Washington State Health Care Authority

Health Technology Assessment

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

Appendix L. Public Comments and Disposition – Draft Report

October 10, 2012

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126

http://www.hta.hca.wa.gov
SHTAP@HCA.WA.GOV

Public Comments and Disposition- Draft Report

Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy

October 10, 2012

Center for Evidence-based Policy
Oregon Health & Science University
3455 SW US Veterans Hospital Road
Mailstop SN-4N, Portland, OR 97239-2941
Phone: 503.494.2182
Fax: 503.494.3807
http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/index.cfm

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Public Comments on Draft Report

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 comments process are included in this response document. Studies were not reviewed for inclusion if there was not a request by the commenter to include them. Submitted references that met inclusion criteria (as outlined in the methods section) were incorporated into the report. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only. To see the full text of a given comment, please use links in the Table of Contents.

This document responds to comments from the following parties:

- American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS)
- American Society for Radiation Oncology (ASTRO)
- CyberKnife® Coalition (CKC)
- Huong Pham, MD (Virginia Mason Medical Center)
- Radiosurgery Society
- Varian Medical Systems, Inc
- Washington State Agency Medical Directors

Table 1. Response to Public Comments on Draft Report

Reviewer	Comment	Disposition
American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS)		
	Summary – AANS and CNS provide information on their organizations and express intent to comment	*Thank you for your comment.* *No changes to the Draft Report.*
	"Overall, the strength of the evidence supporting the use of stereotactic radiosurgery (SRS) for a diverse group of intracranial indications and spinal metastasis is high and overwhelming. Some level 1 and 2 evidence as well as a myriad of level 3, 4, and 5 evidence spanning 40 years demonstrates the efficacy and safety of stereotactic radiosurgery for appropriately selected patients with malignant and benign brain tumors, vascular malformations, functional disorders, and spinal metastases. At this point in time, clinical equipoise will preclude many randomized, prospective trials of SRS versus external beam radiotherapy (EBRT) or resection for various indications when there is four or more decade's worth of data supporting SRS. In addition, the higher cost effectiveness and improved quality of life afforded by SRS as compared to more invasive surgical procedures or broader field radiotherapy approaches have been demonstrated by numerous groups. It is clear that wider field fractionated radiation therapy techniques, which deliver radiation in larger volumes in many treatments to normal cerebral or spinal structures, negatively impact subsequent quality of life compared to the use of tightly confined, highly focused SRS. SRS remains one of the safest and most effective approaches in neurosurgery and radiation oncology. SRS technologies have resulted in a major paradigm shift in the use of both alternative surgical and radiation therapy techniques for a broad array of well-defined clinical indications. During the last 40 years more than 6,000 SRS publications provide this evidence in great detail."	*Thank you for your comment. Please see the appropriate cancer in the report for a summary of the evidence. Our extensive and systematic search for studies found very few randomized controlled trials of SRS and SRT for brain tumors. All but one, involved patients with brain metastates. Not all of these studies report quality of life outcomes. Similarly, the economic studies we identified are summarized in the report. Unfortunately, when the evidence supporting the effectiveness of a treatment is weak, it is difficult to make a strong case for cost-effectiveness.* *A summary judgment for the overall quality of evidence was assigned to each Key Question and outcome using the GRADE system. With a few exceptions, most of the overall strengths of evidence were low to very low indicating that further research is likely to change the estimates of effect and have an important impact on our confidence in the results.* *No changes to the Draft Report.*
	Summary – Background	*Thank you for your comment.*

Reviewer	Comment	Disposition
	• Discusses current state of the evidence for SRS, noting the evidence-based medicine perspective (e.g., Level III) as well as "…evidence derived from a broad array of institutions and hundreds of thousands of patients treated over more than 40 years."	*No changes to the Draft Report.*
	Summary – Quality of Life Issues • "From a quality of life standpoint, there is prospective evidence to support the use of stereotactic radiosurgery for patients with brain metastasis, acoustic neuromas, meningiomas, and pituitary adenomas." • Cites and describes five studies to support claim	*Thank you for your comment. It is difficult to respond without a reference to the comparator for this statement. All studies addressing quality of life outcomes that met inclusion criteria were included in this report. Please see the appropriate tumor type in the report for a summary of the evidence. Acoustic neuromas were not included in the report.* *No changes to the Draft Report.*
	Summary – Cost Effective Analysis • "From an economic standpoint, SRS has been shown to be very cost-effective for multiple indications including brain metastases, acoustic neuromas, meningiomas, arteriovenous malformations, trigeminal neuralgia, and spinal metastases." • Cites and describes 14 studies to support claim.	*To determine if a treatment is cost-effective, there should be strong evidence supporting its effectiveness. Unfortunately, the economic studies we identified were poor quality in part due to the lack of evidence supporting the estimates the authors used for the effectiveness of SRS or SRT.*
	"Conclusion: Stereotactic Radiosurgery in the brain and spine is safe and effective when used in appropriately selected patients. The cost effectiveness and quality of life benefits are also well documented. We thank you again for the opportunity to present our views and are eager to answer any questions the panel may have about the use of SRS by neurosurgeons." Included two attachments: • AANS-CNS Statement on SRS Reimbursement and Coding • January 2007 *Journal of Neurosurgery* article, "Stereotactic	*Thank you for your comment. Please see the comments above.* *No changes to the Draft Report.*

Reviewer	Comment	Disposition
	Radiosurgery—an Organized Neurosurgery-Sanctioned Definition"	
American Society for Radiation Oncology (ASTRO)		
	Summary – ASTRO provides information on its organization and expresses intent to comment	*Thank you for your comment.* *No changes to the Draft Report.*
	Summary – ASTRO describes report conclusions and the method of evidence evaluation used by OHSU CEbP. "…our comments will be primarily focused on the shortcomings of this evaluation based on the NICE and SIGN methodologies. We are very concerned that the OHSU group's reports might lead to a limitation of access to SRS and SBRT for certain underserved populations of patients in the state of Washington, and we wish to avoid disparities in cancer care for socioeconomically disadvantaged groups."	*Thank you for your comment. Please see comments below regarding the use of the quality assessment tools.* *No changes to the Draft Report*
	Summary – Medically inoperable early stage non-small cell lung cancer (NSCLC) • Discusses evidence from the US related to treatment of medically inoperable early stage NSCLC and concerns regarding phase III trials comparing SBRT with a conventional radiotherapy technique. Discusses evidence from the Netherlands related to treatment of medically inoperable early stage NSCLC and inclusion of SBRT within NICE's recommended treatments for patients with this condition. Summary – Brain Metastases • Discusses the history of cranial SRS and the movement toward the use of SRS for CNS neoplasms. • Reports that the oncology community views "…the use of SRS and the use of open surgical resection as equivalent approaches for the treatment of brain metastases" and that "the comparator modality for SRS is not conventional radiotherapy."	*Thank you for your comment.* *No changes to the Draft Report.* *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*

Reviewer	Comment	Disposition
		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.
	Summary – Extracranial indications other than medically inoperable NSCLC • "SBRT is likewise not appropriately compared with conventional radiotherapy but, instead, would be more appropriately compared with surgical resection given that the reported local control outcomes are generally very similar to surgery and so greatly exceed those of conventional radiotherapy. Thus, just as the prospect of randomizing patients between open brain surgery and non-invasive cranial SRS has proven not to be feasible, a randomization between SBRT and surgical resection of a liver, lung, or spine metastasis is unrealistic." • Discusses a few examples of "…attempted randomizations between surgery and convential radiotherapy for extracranial malignancies" and suggests that "it is unrealistic to expect patients to be willing to undergo a coin toss assignment between interventions of such vastly different risk profiles and functional impact."	*Please see comment above.* *Thank you for your comment. Similar comments were made prior to studies of surgical versus medical management ofconditions such as carotid aretery stenosis. However, well done randomized controlled trials were eventually performed.* *No changes to the Draft Report.*
	"Concerning some other aspect of the OHSU report, we disagree with the assessment by this group that nearly all of the studies reviewed, as well as the guidelines evaluated and listed in Appendix G, are of "poor" or at best "fair" quality. Appendix D includes the checklists used as quality assessment tools for the evidence review, and the overall assessment of quality is the reviewer's opinion of the answer to the question "How well was the study done to minimize bias?" or "How well was the study done to minimize the risk of bias or	*In regards to the evidence, the quality assessemt tools are used to assess the methodological quality of the individual studies that met inclusion criteria.The tools are based on a standard set of questions that are similar to the questions asked by many well respected groups such as the Cochrane Collaboration and the*

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	confounding, and to establish a causal relationship between exposure and effect?" for assessments of systematic reviews and cohort studies, respectively. It is ASTRO's opinion that this type of question is impossible to answer, since the reviewers cannot know the state of mind of authors of the studies reviewed, and we submit that any evaluation of published studies should be made based on the objective data reported and not a speculative judgment regarding the authors' state of mind."	*Agency for Healthcare Research and Quality.The items in these tools are key study design features described in textbooks on clinical research design and taught in epidemiology and clinical research design courses.* *In regards to the guidelines, the methodological quality of the guidelines was assessed using an instrument adapted from the Appraisal of Guidelines Research and Evaluation (AGREE) Collaboration. The instrument is recognized internationally as a framework for appraising the quality of the clinical practice guidelines.* *The NCCN guidelines were rated as poor quality. While the NCCN guidelines have a transparent guideline development process and are explicit about guideline panel members and NCCN staff conflicts of interest, the methods for identifying and selecting evidence are unclear. After several email and phone conversations with NCCN staff about their methodology, it is still unclear how evidence is identified (e.g., search strategy and databases searched), what the inclusion/exclusion criteria are, and if individual studies are assessed for quality. As a result, all NCCN guidelines were rated as poor.*
	"ASTRO believes there is established precedent for introducing significant technological developments based on self-evident superiority without the need for randomized clinical trials. Examples include: • CT scanning vs. plain radiographs; • Linear accelerators vs. cobalt machines;	*Thank you for your comment. There are instances of harm caused by relying on "self-evident superiority" of a new treatmentor device. The most recent example of this is metal-on-metal hip replacements (Smith 2012; National Joint Registry of England and Wales). Failure rates*

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	• Minimally invasive surgery vs. conventional surgery."	*of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. Lancet. 2012 Mar 31;379 (9822):1199-204.)* *No changes to the Draft Report.*
	Summary – ASTRO notes that "…there is promotion of a specific vendor's commercially available treatment delivery system that possibly resulted from the OHSU group's fundamental misunderstanding of the nature of the technology described." • Figure 1 – TomoTherapy • Figure 2 – CyberKnife, GammKnife	*Thank you for your comment.* *No changes to the Draft Report.*
	Summary • Discusses difficulty in sustaining equipoise to complete randomized studies of SRS or SBRT	*Thank you for your comment.* *No changes to the Draft Report.*
CyberKnife® Coalition (CKC)		
	"The CyberKnife® Coalition (CKC) respectfully submits our response to the draft evidence report released by the Washington State Health Care Authority, Health Technology Assessment Program (HTA) entitled, "Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy." The CKC is a non-profit association of both hospital-based and freestanding centers that are dedicated to protecting patients'access to robotic stereotactic radiosurgery (R-SRS) and robotic stereotactic body radiotherapy (R-SBRT), performed utilizing CyberKnife technology."	*Thank you for your comment.* *No changes to the Draft Report.*
	"In March 2012, the CKC submitted a response to HTA's request for public comments on Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT). Our response included detailed information surrounding the significant clinical benefits of CyberKnife and the well documented published	*Thank you for your comment.* *No changes to the Draft Report.*

Reviewer	Comment	Disposition
	data that supports SRS/SBRT as a standard of care in the treatment of cancer patients in the United States and around the world."	
	"At this time we would like to provide the HTA with additional information about clinical practice patterns including federal and private payer coverage policies and national guidelines that demonstrate the acceptance of SRS/SBRT. There are several federal and private payers that have deemed SRS/SBRT to be non-experimental and medically necessary for many of the indications that HTA reviewed. Several of the payer policies reviewed by HTA provide coverage for the treatment of benign cranial lesions such as neuromas, meningiomas and malignant brain lesions, while several policies include SBRT for lung, liver, kidney, pancreas and prostate tumors. In addition, Noridian Administrative Services (JH Medicare Contractor) has published a draft Local Coverage Determination (LCD) for SRS/SBRT, which provides coverage for primary and secondary cancers of the brain, spine, lung, liver, pancreas, kidney, and adrenal gland. Noridian has also publicly stated it plans on revising this policy to include coverage of prostate cancer for patients enrolled in a clinical registry. The final LCD is expected this fall, which will be similar to the majority of other published Medicare policies for SRS/SBRT. A complete list of all indications covered by Noridian is provided in Appendix A."	*Thank you for your comment. The report summarizes clinical practice guidelines that met inclusion criteria and payer policiesthat were selected by the WA HTA program.* *No changes to the Draft Report.*
	"We also submit for your consideration guideline information developed by the National Comprehensive Cancer Center (NCCN), a not-for-profit alliance of 21 of the world's leading cancer centers. NCCN promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines. There are several NCCN guidelines (further details in appendix B) that have positive inclusion of SRS/SBRT as an initial treatment option, including: • NCCN non-small cell lung cancer • NCCN hepatocellular carcinoma • NCCN central nervous system"	*Thank you for your comment. All of the NCCN guidelines referenced are included in the guideline section of the report.* *No changes to the Draft Report.*

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	In addition to the NCCN guidelines, there are 3 recent draft Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review reports: stage I non-small cell lung cancer, unresectable primary hepatocellular carcinoma, and metastasis to the liver from unresectable colorectal cancer, which include SBRT as one of the primary treatment options for each of these 3 cancer indications (further details in Appendix CE).1,2,3	*Thank you for your comment. The three AHRQ reports referenced are not final reports and therefore do not meet inclusion criteria.* *No changes to the Draft Report.*
	"Finally, the 2011 California Technology Assessment Forum's (CTAF) report on SBRT for the treatment of early stage NCSLC supports SBRT as a treatment option for stage I inoperable NSCLC.4 The report notes the following: *'It is recommended that stereotactic body radiation therapy for the treatment of early stage non small cell lung cancer in medically inoperable patients with peripheral lesions meets CTAF criteria for safety, effectiveness and improvement in outcomes.'"*	*Thank you for your comment. The CTAF report does not meet inclusion criteria due to study design.* *No changes to the Draft Report.*
	"We strongly support the current federal and private payer coverage policies that provide cancer patients with access to this clinically beneficial treatment option. We also strongly support the current NCCN, AHRQ, and CTAF guidelines and reports that demonstrate the clinically efficacy and safety of SRS and SBRT in the treatment of several cancer types. We urge the Washington State Health Care Authority to allow this same access to care and not deviate from the current federal and private payer SRS/SBRT coverage policies and guidelines within the state of Washington. Thank you for the opportunity to provide comments regarding SRS and SBRT coverage. Our member institutions, including those in Washington State, would welcome a meeting with you in person answer any further questions or concerns that you may have. In addition, please feel free to contact us at the numbers below if we can be of any assistance as your organization finalizes the report." Includes Appendices: Appendix A. ICD-9 Codes for Stereotactic Radiosurgery Services and Stereotactic	*Thank you for your comment.* *No changes to the Draft Report.* *Thank you for your comment.* *No changes to the Draft Report.* *All of the NCCN guidelines references are included in the Draft Report.* *Thank you for your comment. The three AHRQ reports referenced are not final reports and*

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	Body Radiation Therapy (for Cranial Lesions only) Appendix B: NCCN Guidelines (Non-small cell lung cancer, hepatocellular, central nervous system) Appendix C. AHRQ Draft Comparative Effectiveness Review. Local Therapies for Unresectable Primary Hepatocellular Carcinoma. Appendix D. AHRQ Draft Comparative Effectiveness Review. Local Therapies for the Treatment of Stage I Non-Small Cell Lung Cancer and Endobronchial Obstruction due to Advanced Lung Tumors. Appendix E. AHRQ Draft Comparative Effectiveness Review. Local Hepatic Therapies for Metastases to the Liver from Unresectable Colorectal Cancer: Effectiveness and Comparative Effectiveness.	*therefore do not meet inclusion criteria.* *No changes to the Draft Report.*
Huong Pham, MD (Virginia Mason Medical Center)		
	Summary • Discusses the differences between IMRT and SRS/SBRT	*Thank you for your comment. The three AHRQ reports referenced are not final reports and therefore do not meet inclusion criteria. No changes to the Draft Report.*
	• "My observation is that SRS and SBRT are being compared to conventional XRT for the various disease sites and possible indications listed in the document. I do not believe that is a correct comparison analysis for several indications including acoustic neuromas, meningiomas, and solitary primary or metastatic lung tumors since SRS/SRT is used here as an alternative to surgery. There are very few studies published on the use of conventional XRT in these settings.	*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 were summarized regardless of the standard of care. We added additional background context and statements to make it clear that for certain tumors, surgery is*

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	• SRS is a well established treatment for brain metastases and the "Draft Evidence Review" provided a good summary of indications and appropriateness of its use in the guidelines section (NCCN). Other than for primary stage 1 lung cancers and solitary lung metastasis, I believe SBRT is investigational for other disease sites as described in the document.	*the standard of care not external beam radiation.* *Thank you for your comment.* *No changes to the Draft Report.*
	"In acoustic neuromas, SRS or SRT is being used as an alternative to surgery. There are many more patients who have been treated with SRS for acoustic neuromas than with fractionated radiation therapy or hypofractionated SRT. A sentinel paper published in 1998 (N Engl J Med. 1998 Nov 12;339(20):1426-33) by Kondziolka and Flickinger demonstrates excellent outcomes in terms of local control; and hearing preservation improved with lower doses in subsequent reports. Radiosurgery has long been considered a standard treatment option for acoustic neuromas. More recently, reports of using fractionated stereotactic radiotherapy to reduce the risk of hearing loss were reported. These studies are summarized in a review by Dr. Backous and myself (Backous D and Pham HT. Guiding Patients Through the Choices for Treating Vestibular Schwannomas: Balancing Options and Ensuring Informed Consent. In *Otolaryngologic Clinics of North America* Haynes DA; W.B. Saunders: Philadelphia, PA 2007; Vol 40 (3): pp 521- 540). I think controversy exists between SRS and SRT as to which is a better radiotherapeutic option for patients, but there is really no role for conventional radiation therapy for acoustic neuromas as there is very little published using this technique. I do not think it makes any sense to do a comparison of SRS/SRT to conventional radiation therapy for acoustic neuromas. A better comparison is to look at the effectiveness and toxicity of SRS/SRT with surgery."	*See comment above in regards to the comparator.* *The Kondziolka and Flickinger (1998) article does not meet inclusion criteria. The article addresses acoustic neuroma which was not included in the report. No change s to the Draft Report.* *The Backous and Pham (2007) article does not meet inclusion criteria due to study design (narrative review). No change s to the Draft Report.*
	"Same can be said of small meningiomas. Typically, if a patient has a meningioma that can be resected safely and the patient is deemed fit for	*Thank you for your comment.*

Reviewer	Comment	Disposition
	surgery, then surgery is usually recommended. However, often, there are times when a patient has a meningioma in a location that is not safe to operate or the patient could not tolerate the surgery. SRS/SRT would be a good alternative to surgery offering excellent local control rates in the range of 90% at 5 years. Conventional radiation therapy would be an option for larger tumors. Conventional XRT requires 30 fractions over 6 weeks while SRS is a single treatment which is much more conformal reducing the amount of surrounding normal brain tissue being treated. If possible, it seems much more practical and safer for a patient to receive SRS over conventional XRT. The cost of SRS is probably the same or less than a 6 week course of conventional XRT."	*No changes to the Draft Report.*
	"The standard of care for stage 1 lung cancer or for a solitary lung metastasis is surgical resection for curative intent if the patient can tolerate it. What happens if these patients are not fit for surgery? Options include smaller surgeries such as a wedge resection (rather than a standard cancer operation such as lobectomy) or SBRT. Again, there is little data for conventional XRT in this setting. Radiobiological studies demonstrate a dose response for lung tumors which require doses as high as 100cGy (RBE) to obtain good local control for a lung cancer for curative intent. If that were to be done with conventional radiation therapy, it would require 50 fractions or 10 weeks of treatment. In addition, a larger margin of normal lung tissue would be needed around the tumor to account for lung motion resulting in a significant amount of lung treated. Unfortunately, patients who are considered for SBRT are usually because they have poor pulmonary function and cannot afford to have significant lung damage from radiation therapy. With SBRT, the course of the treatment is typically 2-5 fractions over 1 wk with minimal amount of lung damage using gating or breath hold techniques and image guidance. Although I don't have actual cost information, I suspect a course of SBRT would cost less than 10 wks of conventional XRT. Again, SBRT for lung cancer is an alternative to surgery and a better comparison in this setting would be to compare the results of SBRT for lung tumors with surgery, not conventional XRT."	*Thank you for your comment.* *No changes to the Draft Report.*

Reviewer	Comment	Disposition
Radiosurgery Society		
	Background on the Radiosurgery Society and the development of Stereotactic Radiosurgery and Stereotactic body radiation therapy was provided.	*Thank you for your comment.* *No changes to the Draft Report.*
	The current state of data on SRS/SBRT was discussed.	*Thank you for your comment.* *No changes to the Draft Report.*
	"Taken in the aggregate, studies of SRS/SBRT show 70-90% control rates of treated tumors. This almost always compares very favorably with published data for more conventional radiation fractionation schemes. For instance, in non-small cell lung cancers of limited extent, SBRT routinely achieves local control rates of approximately 90% in virtually every published study, while standard radiation struggles to reach a 40% rate. The essential fact is that SRS/SBRT achieves superior results simply because it is better able to deliver the radiation dose precisely to the target while maximally sparing critical nearby tissues, thus allowing a dose of radiation which is biologically different from, and possibly biologically superior to, conventionally fractionated radiation."	*Thank you for your comment.* *No changes to the Draft Report.*
	The non-clincial reasons to consider SRS/SBRT were described.	*Thank you for your comment.* *No changes to the Draft Report.*
	The following recommendation from the California Technology Assessment Forum was included: "It is recommended that stereotactic body radiation therapy for the treatment of early stage non small cell lung cancer in medically inoperable patients with peripheral lesions meets CTAF criteria 2-5 for safety, effectiveness and improvement in outcomes. It is recommended that stereotactic body radiation therapy for the treatment of early stage non small cell lung cancer in medically inoperable patients with central lesions and medically operable patients does not meet CTAF TA criteria 2-5, for safety, effectiveness, and improvement in outcomes."	*Thank you for your comment. The CTAF report does not meet inclusion criteria. No changes to the Draft Report.*
	Guidelines were provided from NCCN on non-small cell lung, hepatocellular carcinoma, central nervous system, prostate, and pancreatic adenocarcinoma.	*Thank you for your comment. All of the NCCN guidelines referenced are included in the*

