Washington State Health Care Authority

Health Technology Assessment

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

Appendix K. Public Comments and Disposition – Key Questions

October 10, 2012

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Public Comments and Disposition- Key Questions

Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy

October 10, 2012

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Public Comments on Key Questions

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. 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 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)[1]
- American College of Radiation Oncology (ARCO)
- American Society for Radiation Oncology (ASTRO)
- Jeanne R. Berry
- Thomas Carlson, MD (Wenachee Valley Medical Center)
- Cyberknife Coalition
- Elekta
- International RadioSurgery Association (IRSA)[2]
- Nancy Lang
- L. Dade Lunsford, MD (University of Pittsburg Physicians, Department of Neurological Surgery)
- Berit Madsen, MD, FACR (Peninsula Cancer Center)
- Dean G. Mastras, MD and Randy D. Sorum, MD (Tacoma/Valley Radiation Oncology Centers)
- James F. Raymond, MD (RadiantCare Radiation Oncology)
- Eric W. Taylor, MD
- Tumor Institute Radiation Oncology Group
- University of Washington Medicine / Seattle Cancer Care Alliance Department of Radiation Oncology, UW Department of Neurological Surgery
- Us TOO International
- Varian Medical Systems
- Sandra Vermeulen, MD (Swedish Radiosurgery Center)
- Virginia Mason Medical Center

[1] This public comment was received in July 2012 in response to revised Key Questions.
[2] This public comment was received in July 2012 in response to revised Key Questions.

Table 1. Response to Public Comments on Key Questions

Reviewer	Comment	Disposition
AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS (AANS) AND THE CONGRESS OF NEUROLOGICAL SURGEONS (CNS)		
	"We are concerned that some of the key questions in the "*DRAFT Key Questions and Background Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy"* are very general and we are eager to provide more specific details in response to the draft technical assessment expected on July 6, 2012."	*Thank you for comments.* *No changes to the Key Questions.*
	Summary KQ1. • Discusses effectiveness of SRS for patients with CNS tumors and non-CNS cancers	*Thank you for comments.* *All references were forwarded to TAC for consideration in the review process.* *No changes to the Key Questions.*
	Summary KQ2. • Discusses harms of SRS compared with EBRT	*Thank you for comments.* *All references were forwarded to TAC for consideration in the review process.* *No changes to the Key Questions.*
	Summary KQ3. • Discusses effectiveness of SRS in subpopulations including gender, age, setting, provider characteristics, equipment, quality assurance standards and procedures.	*Thank you for comments.* *All references were forwarded to TAC for consideration in the review process.* *No changes to the Key Questions.*
	Summary KQ4. • Discusses cost-effectiveness of SRS for patients with brain metastases, spinal metastases, and skull base tumors	*Thank you for comments.* *All references were forwarded to TAC for consideration in the review process.* *No changes to the Key Questions.*
AMERICAN COLLEGE OF RADIATION ONCOLOGY (ACRO)		

