?	☐ Y	X N	☐ NA	Thank you.
V. Results				
Is the presentation of the results well-structured and organized?	X Y	☐ N	☐ NA	Thank you.
Has the evidence been accurately synthesized?	X Y	☐ N	☐ NA	Thank you.
Does the report adequately address effectiveness?	X Y	☐ N	☐ NA	Thank you.
Does the report adequately address harms?	X Y	☐ N	☐ NA	Thank you.
VI. Guidelines				Thank you.
Are the guidelines adequately summarized?	X Y	☐ N	☐ NA	Thank you.
Is the quality of the guidelines clearly described?	X Y	☐ N	☐ NA	Thank you.
Is there an adequate comparison of the	X Y	☐ N	☐ NA	Thank you.

guidelines to the evidence in the report?				
VII. General Conclusions				
Do they summarize the effectiveness of the intervention?	X Y	☐ N	☐ NA	Thank you.
Do they balance the effectiveness with the potential harms?	X Y	☐ N	☐ NA	Thank you.
Do they address the strengths and limitations of the evidence adequately?	X Y	☐ N	☐ NA	Thank you.
VIII. Tables				
Are the figures clear and easy to read?	X Y	☐ N	☐ NA	Thank you.

I X. OVERALL REPORT RATING [1 = Very Poor, 2=Poor, 3=Average, 4=Good, 5 = Excellent]

Overall quality of the report:	☐ **1**	☐ **2**	☐ **3**	☐ **4**	**X 5**
Clarity of the report:	☐ **1**	☐ **2**	☐ **3**	☐ **4**	**X 5**
Presentation (design/formatting):	☐ **1**	☐ **2**	☐ **3**	☐ **4**	**X 5**
Methods:	☐ **1**	☐ **2**	☐ **3**	☐ **4**	**X 5**
Grading of the body of evidence:	☐ **1**	☐ **2**	☐ **3**	☐ **4**	**X 5**
Scientific accuracy:	☐ **1**	☐ **2**	☐ **3**	☐ **4**	**X 5**
Clinical relevance:	☐ **1**	☐ **2**	☐ **3**	☐ **4**	**X 5**

X. Other Comments Well written, comprehensive review of current radiosurgery literature. While the assessment of the level of evidence is fair, it is probable that randomized trials will never be performed for many of the conditions, and retrospective series will be the best level of data available.