Reviewer	Comment	Disposition
		guideline section of the report with the exception of the prostat guideline. The prostate guideline does not make specific recommendations on the use of SBRT and therefore was not included. No changes to the Draft Report.
	Three draft AHRQ reports on non-small cell lung cancer, hepatocellular carcinoma, and colorectal metastases to the liver were referenced.	*Thank you for your comment. The three AHRQ reports referenced are not final reports and therefore do not meet inclusion criteria. No changes to the Draft Report.*
	"We recommend that the Washington Health Care Authority recognize the potential advantages of SRS/SBRT and continue to make these treatments available to patients. If the HCA deems it necessary, it could impose a registry requirement similar to those in place in Medicare regions for certain indications."	*Thank you for your comment.* *No changes to the Draft Report.*
	A white paper titled "Metastatic Cancer of the Liver and Stereotactic Radiosurgery" was provided.	*Thank you for your comment.* *Study design does nto meet inclusion criteria.*
	A white paper titled "SRS for Trigeminal Neuralgia" was provided.	*Thank you for your comment.* *Study design does nto meet inclusion criteria.*
	A white paper titled "Stereotactic Body Radiotherapy Treatment for Head and Neck Cancer" was provided.	*Thank you for your comment.* *Study design does nto meet inclusion criteria.*
	A white paper titled "SRS for Non Small Cell Lung Cancer" was provided.	*Thank you for your comment.* *Study design does nto meet inclusion criteria.*
	A white paper titled "Prostate Cancer and Stereotactic Radiosurgery" was provided.	*Thank you for your comment.* *Study design does nto meet inclusion criteria.*
	A white paper titled "Carcinoma of the Pancreas and Stereotactic Radiosurgery" was provided.	*Thank you for your comment.* *Study design does nto meet inclusion criteria.*

Reviewer	Comment	Disposition
Varian Medical Systems, Inc		
	Summary – Varian provides information on its organization, expresses intent to comment, and notes concerns that the draft report does not properly highlight benefits of SRS and SBRT. "The WSHCA's narrow view of "sufficient clinical evidence" for technologies to include only randomized clinical trials will be to the significant determinant to cancer patients in the state of Washington. Varian recognizes the value of randomized controlled trials or prospective studies to guide the clinical application of new technology. Generating this type of data for radiosurgery, however, is exceedingly difficult as radiosurgery has been developed incrementally which is different from other medical interventions. As is evidenced by our enclosed comments, there are significant clinical peer reviewed publications that demonstrate the clinical effectiveness of SRS and SBRT."	*Thank you for your comment.* *No changes to the Draft Report.* *The report included other study designs (e.g. retrospective and prospective comparative cohort studies and case series for less prevalent tumor types), not just RCTs.*
	The challenges of conducting an evidence-based evaluation are outlined including citations for Bentzen (2008) and Bekelman (2011).	*Thank you for your comment.* *No changes to the Draft Report.*
	Differences between RS and CRT are described, including the types of available evidence on both treatments.	*Thank you for your comment.* *No changes to the Draft Report.*
	"Executive Summary – Background Pages 6 and 38, cost information: These brief sections seems out of place and the particular report by Lanni, et al, is later described as "…a poor quality cost evaluation…", page 98. We suggest removing this section and relying on the discussion on page 98, or developing a larger section that deals with cost information in a more comprehensive fashion."	*Thank you for your comment. There was little cost data identified. This was identified in an Agency for Healthcare Research and Quality report. We deleted this study out of the Executive Summary and Background of the report.*
	Executive Summary – Findings "Page 22, KQ1: This section says "…Since there were no studies comparing SBRT to other therapies, it is uncertain whether SBRT improves survival or other patient-important outcomes compared to conventional EBRT." While not an	*Thank you for your comment.* *No changes to the Draft Report.*

Reviewer	Comment	Disposition
	exhaustive literature search, the following three papers describe comparison of SBRT to sublobar resection; • Fernandez FG, Crabtree TD, Liu J, Meyers BF. Sublobar resection versus definitive radiation in patients with stage IA non-small cell lung cancer. Ann Thorac Surg. 2012 Aug;94(2):354-60; discussion 360-1.	*Study design does not meet inclusion criteria. Reason for exclusion: comparator is not relevant to the key questions addressed in this report. Of note, in the Frenandez (2012) study, the subgroup of patients that were propensity score matched had 3-year overall survivals favoring sublobar resection compared to SBRT (52% versus 41%; p<0.001).*
	• Puri V, Crabtree TD, Kymes S, Gregory M, Bell J, Bradley JD, Robinson C, Patterson GA, Kreisel D, Krupnick AS, Meyers BF. A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis. J Thorac Cardiovasc Surg. 2012 Feb;143(2):428-36.	*Study design does not meet inclusion criteria. Reason for exclusion: comparator is not relevant.*
	• Crabtree TD, Denlinger CE, Meyers BF, El Naqa I, Zoole J, Krupnick AS, Kreisel D, Patterson GA, Bradley JD. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg. 2010 Aug;140(2):377-86."	*Study design does not meet inclusion criteria. Reason for exclusion: comparator is not relevant.*
	Executive Summary – Findings "Page 22, KQ1: The following paper describes the challenges and controversies inherent in doing comparative effectiveness research across very different treatment modalities, such as lung SBRT and sublobular surgical resection; • Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: Recent advances and controversies. J Thorac Dis. 2011 Sep;3(3):189-96."	*Thank you for your comment.* *No changes to the Draft Report.*
	Background "The first paragraph lists the devices that are approved to deliver SRS/SBRT. The	*Thank you for your comment.We deleted Figure 2 and instead updated Firgure 1.*

Reviewer	Comment	Disposition
	list is incomplete and inconsistent with Table 2, on page 35. The list in Table 2 should be expanded to include; TrueBeam, TrueBeam STx, and Clinac iX, all manufactured by Varian Medical Systems, Inc."	*The paragraph on devices was not meant to be all inclusive, but to instead provide a few examples of FDA approved devices. The sentence on page 35 has been revised to reflect this.*
	Background "Pages 33 and 34, figures 1 and 2: These figures show a mixture of generic descriptors and product names. Since this report is intended to provide policy guidance to a broad range of individuals, we recommend using only generic descriptors."	*Thank you for your comment.We deleted Figure 2 and instead updated Firgure 1.*
	Background Differences in terminology for treatment modalities are discussed including: • the definition of Stereotactic Radiosurgery (SRS) approved by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons and the American Society of Therapeutic Radiology and Oncology in 2006 • "By convention, the use of the same treatment methodology in the remaining parts of the body is referred to as Stereotactic Body Radiotherapy (SBRT)." • "Also, some researchers are promoting the use of the term "Stereotactic Ablative Radiotherapy" (SABR), pronounced "sabre"."	*Thank you for your comment.* *No changes to the Draft Report.*
	Background "Page 37, Outcome and Toxicity Measures: This section says "…Outcome measures for the multiple cancers include the primary outcomes of overall survival (OS) and median survival at 1-, 2- and 5-years, and secondary outcomes of local tumor control, disease-free survival (DFS), and quality of life (QoL)…" Multiple modalities, both focal and systemic, are used in the modern management of oncologic disease. In an era of "personalized treatment", it is increasingly rare for mono-therapy to be used exclusively. Thus, overall survival and median survival are better measures for the entire treatment regime. The goals of RS, as described on page 5, are to; "…to improve the targeting of	*Thank you for your comments. Primary outcomes are identified and determined by the authors of the studies. Primary refers to the main outcome for which the study was designed to measure. A surrogate outcome is commonly defined as a surrogate endpoint of a study that may be a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives.As a result, local tumor contro, and disease free survival would be*

Reviewer	Comment	Disposition
	radiation to the tumor to minimize damage to normal tissue and increase the dose of radiation delivered to the tumor…". RS offers ablative dose-escalation to tumor targets with simultaneous dose-restraint to normal tissues that is not possible with conventional radiotherapy. It is axiomatic that reducing dose to normal tissues will result in lower toxicities. Therefore, we recommend that reports of local tumor control, disease-free-survival (DFS) and quality of life (QoL) be incorporated in the discussion of primary outcomes, not secondary outcomes and they should not be described as "surrogate outcome", as is done in the summary section on page 27."	*considered surrogate outcomes versus outcomes important to patients such as quality of life, symptom control, and overall survival. Quality of life was included as an outcome when reported. For almost all of the studies reporting quality of life outcomes, this outcome was not the primary outcome defined by the authors.The term surrogate was deleted on page 27.*
	Liver "Page 57: The following references have been published since the cutoff date for the report, and should comply with the inclusion criteria: • Lee IJ, Seong J. The optimal selection of radiotherapy treatment for hepatocellular carcinoma. Gut Liver. 2012 Apr;6(2):139-48. • Almaghrabi MY, Supiot S, Paris F, Mahé MA, Rio E. Stereotactic Body Radiation Therapy for Abdominal Oligometastases: A biological and clinical review. Radiat Oncol. 2012 Aug 1;7(1):126. • Lock MI, Hoyer M, Bydder SA, Okunieff P, Hahn CA, Vichare A, Dawson LA. An international survey on liver metastases radiotherapy. Acta Oncol. 2012 May;51(5):568-74. • Barney BM, Olivier KR, Miller RC, Haddock MG. Clinical outcomes and toxicity using Stereotactic Body Radiotherapy (SBRT) for advanced cholangiocarcinoma. Radiat Oncol. 2012 May 3;7:67. • O'Connor JK, Trotter J, Davis GL, Dempster J, Klintmalm GB, Goldstein RM. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. Liver Transpl. 2012 Aug;18(8):949-54. • Ibarra RA, Rojas D, Snyder L, Yao M, Fabien J, Milano M, Katz A, Goodman K,Stephans K, El-Gazzaz G, Aucejo F, Miller C, Fung J, Lo S, Machtay M, Sanabria JR. Multicenter results of stereotactic body radiotherapy (SBRT) for non-resectable primary liver tumors. Acta	*Study design does not meet inclusion criteria. Reason for exclusion: study design* *Study design does not meet inclusion criteria. Reason for exclusion: study design* *Study design does not meet inclusion criteria. Reason for exclusion: study design* *Study design does not meet inclusion criteria. Reason for exclusion: sample size* *Study design does not meet inclusion criteria. Reason for exclusion: sample size* *Study design does not meet inclusion criteria. Reason for exclusion: sample size*

Reviewer	Comment	Disposition
	Oncol. 2012 May;51(5):575-83. • Facciuto ME, Singh MK, Rochon C, Sharma J, Gimenez C, Katta U, Moorthy CR,Bentley-Hibbert S, Rodriguez-Davalos M, Wolf DC. Stereotactic body radiation therapy in hepatocellular carcinoma and cirrhosis: evaluation of radiological and pathological response. J Surg Oncol. 2012 Jun 1;105(7):692-8."	*Study does not meet inclusion criteria.* *Reason for exclusion: date of published study*
	Central Nervous System "Page 63: Cranial SRS is routinely used to treat non-oncologic diseases, the primary examples being arteriovenous malformations (AVMs) and trigeminal neuralgia. They are conspicuous in their absence from this section. It is beyond the scope of this review of the draft report to suggest all possible references that should be reviewed, but the usefulness and credibility of the report would be greatly enhanced if it included treatment of non-oncologic disease. Please see the attached bibliography for a list of possible references to consider for inclusion and analysis."	*Thank you for your comment.* *No changes to the Draft Report.*
	Central Nervous System "Page 77, KQ 1: Meningiomas are the most common benign intracranial lesion, and routinely treated with RS, so it is difficult to believe that "...No studies were identified.""	*Thank you for your comment. To address Key Question #1 regarding the effectiveness of SRS and SRT compared to whole brain radiation therapy, we included only comparative studies.No* ***comparative*** *studies were identified that met inclusion criteria.* *No changes to the Draft Report.*
	Central Nervous System "Page 79, KQ4: While the absolute costs may not apply to the US market, the 2011 paper by Tan et al (rated as "good quality"), should be included, since it demonstrates a relative comparison of costs that transcends the healthcare delivery system."	*Thank you for your comment. The results from the Tan (2011) cost study were included in the report. However, the calculation of healthcare costs in the Netherlands, including relative costs across the treatments, may not translate well to the U.S. setting especially given the known variation in costs and charges across healthcare markets in the U.S.*

Reviewer	Comment	Disposition
		No change to Draft Report.
	Lung "Page 94: As mentioned in the general comments section, this population-based study compared overall survival outcomes for elderly patients with stage I NSCLC treated before and after the widespread implementation of SBRT, and detected a 16% absolute increase in radiotherapy utilization, corresponding to a decrease in untreated patients. This suggests that the efficacy, favorable toxicity profile, and convenience associated with SBRT may be key factors influencing treatment uptake. The controlled implementation of SBRT was associated with an improvement in survival that was not readily explained by other potential confounding factors, such as differences in baseline populations or stage migration. • Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of Introducing Stereotactic Lung Radiotherapy for Elderly Patients With Stage I Non-Small-Cell Lung Cancer: A Population-Based Time- Trend Analysis. Journal of clinical oncology 2010;28(35): 5153-9."	*Thank you for your comment.* *No change to Draft Report.* *Study design does not meet inclusion criteria. Reason for exclusion: study design*
	Lung "Page 97, first paragraph: Four studies are summarized that describe the complications from the placement of fiducial markers. Since this applies to only one of the devices used to treat lung SBRT, as noted in the report, the procedure used to introduce the fiducials and the fiducials themselves have evolved, we recommend deleting this section. "	*Thank you for your comment. We summarized the harms identified by the studies included in this review.*
	Lung "Page 98, KQ 4: The following two studies, one that address patients that are older than 75 and the other that looks at patients with concurrent COPD, should be included in this section on subpopulations. • Palma DA, Tyldesley S, Sheehan F, Mohamed IG, Smith S, Wai E, Murray N, Senan S. Stage I non-small cell lung cancer (NSCLC) in patients aged 75 years and older: does age determine survival after radical treatment? J Thorac Oncol. 2010 Jun;5(6):818-24.	*Study design does not meet inclusion criteria. Reason for exclusion: comparator not relevant* *Study design does not meet inclusion criteria.*

Reviewer	Comment	Disposition
	• Louie AV, Rodrigues G, Hannouf M, Lagerwaard F, Palma D, Zaric GS, Haasbeek C, Senan S. Withholding stereotactic radiotherapy in elderly patients with stage I non-small cell lung cancer and co-existing COPD is not justified: outcomes of a Markov model analysis. Radiother Oncol. 2011 May;99(2):161-5."	*Reason for exclusion: comparator not relevant*
	Prostate "Page 99, KQ1: There has been considerable clinical research on prostate SBRT, so it is surprising to see that "No studies were identified." There are studies mentioned in "Subsequently Published Studies" section, so perhaps this is an editorial oversight. The following studies may comply with the inclusion criteria; • Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. Radiat Oncol. 2011 Jan 10;6:3.	*Thank you for your comment. To address Key Question #1 on the effectiveness of SBRT compared to conventional EBRT, we included only comparative studies. No **comparative** studies were identified that met inclusion criteria.*
	• King C. Stereotactic body radiotherapy for prostate cancer: current results of a phase II trial. Front Radiat Ther Oncol. 2011;43:428-37. Epub 2011 May 20.	*Study design does not meet inclusion criteria. Reason for exclusion: sample size*
	• Boike TP, Lotan Y, Cho LC, Brindle J, DeRose P, Xie XJ, Yan J, Foster R, Pistenmaa D, Perkins A, Cooley S, Timmerman R. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer, J Clin Oncol. 2011 May 20;29(15):2020-6.	*Study design does not meet inclusion criteria. Reason for exclusion: study design*
	• Ray C. Long-term outcomes of SBRT in low-risk prostate cancer, Nat Rev Urol. 2011 Apr;8(4):174. No abstract available.	*Study design does not meet inclusion criteria. Reason for exclusion: sample size*
	• Kang JK, Cho CK, Choi CW, Yoo S, Kim MS, Yang K, Yoo H, Kim JH, Seo YS, Lee DH, Jo M., Image-guided stereotactic body radiation therapy for localized prostate cancer,Tumori. 2011 Jan-Feb;97(1):43-8.	*Study design does not meet inclusion criteria. Reason for exclusion: study design*
	• King CR, Brooks JD, Gill H, Presti JC Jr. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer, Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):877-82. Epub 2011	*Study design does not meet inclusion criteria. Reason for exclusion: sample size*

Reviewer	Comment	Disposition
	Feb 6. • Katz AJ, Santoro M, Ashley R, Diblasio F. Stereotactic Body Radiation Therapy for Low- and Low-Intermediate-Risk Prostate Cancer: Is there a Dose Effect? Front Oncol. 2011;1:49. Epub 2011 Dec 5. • Jabbari S, Weinberg VK, Kaprealian T, Hsu IC, Ma L, Chuang C, Descovich M, Shiao S, Shinohara K, Roach M 3rd, Gottschalk AR. Stereotactic body radiotherapy as monotherapy or post-external beam radiotherapy boost for prostate cancer: technique, early toxicity, and PSA response, Int J Radiat Oncol Biol Phys. 2012 Jan 1;82(1):228-34. Epub 2010 Dec 22. • Bolzicco G, Favretto MS, Scremin E, Tambone C, Tasca A, Guglielmi R. Image-guided stereotactic body radiation therapy for clinically localized prostate cancer: preliminary clinical results, Technol Cancer Res Treat. 2010 Oct;9(5):473-7. • Katz AJ. CyberKnife radiosurgery for prostate cancer, Technol Cancer Res Treat. 2010 Oct;9(5):463-72. • Oermann EK, Slack RS, Hanscom HN, Lei S, Suy S, Park HU, Kim JS, Sherer BA, Collins BT, Satinsky AN, Harter KW, Batipps GP, Constantinople NL, Dejter SW, Maxted WC, Regan JB, Pahira JJ, McGeagh KG, Jha RC, Dawson NA, Dritschilo A, Lynch JH, Collins SP. A pilot study of intensity modulated radiation therapy with hypofractionated stereotactic body radiation therapy (SBRT) boost in the treatment of intermediate- to high-risk prostate cancer, Technol Cancer Res Treat. 2010 Oct;9(5):453-62. • Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M. Stereotactic body radiotherapy for organ-confined prostate cancer.BMC Urol. 2010 Feb 1;10:1."	*Study was already included* *Study design does not meet inclusion criteria. Reason for exclusion: comparator* *Study design does not meet inclusion criteria. Reason for exclusion: sample size* *Study design does not meet inclusion criteria. Reason for exclusion: sample size* *Study design does not meet inclusion criteria. Reason for exclusion: study design* *Study design does not meet inclusion criteria. Reason for exclusion: sample size* *Study design does not meet inclusion criteria. Reason for exclusion: study design*
	Prostate "In addition, the following review articles may comply with the inclusion criteria;	

Reviewer	Comment	Disposition
	• Spyropoulou D, Kardamakis D Review of hypofractionated radiotherapy for prostate cancer. ISRN Oncol. 2012;2012:410892	*Study design does not meet inclusion criteria. Reason for exclusion: study design*
	• Arcangeli S, Scorsetti M, Alongi F, Will SBRT replace conventional radiotherapy in patients with low-intermediate risk prostate cancer? A review. Crit Rev Oncol Hematol. 2012 Oct;84(1):101-8.	*Study design does not meet inclusion criteria. Reason for exclusion: study design*
	• Ishiyama H, Teh BS, Lo SS, Mathews T, Blanco A, Amato R, Ellis RJ, Mayr NA, Paulino AC, Xu B, Butler BE Stereotactic body radiation therapy for prostate cancer. Future Oncol. 2011 Sep;7(9):1077-86.	*Study design does not meet inclusion criteria. Reason for exclusion: study design*
	• Teh BS, Ishiyama H, Mathews T, Xu B, Butler EB, Mayr NA, Lo SS, Lu JJ, Blanco AI, Paulino AC, Timmerman RD.Stereotactic body radiation therapy (SBRT) for genitourinary malignancies. Discov Med. 2010 Sep;10(52):255-62.	*Study design does not meet inclusion criteria. Reason for exclusion: study design*
	• Biagioli MC, Hoffe SE. Emerging technologies in prostate cancer radiation therapy: improving the therapeutic window. Cancer Control. 2010 Oct;17(4):223-32.	*Study design does not meet inclusion criteria. Reason for exclusion: study design*
	• Choe KS, Liauw SL Radiotherapeutic strategies in the management of low-risk prostate cancer. ScientificWorldJournal. 2010 Sep 14;10:1854-69.	*Study design does not meet inclusion criteria. Reason for exclusion: study design*
	• Wiegner EA, King CR Sexual function after stereotactic body radiotherapy for prostate cancer: results of a prospective clinical trial. Int J Radiat Oncol Biol Phys. 2010 Oct 1;78(2):442-8."	*Study design does not meet inclusion criteria. Reason for exclusion: sample size*
	Prostate "Page 100, KQ4: The following studies may comply with the inclusion criteria; • Hodges JC, Lotan Y, Boike TP, Benton R, Barrier A, Timmerman RD, Cost-effectiveness analysis of stereotactic body radiation therapy versus intensity-modulated radiation therapy: an emerging initial radiation treatment option for organ-confined prostate cancer, J Oncol Pract. 2012 May;8(3 Suppl):e31s-7s.	*Study design does not meet inclusion criteria. Reason for exclusion: search dates*
	• Parthan A, Pruttivarasin N, Davies D, Taylor DC, Pawar V, Bijlani A, Lich	*Study design does not meet inclusion criteria.*

Reviewer	Comment	Disposition
	KH, Chen RC. Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer, Front Oncol. 2012;2:81. Epub 2012 Aug 20. • Hodges JC, Lotan Y, Boike TP, Benton R, Barrier A, Timmerman RD. Cost-effectiveness analysis of SBRT versus IMRT: an emerging initial radiation treatment option for organ-confined prostate cancer. Am J Manag Care. 2012 May 1;18(5):e186-93."	*Reason for exclusion: search dates* *Study design does not meet inclusion criteria. Reason for exclusion: search dates*
	Spine "Page 101, KQ1: The following study is discussed KQ2 and should also be included in KQ1; • Ryu S, Rock J, Jain R, Lu M, Anderson J, Jin JY, Rosenblum M, Movsas B, Kim JH. Radiosurgical decompression of metastatic epidural compression. Cancer. 2010 May 1;116(9):2250-7."	*Study design does not meet inclusion criteria. Reason for exclusion: study design*
	Spine "Page 102, KQ2: The following study should be included in KQ2; • Ryu S, Jin R, Jin JY, Chen Q, Rock J, Anderson J, Movsas B. Pain control by image-guided radiosurgery for solitary spinal metastasis. J Pain Symptom Manage.2008 Mar;35(3):292-8."	*Study design does not meet inclusion criteria. Reason for exclusion: sample size*
	Spine "Page 105, KQ3: The following study should be included in KQ3, as is it discusses a particular subpopulation, postoperative patients. • Sahgal A, Bilsky M, Chang EL, Ma L, Yamada Y, Rhines LD, Létourneau D, Foote M, Yu E, Larson DA, Fehlings MG. Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient. J Neurosurg Spine. 2011 Feb;14(2):151-66."	*Study design does not meet inclusion criteria. Reason for exclusion: study design*
	Spine "Page 105, KQ4: Since costs are typically reported on a per-patient basis, the reported Haley 2011 study results should be revised such that they are per-patient, not per 100 patients. This will avoid the potential for significant	*Thank you for your comment. We agree with the comment about the potential for confusion about the study results.The authors used statistical modeling to arrive at these results. The*

Reviewer	Comment	Disposition
	confusion."	*assumptions and specific modeling technique were not well described in the article, so we chose to report the results as they did. We can not determine from the article if it is appropriate to divide each of the reported numbers by 100.* *No change to Draft Report.*
	Guidelines Page 108: The following study should be included; • Sahgal A, Roberge D, Schellenberg D, Purdie TG, Swaminath A, Pantarotto J, Filion E, Gabos Z, Butler J, Letourneau D, Masucci GL, Mulroy L, Bezjak A, Dawson LA, Parliament M. The Canadian Association of Radiation Oncology Scope of Practice Guidelines for Lung, Liver and Spine Stereotactic Body Radiotherapy. Clin Oncol (R Coll Radiol). 2012 May 23"	*Thank you for your comment. Only US based guidelines were included in the report.* *No change to Draft Report*
Washington State Agency Medical Directors		
	"This is a comprehensive evidence review which reflects the overall lack of high quality evidence addressing concerns of safety, comparative effectiveness, and cost for stereotactic radiosurgery and stereotactic body radiation therapy. In its present format the report does not prioritize the areas of greatest clinical relevance which are supported by at least a fair to good level of evidence. Restructuring the report will assist the Health Technology Clinical Committee members in their decision making process. The proposed areas of prioritization in the report include the use of stereotactic radiosurgery in the treatment of medically inoperable or unresectable primary brain neoplasms or metastatic disease for patients with a good Karnofsky performance status, treatment of early stage NSCLC in patients with a favorable live expectancy who are otherwise medically inoperable or unresectable, and treatment of primary or metastatic vertebral body, spinal or paraspinal tumors with either a history of previous radiation therapy or requiring high-dose radiotherapy."	*Thank you for your comment.* *No change to Draft Report.*

Reviewer	Comment	Disposition
	"p. 6 The article "Stereotactic Radiotherapy Reduces Treatment Cost While Improving Overall Survival and Local Control over Standard Fractionated Radiation Therapy for Medically Inoperable Non-Small-Cell Lung Cancer," is misquoted in the *Cost information* section in paragraph 2. This data should be omitted from the Executive Summary for the following reasons: 1. There is no mention made of whether or not these patients received adjuvant chemotherapy and therefore the survival conclusion must be questioned. 2. Indirect costs such as ancillary tests and associated imaging studies were not included in this cost analysis. 3. The executive summary should not contain a reference to a specific journal article, particularly if the article is of poor quality and unclear clinical significance."	*Thank you for your comment. We agree that there was very little information regarding the cost or charges for SRS, SRT or SBR. As a result, we included everything we identified. This section was removed from the Executive Summary and Background.*
	"p. 6 Please specify whether or not the EBRT comparator included IMRT."	*Thank you for your comment. The EBRT comparator for the cost data from Lanni (2010) does not include IMRT.*
	"p. 9 The findings should be listed either according to frequency of use based upon the state agency data or to quality of supporting medical evidence, rather than alphabetically."	*Thank you for your comment.* *The listing of the findings was changed. The findings were separated by the overall strengths of evidence. Tumor types with the highest overall strengths of evidence are listed first.*
	"p. 10 A summary table of findings, organized by diagnosis or prioritized by the level of evidence, such as was performed for the IMRT review, would be helpful. The present organization of the report is very difficult to follow."	*Thank you for your comment. The report is reorganized as stated above and a summary table will be provided in the Final Report.*
	"p. 12 The Central Nervous System section should be divided into primary CNS tumors and "brain metastases."	*Thank you for your comment. We made the changes to the report as recommended and able based on the study populations.*
	"pp. 10-24 Information should be incorporated into a table, as stated previously. Table should be reinserted before p. 55 Study results."	*Thank you for your comment. We have two summary of findings tables in the Appendix of the report. The table is separated by tumor types with comparative studies and those without. We*

Reviewer	Comment	Disposition
		will also insert the table where there are comparative studies before the findings section as recommended.
	"p. 64. The "Brain metastases" section needs to elucidate if the patient populations were limited to single metastasis versus multiple metastases. This section requires expansion as this will be an area of focus for the Clinical committee. Please add the following in a summary table: single vs. multiple metastases, resectable vs. unresectable disease, size of metastasis and histologic type."	*Thank you for your comment. We agree that an expansion as recommended would be ideal however, only one study (Andrews 2004) reported stratified results.* *Most studies included patients with 1- 4 mets and did not analyze their results by one vs. more than one met. The same is true for histology. None of the studies described whether patients had resectable or unresectable brain mets. Most of the studies only included patients with mets less than or equal to four centimeters.We separated them as we were able based on the study designs.*
	"p. 79 "Multiple CNS Tumors" is unclear. Does this mean Synchronous primary brain tumors? Metachronous primary brain tumors? Multiple brain metastases? Either clarify or omit this section."	*Thank you for your comment. This was clarified in the report as able. Many of the studiesincluded heterogenous population.*
	"There is no reference to the pediatric population in this report. Please clarify if (1) no literature exists (2) literature is present but did not meet the minimum sample size requirements. If literature is present but did not meet the minimum sample size requirements please include this comment, particularly in the sections for abdominal, brain and spinal tumors."	*Thank you for your comment. The majority of cancers addressed by the studies in this report occur predominantly in adults. There were 53 studies that included children, adolescents, and adults but they did not stratify the results by age. In addition, the median and mean ages for those studies were over 50 years old. Only one study (Kano 2010) on ependymomas included a pediatric population. Another study (Marcus 2005)included patients aged 2-26 with a sample size of 50. A list of studies is provided in the first paragraph of the Findings section. In addition,*

Reviewer	Comment	Disposition
		Marcus and Kano are well described in the report and highlighted in the presentation to the committee.

Full Public Comments

American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS)

AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS
THOMAS A. MARSHALL, *Executive Director*
9550 Meadowbrook Drive
Rolling Meadows, IL 60008
Phone: 888-566-AANS
Fax: 847-378-0600
info@aans.org

President
MITCHEL S. BERGER, MD
San Francisco, California

American Association of Neurological Surgeons

CONGRESS OF NEUROLOGICAL SURGEONS
REGINA GHURANI, *Acting Executive Director*
10 North Martingale Road, Suite 190
Schaumburg, IL 60173
Phone: 877-517-CNS
Fax: 847-240-0804
info@CNS.org

President
CHRISTOPHER E. WOLTJA, MD
Milwaukee, Wisconsin

September 28, 2012

Josh Morse, MPH, Program Director
WA Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 4282
Olympia, WA 98504-2682
E-mail: shtap@hca.wa.gov

RE: Draft Health Technology Assessment for Stereotactic Radiosurgery

Dear Mr. Morse:

On behalf of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), we would like to thank the Washington State Health Care Authority for the opportunity to comment on the draft Health Technology Assessment (HTA) regarding the use of Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiotherapy (SBRT). As you may know, stereotactic radiosurgery was pioneered by neurosurgeons and we are the leaders in using SRS to treat patients with a variety of neurologic diseases. For years, the AANS and CNS have worked with policymakers to help ensure that neurosurgical patients have access to this important treatment when appropriate, and we appreciate the opportunity to reiterate our thoughts on this topic to you now.

Summary

Overall, the strength of the evidence supporting the use of stereotactic radiosurgery (SRS) for a diverse group of intracranial indications and spinal metastasis is high and overwhelming. Some level 1 and 2 evidence as well as a myriad of level 3, 4, and 5 evidence spanning 40 years demonstrates the efficacy and safety of stereotactic radiosurgery for appropriately selected patients with malignant and benign brain tumors, vascular malformations, functional disorders, and spinal metastases. At this point in time, clinical equipoise will preclude many randomized, prospective trials of SRS versus external beam radiotherapy (EBRT) or resection for various indications when there is four or more decade's worth of data supporting SRS. In addition, the higher cost effectiveness and improved quality of life afforded by SRS as compared to more invasive surgical procedures or broader field radiotherapy approaches have been demonstrated by numerous groups. It is clear that wider field fractionated radiation therapy techniques, which deliver radiation in larger volumes in many treatments to normal cerebral or spinal structures, negatively impact subsequent quality of life compared to the use of tightly confined, highly focused SRS. SRS remains one of the safest and most effective approaches in neurosurgery and radiation oncology. SRS technologies have resulted in a major paradigm shift in the use of both alternative surgical and radiation therapy techniques for a broad array of well-defined clinical indications. During the last 40 years more than 6,000 SRS publications provide this evidence in great detail.

Background

From a strict evidence based medicine standpoint, most of the evidence regarding stereotactic radiosurgery (SRS) is level III or higher. The majority of level I evidence for SRS exists for brain

WASHINGTON OFFICE
KATIE O. ORRICO, *Director*
725 Fifteenth Street, NW, Suite 500 Washington, DC 20005
Phone: 202-628-2072 Fax: 202-628-5284 E-mail: korrico@neurosurgery.org

metastasis and glioblastomas. SRS was introduced more than 40 years ago, an era in which evidence based approaches were less of a priority. In 2012, if a prospective trial of patients with small to moderately sized meningiomas was designed to randomize patients to SRS, EBRT, and microsurgical resection, it would be unlikely to accrue secondary to clinical equipoise issues. While it may seem humbling that the majority of the practice of SRS is supported by class III evidence and a small amount of class I and II data, evidence based methodologies are useful to organize existing literature and to see if there is truly objective data to answer specific questions. However, there is overwhelming evidence derived from a broad array of institutions and hundreds of thousands of patients treated over more than 40 years to support the clinical benefits, cost effectiveness, and safety of SRS in patients who may be eligible for SRS, EBRT, and/or microsurgery. The clinical efficacy and safety of SRS and, to a lesser extent, the cost effectiveness and quality of life benefits of it compared to EBRT or resection are well documented by the report prepared by the Center for Evidenced-Based Policy at the Oregon Health & Science University.

Quality of Life Issues

From a quality of life standpoint, there is prospective evidence to support the use of stereotactic radiosurgery for patients with brain metastasis, acoustic neuromas, meningiomas, and pituitary adenomas. In a randomized, prospective trial of patients with brain metastasis, Chang and colleagues found significant benefit in terms of neurocognition in patients treated with SRS alone over SRS plus whole brain radiation therapy (WBRT) (Chang et al., 2009). In a study constituting level II evidence, radiosurgery afforded a higher quality of life for vestibular schwannoma patients as compared to microsurgery (Pollock et al., 2006). In a case controlled study of patients with small to medium sized meningiomas, SRS was also demonstrated to provide better neurological preservation than surgical resection for patients with small to moderately size meningiomas (Pollock et al., 2003). In a nonrandomized, prospective study of pituitary adenoma patients, SRS afforded neurocognitive preservation as compared to patients undergoing external beam radiotherapy (EBRT) or being left untreated for their pituitary adenoma (Tooze et al., 2012). With regard to spinal metastases patients, spinal radiosurgery has been demonstrated in a recently published phase 1-2 study to lead to significant reductions in pain and other symptoms and provide a high rate of progression free survival while at the same time resulting in a low rate of spinal cord toxicity (Wang et al., 2012).

Cost Effective Analysis

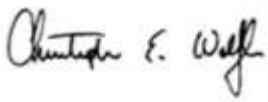
From an economic standpoint, SRS has been shown to be very cost-effective for multiple indications including brain metastases, acoustic neuromas, meningiomas, arteriovenous malformations, trigeminal neuralgia, and spinal metastases (Tarricone et al., 2008; Wellis et al., 2003, van Roijen et al., 1997). In a comparison of surgical and follow up costs associated with vestibular schwannoma patients, radiosurgery was shown to be less expensive than microsurgery even when factoring in long-term follow up expenses (Banerjee et al., 2008). In a cost-effectiveness analysis of the Chang et al. study (Lancet Oncology, 2009), SRS alone had a higher average effectiveness than when added to WBRT (Lal et al., 2012). This finding of a high cost-effectiveness of SRS for brain metastases patients is consistent with prior publications (Lee et al., 2009; Mehta et al., 1997). SRS has also been shown to be more cost effective than resection for patients with brain metastases (Vuong et al., 2012; Rutigliano et al., 1995). Cho et al. (2006) evaluated the socioeconomic costs of open surgery and SRS for 174 patients with benign skull based tumors. They found shorten hospital stays, reduced complications, improvements in return to work, and an overall better cost-effectiveness with SRS over resection for comparable groups of patients (Cho et al., 2006). It is also well accepted, as noted in recent meta-analyses, that radiosurgery provides a faster rate of endocrine remission compared to EBRT for patients with functioning pituitary adenomas thereby allowing radiosurgery patients to be removed from costly antisecretory medications much more quickly than comparable patients treated with EBRT (Loeffler et al., 2011; Sheehan et al., 2005). In an analysis of the cost-effectiveness of SRS for patients with spinal

metastasis, spinal radiosurgery was found to be superior to conventional EBRT for appropriately selected patients (Papatheofanis et al., 2009).

Conclusion

Stereotactic Radiosurgery in the brain and spine is safe and effective when used in appropriately selected patients. The cost effectiveness and quality of life benefits are also well documented. We thank you again for the opportunity to present our views and are eager to answer any questions the panel may have about the use of SRS by neurosurgeons.

Sincerely,



Mitchel S. Berger, MD, President
American Association of Neurological Surgeons

Christopher E. Wolfla, MD, President
Congress of Neurological Surgeons

Attachments:

- AANS-CNS Statement on SRS Reimbursement and Coding
- January 2007 *Journal of Neurosurgery* article, "Stereotactic Radiosurgery—an Organized Neurosurgery-Sanctioned Definition"

Staff Contact:

Catherine Jeakle Hill
Senior Manager, Regulatory Affairs
AANS/CNS Washington Office
725 15th Street, NW, Suite 500
Washington, DC 20005
Phone: 202-446-2026
E-mail: chill@neurosurgery.org

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AMERICAN ASSOCIATION OF
NEUROLOGICAL SURGEONS
THOMAS A. MARSHALL, Executive Director
5550 Meadowbrook Drive
Rolling Meadows, IL 60008
Phone: 888-566-AANS
Fax: 847-378-0600
info@aans.org

President
JAMES R. BEAN, MD
Lexington, Kentucky

American Association of Neurological Surgeons

CONGRESS OF
NEUROLOGICAL SURGEONS
LAURIE BEHNCKE, Executive Director
10 North Martingale Road, Suite 190
Schaumburg, IL 60173
Phone: 877-517-1CNS
FAX: 847-240-0804
info@1CNS.org

President
P. DAVID ADELSON, MD
Pittsburgh, Pennsylvania

American Association of Neurological Surgeons and Congress of Neurological Surgeons

Statement on Coding and Reimbursement for

Stereotactic Radiosurgery

Background

Stereotactic Radiosurgery (SRS) is a multispecialty discipline pioneered by neurosurgeons, and the roles of the neurosurgeon, radiation oncologist and physicist are essential. As with other 90-day global cranial and spinal procedures performed by neurosurgeons, the neurosurgeon is responsible for the pre-operative assessment of the patient, treatment planning, oversight of the procedure itself, and health needs of the patient during the 90-day global period related to the SRS procedure. As the primary responsible health care provider, the neurosurgeon assumes responsibility for the patient's record and conducts follow up visits as deemed clinically appropriate following the SRS procedure.

Definition of Stereotactic Radiosurgery

The American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) support the following definition of stereotactic radiosurgery developed by the AANS, CNS, and the American Society for Therapeutic Radiology and Oncology (ASTRO) in March 20, 2006:

> ***Stereotactic Radiosurgery is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate (a) defined target(s) in the head or spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist.***
>
> ***Stereotactic Radiosurgery (SRS) typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five.***
>
> ***Technologies that are used to perform SRS include linear accelerators, particle beam accelerators, and multisource Cobalt 60 units. In order to enhance precision, various devices may incorporate robotics and real time imaging.***

Coding for Radiosurgery

As of January 1, 2009, CPT Code 61793, which was formerly used to report SRS, has been deleted from AMA *Current Procedural Terminology*, Fourth Edition (CPT®)[1] Current Procedural Terminology

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WASHINGTON OFFICE
KATIE G. ORRICO, Director
725 Fifteenth Street, NW, Suite 500 Washington, DC 20005
Phone: 202-628-2072 Fax: 202-628-5264 E-mail: korrico@neurosurgery.org

(CPT) and replaced with new codes[2]. The new codes are part of the 2009 CPT and beginning on January 1, 2009, the appropriate codes for reporting SRS are as follows:

CPT Code	Description
61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in additional to code for primary procedure)
61800	Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
63620	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)

With the new coding structure, one can report the work involved with treating more than one lesion. The maximum number of cranial lesions that can be treated at any one time is five and the maximum number of spinal lesions that can be treated at any one time is three. The primary code (61796, 61798 or 63620) should be reported for the first lesion. The cranial add-on codes (61797 or 61799) are used for each additional lesion and the spinal add-on code (63621) is used for each additional lesion in the spine.

This entire new code structure has also been incorporated into the 2009 Medicare Physician Fee Schedule and each of these codes is designated as an "Active" code.

The above SRS codes should be reported only once per lesion treated, regardless of the number of treatment delivery sessions that are used to treat that lesion. Note, however, that the definition of SRS states that SRS is delivered in one to five sessions. If a lesion is treated in more than five sessions then that procedure is, by definition, ***not*** radiosurgery – it is radiation therapy – and thus cannot be reported using the SRS codes. In addition, the SRS codes should be reported only once per lesion treated, regardless of the number of treatment planning sessions that are required to plan for the treatment of that lesion.

[2] See Stereotactic Radiosurgery Appendix for the complete code description for the Stereotactic Radiosurgery (Cranial) and Stereotactic Radiosurgery (Spinal) codes as published in CPT 2009.

With the new code structure, the neurosurgeon only bills for SRS using the above codes. The neurosurgeon should not report any of the radiation oncology codes (77XXX codes) in addition to the radiosurgery codes. The neurosurgeon should also not report SRS using any other codes in addition to the above codes.

For example, the following codes are bundled into the radiosurgery codes and therefore ***cannot*** be reported with the SRS codes:

61720 Creation of lesion by stereotactic method, including burr hole(s) and localizing and recording techniques, single or multiple stages; globus pallidus or thalamus

61735 Creation of lesion by stereotactic method, including burr hole(s) and localizing and recording techniques, single or multiple stages; subcortical structure(s) other than globus pallidus or thalamus

61770 Stereotactic localization, including burr hole(s), with insertion of catheter(s) or probe(s) for placement of radiation source

61790 Creation of lesion by stereotactic method, percutaneous, by neurolytic agent (eg, alcohol, thermal, electrical, radiofrequency); gasserian ganglion

61795 Stereotactic computer-assisted volumetric (navigational) procedure, intracranial, extracranial, or spinal (List separately in addition to code for primary procedure)

Summary

Neurosurgeons use SRS as a definitive or adjuvant modality for their patients, as deemed appropriate by the clinical needs of the individual patient. The procedure requires a collaborative effort, combining the neurosurgeon's expertise in neuroanatomy and physiology with the expertise in dose selection and radiation safety possessed by the radiation oncologist and radiation physicist. Beginning January 1, 2009, the neurosurgeon should report the procedure using the codes in the 2009 CPT book, as CPT Code 61793 has been deleted. All third party payers, including Medicare, Medicaid and private insurers should likewise reimburse neurosurgeons for SRS based on the new code structure.

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Stereotactic radiosurgery—an organized neurosurgery-sanctioned definition

GENE H. BARNETT, M.D.,[1] MARK E. LINSKEY, M.D.,[2] JOHN R. ADLER, M.D.,[3] JEFFREY W. COZZENS, M.D.,[4] WILLIAM A. FRIEDMAN, M.D.,[5] M. PETER HEILBRUN, M.D.,[6] L. DADE LUNSFORD, M.D.,[7] MICHAEL SCHULDER, M.D.,[8] AND ANDREW E. SLOAN, M.D.,[9] THE AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS/CONGRESS OF NEUROLOGICAL SURGEONS WASHINGTON COMMITTEE STEREOTACTIC RADIOSURGERY TASK FORCE

[1]Brain Tumor Institute and Department of Neurological Surgery, Cleveland Clinic, Cleveland, Ohio; [2]Department of Neurological Surgery, University of California Irvine Medical Center, Orange; [3]Department of Neurological Surgery, Stanford University Medical Center, Palo Alto; and [4]Tiburon, California; [5]Department of Neurological Surgery, Evanston Northwestern Healthcare, Evanston, Illinois; [6]Department of Neurosurgery, University of Florida, Gainesville; and [8]Neuro-oncology Program, Moffitt Cancer Center, Tampa, Florida; [7]Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; and [9]Department of Neurological Surgery, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey

KEY WORDS • **stereotactic radiosurgery** • **American Association of Neurological Surgeons** • **Congress of Neurological Surgeons**

> Change is the law of life. And those who look only to the past or present are certain to miss the future.
>
> JOHN F. KENNEDY

Since its introduction five decades ago, stereotactic radiosurgery (SRS) has evolved from an investigational concept into a mainstream neurosurgical procedure for the management of a wide variety of brain disorders. Contemporary neurosurgeons routinely use radiosurgery either as a definitive or adjuvant treatment modality in the fields of neurooncology and cerebrovascular and functional neurosurgery. Stereotactic radiosurgery offers the surgical neurooncologist a precise and established treatment that, in combination with fractionated radiotherapy, chemotherapy, and conventional surgery, offers additional management options for the treatment of patients with brain tumors.[4,5,12] The role of SRS in the management of vascular malformations is also well established. Furthermore, this modality has had a significant impact on the treatment of patients with brain metastases;[5,20,51] in cases in which SRS is possible, these patients more commonly succumb to their uncontrolled extracranial disease than to their intracranial disease.

Recently there has been a spate of reports attempting to clarify or to (re)define the terms "stereotactic radiosurgery" and "stereotactic radiotherapy" (SRT).[1,48,66] It has become increasingly clear that the evolution of radiosurgery and radiotherapeutic techniques demands a reevaluation of the definition of radiosurgery by organized neurosurgery. These factors led the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) to form the Stereotactic Radiosurgery Task Force under the auspices of the AANS/CNS Washington Committee. Members of the Stereotactic Radiosurgery Task Force were directed to review, clarify, and recommend to their parent organizations a contemporary definition of SRS, which would take into account historical, current, and potential applications of SRS. The purpose of this paper is to express the position of the AANS as well as that of the CNS on the definition of SRS.

Historical Review

"Stereotactic radiosurgery" was defined by the Swedish neurosurgeon Lars Leksell in 1951.[37] At that time, Leksell sought to mimic destructive lesions in the brain produced by mechanically invasive stereotactic surgical procedures for movement and pain disorders by delivering a high dose of photon or proton energy to the intended target in a single session, while steep fall-off dose gradients protected the adjacent brain. Early efforts involving stereotactically applied ultrasound, orthovoltage x-ray, and accelerated particles such as protons proved inadequate to create these lesions deep in the brain or were otherwise too cumbersome. To overcome these shortcomings, Leksell, Liden, Larsson, and colleagues developed the Gamma Knife in 1967. This device focuses multiple beams of high-energy gamma rays to a common point directed by frame-based stereotactic guidance.[35,38] Contemporaries such as Kjellberg, Winston, Lutz, Loeffler, Fabrikant, and others also developed systems using x-rays or particles to achieve the same ends.[22,26,48,73,78]

For decades, stereotactic localization was limited to information derived from atlases, plain radiographs, pneumoencephalograms, and angiograms.[37,39,65,67,71] Throughout his life, Leksell remained active in advancing the state of the art

of SRS and was one of several visionaries who developed methods of exploiting the spatial information provided by computed tomography and, later, magnetic resonance (MR) imaging, thereby creating the field of image-guided stereotaxy.[60] Although the radiosurgical treatment of intracranial malignancies became feasible, Leksell believed that SRS was best used for functional neurosurgery or to treat benign tumors and lesions such as arteriovenous malformations and not to treat malignant tumors.

Early neurosurgeons who performed radiosurgery found that collateral damage to adjacent structures occasionally occurred when treating benign disease; several strategies were devised to reduce complications.[47,59] Stereotactic MR imaging was used to provide better visualization and definition of targets and anatomical structures at risk.[23] Radiation doses directed to the lesion's margin were gradually reduced while maintaining therapeutic efficacy.[23,25] Computer-assisted planning systems aided the design of treatment plans that better conformed to the shape of the radiosurgery target.[23,25] Rigid skull fixation, the "gold-standard" for stereotactic accuracy, was supplemented by relocatable frames that allowed radiosurgery to be performed in multiple sessions.[15,18,23,24,38,43,53,63–65,69,70,77,78]

Stereotactic radiosurgery became established and accepted as an important neurosurgical technique in the 1980s and 1990s.[58,61] Its value transcended the original indications posed by Leksell to include proven efficacy for the most common central nervous system malignancy—metastatic disease.[6,66,72] Neurosurgeons wished to extend the reach of this technology beyond the limits of cranial disease. The use of extracranial radiosurgery with the aid of a frame was first reported by Hamilton in 1996.[31,72] Concurrently, conventional surgical stereotaxy was revolutionized by the neurosurgical development of frameless stereotactic techniques.[8,42,67,74] The notion that radiosurgery could also be delivered without a stereotactic frame was brought to fruition by Adler and others.[2,15,31,64,75] New linear accelerator (LINAC)–based radiosurgical instruments rely on image-guided stereotactic targeting and advanced beam delivery methods. In one system, radiosurgical delivery is performed by a lightweight LINAC that is robotically positioned,[15,36,75] and in another, by a LINAC whose output is modulated by computer-controlled multileaf collimators.[10] Today, radiosurgery can and has been performed on virtually any part of the body, and the fewer fixation requirements facilitate the performance of the procedure in multiple sessions.[9–11,13,18,27–29,31–34,40,47,52,68,69,74]

Recently developed alternative forms of energy include high-intensity focused ultrasound.[37,44,45] When delivered stereotactically to destroy or injure tissue, these other forms of energy could be interpreted by some as falling within the umbrella of SRS.

Role of the Neurosurgeon in SRS

These advances notwithstanding, SRS remains a "team" discipline in which the roles of the surgeon, radiation oncologist, and physicist are essential, regardless of the target organ or site of service. As in any surgical procedure involving the brain or spine, the neurological surgeon provides preoperative assessment of the patient and a review of pertinent imaging studies so that therapeutic alternatives can be presented to the patient and informed consent can be obtained. After the procedure, the neurosurgeon provides continued reevaluation and follow-up review at clinically appropriate intervals in order to assess outcomes on a long-term basis. During the radiosurgical procedure itself, the neurosurgeon serves as the primary responsible healthcare provider. Separate tasks of a radiosurgical procedure, including the treatment setup, planning, and delivery that are performed by or directly supervised by the neurosurgeon, comprise the following: delivery of agents for appropriate conscious sedation; application of the stereotactic coordinate frame (when pertinent) based on lesion location; selection and creation of the appropriate imaging data set (for example, computed tomography scans, MR images, angiograms, or positron emission tomography images) necessary for radiosurgical planning; computer-assisted delineation of target volumes and adjacent critical anatomical structures; creation of the 3D volumetric radiosurgical effect assisted by computer planning; setup, confirmation, and delivery of radiation; provision of additional sedation as required; monitoring of the patient's vital signs during radiation delivery; removal of the stereotactic frame followed by bandaging or other wound care as needed; and standard postradiosurgery 90-day follow-up care. As the primary responsible healthcare provider, the neurosurgeon assumes responsibility for chart completion as required by the patient's inpatient or ambulatory status after radiosurgery.

Recent Publications on the Role of Radiosurgery Versus SRT

Because new technology now enables radiosurgery to be delivered in more than one session and because "radiation therapy" is sometimes administered with the aid of stereotactic localization, there have been several attempts in the neurosurgical literature during the past few years to define, redefine, or clarify the term SRS.[7,68,69] At present there are "purists" who prefer the original definition of SRS offered by Lars Leksell some 50 years ago, while others subscribe to the concept of a procedure that has evolved with the emergence of new technology.

The Traditional Perspective

The principal argument made by authors espousing the traditional perspective is that the term radiosurgery must be restricted to a high dose of ionizing radiation delivered to a defined target in a single session.[48,64] Stereotactic radiosurgery derives its safety by its high degree of conformality and high selectivity (shown by the steep dose falloff in the adjacent normal tissue), such that dose homogeneity within the target area is irrelevant. On the other hand, these authors contend that the delivery of fractionated radiation delivered in multiple sessions by daily application of a non–skeleton-affixed guiding device (SRT) is usually less conformal and precise than conventional frame-based SRS. This presumably makes dose homogeneity desirable. This group also maintains that the rationale for SRT is primarily an attempt to reduce the risks of radiation damage to the surrounding normal tissue. Finally, they state that the term "(hypo-)fractionated stereotactic radiosurgery" is an oxymoron.

Alternative Perspectives

All will agree that a high dose of ionizing radiation deliv-

ered to a stereotactically defined target in a single session is (a form of) SRS. Contemporary controversies focus on two areas: can "radiosurgery" be delivered in more than one session, and, if so, where does SRS delivered in multiple sessions end and SRT begin?

The historical review presented earlier demonstrates the evolutionary process of thought and practice in SRS throughout the past five decades. We believe that a reasonable person will recognize that this evolution includes radiosurgery delivered in more than one session. In his original description of SRS in 1951, Lars Leksell did not specifically state that the procedure needed be performed in a single session. In 1983, Leksell described SRS as "a technique for the non-invasive destruction of intracranial tissues or lesions . . . [in which] the open stereotactic method provides the basis. . . ."[28]—again without explicitly restricting its use to a single session. Statements limiting SRS to a single session arose years later, in describing the state of practice at that time.[4,7,20,33] Today, the American Medical Association recognizes that SRS may be undertaken in one or more sessions according to Current Procedural Terminology,[3] as does the Centers for Medicare and Medicaid Services.[14]

Ionizing radiation has been used for longer than a century in medical therapy. Much has been made of the differential radiobiology of SRS and fractionated radiotherapy—the "Four Rs" of reoxygenation, reassortment, repopulation, and repair[5,38]—to distinguish SRS from SRT. In truth, little is known about the true radiobiology of radiosurgery and these arguments are theoretical at best.[49,54]

What is known is the intent of the treatment. Radiosurgery aims to injure or destroy tissue at the target and preserve adjacent critical tissue, primarily due to steep dose gradients. Homogeneity within the lesion is generally not considered important and can be a disadvantage for achieving tumor shrinkage when treating lesions that do not contain normal tissue or for treating internal tumor areas of necrosis or hypoxemia. Tumors that may be resistant to fractionated radiotherapy may respond well to radiosurgery. Multiple sessions may be used to further reduce injury to adjacent normal tissue while maintaining the efficacy of radiosurgery. In fractionated radiotherapy abnormal tissue is differentiated from normal tissue within the target site by the differential sensitivity of these tissues to fractionated ionizing radiation.[21] Dose homogeneity is desirable when the treatment volume contains sensitive normal tissue (either in the tumor or closely adjacent). Deleterious effects outside the treatment area may be further reduced by enhancing treatment conformality and by increasing the dose gradient. Either technique may be directed stereotactically (SRS and SRT).

Few would disagree that the precise stereotactic delivery of a high dose of radiation for the purpose of tissue inactivation or destruction in a single session is within the scope of SRS, and that the precise stereotactic delivery of radiation in 30 sessions is not SRS but is better described as SRT. Conversely, such a single-session delivery should fall outside the scope of SRT. Between these extremes, however, are cases of potential overlap between the techniques. We believe that these are best differentiated by the intended mechanism of action and that data in the literature, federal policy, and contemporary practice indicate that the upper limit of sessions in which SRS may be delivered is five.[14]

After considerable debate and discussions, on June 29, 2005, the members of the AANS/CNS Stereotactic Radiosurgery Task Force *(Appendix A)* met in Chicago and arrived at a contemporary definition of SRS, which has subsequently been approved by both parent organizations. Thereafter, on March 20, 2006, representatives of the AANS/CNS met with the corresponding body of the American Society for Therapeutic Radiology and Oncology (ASTRO; *Appendix B*) and refined this definition of radiosurgery, subsequently sanctioned by the AANS, CNS, and ASTRO:

> Stereotactic Radiosurgery is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate (a) defined target(s) in the head or spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist.
>
> Stereotactic Radiosurgery (SRS) typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five.
>
> Technologies that are used to perform SRS include linear accelerators, particle beam accelerators and multisource Cobalt 60 units. In order to enhance precision, various devices may incorporate robotics and real time imaging.

Appendix A

Members of the AANS/CNS Washington Committee Stereotactic Radiosurgery Task Force

Gene H. Barnett, M.D., Chair
Mark E. Linskey, M.D., Vice-Chair
John R. Adler, M.D.
Jeffrey W. Cozzens, M.D.
William A. Friedman, M.D.
M. Peter Heilbrun, M.D.
L. Dade Lunsford, M.D.
Michael Schulder, M.D.
Andrew E. Sloan, M.D.

Appendix B

Representatives at the March 20, 2006 Meeting of the AANS/CNS and the ASTRO

AANS/CNS
Gene Barnett, M.D., Chair, AANS/CNS Stereotactic Radiosurgery Task Force; Chair, AANS Representative Board of Directors
Mark Linskey, M.D., Vice-Chair, AANS/CNS Stereotactic Radiosurgery Task Force; Co-Chair, CNS Representative Executive Committee
Greg Przybylski, M.D., Chair AANS/CNS Coding and Reimbursement Committee; Member, AANS Relative Value Update Committee
Jeff Cozzens, M.D., Member, AANS/CNS Coding and Reimbursement Committee; Advisor, AANS Current Procedural Terminology
Troy Tippett, M.D., Chair, AANS/CNS Washington Committee; Member, AANS Board of Directors
Cathy Hill, Senior Manager for Regulatory Affairs, AANS/CNS
Katie Orrico, Director, AANS/CNS Washington Office

ASTRO
K. Kian Ang, M.D., Ph.D., President, ASTRO
Michael Steinberg, M.D., Member, ASTRO Board of Directors; Chair, Health Policy Council; Advisor, Current Procedural Terminology
Louis Potters, M.D., Member, ASTRO Board of Directors; Vice-

Chair, Health Policy Council; Member, Ambulatory Payment Classification Panel
Timothy Williams, M.D., Co-Chair, Health Policy Committee
David Beyer, M.D., Co-Chair, Health Policy Committee; Advisor, Current Procedural Terminology
Najeeb Mohideen, M.D., Chair, Code Utilization, Application, Development and Valuation Committee; Representative, Relative Value Update Committee
Joel Cherlow, M.D., Chair, Regulatory Committee
Trisha Crishock, Director of Health Policy, ASTRO
Debra Lansey, Assistant Director of Health Policy, ASTRO

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Address reprint requests to: Gene H. Barnett, M.D., Brain Tumor Institute, Taussig Cancer Center, R20, 9500 Euclid Avenue, Cleveland, Ohio 44195. email: barnett@neus.ccf.org.

American Society for Radiation Oncology (ASTRO)

September 28, 2012

Christine Valkyrie Masters
Program Specialist
Health Technology Assessment
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

BY ELECTRONIC SUBMISSION to shtap@hca.wa.gov

Dear Ms. Masters:

The American Society for Radiation Oncology (ASTRO), the largest radiation oncology society in the world representing more than 10,000 members who specialize in treating patients with radiation therapies, appreciates the opportunity to comment on the Washington State Health Care Authority Health Technology Assessment Program Draft Evidence Report on stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT), published on August 29, 2012.

The draft evidence report from the Oregon Health & Science University (OHSU) Center for Evidence-based Policy compares SRS and SBRT with conventional radiation therapy in the areas of efficacy, safety and cost effectiveness for multiple cancer types. The report concludes that the strength of the evidence for SRS and SBRT is very low or low for most of the findings according to a method of evaluation that the OHSU group developed as a modification of the British systems used by the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN). ASTRO believes there is ample evidence of efficacy and safety for SRS and SBRT, and our comments will be primarily focused on the shortcomings of this evaluation based on the NICE and SIGN methodologies. We are very concerned that the OHSU group's reports might lead to a limitation of access to SRS and SBRT for certain underserved populations of patients in the state of Washington, and we wish to avoid disparities in cancer care for socioeconomically disadvantaged groups.

First of all, it should be appreciated that for many of the most important indications for which SRS and SBRT have emerged as a standard of care, they were developed to meet otherwise unmet medical needs. For example, regarding the case of medically inoperable early stage non-small cell lung cancer (NSCLC), if left untreated the disease kills more than half of afflicted patients [1]. Data from the Surveillance, Epidemiology, and End Results (SEER) registry indicate that with the use of conventional radiotherapy for stage I NSCLC the incremental survival gain above observation is a meager 7 months, for a median survival of only 21 months [2]. Against the background of these entirely unsatisfactory results, when carefully executed multi-institutional cooperative group studies involving SBRT in the management of early stage medically inoperable NSCLC were completed and revealed a median overall survival exceeding

AMERICAN SOCIETY FOR RADIATION ONCOLOGY
8280 WILLOW OAKS CORPORATE DRIVE • SUITE 500 • FAIRFAX, VA 22031 • 800.962.7876 • 703.502.1550 • FAX: 703.502.7852
www.astro.org • www.rtanswers.org

3 years [3,4], it is not surprising that patient advocates objected to randomized studies comparing SBRT with a conventional radiotherapy technique, effectively eliminating the possibility of a phase III study of that type in the US given the overwhelming body of evidence favoring the superiority of SBRT in that setting.

Additional compelling evidence supporting the US observations is available from the published reports of the Dutch experience of SBRT for early stage medically inoperable NSCLC. An analysis of 4605 patients followed in the Netherlands Cancer Registry revealed a significant improvement in overall survival for patients with stage I NSCLC treated with radiotherapy since the implementation of SBRT methods for treating this disease [5, 6]. In view of these and the multitude of other supporting published reports documenting the safety and efficacy of SBRT in this setting, NICE has now included SBRT within its recommended treatments for patients with medically inoperable early stage NSCLC [7].

It is likewise worth noting that cranial SRS was similarly developed as a means of addressing unmet medical needs. Specifically, the individual universally credited as the inventor of the technique, Lars Leksell, initially focused on the use of SRS as a means of treating anatomic irregularities such as arteriovenous malformations and a variety of functional disorders of the central nervous system, and only a minority of his initial patients in the late 1960s through early 1980s were treated for neoplastic disease [8]. Once the safety and efficacy of administering SRS had been established as an effective non-surgical alternative in a wide range of neurosurgical applications, the technique began to proliferate with emphasis on the use of SRS for CNS neoplasms in particular. Decades of accumulated experience have led the oncology community to view the use of SRS and the use of open surgical resection as equivalent approaches for the treatment of brain metastases. For example, in the randomized EORTC study comparing observation versus adjuvant whole brain radiotherapy following local treatment for limited cranial metastases, either SRS or open surgery could be employed as the initial treatment modality [9].

In other words, the comparator modality for SRS is not conventional radiotherapy but, instead, open surgical resection. It is unrealistic to think that a randomized clinical trial would ever be accomplished in the comparison of two modalities of such widely disparate nature. To our knowledge, the only study of this type ever reported is the noble, ambitious but ultimately futile efforts of Roos and colleagues [10], who were obliged to close their trial long before reaching the intended accrual as a result of the difficulty in identifying patients willing to undergo this type of randomization. Indeed, in their discussion the authors articulated the essential insurmountable obstacle elegantly: "The high rate of patient refusals (18/40 - 45% of those deemed eligible) reflects the strong preferences of some patients to avoid an invasive procedure, some want the lesion removed and others want neither surgery nor radiosurgery."

For extracranial indications other than medically inoperable NSCLC, SBRT is likewise not appropriately compared with conventional radiotherapy but, instead, would be more appropriately compared with surgical resection given that the reported local control outcomes are generally very similar to surgery and so greatly exceed those of conventional radiotherapy. Thus, just as the prospect of randomizing patients between open brain surgery and non-invasive cranial

SRS has proven not to be feasible, a randomization between SBRT and surgical resection of a liver, lung, or spine metastasis is unrealistic.

There have been a few notable and instructive examples of attempted randomizations between surgery and conventional radiotherapy for extracranial malignancies. A rare example of a successfully completed study of surgery versus radiotherapy is the Department of Veterans Affairs Laryngeal Cancer Study, which demonstrated higher larynx preservation and equal survival with non-surgical treatment [11]. That study, however, is the exception and not the rule, and it is a singular example of an instance where patients agreed to undergo randomization between interventions with such extremely different anatomic impact. While a completed intergroup study for lung cancer involved a randomization between full dose chemotherapy and radiotherapy versus a lower pre-operative dose of radiotherapy and chemotherapy prior to surgery [12], there is far less difference in net physiologic or psychological impact between high dose radiotherapy and lower dose radiotherapy plus partial lung resection than between surgery that removes a voicebox and radiotherapy that preserves oral speech. On the other hand, numerous other studies attempting randomization between surgery and radiotherapy for prostate or esophageal cancer have failed to accrue. It is unrealistic to expect patients to be willing to undergo a coin toss assignment between interventions of such vastly different risk profiles and functional impact.

Concerning some other aspect of the OHSU report, we disagree with the assessment by this group that nearly all of the studies reviewed, as well as the guidelines evaluated and listed in Appendix G, are of "poor" or at best "fair" quality. Appendix D includes the checklists used as quality assessment tools for the evidence review, and the overall assessment of quality is the reviewer's opinion of the answer to the question "How well was the study done to minimize bias?" or "How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect?" for assessments of systematic reviews and cohort studies, respectively. It is ASTRO's opinion that this type of question is impossible to answer, since the reviewers cannot know the state of mind of authors of the studies reviewed, and we submit that any evaluation of published studies should be made based on the objective data reported and not a speculative judgment regarding the authors' state of mind.

Furthermore, as we discussed in our comment letter on the IMRT draft evidence report dated August 2, 2012, ASTRO believes there is established precedent for introducing significant technological developments based on self-evident superiority without the need for randomized clinical trials. Examples include:

- CT scanning vs. plain radiographs;
- Linear accelerators vs. cobalt machines;
- Minimally invasive surgery vs. conventional surgery.

Of lesser importance in the OHSU draft report, but still worth noting, are instances where there is promotion of a specific vendor's commercially available treatment delivery system that possibly resulted from the OHSU group's fundamental misunderstanding of the nature of the technology described. In figure 1, the trade name Tomotherapy is isolated as a category of so-called newer image-guided conformal methods with an implication that it is somehow different from IMRT, when in fact that particular commercial delivery platform administers treatment that is properly

called either SBRT or IMRT, depending on the clinical indication and schedule of treatment. Likewise, Figure 2 separates out CyberKnife and GammaKnife from other treatment delivery platforms that administer stereotactic radiation, but these systems are simply examples of vendor-specific commercially available systems capable of either cranial SRS (GammaKnife) or both SRS and SBRT (CyberKnife).

In summary, ASTRO agrees that in general, prospective studies and randomized controlled trials are the most reliable way of assessing the efficacy and safety of new technologies. However, in the case of transformative technologies such as SRS or SBRT, it is often impossible to sustain the necessary equipoise to complete a randomized study if the clinical outcomes of the new treatment so far exceed prior forms of intervention. Additionally, in some cases the nature of the new technology is so fundamentally different from the most relevant comparator that it is unrealistic to expect patients to be willing to undergo randomization, as in the case when open surgical resection—with its attendant risks of immediate perioperative mortality—would have to be compared with the less invasive interventions of SRS and SBRT. Ultimately, then, not all technology questions will be addressed by phase III trials, and other high quality levels of evidence are employed to facilitate the evolution of practice standards.

We appreciate your consideration of our comments and look forward to the November 16, 2012 public meeting on this topic.

Sincerely,

Gregory Patton, MD
Chair, Regulatory Committee

Michael Dzeda, MD
Vice-Chair, Regulatory Committee

cc: Thomas Eichler, MD
Joel Cherlow, MD
Najeeb Mohideen, MD
Brian Kavanagh, MD

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CyberKnife® Coalition (CKC)

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CYBERKNIFE CKC COALITION

September 27, 2012

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712

Re: Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy (SRS/SBRT) Draft Evidence Report

The CyberKnife® Coalition (CKC) respectfully submits our response to the draft evidence report released by the Washington State Health Care Authority, Health Technology Assessment Program (HTA) entitled, "Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy." The CKC is a non-profit association of both hospital-based and freestanding centers that are dedicated to protecting patients' access to robotic stereotactic radiosurgery (R-SRS) and robotic stereotactic body radiotherapy (R-SBRT), performed utilizing CyberKnife technology.

In March 2012, the CKC submitted a response to HTA's request for public comments on Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT). Our response included detailed information surrounding the significant clinical benefits of CyberKnife and the well documented published data that supports SRS/SBRT as a standard of care in the treatment of cancer patients in the United States and around the world.

At this time we would like to provide the HTA with additional information about clinical practice patterns including federal and private payer coverage policies and national guidelines that demonstrate the acceptance of SRS/SBRT. There are several federal and private payers that have deemed SRS/SBRT to be non-experimental and medically necessary for many of the indications that HTA reviewed. Several of the payer policies reviewed by HTA provide coverage for the treatment of benign cranial lesions such as neuromas, meningiomas and malignant brain lesions, while several policies include SBRT for lung, liver, kidney, pancreas and prostate tumors. In addition, Noridian Administrative Services (JH Medicare Contractor) has published a draft Local Coverage Determination (LCD) for SRS/SBRT, which provides coverage for primary and secondary cancers of the brain, spine, lung, liver, pancreas, kidney, and adrenal gland. Noridian has also publicly stated it plans on revising this policy to include coverage of prostate cancer for patients enrolled in a clinical registry. The final LCD is expected this fall, which will be similar to the majority of other published Medicare policies for SRS/SBRT. A complete list of all indications covered by Noridian is provided in Appendix A.

info@ckcoalition.org

We also submit for your consideration guideline information developed by the National Comprehensive Cancer Center (NCCN), a not-for-profit alliance of 21 of the world's leading cancer centers. NCCN promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines. There are several NCCN guidelines (further details in appendix B) that have positive inclusion of SRS/SBRT as an initial treatment option, including:

- NCCN non-small cell lung cancer
- NCCN hepatocellular carcinoma
- NCCN central nervous system

In addition to the NCCN guidelines, there are 3 recent draft Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review reports: stage I non-small cell lung cancer, unresectable primary hepatocellular carcinoma, and metastasis to the liver from unresectable colorectal cancer, which include SBRT as one of the primary treatment options for each of these 3 cancer indications (further details in Appendix C-E).[1,2,3]

Finally, the 2011 California Technology Assessment Forum's (CTAF) report on SBRT for the treatment of early stage NCSLC supports SBRT as a treatment option for stage I inoperable NSCLC.[4] The report notes the following:

"It is recommended that stereotactic body radiation therapy for the treatment of early stage non small cell lung cancer in medically inoperable patients with peripheral lesions meets CTAF criteria for safety, effectiveness and improvement in outcomes."

We strongly support the current federal and private payer coverage policies that provide cancer patients with access to this clinically beneficial treatment option. We also strongly support the current NCCN, AHRQ, and CTAF guidelines and reports that demonstrate the clinically efficacy and safety of SRS and SBRT in the treatment of several cancer types. We urge the Washington State Health Care Authority to allow this same

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[1] AHRQ. Draft Comparative Effectiveness Review. Local Therapies for Unresectable Primary Hepatocellular Carcinoma. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1012&pageaction=displayproduct Accessed September 25, 2012.

[2] ARHQ. Draft Comparative Effectiveness Review. Local Hepatic Therapies for Metastases to the Liver from Unresectable Colorectal Cancer: Effectiveness and Comparative Effectiveness. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=949 Accessed September 25, 2012.

[3] AHRQ. Draft Comparative Effectiveness Review. Local Therapies for the Treatment of Stage I Non-Small Cell Lung Cancer and Endobronchial Obstruction due to Advanced Lung Tumors. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=965&pageaction=displayproduct Accessed September 25, 2012.

[4] Walsh, J. CTAF. Stereotactic Body Therapy Radiation for the Treatment of Early Stage Non-Small Cell Lung Cancer. June 2011. http://www.ctaf.org/assessments/stereotactic-body-radiation-therapy-treatment-early-stage-non-small-cell-lung-cancer-0 Accessed September 25, 2012.

access to care and not deviate from the current federal and private payer SRS/SBRT coverage policies and guidelines within the state of Washington.

Thank you for the opportunity to provide comments regarding SRS and SBRT coverage. Our member institutions, including those in Washington State, would welcome a meeting with you in person answer any further questions or concerns that you may have. In addition, please feel free to contact us at the numbers below if we can be of any assistance as your organization finalizes the report.

Sincerely,

Linda F. Winger, MSc, FACHE
President, CyberKnife Coalition
Vice President, Washington Region Oncology Svcs.
MedStar Health
3800 Reservoir Road, NW
Washington, DC 20007-2197
202-412-3191
Linda.F.Winger@medstar.net

John W. Rieke, MD, FACR
Board of Directors, CyberKnife Coalition
Medical Director, MultiCare Regional Cancer Center
1003 South 5th Street
Tacoma, Washington 98405
253-403-4994
John.Rieke@Multicare.org

Appendix A

Stereotactic Radiosurgery Services and Stereotactic Body Radiation Therapy (for Cranial Lesions only) - (CPT 77371, 77372, 77373, 77432, 77435, G0173, G0251, G0339, and G0340)

147.0	MALIGNANT NEOPLASM OF SUPERIOR WALL OF NASOPHARYNX
147.1	MALIGNANT NEOPLASM OF POSTERIOR WALL OF NASOPHARYNX
147.2	MALIGNANT NEOPLASM OF LATERAL WALL OF NASOPHARYNX
147.3	MALIGNANT NEOPLASM OF ANTERIOR WALL OF NASOPHARYNX
147.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF NASOPHARYNX
147.9	MALIGNANT NEOPLASM OF NASOPHARYNX UNSPECIFIED SITE
160.0	MALIGNANT NEOPLASM OF NASAL CAVITIES
160.1	MALIGNANT NEOPLASM OF AUDITORY TUBE MIDDLE EAR AND MASTOID AIR CELLS
160.2	MALIGNANT NEOPLASM OF MAXILLARY SINUS
160.3	MALIGNANT NEOPLASM OF ETHMOIDAL SINUS
160.4	MALIGNANT NEOPLASM OF FRONTAL SINUS
160.5	MALIGNANT NEOPLASM OF SPHENOIDAL SINUS
160.8	MALIGNANT NEOPLASM OF OTHER ACCESSORY SINUSES
160.9	MALIGNANT NEOPLASM OF ACCESSORY SINUS UNSPECIFIED
191.0	MALIGNANT NEOPLASM OF CEREBRUM EXCEPT LOBES AND VENTRICLES
191.1	MALIGNANT NEOPLASM OF FRONTAL LOBE
191.2	MALIGNANT NEOPLASM OF TEMPORAL LOBE
191.3	MALIGNANT NEOPLASM OF PARIETAL LOBE
191.4	MALIGNANT NEOPLASM OF OCCIPITAL LOBE
191.5	MALIGNANT NEOPLASM OF VENTRICLES
191.6	MALIGNANT NEOPLASM OF CEREBELLUM NOS
191.7	MALIGNANT NEOPLASM OF BRAIN STEM
191.8	MALIGNANT NEOPLASM OF OTHER PARTS OF BRAIN
191.9	MALIGNANT NEOPLASM OF BRAIN UNSPECIFIED SITE
192.0	MALIGNANT NEOPLASM OF CRANIAL NERVES
192.1	MALIGNANT NEOPLASM OF CEREBRAL MENINGES
194.3	MALIGNANT NEOPLASM OF PITUITARY GLAND AND CRANIOPHARYNGEAL DUCT
194.4	MALIGNANT NEOPLASM OF PINEAL GLAND
194.6	MALIGNANT NEOPLASM OF AORTIC BODY AND OTHER PARAGANGLIA
198.3	SECONDARY MALIGNANT NEOPLASM OF BRAIN AND SPINAL CORD
198.4*	SECONDARY MALIGNANT NEOPLASM OF OTHER PARTS OF NERVOUS SYSTEM
198.5*	SECONDARY MALIGNANT NEOPLASM OF BONE AND BONE MARROW
198.89*	SECONDARY MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES
225.0	BENIGN NEOPLASM OF BRAIN
225.1	BENIGN NEOPLASM OF CRANIAL NERVES
225.2	BENIGN NEOPLASM OF CEREBRAL MENINGES
227.3	BENIGN NEOPLASM OF PITUITARY GLAND AND CRANIOPHARYNGEAL DUCT

227.4	BENIGN NEOPLASM OF PINEAL GLAND
227.5	BENIGN NEOPLASM OF CAROTID BODY
227.6*	BENIGN NEOPLASM OF AORTIC BODY AND OTHER PARAGANGLIA
228.02	HEMANGIOMA OF INTRACRANIAL STRUCTURES
237.0	NEOPLASM OF UNCERTAIN BEHAVIOR OF PITUITARY GLAND AND CRANIOPHARYNGEAL DUCT
237.1	NEOPLASM OF UNCERTAIN BEHAVIOR OF PINEAL GLAND
237.3*	NEOPLASM OF UNCERTAIN BEHAVIOR OF PARAGANGLIA
237.5*	NEOPLASM OF UNCERTAIN BEHAVIOR OF BRAIN AND SPINAL CORD
237.6*	NEOPLASM OF UNCERTAIN BEHAVIOR OF MENINGES
239.6*	NEOPLASM OF UNSPECIFIED NATURE OF BRAIN
239.7*	NEOPLASM OF UNSPECIFIED NATURE OF ENDOCRINE GLANDS AND OTHER PARTS OF NERVOUS SYSTEM
332.0*	PARALYSIS AGITANS
333.1*	ESSENTIAL AND OTHER SPECIFIED FORMS OF TREMOR
345.11	GENERALIZED CONVULSIVE EPILEPSY WITH INTRACTABLE EPILEPSY
345.3	GRAND MAL STATUS EPILEPTIC
345.91	EPILEPSY UNSPECIFIED WITH INTRACTABLE EPILEPSY
350.1	TRIGEMINAL NEURALGIA
350.8	OTHER SPECIFIED TRIGEMINAL NERVE DISORDERS
350.9	TRIGEMINAL NERVE DISORDER UNSPECIFIED
351.0	BELL'S PALSY
351.1	GENICULATE GANGLIONITIS
351.8	OTHER FACIAL NERVE DISORDERS
351.9	FACIAL NERVE DISORDER UNSPECIFIED
352.0*	DISORDERS OF OLFACTORY (1ST) NERVE
352.1*	GLOSSOPHARYNGEAL NEURALGIA
352.2*	OTHER DISORDERS OF GLOSSOPHARYNGEAL (9TH) NERVE
352.3*	DISORDERS OF PNEUMOGASTRIC (10TH) NERVE
352.4*	DISORDERS OF ACCESSORY (11TH) NERVE
352.5*	DISORDERS OF HYPOGLOSSAL (12TH) NERVE
352.6*	MULTIPLE CRANIAL NERVE PALSIES
352.9*	UNSPECIFIED DISORDER OF CRANIAL NERVES
747.81*	CONGENITAL ANOMALIES OF CEREBROVASCULAR SYSTEM
990*	EFFECTS OF RADIATION UNSPECIFIED

* ICD-9-CM Codes 198.4, 198.5, 198.89, 227.6, 237.3, 237.5, 237.6, 239.6, 239.7, 352.0, 352.1, 352.2, 352.3, 352.4, 352.5, 352.6, 352.9 and 747.81 are all limited to use for lesions occurring either above the neck or in the spine.

* ICD-9-CM Codes 333.1 and 332.0 codes are limited to the patient who cannot be controlled with medication, has major systemic disease or coagulopathy, and who is unwilling or unsuited for open surgery.

*ICD-9-CM Code 990 may only be used where prior radiation therapy to the site is the governing factor necessitating SRS in lieu of other radiotherapy. An ICD-9-CM code for the anatomic diagnosis must also be used.

Stereotactic Body Radiation Therapy (SBRT) Services (CPT 77373, 77435, G0339, and G0340

140.0*	MALIGNANT NEOPLASM OF UPPER LIP VERMILION BORDER
140.1*	MALIGNANT NEOPLASM OF LOWER LIP VERMILION BORDER
140.3*	MALIGNANT NEOPLASM OF UPPER LIP INNER ASPECT
140.4*	MALIGNANT NEOPLASM OF LOWER LIP INNER ASPECT
140.5*	MALIGNANT NEOPLASM OF LIP UNSPECIFIED INNER ASPECT
140.6*	MALIGNANT NEOPLASM OF COMMISSURE OF LIP
140.8*	MALIGNANT NEOPLASM OF OTHER SITES OF LIP
140.9*	MALIGNANT NEOPLASM OF LIP UNSPECIFIED VERMILION BORDER
141.0*	MALIGNANT NEOPLASM OF BASE OF TONGUE
141.1*	MALIGNANT NEOPLASM OF DORSAL SURFACE OF TONGUE
141.2*	MALIGNANT NEOPLASM OF TIP AND LATERAL BORDER OF TONGUE
141.3*	MALIGNANT NEOPLASM OF VENTRAL SURFACE OF TONGUE
141.4*	MALIGNANT NEOPLASM OF ANTERIOR TWO-THIRDS OF TONGUE PART UNSPECIFIED
141.5*	MALIGNANT NEOPLASM OF JUNCTIONAL ZONE OF TONGUE
141.6*	MALIGNANT NEOPLASM OF LINGUAL TONSIL
141.8*	MALIGNANT NEOPLASM OF OTHER SITES OF TONGUE
141.9*	MALIGNANT NEOPLASM OF TONGUE UNSPECIFIED
142.0*	MALIGNANT NEOPLASM OF PAROTID GLAND
142.1*	MALIGNANT NEOPLASM OF SUBMANDIBULAR GLAND
142.2*	MALIGNANT NEOPLASM OF SUBLINGUAL GLAND
142.8*	MALIGNANT NEOPLASM OF OTHER MAJOR SALIVARY GLANDS
142.9*	MALIGNANT NEOPLASM OF SALIVARY GLAND UNSPECIFIED
143.0*	MALIGNANT NEOPLASM OF UPPER GUM
143.1*	MALIGNANT NEOPLASM OF LOWER GUM
143.8*	MALIGNANT NEOPLASM OF OTHER SITES OF GUM
143.9*	MALIGNANT NEOPLASM OF GUM UNSPECIFIED
144.0*	MALIGNANT NEOPLASM OF ANTERIOR PORTION OF FLOOR OF MOUTH
144.1*	MALIGNANT NEOPLASM OF LATERAL PORTION OF FLOOR OF MOUTH
144.8*	MALIGNANT NEOPLASM OF OTHER SITES OF FLOOR OF MOUTH
144.9*	MALIGNANT NEOPLASM OF FLOOR OF MOUTH PART UNSPECIFIED
145.0*	MALIGNANT NEOPLASM OF CHEEK MUCOSA
145.1*	MALIGNANT NEOPLASM OF VESTIBULE OF MOUTH
145.2*	MALIGNANT NEOPLASM OF HARD PALATE
145.3*	MALIGNANT NEOPLASM OF SOFT PALATE
145.4*	MALIGNANT NEOPLASM OF UVULA
145.5*	MALIGNANT NEOPLASM OF PALATE UNSPECIFIED
145.6*	MALIGNANT NEOPLASM OF RETROMOLAR AREA

145.8*	MALIGNANT NEOPLASM OF OTHER SPECIFIED PARTS OF MOUTH
145.9*	MALIGNANT NEOPLASM OF MOUTH UNSPECIFIED
146.0*	MALIGNANT NEOPLASM OF TONSIL
146.1*	MALIGNANT NEOPLASM OF TONSILLAR FOSSA
146.2*	MALIGNANT NEOPLASM OF TONSILLAR PILLARS (ANTERIOR) (POSTERIOR)
146.3*	MALIGNANT NEOPLASM OF VALLECULA EPIGLOTTICA
146.4*	MALIGNANT NEOPLASM OF ANTERIOR ASPECT OF EPIGLOTTIS
146.5*	MALIGNANT NEOPLASM OF JUNCTIONAL REGION OF OROPHARYNX
146.6*	MALIGNANT NEOPLASM OF LATERAL WALL OF OROPHARYNX
146.7*	MALIGNANT NEOPLASM OF POSTERIOR WALL OF OROPHARYNX
146.8*	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF OROPHARYNX
146.9*	MALIGNANT NEOPLASM OF OROPHARYNX UNSPECIFIED SITE
155.0	MALIGNANT NEOPLASM OF LIVER PRIMARY
155.1	MALIGNANT NEOPLASM OF INTRAHEPATIC BILE DUCTS
155.2	MALIGNANT NEOPLASM OF LIVER NOT SPECIFIED AS PRIMARY OR SECONDARY
157.0	MALIGNANT NEOPLASM OF HEAD OF PANCREAS
157.1	MALIGNANT NEOPLASM OF BODY OF PANCREAS
157.2	MALIGNANT NEOPLASM OF TAIL OF PANCREAS
157.3	MALIGNANT NEOPLASM OF PANCREATIC DUCT
157.4	MALIGNANT NEOPLASM OF ISLETS OF LANGERHANS
157.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF PANCREAS
157.9	MALIGNANT NEOPLASM OF PANCREAS PART UNSPECIFIED
162.2	MALIGNANT NEOPLASM OF MAIN BRONCHUS
162.3	MALIGNANT NEOPLASM OF UPPER LOBE BRONCHUS OR LUNG
162.4	MALIGNANT NEOPLASM OF MIDDLE LOBE BRONCHUS OR LUNG
162.5	MALIGNANT NEOPLASM OF LOWER LOBE BRONCHUS OR LUNG
162.8	MALIGNANT NEOPLASM OF OTHER PARTS OF BRONCHUS OR LUNG
162.9	MALIGNANT NEOPLASM OF BRONCHUS AND LUNG UNSPECIFIED
189.0	MALIGNANT NEOPLASM OF KIDNEY EXCEPT PELVIS
189.1	MALIGNANT NEOPLASM OF RENAL PELVIS
194.0	MALIGNANT NEOPLASM OF ADRENAL GLAND
194.6	MALIGNANT NEOPLASM OF AORTIC BODY AND OTHER PARAGANGLIA
196.1	SECONDARY AND UNSPECIFIED MALIGNANT NEOPLASM OF INTRATHORACIC LYMPH NODES
197.0	SECONDARY MALIGNANT NEOPLASM OF LUNG
197.7	MALIGNANT NEOPLASM OF LIVER SECONDARY
198.0	SECONDARY MALIGNANT NEOPLASM OF KIDNEY
198.7	SECONDARY MALIGNANT NEOPLASM OF ADRENAL GLAND
990*	EFFECTS OF RADIATION UNSPECIFIED

*ICD-9-CM Codes 140.0-146.9 and 990 due to recurrence after prior conventional fractionated RT.

ICD-9-CM Code 990 may only be used where prior radiation therapy to the site is the governing factor necessitating SBRT in lieu of other radiotherapy. An ICD-9-CM code for the anatomic diagnosis must also be used.

Diagnoses that Support Medical Necessity
All diagnoses listed in ICD-9-CM Codes that Support Medical Necessity above.
ICD-9 Codes that DO NOT Support Medical Necessity
All ICD-9-CM codes not listed in this policy under ICD-9-CM Codes that Support Medical Necessity above.

ICD-9 Codes that DO NOT Support Medical Necessity Asterisk Explanation

Diagnoses that DO NOT Support Medical Necessity
All ICD-9-CM codes not listed in this policy under ICD-9-CM Codes that Support Medical Necessity above.

Appendix B: NCCN Guidelines

Guideline indication	Key highlights
Non-small cell lung	**Early stage Lung Cancer (Stage I)** "SABR (traditionally known as SBRT) is recommended for patients who are medically inoperable and is also an appropriate option for many older patients (eg, ≥ age 75). SABR has achieved high primary tumor control rates and favorable overall survival in prospective studies, comparable to surgery and higher than #DCRT in non-randomized comparisons. An analysis of cost-effectiveness found SABR more cost-effective than 3DCRT and radiofrequency ablation, largely owing to its high efficacy." "For patients with high survival risk (able to tolerate sublobar resection but not lobectomy), SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control in non-randomized comparisons. A prospective randomized cooperative group trial of sublobar resection vs. SABR has been initiated. (ACOSOG Z4099/RTOG 1021)." "For potentially operable patients who refuse surgical therapy despite a complete thoracic surgery consultation, SABR is recommended based on comparable outcomes in non-randomized retrospective comparisons, especially in older patients." **Early stage/SABR** "For SABR, intensive regimens of BED ≥ 100 Gy are associated with significantly better local control and survival than less intensive regimens. In the United States, only regimens of ≤ 5 fractions meet the arbitrary billing code definition of SBRT but slightly more protracted regimens are appropriate as well." "SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected." **Stereotactic Ablative Radiotherapy (SABR)** SABR (traditionally known as SBRT), uses short courses of very high dose RT that are precisely delivered to the target. Studies have shown that SABR is very useful for patients with inoperable stage I NSCLC, or those who refuse surgery. With conventional treatment, 3-year survival is only about 20-35% in these patients. There is a high rate of local failure in patients receiving conventional RT. However, local control is increased after SABR. In patients with stage I NSCLC, SABR provides a significantly longer 5-year survival than 3-D conformal RT. SABR yields median survival of 32 months and 3-year overall survival of about 43% in patients with stage I disease; patients with T1 tumors survive longer than those with T2 tumors (39 versus 25 months). Randomized clinical trials are currently comparing SABR to surgery. SABR can also be used for patients with limited lung metastases and for palliative therapy. Studies also suggest that SABR can be used for bone, liver, and brain metastases. A recent study reported that SABR increased survival in elderly patients (75 years or older) with stage I NSCLC who otherwise would not have received treatment."

Hepatocellular carcinoma	**Principles of locoregional therapy** "There is growing evidence for the usefulness of radiotherapy in the management of HCC. All tumors irrespective of location may be amenable to SBRT or external-bean conformal radiation. SBRT is often used for 1-3 tumors with a cumulative diameter under 6 cm. SBRT could be considered for larger lesions, if there is at least 800 cc of uninvolved liver and liver radiation tolerance can be respected. There should be no extra-hepatic disease or it should be minimal and addressed in a comprehensive management plan. Most patients treated today were in the Child-Pugh A category. Radiotherapy can be considered as an alternative to the ablation/embolization techniques..." **External beam radiation therapy** "The panel recommends that radiation therapy can be considered (category 2B) as an alternative to ablation/embolization techniques or when these therapies have failed in patients with unresectable disease characterized as extensive or otherwise no suitable for liver transplantation and those with local disease who are not operable due to performance status or comorbidity."

Central nervous system	**Brain Metastases – Stereotactic radiosurgery** "The advent of SRS offered a minimally invasive option as opposed to surgery. Patients undergoing SRS avoid the risk of surgery-related morbidity. Late side effects such as edema and radiation necrosis are uncommon. SRS is most successful for small, deep tumors. In a randomized Japanese study of 132 patients with 1 to 4 metastatic brain tumors smaller than 3 cm, addition of WBRT to SRS did not prolong median survival compared to SRS along (7.5 months vs. 8.0 months, respectively). However, 1-year brain recurrence rate was lowered in the WBRT plus SRS arm (47% vs. 76%; P < 0.001). This likely served to decrease the need for salvage therapy in this group (10/65) compared to patients receiving no upfront WBRT (29/67)." "Retrospective comparative studies showed that SRS plus WBRT resulted in equivalent if not better survival compared with surgery and WBRT. SRS also conferred a significant improvement in local control, especially for patients with radiosensitive tumors or solitary brain lesions." **Metastatic Spinal Tumors** The advent of SRS allowed precise high-dose targeting in one or two fractions while minimizing exposure of surrounding cord. This is especially important in pre-irradiated patients. The largest prospective study involved a cohort of nearly 400 patients with 500 spinal metastases, 70% of whom had previous conventional irradiation. At a median follow-up of 21 months, radiosurgery resulted in long-term pain improvement and tumor control in 85% and 90% of cases, respectively. Other single-institution reports also suggest that SRS is safe and offers more durable response than conventional therapy." "Patients experiencing intractable pain or rapid neurological decline during RT should consider surgery or SRS." **Overall** SRS included in the following areas as primary treatment: • Adult intracranial ependymoma • Meningiomas • Limited (1-3) metastatic lesions • Multiple (>3) metastatic lesions

APPENDIX C

AHRQ Draft Comparative Effectiveness Review. Local Therapies for Unresectable Primary Hepatocellular Carcinoma.

Table 4. Local radiotherapies for primary hepatocellular carcinoma reviewed in this report*

Treatment strategy	Mechanism of cell death	Setting	Performed by	Specific Harms
External-beam three-dimensional conformal radiation therapy (3D-CRT)	This type of radiotherapy uses computer-assisted tomography (CT or CAT) and/or magnetic resonance imaging (MR or MRI), or both to create detailed, 3D representations of the tumor and the surrounding organs. The radiation oncologist uses these computer-generated images to shape radiation beams to the exact size and shape of the tumor, which is intended to spare nearby healthy tissues.	Each treatment lasts only a few minutes, although the setup time usually takes longer. Most often, radiation treatments are given 5 days a week for several weeks. The patient's diagnosis determines the total duration of treatment.[10,11]	Radiation oncologist, medical physicist, dosimetrist, radiation therapist, and radiation therapy nurse	Possible side effects of external radiation therapy include sunburn-like skin problems, nausea, vomiting, and fatigue. These typically diminish posttreatment. Radiation might also make the side effects of chemotherapy worse.[1] Radiation-induced liver disease is the major dose-limiting toxicity.[1]
External-beam intensity-modulated radiotherapy (IMRT)	This approach to radiotherapy allows the radiation oncologist to vary both the intensity of a radiation beam and the angle at which it is delivered to the patient. This is intended to deliver a high dose of radiation to a tumor while significantly reducing the dose to surrounding normal tissue. IMRT offers a better defined radiation dose over traditional 3D-CRT.	Same as 3D-CRT, but IMRT requires slightly longer daily treatment times and additional planning and safety checks before the patient can start the treatment.[11]	Radiation oncologist, medical physicist, dosimetrist, radiation therapist, and radiation therapy nurse	Same as for 3D-CRT
Stereotactic body radiation therapy (SBRT)	This type of external-beam radiation therapy delivers a high dose of radiation with high targeting accuracy to an extracranial target within the body in either a single dose or a small number of dose fractions.[12]	SBRT typically consists of one to five treatment sessions over the course of 1 to 2 weeks.[12]	Radiation oncologist, medical physicist, dosimetrist, radiation therapist, and radiation therapy nurse	Same as above for 3D-CRT and IMRT
Hypofractionated proton beam therapy	This is a type of external-beam radiation therapy that delivers high doses of radiation to the tumor target while simultaneously reducing the number of photons reaching normal surrounding tissue, delivered in fewer sessions of larger dose fractions than are delivered in standard regimens.[13]	Proton beam therapy is performed typically on an outpatient basis. For most tumor sites, the average course of treatment is usually 5 to 7 weeks, with varying length of each treatment depending on the tumor type and stage. The delivery of the proton beam lasts only 1 minute.[13]	Radiation oncologist, radiation physicist, dosimetrist, immobilization specialist, radiation therapist, nurse	Same as above for 3D-CRT, IMRT and SBRT

Treatment strategy	Mechanism of cell death	Setting	Performed by	Specific Harms
Intraluminal brachytherapy	This type of radiotherapy places a radiation source within the body lumen, allowing the delivery of higher doses of radiation directly to a specific tumor. Brachytherapy can be administered as a permanent or temporary treatment.	In permanent brachytherapy, a radioactive "seed" is permanently implanted in the tumor. Seeds may also be implanted at regular intervals in temporary brachytherapy. Treatments may be delivered at a high dose-rate (HDR) in 10 to 20 minutes per session or a low dose-rate (LDR) in 20 to 50 hours. HDR brachytherapy is usually an outpatient procedure where the treatment is repeated two times a day for up to 10 separate treatments in 1 or more weeks. LDR brachytherapy, an inpatient procedure, delivers radiation at a continuous rate in 1 to 2 days. Pulsed dose-rate (PDR) brachytherapy delivers radiation in periodic pulses (usually 1 per hour) rather than continuously.[14]	Radiation oncologist, medical physicist, dosimetrist, radiation therapist, radiation therapy nurse, and in some cases, a surgeon	Brachytherapy typically causes fewer side effects than does external-beam radiation. Patients may experience tenderness and swelling in the treatment area and other symptoms depending on the site of brachytherapy and can resume normal activities within days or weeks of brachytherapy.

*The radiotherapy presented in this report is focused on focal treatment of the lesion or lesions and not whole liver irradiation.

Appendix D

AHRQ Draft Comparative Effectiveness Review. Local Therapies for the Treatment of Stage I Non-Small Cell Lung Cancer and Endobronchial Obstruction due to Advanced Lung Tumors.

Analytic Framework

Figure ES1. Analytical framework for comparative effectiveness of local nonsurgical definitive therapies for adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 or T2N0M0) medically inoperable NSCLC or those with documented stage I NSCLC who are deemed operable but elect nonsurgical intervention

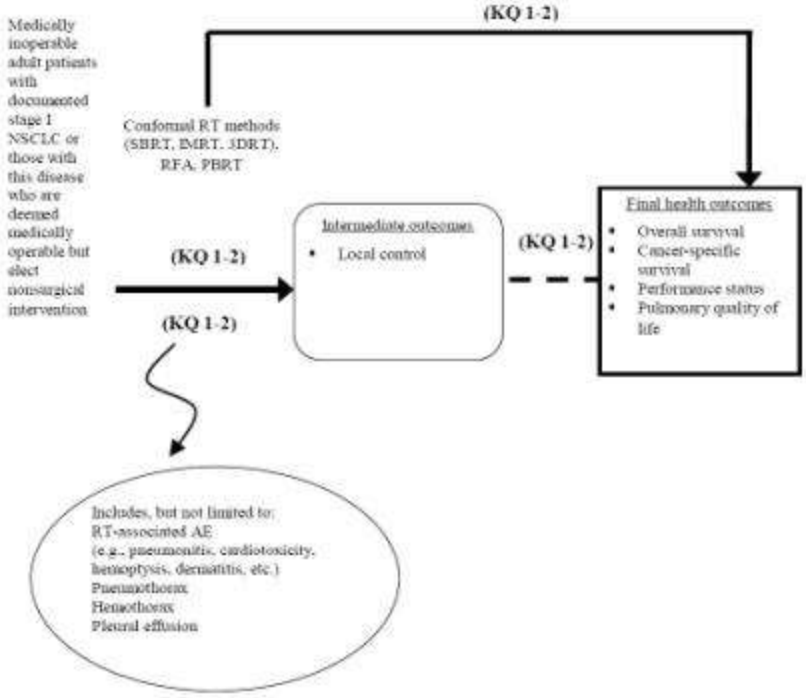
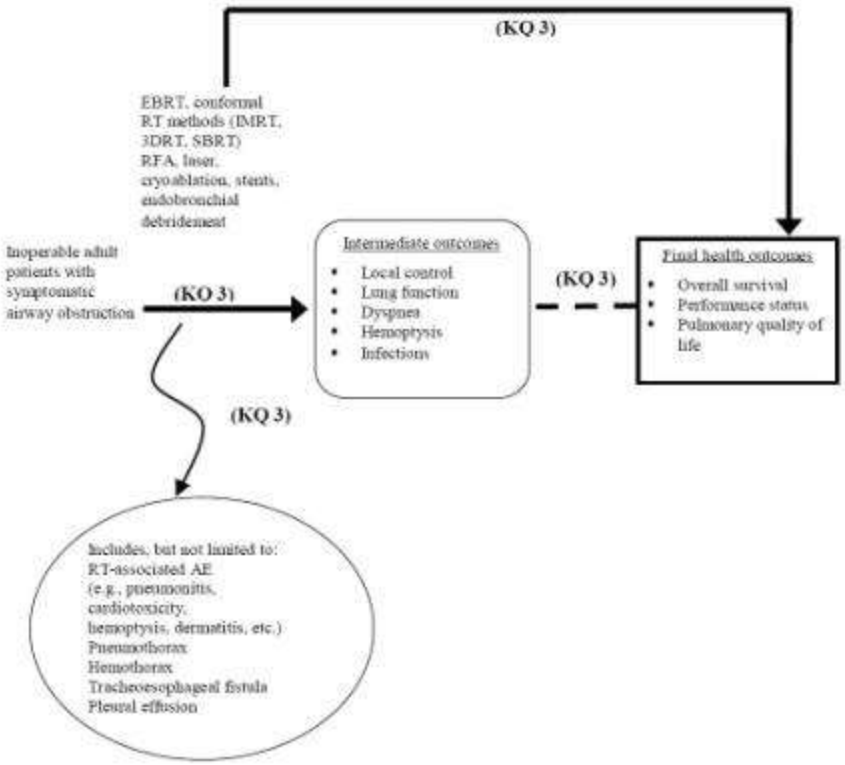


Figure ES2. Analytical framework for comparative effectiveness of local curative or palliative therapies for adult patients (age 18 years or older) with symptomatic inoperable airway obstruction due to NSCLC.



Appendix E

AHRQ Draft Comparative Effectiveness Review. Local Hepatic Therapies for Metastases to the Liver from Unresectable Colorectal Cancer: Effectiveness and Comparative Effectiveness.

Table ES-2. Characteristics of studies included in this review by intervention.

Characteristic	RFA	TACE	HAI	RE	DEB	SBRT	RFA with SC	HAI with SC	RE with SC	Total*
Total	2	2[a]	2	12[a]	3	3	2	2	2	30
Study Design										
Prospective case series	1	0	0	6	2	1	2[c]	1	1	14
Retrospective case series	1	2	2	6[b]	1	2	0	1	1	16
Outcomes Reported										
Overall Survival	2	2	2	12	3	3	2	2	2	30
Quality of Life	0	0	0	1	1	0	1	0	0	3
Time to Recurrence	1	0	0	0	0	0	0	0	0	1
Length of Stay	0	1	0	0	1	0	0	0	0	2
Local Recurrence	2	0	0	0	0	2	2	0	0	6
Adverse Events	2	2	2	12	3	3	2	2	2	30
Study population										
United States	0	2	0	6	1	0	0	0	0	9
Europe	2	0	1	5	2	2	1	0	1	14
Australia	0	0	0	1	0	0	1	0	1	3
Asia	0	0	1	0	0	1	0	2	0	4
Total N participants	190	142	67	416	157	43	73	36	159	1283

RFA: Radiofrequency ablation, TACE: Transarterial chemoembolization, HAI: Hepatic arterial infusion, RE: Radioembolization, DEB: Drug-eluting beads; SBRT: Stereotactic body radiotherapy, SC: Systemic chemotherapy, N: Number
No studies reporting on cryoablation, microwave ablation, transarterial embolization, 3D-CRT, or IMRT met inclusion criteria for this review
*The total number of articles included in this review is 29, but the study by Hong et al., reports on both TACE and RE interventions
[a] Hong et al., reports on both TACE and RE interventions
[b] Heleniliz et al., is an RCT that was extracted as a single-arm case-series
[c] The study by Ruers et al., is an RCT that was extracted as a single-arm case series

Table ES-31. Core dataset elements for local hepatic therapy registry by PICOTS

Population	Intervention	Comparators	Outcomes	Timing	Setting
Patient Characteristics	**Type of local hepatic therapy**	Same as intervention	Overall survival	Ongoing	Hospital type
Age	Cryosurgical ablation		Quality of life		Number of procedures by practitioner
Sex	RFA		Response (e.g. complete, partial, no response)		Type of practitioner
Race	Microwave ablation				Local hepatic therapy availability
Ethnicity	TAE		Recovery time		Inpatient or outpatient procedure
Performance status	TACE				
LDH	HAI		Length of Stay		
CEA	RE				
Clinical risk scores (e.g., Fong[9]	DEB		Adverse effects (Short term and long-term harms		
Tumor characteristics	3D-CRT				
Location of tumor	IMRT		Treatment holidays*		
Size of lesions	SBRT				
Number of lesions	**Characteristics of local hepatic therapy**				
Tumor volume	Dose				
Portal vein obstruction	Duration				
Course of disease(stabilization, rapid progression)	Surgical site				
Other treatments					
Number, dose, duration, for lines of prior therapy by drug					
Number, dose, duration for lines of adjunctive therapy by drug					
Previous liver-directed therapy					

* Treatment holidays refer to new-onset dose-volume chemotherapy and may result from successful treatment with a local hepatic therapy. cd LDH: lactate dehydrogenase; CEA: carcinoembryonic antigen; RFA: Radiofrequency ablation; TAE: Transarterial embolization; TACE: transarterial chemoembolization; HAI: Hepatic artery infusion; RE: Radioembolization; DEB: Drug-eluting bead; 3D-CRT: three dimensional conformal radiation therapy; IMRT: Intensity modulated radiation therapy; SBRT: Stereactic body radiation therap

Huong Pham, MD (Virginia Mason Medical Center)

Public Comment for: Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy
Pham, Huong [Huong.Pham@vmmc.org]

Sun 9/30/2012 4:09 PM
HCA ST Health Tech Assessment Prog

Dear members of the Health Technology Clinical Committee:

Thank you for performing an assessment of the benefits and appropriateness of SRS and SBRT. I've reviewed the "Draft Evidence Review" for this topic. I would like to emphasize that SRS and SBRT is not the same as IMRT. Stereotactic treatments require special equipment (Gamma Knife, Cyber Knife) or modifications to the linear accelerator to ensure the accuracy of the radiation beams coming from any direction is less than 1 mm. That is not the case with standard linear accelerators used for standard radiation therapy whose accuracy could be up to 2-3 mm depending on how it was calibrated. IMRT is a technique of conforming the dose to the target but does not necessarily employ a stereotactic approach. SRS and SBRT can however use IMRT if necessary to increase conformality of dose to the target. My observation is that SRS and SBRT are being compared to conventional XRT for the various disease sites and possible indications listed in the document. I do not believe that is a correct comparison analysis for several indications including acoustic neuromas, meningiomas, and solitary primary or metastatic lung tumors since SRS/SRT is used here as an alternative to surgery. There are very few studies published on the use of conventional XRT in these settings. SRS is a well established treatment for brain metastases and the "Draft Evidence Review" provided a good summary of indications and appropriateness of its use in the guidelines section (NCCN). Other than for primary stage 1 lung cancers and solitary lung metastasis, I believe SBRT is investigational for other disease sites as described in the document.

In acoustic neuromas, SRS or SRT is being used as an alternative to surgery. There are many more patients who have been treated with SRS for acoustic neuromas than with fractionated radiation therapy or hypofractionated SRT. A sentinel paper published in 1998 (N Engl J Med. 1998 Nov 12;339(20):1426-33) by Kondziolka and Flickinger demonstrates excellent outcomes in terms of local control; and hearing preservation improved with lower doses in subsequent reports. Radiosurgery has long been considered a standard treatment option for acoustic neuromas. More recently, reports of using fractionated stereotactic radiotherapy to reduce the risk of hearing loss were reported. These studies are summarized in a review by Dr. Backous and myself (Backous D and **Pham HT**. Guiding Patients Through the Choices for Treating Vestibular Schwannomas: Balancing Options and Ensuring Informed Consent. In *Otolaryngologic Clinics of North America* Haynes DA; W.B. Saunders: Philadelphia, PA 2007; Vol 40 (3): pp 521-540.). I think controversy exists between SRS and SRT as to which is a better radiotherapeutic option for patients, but there is really no role for conventional radiation therapy for acoustic neuromas as there is very little published using this technique. I do not think it makes any sense to do a comparison of SRS/SRT to conventional radiation therapy for acoustic neuromas. A better comparison is to look at the effectiveness and toxicity of SRS/SRT with surgery.

Same can be said of small meningiomas. Typically, if a patient has a meningioma that can be resected safely and the patient is deemed fit for surgery, then surgery is usually recommended. However, often, there are times when a patient has a meningioma in a location that is not safe to operate or the patient could not tolerate the surgery. SRS/SRT would be a good alternative to surgery offering excellent local control rates in the range of 90% at 5 years. Conventional radiation therapy would be an option for larger tumors. Conventional XRT requires 30 fractions over 6 weeks while SRS is a single treatment which is much more conformal reducing the amount of surrounding normal brain tissue being treated. If possible, it seems much more practical and safer for a patient to receive SRS over conventional XRT. The cost of SRS is probably the same or less than a 6 week course of conventional XRT.

The standard of care for stage 1 lung cancer or for a solitary lung metastasis is surgical resection for curative intent if the patient can tolerate it. What happens if these patients are not fit for surgery ? Options include smaller surgeries such as a wedge resection (rather than a standard cancer operation such as lobectomy) or SBRT. Again, there is little data for conventional XRT in this setting. Radiobiological studies demonstrate a dose response for lung tumors which require doses as high as 100cGy (RBE) to obtain good local control for a lung cancer for curative intent. If that were to be done with conventional radiation therapy, it would require 50 fractions or 10 weeks of treatment. In addition, a larger margin of normal lung tissue would be needed around the tumor to account for lung motion resulting in a significant amount of lung treated. Unfortunately, patients who are considered for SBRT are usually because they have poor pulmonary function and cannot afford to have significant lung damage from radiation therapy. With SBRT, the course of the treatment is typically 2-5 fractions over 1 wk with minimal amount of lung damage using gating or breath hold techniques and image guidance. Although I don't have actual cost information, I suspect a course of SBRT would cost less than 10 wks of conventional XRT. Again, SBRT for lung cancer is an alternative to surgery and a better comparison in this setting would be to compare the results of SBRT for lung tumors with surgery, not conventional XRT.

Thank you for allowing me to submit my comments on this topic.

Huong Pham, MD
Section Head, Section of Radiation Oncology
Virginia Mason Medical Center
1100 Ninth Ave, PO Box 900
Mailstop : CB-RO
Seattle, WA 98101
(206) 223-6801

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Radiosurgery Society

I am writing in response to the Washington State Health Authority Draft Evidence Review of Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy. I am the Chairman of the Radiosurgery Society. The RSS is the world's largest SRS/SBRT society, and through its white papers like those attached has become the authoritative voice in this field. We appreciate the work that has gone into this review. In many ways, we agree with the conclusions that the quality of the evidence that is available is less than we would wish. Despite the lack of level I evidence, there are several indications for which SRS/SBRT has become a standard of care - and years of clinical practice and published data that do exist, have allowed conclusions to be drawn reflecting the safety and efficacy of these treatments.

Stereotactic radiosurgery (SRS, which we will use to refer to intracranial treatments only) started with Gamma Knife, which in this country became available at the University of Pittsburgh in 1987. Since its inception, the Gamma Knife center there has treated over 10,000 patients and the physicians and scientists there have published over 600 articles on their experience.

Stereotactic body radiation therapy (SBRT, which will be used here to refer to all extracranial treatments) began with the CyberKnife at Stanford in 1987, with the first patient treated in 1994. The CyberKnife has been commercially available with FDA clearance for full body treatment since 2001, and since that time, over 100,000 patients worldwide have been treated.

Building on the clinical success of the CyberKnife, multiple other manufacturers have devised other methods of delivering high dose, extremely hypofractionated treatment to intracranial and extracranial sites. These usually consist of an imaging system, a gantry-based linear accelerator with enhanced accuracy, and a multi-leaf collimator with small leaf sizes than are commonly employed for more conventionally fractionated treatment. Examples include the Novalis system, Accuknife, X-Knife, and Peacock. Other systems with novel designs are approaching FDA clearance.

These devices, and the treatments they can deliver, should be considered disruptive technologies. They have not simply changed the way we deliver radiation, they have redefined an entirely new approach wherein radiation is used like a surgical tool, with large doses delivered over a short time frame with the intention of total tumor ablation. Like many disruptive technologies, their inroads into clinical practice have taken place more rapidly than top-level evidence of effectiveness could be developed. With advanced technologies such as these, this is going to be an ongoing problem. It takes nearly ten years to develop, deploy, carry out, follow, and publish a randomized clinical trial. By the time that is done, the technology has advance and changed so much that the conclusions are no longer relevant. CMS has explicitly acknowledged this fact in their discussions with us, and they are moving more toward the use of validated registries as a means of developing the necessary clinical evidence in instances where CMS seeks to answer additional questions of comparative effectiveness among existing therapies or to determine generalizability of data to certain patient populations.

The Radiosurgery Society has developed such a registry, called RSSearch. It contains over 10,000 patients, and we have just begun the process of mining the information it contains to establish

efficacy and safety data for indications commonly treated with SRS/SBRT. As an example, the first aggregate data study has been initiated with a study of 2800 non-small cell lung cancer patients. Over 800 of these are T1 patients, and to accrue that number on a randomized protocol would be impossible.

Multiple institutions are attempting randomized trials. In some cases, these will result in publishable Level I evidence, but some may never be completed because of the difficulty inherent in trying to convince a patient that they should allow random selection of their treatment when the possible treatments are as different as a surgical procedure and a completely non-invasive treatment.

With regard to the existing clinical published data, there is little that would be considered Level I evidence. What exists is largely single institution reviews of institutional experience. These should not be discounted as insufficient evidence for the following reasons:

1. Many of these have 5-10 year follow-up data, making conclusions more valid and valuable
2. 2. Many (perhaps most) have been validated by publication of similar results from other centers

Taken in the aggregate, studies of SRS/SBRT show 70-90% control rates of treated tumors. This almost always compares very favorably with published data for more conventional radiation fractionation schemes. For instance, in non-small cell lung cancers of limited extent, SBRT routinely achieves local control rates of approximately 90% in virtually every published study, while standard radiation struggles to reach a 40% rate. The essential fact is that SRS/SBRT achieves superior results simply because it is better able to deliver the radiation dose precisely to the target while maximally sparing critical nearby tissues, thus allowing a dose of radiation which is biologically different from, and possibly biologically superior to, conventionally fractionated radiation.

There are compelling non-clinical reasons to consider SRS/SBRT, including the following:

1. It is usually less expensive than the available alternatives. For instance, a course of IMRT radiation for prostate cancer will cost over $40,000, while SBRT is only about $30,000. Single fraction or multiple fraction SRS for a skullbase meningioma will be significantly less expensive than a skullbase surgery and the protracted rehabilitation that frequently ensures.
2. It is more convenient for patients. In western states such as Washington and others, patients often have to travel great distances for treatment. This is especially important for patients covered under the Washington Medicaid program with limited financial resources, where travel and extended treatment times associated with conventional radiation frequently results in large unnecessary expense for the patient, or all too frequently results in poor treatment compliance or the patient not seeking treatment at all.
3. It uses less of the health system's resources. It is obviously more efficient for a center to treat a patient in 1-5 days than to treat them daily for 6-9 weeks.

The California Technology Assessment Forum also considered similar questions of efficacy and safety for SRS/SBRT for non-small cell lung cancer. Their recommendations were:

It is recommended that stereotactic body radiation therapy for the treatment of early stage non small cell lung cancer in medically inoperable patients with peripheral lesions meets CTAF criteria 2-5 for safety, effectiveness and improvement in outcomes.
It is recommended that stereotactic body radiation therapy for the treatment of early stage non small cell lung cancer in medically inoperable patients with central lesions and medically operable patients does not meet CTAF TA criteria 2-5, for safety, effectiveness, and improvement in outcomes**.**

There is also information in the NCCN guidelines:

Non-small cell lung	**Early stage Lung Cancer (Stage I)** "SABR (traditionally known as SBRT) is recommended for patients who are medically inoperable and is also an appropriate option for many older patients (eg, ≥ age 75). SABR has achieved high primary tumor control rates and favorable overall survival in prospective studies, comparable to surgery and higher than #DCRT in non-randomized comparisons. An analysis of cost-effectiveness found SABR more cost-effective than 3DCRT and radiofrequency ablation, largely owing to its high efficacy." "For patients with high survival risk (able to tolerate sublobar resection but not lobectomy), SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control in non-randomized comparisons. A prospective randomized cooperative group trial of sublobar resection vs. SABR has been initiated. (ACOSOG Z4099/RTOG 1021)." "For potentially operable patients who refuse surgical therapy despite a complete thoracic surgery consultation, SABR is recommended based on comparable outcomes in non-randomized retrospective comparisons, especially in older patients." **Early stage/SABR** "For SABR, intensive regimens of BED ≥ 100 Gy are associated with significantly better local control and survival than less intensive regimens. In the United States, only regimens of ≤ 5 fractions meet the arbitrary billing code definition of SBRT but slightly more protracted regimens are appropriate as well." "SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected." **Stereotactic Ablative Radiotherapy (SABR)** SABR (traditionally known as SBRT), uses short courses of very high dose

	RT that are precisely delivered to the target. Studies have shown that SABR is very useful for patients with inoperable stage I NSCLC, or those who refuse surgery. With conventional treatment, 3-year survival is only about 20-35% in these patients. There is a high rate of local failure in patients receiving conventional RT. However, local control is increased after SABR. In patients with stage I NSCLC, SABR provides a significantly longer 5-year survival than 3-D conformal RT. SABR yields median survival of 32 months and 3-year overall survival of about 43% in patients with stage I disease; patients with T1 tumors survive longer than those with T2 tumors (39 versus 25 months). Randomized clinical trials are currently comparing SABR to surgery. SABR can also be used for patients with limited lung metastases and for palliative therapy. Studies also suggest that SABR can be used for bone, liver, and brain metastases. A recent study reported that SABR increased survival in elderly patients (75 years or older) with stage I NSCLC who otherwise would not have received treatment."
Hepatocellular carcinoma	**Principles of locoregional therapy** "There is growing evidence for the usefulness of radiotherapy in the management of HCC. All tumors irrespective of location may be amenable to SBRT or external-bean conformal radiation. SBRT is often used for 1-3 tumors with a cumulative diameter under 6 cm. SBRT could be considered for larger lesions, if there is at least 800 cc of uninvolved liver and liver radiation tolerance can be respected. There should be no extra-hepatic disease or it should be minimal and addressed in a comprehensive management plan. Most patients treated today were in the Child-Pugh A category. Radiotherapy can be considered as an alternative to the ablation/embolization techniques…" **External beam radiation therapy** "The panel recommends that radiation therapy can be considered (category 2B) as an alternative to ablation/embolization techniques or when these therapies have failed in patients with unresectable disease characterized as extensive or otherwise no suitable for liver transplantation and those with local disease who are not operable due to performance status or comorbidity."
Central nervous system	**Brain Metastases – Stereotactic radiosurgery** "The advent of SRS offered a minimally invasive option as opposed to surgery. Patients undergoing SRS avoid the risk of surgery-related morbidity. Late side effects such as edema and radiation necrosis are uncommon. SRS is most successful for small, deep tumors. In a randomized Japanese study of 132 patients with 1 to 4 metastatic brain tumors smaller than 3 cm, addition of WBRT to SRS did not prolong median survival compared to SRS along (7.5 months vs. 8.0 months, respectively). However, 1-year brain recurrence rate was lowered in the

	WBRT plus SRS arm (47% vs. 76%; P < 0.001). This likely served to decrease the need for salvage therapy in this group (10/65) compared to patients receiving no upfront WBRT (29/67)." "Retrospective comparative studies showed that SRS plus WBRT resulted in equivalent if not better survival compared with surgery and WBRT. SRS also conferred a significant improvement in local control, especially for patients with radiosensitive tumors or solitary brain lesions." **Metastatic Spinal Tumors** The advent of SRS allowed precise high-dose targeting in one or two fractions while minimizing exposure of surrounding cord. This is especially important in pre-irradiated patients. The largest prospective study involved a cohort of nearly 400 patients with 500 spinal metastases, 70% of whom had previous conventional irradiation. At a median follow-up of 21 months, radiosurgery resulted in long-term pain improvement and tumor control in 85% and 90% of cases, respectively. Other single-institution reports also suggest that SRS is safe and offers more durable response than conventional therapy." "Patients experiencing intractable pain or rapid neurological decline during RT should consider surgery or SRS." **Overall** SRS included in the following areas as primary treatment: · Adult intracranial ependymoma · Meningiomas · Limited (1-3) metastatic lesions · Multiple (>3) metastatic lesions

There are additional NCCN guidelines that do not include SBRT as the first line of therapy; however, there is positive language within these guidelines about SBRT, which is noted below.

Prostate	Not included in the guidelines as a standard therapy option; however, there is a statement about the SBRT within the guidelines, which reads: "The relatively slow proliferation of prostate cancer is reflected in a low α/β ratio, most commonly reported between 1 and 4. These values are similar to that for the rectal mucosa. Since the α/β ratio for prostate cancer is similar to or lower than the surrounding tissues responsible for most of the toxicity reported with radiation therapy, appropriately designed radiation treatment fields and schedules using hypofractionated regimens should result in similar cancer control rates

	without an increased risk of late toxicity. Stereotactic body radiotherapy (SBRT) delivers highly conformal, high dose radiation in 5 or fewer treatment fractions, that is possible to do safely only with precise delivery. Single institution series with median follow-up as long as 5-years report that biochemical progression free-survival is 90-100% and early toxicity (bladder, rectal, and quality of life) is similar to other standard radiation techniques. Longer follow-up and prospective multi-institutional data are required to evaluate longer term results especially since late toxicity theoretically could be worse in hypofractionated regimens compared to conventional fractionation (1.8 to 2.0 Gy per fraction)."
Pancreatic adenocarcinoma	General principles: "Ideally, patients should be treated on clinical trials when available. Radiation is typically given concurrently with chemotherapy, except in the palliative setting, with intraoperative radiation therapy (IORT), or with stereotactic body radiation therapy (SBRT)." Unresectable/locally advanced (non-metastatic): **"No standard total dose or dose per fraction has been established for SBRT; therefore, it should be utilized as part of a clinical trial."** Principles of radiation therapy: "SBRT is often delivered in 1-5 fractions ranging from 5-25 Gy per fraction."

In addition, there are 3 recent **draft** (not finalized) AHRQ reports: non-small cell lung cancer, hepatocellular carcinoma, and colorectal metastases to the liver, in which SBRT is included as one of the primary treatment options for each of these 3 cancer indications.

We recommend that the Washington Health Care Authority recognize the potential advantages of SRS/SBRT and continue to make these treatments available to patients. If the HCA deems it necessary, it could impose a registry requirement similar to those in place in Medicare regions for certain indications.

Other references submitted:

- The Radiosurgery Society (November 2011). WHITE PAPER - Stereotactic Body Radiotherapy Treatment for Head and Neck Cancer,1-19
- The Radiosurgery Society (March 2010). WHITE PAPER – Metastatic Cancer of the Liver and Stereotactic Radiosurgery, 1-14
- The Radiosurgery Society (March 2010). WHITE PAPER - SRS for Non Small Cell Lung Cancer, 1- 56

- The Radiosurgery Society (March 2010). WHITE PAPER - Carcinoma of the Pancreas and Stereotactic Radiosurgery, 1-16

- The Radiosurgery Society (March 2010). WHITE PAPER - Prostate Cancer and Stereotactic Radiosurgery, 1- 34

- The Radiosurgery Society (September 2010). WHITE PAPER - SRS for Spinal Tumors, 1-22

- The Radiosurgery Society (September 2011). WHITE PAPER - SRS for Trigeminal Neuralgia, 1- 19

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Varian Medical Systems, Inc
525 9th Street NW, Suite 450
Washington, DC 20004
Telephone: 202 629 3459
www.varian.com

October 1, 2012

BY ELECTRONIC DELIVERY

Christine V. Masters
Program Specialist
Health Technology Assessment
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

Re: Washington State Health Care Authority Health Technology Assessment Program Draft Evidence Report on Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

Dear Ms. Masters:

Varian Medical Systems (Varian) is pleased to offer comments on the Center for Evidence-based Policy, Oregon Health & Science University, draft report entitled, "Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy", dated August 27, 2012, as commissioned by the Washington State Health Care Authority (WSHCA), Health Technology Assessment Program (HTA). Varian is the world's leading supplier of radiotherapy products for treating cancer. Our products include linear accelerators, simulators, proton therapy systems, and a broad range of accessories and interconnected software tools for planning, verifying, and delivering the most advanced radiation, radiosurgical, and brachytherapy treatments.

Varian has significant concerns that the draft report does not properly highlight the immense benefits of the use of Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT) for treating cancer. Varian strongly supports comparative effectiveness research that can assist policy makers, healthcare providers and consumers make sound judgments about healthcare choices. Our comments are intended to contribute to the balance, completeness and usefulness of the Technology Assessment.

The WSHCA's narrow view of "sufficient clinical evidence" for technologies to include only randomized clinical trials will be to the significant determinant to cancer patients in the state of Washington. Varian recognizes the value of randomized controlled trials or prospective studies to guide the clinical application of new technology. Generating this type of data for radiosurgery, however, is exceedingly difficult as radiosurgery has been developed incrementally which is different from other medical interventions. As is evidenced by our

enclosed comments, there are significant clinical peer reviewed publications that demonstrate the clinical effectiveness of SRS and SBRT.

Attached, please find several edits to the report as well as additional pieces of evidence that should be considered before the report is finalized. Varian appreciates the opportunity to comment on Center for Evidence-based Policy, draft report entitled, "Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy." We stand prepared to answer any questions you may have about our comments or to provide any additional information. Thank you for your consideration.

Sincerely,

Andrew M. Whitman
Vice President, Government Affairs

Edits for Draft Evidence Report:

General Comments

The evidence-based evaluation of new medical technologies can be challenging and controversial. The 2008 paper by Bentzen describes many of the challenges, using an analogous comparison of proton and photon therapy. Many of the same challenges apply to a comparative evaluation of SRS/SBRT (radiosurgery, RS) and 3D Conformal Radiotherapy (CRT).

- Bentzen SM. Randomized controlled trials in health technology assessment: overkill or overdue? Radiother Oncol. 2008 Feb;86(2):142-7

Bekelman et al updated and expanded on this effort with their 2011 study, whose objective was to introduce the relative strengths and weaknesses of several forms of evidence to illustrate the potential for comparative effectiveness research generation within radiation oncology.

- Bekelman J, Shah A, Hahn S, Implications of comparative effectiveness research for radiation oncology, Prac Rad Onc, vol 1,Iss 2, p72-80, April 2011

In particular, the draft report makes the implicit assumption that RS and CRT are single treatment entities, analogous to a new drug, and that randomized controlled trials can be used to define their respective indications for use.

Rather, RS and CRT are both clinical processes comprised of numerous discrete technologies in the areas of modern oncologic imaging, pretreatment simulation, treatment planning, treatment beam delivery and quality assurance. This situation is quite different from that of a single therapeutic technology or biological agent.

- Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, Keall P, Lovelock M, Meeks S, Papiez L, Purdie T, Sadagopan R, Schell MC, Salter B, Schlesinger DJ, Shiu AS, Solberg T, Song DY, Stieber V, Timmerman R, Tomé WA, Verellen D, Wang L, Yin FF. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010 Aug;37(8):4078-101.

While the clinical use of RS was first described in the 1940's, the enabling technologies continue to evolve at a rapid rate. RS continually evolves, typically on time scales that are much faster than the timeframes needed to collect long-term clinical outcomes, making it very challenging to conduct long-term comparative effectiveness trials.

With few high-quality controlled trial comparisons of RS and CRT, population studies can take on a high level of importance: the National Cancer Institute considers them the strongest study design after randomized controlled trials or non- randomized controlled trials. Such a study of lung SBRT implementation in a Dutch population was published during the time period

examined by this report, but not included in this draft. It will be discussed further in the following section on lung.

http://www.cancer.gov/cancertopics/pdq/levels-evidence-adult-treatment/HealthProfessional/page2

Executive Summary - Background

Pages 6 and 38, cost information;

- These brief sections seems out of place and the particular report by Lanni, et al, is later described as "...a poor quality cost evaluation...", page 98. We suggest removing this section and relying on the discussion on page 98, or developing a larger section that deals with cost information in a more comprehensive fashion.

Executive Summary - Findings

Page 22, KQ1;

- This section says "...Since there were no studies comparing SBRT to other therapies, it is uncertain whether SBRT improves survival or other patient-important outcomes compared to conventional EBRT." While not an exhaustive literature search, the following three papers describe comparison of SBRT to sublobar resection;
  - Fernandez FG, Crabtree TD, Liu J, Meyers BF. Sublobar resection versus definitive radiation in patients with stage IA non-small cell lung cancer. Ann Thorac Surg. 2012 Aug;94(2):354-60; discussion 360-1.
  - Puri V, Crabtree TD, Kymes S, Gregory M, Bell J, Bradley JD, Robinson C, Patterson GA, Kreisel D, Krupnick AS, Meyers BF. A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis. J Thorac Cardiovasc Surg. 2012 Feb;143(2):428-36.
  - Crabtree TD, Denlinger CE, Meyers BF, El Naqa I, Zoole J, Krupnick AS, Kreisel D, Patterson GA, Bradley JD. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg. 2010 Aug;140(2):377-86.

5

- The following paper describes the challenges and controversies inherent in doing comparative effectiveness research across very different treatment modalities, such as lung SBRT and sublobular surgical resection;
    - Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: Recent advances and controversies. J Thorac Dis. 2011 Sep;3(3):189-96.

Background

- The first paragraph lists the devices that are approved to deliver SRS/SBRT. The list is incomplete and inconsistent with Table 2, on page 35. The list in Table 2 should be expanded to include; TrueBeam, TrueBeam STx, and Clinac iX, all manufactured by Varian Medical Systems, Inc.

Pages 33 and 34, figures 1 and 2;

- These figures show a mixture of generic descriptors and product names. Since this report is intended to provide policy guidance to a broad range of individuals, we recommend using only generic descriptors.

Page 34;

- The American Association of Neurological Surgeons, the Congress of Neurological Surgeons and the American Society of Therapeutic Radiology and Oncology approved a definition of Stereotactic Radiosurgery (SRS) in 2006. That definition reads as follows:
    - Stereotactic radiosurgery is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate (a) defined target(s) in the head and spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist.
    - Stereotactic radiosurgery typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five.
    - Technologies that are used to perform stereotactic radiosurgery include linear accelerators, particle beam accelerators, and multisource Cobalt 60 units. In order

to enhance precision, various devices may incorporate robotics and real time imaging.

- AANS/CNS/ASTRO Definition of Stereotactic Radiosurgery, Position Statement: 2006 June 2, available as Article 38198, AANS.org/Library (http://www.aans.org/Media/Article.aspx?ArticleId=38198).

- By convention, the use of the same treatment methodology in the remaining parts of the body is referred to as Stereotactic Body Radiotherapy (SBRT).
- Also, some researchers are promoting the use of the term "Stereotactic Ablative Radiotherapy" (SABR), pronounced "sabre".
  - Loo B, Chang J, Dawson L, Kavanagh B, Koong A, Senan S, Timmerman R, Stereotactic ablative radiotherapy: what's in a name? Practical Rad Onc Vol. 1, Is 1, Pages 38-39

Page 37, Outcome and Toxicity Measures;

- This section says "...Outcome measures for the multiple cancers include the primary outcomes of overall survival (OS) and median survival at 1-, 2- and 5-years, and secondary outcomes of local tumor control, disease-free survival (DFS), and quality of life (QoL)..." Multiple modalities, both focal and systemic, are used in the modern management of oncologic disease. In an era of "personalized treatment", it is increasingly rare for mono-therapy to be used exclusively. Thus, overall survival and median survival are better measures for the entire treatment regime. The goals of RS, as described on page 5, are to; "...to improve the targeting of radiation to the tumor to minimize damage to normal tissue and increase the dose of radiation delivered to the tumor...". RS offers ablative dose-escalation to tumor targets with simultaneous dose-restraint to normal tissues that is not possible with conventional radiotherapy. It is axiomatic that reducing dose to normal tissues will result in lower toxicities. Therefore, we recommend that reports of local tumor control, disease-free-survival (DFS) and quality of life (QoL) be incorporated in the discussion of primary outcomes, not secondary outcomes and they should not be described as "surrogate outcome", as is done in the summary section on page 27.

Liver

Page 57;

- The following references have been published since the cutoff date for the report, and should comply with the inclusion criteria;

7

- Lee IJ, Seong J. The optimal selection of radiotherapy treatment for hepatocellular carcinoma. Gut Liver. 2012 Apr;6(2):139-48.
- Almaghrabi MY, Supiot S, Paris F, Mahé MA, Rio E. Stereotactic Body Radiation Therapy for Abdominal Oligometastases: A biological and clinical review. Radiat Oncol. 2012 Aug 1;7(1):126.
- Lock MI, Hoyer M, Bydder SA, Okunieff P, Hahn CA, Vichare A, Dawson LA. An international survey on liver metastases radiotherapy. Acta Oncol. 2012 May;51(5):568-74.
- Barney BM, Olivier KR, Miller RC, Haddock MG. Clinical outcomes and toxicity using Stereotactic Body Radiotherapy (SBRT) for advanced cholangiocarcinoma. Radiat Oncol. 2012 May 3;7:67.
- O'Connor JK, Trotter J, Davis GL, Dempster J, Klintmalm GB, Goldstein RM. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. Liver Transpl. 2012 Aug;18(8):949-54.
- Ibarra RA, Rojas D, Snyder L, Yao M, Fabien J, Milano M, Katz A, Goodman K,Stephans K, El-Gazzaz G, Aucejo F, Miller C, Fung J, Lo S, Machtay M, Sanabria JR. Multicenter results of stereotactic body radiotherapy (SBRT) for non-resectable primary liver tumors. Acta Oncol. 2012 May;51(5):575-83.
- Facciuto ME, Singh MK, Rochon C, Sharma J, Gimenez C, Katta U, Moorthy CR,Bentley-Hibbert S, Rodriguez-Davalos M, Wolf DC. Stereotactic body radiation therapy in hepatocellular carcinoma and cirrhosis: evaluation of radiological and pathological response. J Surg Oncol. 2012 Jun 1;105(7):692-8.

Central Nervous System

Page 63;

- Cranial SRS is routinely used to treat non-oncologic diseases, the primary examples being arteriovenous malformations (AVMs) and trigeminal neuralgia. They are conspicuous in their absence from this section. It is beyond the scope of this review of the draft report to suggest all possible references that should be reviewed, but the usefulness and credibility of the report would be greatly enhanced if it included treatment of non-oncologic disease. Please see the attached bibliography for a list of possible references to consider for inclusion and analysis.

Page 77, KQ 1;

- Meningiomas are the most common benign intracranial lesion, and routinely treated with RS, so it is difficult to believe that "...No studies were identified."

Page 79, KQ4;

- While the absolute costs may not apply to the US market, the 2011 paper by Tan et al (rated as "good quality"), should be included, since it demonstrates a relative comparison of costs that transcends the healthcare delivery system.

Lung

Page 94;

- As mentioned in the general comments section, this population-based study compared overall survival outcomes for elderly patients with stage I NSCLC treated before and after the widespread implementation of SBRT, and detected a 16% absolute increase in radiotherapy utilization, corresponding to a decrease in untreated patients. This suggests that the efficacy, favorable toxicity profile, and convenience associated with SBRT may be key factors influencing treatment uptake. The controlled implementation of SBRT was associated with an improvement in survival that was not readily explained by other potential confounding factors, such as differences in baseline populations or stage migration.
  - Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of Introducing Stereotactic Lung Radiotherapy for Elderly Patients With Stage I Non-Small-Cell Lung Cancer: A Population-Based Time- Trend Analysis. Journal of clinical oncology 2010;28(35): 5153-9.

Page 97, first paragraph;

- Four studies are summarized that describe the complications from the placement of fiducial markers. Since this applies to only one of the devices used to treat lung SBRT, as noted in the report, the procedure used to introduce the fiducials and the fiducials themselves have evolved, we recommend deleting this section.

Page 98, KQ 4;

9

- The following two studies, one that address patients that are older than 75 and the other that looks at patients with concurrent COPD, should be included in this section on subpopulations.
  - Palma DA, Tyldesley S, Sheehan F, Mohamed IG, Smith S, Wai E, Murray N, Senan S. Stage I non-small cell lung cancer (NSCLC) in patients aged 75 years and older: does age determine survival after radical treatment? J Thorac Oncol. 2010 Jun;5(6):818-24.
  - Louie AV, Rodrigues G, Hannouf M, Lagerwaard F, Palma D, Zaric GS, Haasbeek C, Senan S. Withholding stereotactic radiotherapy in elderly patients with stage I non-small cell lung cancer and co-existing COPD is not justified: outcomes of a Markov model analysis. Radiother Oncol. 2011 May;99(2):161-5.

Prostate

Page 99, KQ1;

- There has been considerable clinical research on prostate SBRT, so it is surprising to see that "No studies were identified." There are studies mentioned in "Subsequently Published Studies" section, so perhaps this is an editorial oversight. The following studies may comply with the inclusion criteria;
  - Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. Radiat Oncol. 2011 Jan 10;6:3.
  - King C. Stereotactic body radiotherapy for prostate cancer: current results of a phase II trial. Front Radiat Ther Oncol. 2011;43:428-37. Epub 2011 May 20.
  - Boike TP, Lotan Y, Cho LC, Brindle J, DeRose P, Xie XJ, Yan J, Foster R, Pistenmaa D, Perkins A, Cooley S, Timmerman R. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer, J Clin Oncol. 2011 May 20;29(15):2020-6.
  - Ray C. Long-term outcomes of SBRT in low-risk prostate cancer, Nat Rev Urol. 2011 Apr;8(4):174. No abstract available.
  - Kang JK, Cho CK, Choi CW, Yoo S, Kim MS, Yang K, Yoo H, Kim JH, Seo YS, Lee DH, Jo M., Image-guided stereotactic body radiation therapy for localized prostate cancer,Tumori. 2011 Jan-Feb;97(1):43-8.
  - King CR, Brooks JD, Gill H, Presti JC Jr. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer, Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):877-82. Epub 2011 Feb 6.

- Katz AJ, Santoro M, Ashley R, Diblasio F. Stereotactic Body Radiation Therapy for Low- and Low-Intermediate-Risk Prostate Cancer: Is there a Dose Effect? Front Oncol. 2011;1:49. Epub 2011 Dec 5.
- Jabbari S, Weinberg VK, Kaprealian T, Hsu IC, Ma L, Chuang C, Descovich M, Shiao S, Shinohara K, Roach M 3rd, Gottschalk AR. Stereotactic body radiotherapy as monotherapy or post-external beam radiotherapy boost for prostate cancer: technique, early toxicity, and PSA response, Int J Radiat Oncol Biol Phys. 2012 Jan 1;82(1):228-34. Epub 2010 Dec 22.
- Bolzicco G, Favretto MS, Scremin E, Tambone C, Tasca A, Guglielmi R. Image-guided stereotactic body radiation therapy for clinically localized prostate cancer: preliminary clinical results, Technol Cancer Res Treat. 2010 Oct;9(5):473-7.
- Katz AJ. CyberKnife radiosurgery for prostate cancer, Technol Cancer Res Treat. 2010 Oct;9(5):463-72.
- Oermann EK, Slack RS, Hanscom HN, Lei S, Suy S, Park HU, Kim JS, Sherer BA, Collins BT, Satinsky AN, Harter KW, Batipps GP, Constantinople NL, Dejter SW, Maxted WC, Regan JB, Pahira JJ, McGeagh KG, Jha RC, Dawson NA, Dritschilo A, Lynch JH, Collins SP. A pilot study of intensity modulated radiation therapy with hypofractionated stereotactic body radiation therapy (SBRT) boost in the treatment of intermediate- to high-risk prostate cancer, Technol Cancer Res Treat. 2010 Oct;9(5):453-62.
- Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M. Stereotactic body radiotherapy for organ-confined prostate cancer.BMC Urol. 2010 Feb 1;10:1.

- In addition, the following review articles may comply with the inclusion criteria;

  - Spyropoulou D, Kardamakis D Review of hypofractionated radiotherapy for prostate cancer. ISRN Oncol. 2012;2012:410892
  - Arcangeli S, Scorsetti M, Alongi F, Will SBRT replace conventional radiotherapy in patients with low-intermediate risk prostate cancer? A review. Crit Rev Oncol Hematol. 2012 Oct;84(1):101-8.
  - Ishiyama H, Teh BS, Lo SS, Mathews T, Blanco A, Amato R, Ellis RJ, Mayr NA, Paulino AC, Xu B, Butler BE Stereotactic body radiation therapy for prostate cancer. Future Oncol. 2011 Sep;7(9):1077-86.

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- Teh BS, Ishiyama H, Mathews T, Xu B, Butler EB, Mayr NA, Lo SS, Lu JJ, Blanco AI, Paulino AC, Timmerman RD.Stereotactic body radiation therapy (SBRT) for genitourinary malignancies. Discov Med. 2010 Sep;10(52):255-62.
- Biagioli MC, Hoffe SE. Emerging technologies in prostate cancer radiation therapy: improving the therapeutic window. Cancer Control. 2010 Oct;17(4):223-32.
- Choe KS, Liauw SL Radiotherapeutic strategies in the management of low-risk prostate cancer. ScientificWorldJournal. 2010 Sep 14;10:1854-69.
- Wiegner EA, King CR Sexual function after stereotactic body radiotherapy for prostate cancer: results of a prospective clinical trial. Int J Radiat Oncol Biol Phys. 2010 Oct 1;78(2):442-8.

Page 100, KQ4;

- The following studies may comply with the inclusion criteria;
  - Hodges JC, Lotan Y, Boike TP, Benton R, Barrier A, Timmerman RD, Cost-effectiveness analysis of stereotactic body radiation therapy versus intensity-modulated radiation therapy: an emerging initial radiation treatment option for organ-confined prostate cancer, J Oncol Pract. 2012 May;8(3 Suppl):e31s-7s.
  - Parthan A, Pruttivarasin N, Davies D, Taylor DC, Pawar V, Bijlani A, Lich KH, Chen RC. Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer, Front Oncol. 2012;2:81. Epub 2012 Aug 20.
  - Hodges JC, Lotan Y, Boike TP, Benton R, Barrier A, Timmerman RD. Cost-effectiveness analysis of SBRT versus IMRT: an emerging initial radiation treatment option for organ-confined prostate cancer. Am J Manag Care. 2012 May 1;18(5):e186-93.

Spine

Page 101, KQ1;

- The following study is discussed KQ2 and should also be included in KQ1;
  - Ryu S, Rock J, Jain R, Lu M, Anderson J, Jin JY, Rosenblum M, Movsas B, Kim JH. Radiosurgical decompression of metastatic epidural compression. Cancer. 2010 May 1;116(9):2250-7.

12

Page 102, KQ2;

- The following study should be included in KQ2;
    - Ryu S, Jin R, Jin JY, Chen Q, Rock J, Anderson J, Movsas B. Pain control by image-guided radiosurgery for solitary spinal metastasis. J Pain Symptom Manage. 2008 Mar;35(3):292-8.

Page 105, KQ3;

- The following study should be included in KQ3, as is it discusses a particular subpopulation, postoperative patients.
    - Sahgal A, Bilsky M, Chang EL, Ma L, Yamada Y, Rhines LD, Létourneau D, Foote M, Yu E, Larson DA, Fehlings MG. Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient. J Neurosurg Spine. 2011 Feb;14(2):151-66.

Page 105, KQ4;

- Since costs are typically reported on a per-patient basis, the reported Haley 2011 study results should be revised such that they are per-patient, not per 100 patients. This will avoid the potential for significant confusion.

Guidelines

Page 108;

- The following study should be included;
    - Sahgal A, Roberge D, Schellenberg D, Purdie TG, Swaminath A, Pantarotto J, Filion E, Gabos Z, Butler J, Letourneau D, Masucci GL, Mulroy L, Bezjak A, Dawson LA, Parliament M. The Canadian Association of Radiation Oncology Scope of Practice Guidelines for Lung, Liver and Spine Stereotactic Body Radiotherapy. Clin Oncol (R Coll Radiol). 2012 May 23

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SRS & SBRT BIBLIOGRAPHY

CLINICAL AND TECHNICAL JOURNAL PUBLICATIONS JAN 2010 THROUGH SEPT 2012

WHERE VARIAN LINACS WERE USED FOR SRS & SBRT OR WHERE VARIAN TECHNIQUES ARE USED FOR RADIOSURGERY / SBRT

BRAIN TUMORS – BENIGN

Benign Meningioma & Other Benign Tumors

Published

Kimball MM, Foote KD, Bova FJ, Chi YY, Friedman WA. Linear accelerator radiosurgery for nonvestibular schwannomas. Neurosurgery. 2011 Apr;68(4):974-84; discussion 984.*University of Florida, Gainsville*

Korah MP, Nowlan AW, Johnstone PA, Crocker IR. Radiation Therapy Alone for Imaging-Defined Meningiomas. *Int J Radiat Oncol Biol Phys.* 2010 Jan 1;76(1):181-6. *Emory University, Atlanta*

BRAIN TUMORS – BENIGN

Vestibular Schwannoma (Acoustic Neuroma)

Published

Kopp C, Fauser C, Müller A, Astner ST, Jacob V, Lumenta C, Meyer B, Tonn JC, Molls M, Grosu AL. Stereotactic Fractionated Radiotherapy and LINAC Radiosurgery in the Treatment of Vestibular Schwannoma-Report About Both Stereotactic Methods From a Single Institution. *Int J Radiat Oncol Biol Phys.* 2011 Aug 1;80(5):1485-91. *Klinikum rechts der Isar der Technische Universität München, Munich, Germany*

Bassim MK, Berliner KI, Fisher LM, Brackmann DE, Friedman RA. Radiation therapy for the treatment of vestibular schwannoma: a critical evaluation of the state of the literature. *Otol Neurotol.* 2010 Jun;31(4):567-73. Review. *American University of Beirut, Beirut,*

Hsu PW, Chang CN, Lee ST, Huang YC, Chen HC, Wang CC, Hsu YH, Tseng CK, Chen YL, Wei KC. Outcomes of 75 patients over 12 years treated for acoustic neuromas with linear accelerator-based radiosurgery. *J Clin Neurosci.* 2010 May;17(5):556-60. *Chang Gung University, Kweishan, Taoyuan, TW*

Lin YC, Wang CC, Wai YY, Wan YL, Ng SH, Chen YL, Liu HL, Wang JJ. Significant Temporal Evolution of Diffusion Anisotropy for Evaluating Early Response to Radiosurgery in Patients with Vestibular Schwannoma: Findings from Functional Diffusion Maps. *AJNR Am J Neuroradiol.* 2010 Feb;31(2):269-74. *Chang Gung University, Taiwan, Republic of China.*

BRAIN TUMORS – BENIGN

Pituitary Adenoma, Craniopharyngioma and Cushing's Disease

Published

Yang I, Kim W, De Salles A, Bergsneider M. A systematic analysis of disease control in acromegaly treated with radiosurgery. *Neurosurg Focus.* 2010 Oct;29(4):E13. *University of California, Los Angeles, California*

BRAIN TUMORS – MALIGNANT & METASTATIC

Glioma / Glioblastoma / Malignant Meningioma

Published

Cabrera AR, Cuneo KC, Vredenburgh JJ, Sampson JH, Kirkpatrick JP. Stereotactic radiosurgery and bevacizumab for recurrent glioblastoma multiforme. *J Natl Compr Canc Netw.* 2012 Jun 1;10(6):695-9. *Duke University Medical Center, Durham, NC*

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Cuneo KC, Vredenburgh JJ, Sampson JH, Reardon DA, Desjardins A, Peters KB, Friedman HS, Willett CG, Kirkpatrick JP. Safety and Efficacy of Stereotactic Radiosurgery and Adjuvant Bevacizumab in Patients with Recurrent Malignant Gliomas. *Int J Radiat Oncol Biol Phys*. 2012 Apr 1;82(5):2018-24. *Duke University Medical Center, Durham, NC.*

Fields EC, Damek D, Gaspar LE, Liu AK, Kavanagh BD, Waziri A, Lillehei K, Chen C. Phase I Dose Escalation Trial of Vandetanib With Fractionated Radiosurgery in Patients With Recurrent Malignant Gliomas. *Int J Radiat Oncol Biol Phys*. 2012 Jan 1;82(1):51-7. *University of Colorado, Aurora*

Shaffer R, Nichol AM, Vollans E, Fong M, Nakano S, Moiseenko V, Schmuland M, Ma R, McKenzie M, Otto K. A Comparison of Volumetric Modulated Arc Therapy and Conventional Intensity-Modulated Radiotherapy for Frontal and Temporal High-Grade Gliomas. *Int J Radiat Oncol Biol Phys*. 2010 Mar 15;76(4):1177-84. *BC Cancer Agency, Vancouver, British Columbia*

BRAIN TUMORS – MALIGNANT & METASTATIC

Metastatic Disease

Published

Pan H, Cerviño LI, Pawlicki T, Jiang SB, Alksne J, Detorie N, Russell M, Carter BS, Murphy KT, Mundt AJ, Chen C, Lawson JD. Frameless, real-time, surface imaging-guided radiosurgery: clinical outcomes for brain metastases. *Neurosurgery*. 2012 Oct;71(4):844-52 *University of California San Diego, La Jolla, California*

Liepa Z, Auslands K, Apskalne D, Ozols R. Initial experience with using frameless image-guided radiosurgery for the treatment of brain metastases. *Exp Oncol*. 2012 Jul;34(2):125-8. *Riga East Clinical University Hospital, Riga, Latvia.*

Wang JZ, Pawlicki T, Rice R, Mundt AJ, Sandhu A, Lawson J, Murphy KT. Intensity-modulated radiosurgery with RapidArc® for multiple brain metastases and comparison with static approach. *Med Dosim*. 2012 Spring;37(1):31-6. *University of California, San Diego, La Jolla, CA.*

Lal LS, Byfield SD, Chang EL, Franzini L, Miller LA, Arbuckle R, Reasonda L, Feng C, Adamus A, Swint JM. Cost-effectiveness Analysis of a Randomized Study Comparing Radiosurgery With Radiosurgery and Whole Brain Radiation Therapy in Patients With 1 to 3 Brain Metastases. *Am J Clin Oncol*. 2012 Feb;35(1):45-50.*The University of Texas School of Public Health, Houston, TX*

Kelly PJ, Lin YB, Yu AY, Alexander BM, Hacker F, Marcus KJ, Weiss SE. Stereotactic Irradiation of the Postoperative Resection Cavity for Brain Metastasis: A Frameless Linear Accelerator-Based Case Series and Review of the Technique. *Int J Radiat Oncol Biol Phys*. 2012 Jan 1;82(1):95-101. *Dana-Farber/Brigham and Women's Cancer Center, Boston*

Audet C, Poffenbarger BA, Chang P, Jackson PS, Lundahl RE, Ryu SI, Ray GR. Evaluation of volumetric modulated arc therapy for cranial radiosurgery using multiple noncoplanar arcs. *Med Phys*. 2011 Nov;38(11):5863-72. *Palo Alto Medical Foundation, Palo Alto, CA*

Kelly PJ, Lin YB, Yu AY, Ropper AE, Nguyen PL, Marcus KJ, Hacker FL, Weiss SE. Linear accelerator-based stereotactic radiosurgery for brainstem metastases: the Dana-Farber/Brigham and Women's Cancer Center experience. *J Neurooncol*. 2011 Sep;104(2):553-7.*Dana-Farber/Brigham and Women's Cancer Center, Boston*

Roberge D, Souhami L. Tumor bed radiosurgery following resection of brain metastases: a review. *Technol Cancer Res Treat*. 2010 Dec;9(6):597-602. *McGill University, Montreal*

Ma Y, Li M, Yin Y, Kong L, Sun X, Lin X, Yu J. Hypofractionated stereotactic radiotherapy for brain metastases: a dosimetric and treatment efficiency comparison between volumetric modulated arc therapy and intensity modulated radiotherapy. *Technol Cancer Res Treat*. 2010 Oct;9(5):499-507. *Shandong Tumor Hospital and Institute, Shandong Province, China.*

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Stewart JG, Sawrie SM, Bag A, Han X, Fiveash JB. Management of brain metastases. *Curr Treat Options Neurol.* 2010 Jul;12(4):334-46. *University of Alabama at Birmingham, Birmingham, AL*

Nath SK, Lawson JD, Simpson DR, Vanderspek L, Wang JZ, Alksne JF, Ciacci J, Mundt AJ, Murphy KT. Single-isocenter frameless intensity-modulated stereotactic radiosurgery for simultaneous treatment of multiple brain metastases: clinical experience. *Int J Radiat Oncol Biol Phys.* 2010 Sep 1;78(1):91-7. *UCSD, San Diego, CA*

Hsu F, Carolan H, Nichol A, Cao F, Nuraney N, Lee R, Gete E, Wong F, Schmuland M, Heran M, Otto K. Whole Brain Radiotherapy with Hippocampal Avoidance and Simultaneous Integrated Boost for 1-3 Brain Metastases: A Feasibility Study Using Volumetric Modulated Arc Therapy. *Int J Radiat Oncol Biol Phys.* 2010 Apr;76(5):1480-5 *BC Cancer Agency, Vancouver, British Columbia*

Nath SK, Lawson JD, Wang JZ, Simpson DR, Newman CB, Alksne JF, Mundt AJ, Murphy KT. Optically-guided frameless linac-based radiosurgery for brain metastases: clinical experience. *J Neurooncol.* 2010 Mar;97(1):67-72. *University of California, San Diego*

Clark GM, Popple RA, Young PE, Fiveash JB. Feasibility of single-isocenter volumetric modulated arc radiosurgery for treatment of multiple brain metastases. *Int J Radiat Oncol Biol Phys.* 2010 Jan 1;76(1):296-302. *University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

BRAIN – PEDIATRIC
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Mirza B, Mønsted A, Harding J, Ohlhues L, Roed H, Juhler M. Stereotactic radiotherapy and radiosurgery in pediatric patients: analysis of indications and outcome. *Childs Nerv Syst.* 2010 Dec;26(12):1785-93. *Rigshospitalet, Copenhagen University Hospital, Copenhagen, DN*

BRAIN – FUNCTIONAL DISEASE

Trigeminal Neuralgia and other Pain

Published
Smith ZA, Gorgulho AA, Bezrukiy N, McArthur D, Agazaryan N, Selch MT, De Salles AA. Dedicated Linear Accelerator Radiosurgery for Trigeminal Neuralgia: A Single-Center Experience in 179 Patients with Varied Dose Prescriptions and Treatment Plans. *Int J Radiat Oncol Biol Phys.* 2011 Sep 1;81(1):225-31. *UCLA Medical Center, Los Angeles, CA*

Dos Santos MA, Pérez de Salcedo JB, Gutiérrez Díaz JA, Nagore G, Calvo FA, Samblás J, Marsiglia H, Sallabanda K. Outcome for Patients with Essential Trigeminal Neuralgia Treated with Linear Accelerator Stereotactic Radiosurgery. *Stereotact Funct Neurosurg.* 2011 May 25;89(4):220-225. *Instituto Madrileño de Oncología/Grupo IMO, Madrid, Spain.*

Chen JC, Rahimian J, Rahimian R, Arellano A, Miller MJ, Girvigian MR. Frameless image-guided radiosurgery for initial treatment of typical trigeminal neuralgia. *World Neurosurg.* 2010 Oct-Nov;74(4-5):538-43. *Southern California Permanente Medical Group, Los Angeles, CA*

BRAIN – FUNCTIONAL DISEASE

Arteriovenous Malformations and Cavernomas

In-Press
Gross BA, Ropper AE, Du R. Vascular complications of stereotactic radiosurgery for arteriovenous malformations. *Clin Neurol Neurosurg.* 2012 Aug 18. *Brigham and Women's Hospital and Harvard Medical School, Boston, MA* [Epub ahead of print]

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Blamek S, Tarnawski R, Miszczyk L. Linac-based Stereotactic Radiosurgery for Brain Arteriovenous Malformations. *Clin Oncol (R Coll Radiol).* 2011 Oct;23(8):525-31.. *Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, PO*

Yuki I, Kim RH, Duckwiler G, Jahan R, Tateshima S, Gonzalez N, Gorgulho A, Diaz JL, De Salles AA, Viñuela F. Treatment of brain arteriovenous malformations with high-flow arteriovenous fistulas: risk and complications associated with endovascular embolization in multimodality treatment. *J Neurosurg.* 2010 Oct;113(4):715-22. *UCLA, Los Angeles, CA*

BRAIN – FUNCTIONAL DISEASE

BRAIN – Seizure Treatment: Thalamotomy & Corpus Callosotomy

Published
Golanov AV, Kornienko VN, Trunin Iulu, Kostiuchenko VV, Gorlachev GE, Gorelyshev SK, Melikian AG, Khukhlaeva EA, Mazerkina NA, Sorokin VA. [Stereotactic radiosurgery in treatment of patients with hypothalamic hamartomas] *Zh Vopr Neirokhir Im N N Burdenko.* 2010 Jan-Mar;(1):24-9.

SPINE

Spine – Metatatic Spinal Disease, Primary Spine Tumors, Vascular Spine Disease

In-Press
Schipani S, Wen W, Jin JY, Kim JK, Ryu S.Spine Radiosurgery: A Dosimetric Analysis in 124 Patients Who Received 18 Gy. *Int J Radiat Oncol Biol Phys.* 2012 Sep 10. pii: *University of Glasgow, Glasgow, United Kingdom* [Epub ahead of print]

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Selch MT, Tenn S, Agazaryan N, Lee SP, Gorgulho A, De Salles AA. Image-guided linear accelerator-based spinal radiosurgery for hemangioblastoma. *Surg Neurol Int.* 2012;3:73. *UCLA, Los Angeles, California*

Niazi TN, Bowers CA, Schmidt MH. Role of adjuvant radiosurgery after thoracoscopic microsurgical resection of a spinal schwannoma. *Case Report Neurol Med.* 2012;2012:345830
University of Utah, Salt Lake City, UT

Cox BW, Spratt DE, Lovelock M, Bilsky MH, Lis E, Ryu S, Sheehan J, Gerszten PC Chang E, Gibbs I, Soltys S, Sahgal A, Deasy J, Flickinger J, Quader M, Mindea S, Yamada Y. International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys.* 2012 Aug 1;83(5):e597-605. *Memorial Sloan-Kettering Cancer Center, New York, NY*

Dahdal S, Andres RH, Hewer E, Reubi JC, Klaeser B, Raabe A, Cihoric N, Schmid R, Tänzler K, Krause T, Aebersold DM, Schmuecking M. A rare case of a large spinal meningioma with mediastinal extension and malignant behavior classified histologically as benign. *Recent Results Cancer Res.* 2012;194:443-55
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PROSTATE, KIDNEY AND GU CANCERS

Primary and Metastatic GU Neoplasms

In-Press

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EXTRACRANIAL DISEASE – MIXED TARGETS

X-CRANIAL/nonCNS-OTHER

In-Press

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GENERAL RADIOSURGERY & SABR

General Applications of Radiosurgery & Stereotactic Ablative Radiotherapy

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TECHNICAL

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Tumor Targeting & Treatment Accuracy & Delivery Speed

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Image-Guidance

Published

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TECHNICAL

MOTION TRACKING, MANAGEMENT & COMPENSATION

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Dose - Radiation Delivery - Radiobiology

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TECHNICAL

PERFORMANCE – QA/QC

Published

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Washington State Agency Medical Directors

Agency Director Comments on Draft Report: Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

This is a comprehensive evidence review which reflects the overall lack of high quality evidence addressing concerns of safety, comparative effectiveness, and cost for stereotactic radiosurgery and stereotactic body radiation therapy. In its present format the report does not prioritize the areas of greatest clinical relevance which are supported by at least a fair to good level of evidence. Restructuring the report will assist the Health Technology Clinical Committee members in their decision making process. The proposed areas of prioritization in the report include the use of stereotactic radiosurgery in the treatment of medically inoperable or unresectable primary brain neoplasms or metastatic disease for patients with a good Karnofsky performance status, treatment of early stage NSCLC in patients with a favorable live expectancy who are otherwise medically inoperable or unresectable, and treatment of primary or metastatic vertebral body, spinal or paraspinal tumors with either a history of previous radiation therapy or requiring high-dose radiotherapy.

List of comments:

p. 6 The article "Stereotactic Radiotherapy Reduces Treatment Cost While Improving Overall Survival and Local Control over Standard Fractionated Radiation Therapy for Medically Inoperable Non-Small-Cell Lung Cancer," is misquoted in the *Cost information* section in paragraph 2. This data should be omitted from the Executive Summary for the following reasons: 1. There is no mention made of whether or not these patients received adjuvant chemotherapy and therefore the survival conclusion must be questioned. 2. Indirect costs such as ancillary tests and associated imaging studies were not included in this cost analysis. 3. The executive summary should not contain a reference to a specific journal article, particularly if the article is of poor quality and unclear clinical significance.

p. 6 Please specify whether or not the EBRT comparator included IMRT.

p. 9 The findings should be listed either according to frequency of use based upon the state agency data or to quality of supporting medical evidence, rather than alphabetically.

p. 10 A summary table of findings, organized by diagnosis or prioritized by the level of evidence, such as was performed for the IMRT review, would be helpful. The present organization of the report is very difficult to follow.

p. 12 The Central Nervous System section should be divided into primary CNS tumors and "brain metastases."

pp. 10-24 Information should be incorporated into a table, as stated previously. Table should be reinserted before p. 55 Study results.

p. 64. The "Brain metastases" section needs to elucidate if the patient populations were limited to single metastasis versus multiple metastases. This section requires expansion as this will be an area of focus for the Clinical committee. Please add the following in a summary table: single vs. multiple metastases, resectable vs. unresectable disease, size of metastasis and histologic type.

p. 79 "Multiple CNS Tumors" is unclear. Does this mean Synchronous primary brain tumors? Metachronous primary brain tumors? Multiple brain metastases? Either clarify or omit this section.

There is no reference to the pediatric population in this report. Please clarify if (1) no literature exists (2) literature is present but did not meet the minimum sample size requirements. If

literature is present but did not meet the minimum sample size requirements please include this comment, particularly in the sections for abdominal, brain and spinal tumors.