Reviewer	Comment	Disposition
	"There is clear and increasing evidence that in certain circumstances, SBRT and SRS may be equivalent and/or preferable to conventional fractionated and protracted radiation. SBRT and SRS, unlike IMRT, relate to "biology" and not "technology," in that they merely represent the delivery of high-dose, short-course radiation (5 or fewer treatments, rather than daily, protracted, lower-dose, longer-course therapies). Evidence mounts that numerous sites, including brain, spinal cord, liver, and lung, as well as other emerging indications, are appropriately treated by SRS (for central nervous system) and SBRT (for non-central nervous system). We understand that the American Society for Radiation Oncology (ASTRO) has included its own model coverage policies on SRS, SBRT and IMRT for your review that outline specific technology of each treatment, clinical indications, coding considerations and references. ACRO supports your review of these materials and their conclusions. We also are aware that physicians with the Swedish Medical Center are submitting information regarding studies that have been performed relating to SRS, SBRT and IMRT. We would encourage the committee to review these in detail."	*Thank you for comments.* *No changes to the Key Questions.*
AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)		
	"The Key Questions posed for the SRS, SBRT, and IMRT are extensive and ask for a level of detail that we can not produce within the time frame allotted. The information requested for all three technologies, specifically comparisons to external beam radiation therapy) benefits and harms), and diferential efficacy or safety issues in subpopulations including consideration of gender, age, site and type of cancer, stage and grade of cancer and setting, provider characteristics, equipment, quality assurance standards and procedures, constitutes a full research study that would take many months to produce. While ASTRO believes these technologies offer clear benefits to many of the cancer patients our members treat, we would require significantly more time to adequately address the important issues raised in the Key Questions. ASTRO plans on reviewing the draft report that will be produced as a result of the public comment period and we look forward to reviewing this report in early July.	*Thank you for comments.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	We have noted that the Health Technology Clinical Committee that will be reviewing the technology assessment reports and making coverage decisions does not include a radiation oncologist and we strongly recommend that a radiation oncologist be added to this committee. In anticipation of the more detailed comments that we will submit in response to the draft report, we offer a general observation relating to the fundamental basis of some of our positions about IMRT in particular. During the past two decades, an abundant number of clinical studies have characterized the relationship between the dose given to various normal tissues using 3D EBRT and the risk of toxicity to those tissues. There are recogonized dose thresholds know to relate to the risk of toxicity for bowel, bladder, spinal cord, and other important organs. Whereas IMRT offers the capacity to avoid exceeding those recognized thresholds for toxicity, it is considered an appropriate standard for numberous indications as a result of this property. The field of radiation oncology has not considred it ethical or resource-efficient to conduct head-to-head tcomparisons of 3D EBRT vs. IMRT in all settings where a clear improvement in a surrogate measure of toxicity risk is easily demonstrated. We have included ASTRO's model coverage policies on SRS, SBRT, and IMRT for your review that outline the specific technology of each treatment, clinical indications, coding considerations, and references."	
JEANNE R. BERRY		
	Summary – Shared story of husband's experience with prostate cancer and Cyberknife treatment.	*Thank you for your comment.* *No changes to Key Questions.*
THOMAS CARLSON, MD (WENATCHEE VALLEY MEDICAL CENTER)		
	"I am concerned with respect to the path we have been going down regarding the complexity of reimbursement evaluation. We seem to be reimbursing physicians based on the tools they are using to accomplish a task as opposed to the task itself. In the case of IMRT, Stereotactic Radiosurgery (in the brain or body) or	*Thank you for your comment.* *No changes to Key Questions.*

Reviewer	Comment	Disposition
	brachytherapy, we are reimbursing based on the tool. Do we reimburse a surgeon for using one scalpel blade over another? No. The surgeon chooses what's most appropriate for the situation and is paid for the job. I believe a tremendous amount of waste could be removed from the system if a case rate reimbursement model was initiated."	
CYBERKNIFE COALITION (JOHN RIEKE, MD FACR [MULTICARE REGIONAL CANCER CENTER] AND LINDA F WINGER, MSC, FACHE)		
	Summary: General background information on CyberKnife system.	*Thank you for your comment.*
	Summary KQ1. • Comparative data of conventional external beam radiation treatment (EBRT)versus CyberKnife Clinical Outcomes for Spine • Comparative data of conventional external beam radiation treatment (EBRT)versus CyberKnife Clinical Outcomes for Non-Small Cell Lung • Comparative data of conventional external beam radiation treatment (EBRT)versus CyberKnife Clinical Outcomes for Liver Metastases • Comparative data of conventional external beam radiation treatment (EBRT)versus CyberKnife Clinical Outcomes for Prostate Cancer • Comparative data of conventional external beam radiation treatment (EBRT)versus CyberKnife Clinical Outcomes for Pancreatic Cancer	*Thank youfor your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*
	Summary KQ 2. • Discussion of harms from SBRT, SRS, EBRT and CyberKnife	*Thank you for your comment.* *No changes to Key Questions.*
	"The unique codes CMS created for Robotic Stereotactic Radiosurgery are G0339 and G0340. While the majority of fractionated SRS and SBRT in the United States are performed with the CyberKnife, curiously G0339 and G0340 are not listed on the Washington Medicaid Fee Schedule, and the codes for gantry-based SRS and SBRT (G0251 and G0173) are."	*Thank you for your comment.* *No changes to Key Questions.*
	Summary KQ3.	*Thank you for your comment.*

Reviewer	Comment	Disposition
	• Discussion of Food and Drug Administration clearance for CyberKnife System • Provided summary of Aetna's national SBRT policy	*No changes to Key Questions.*
	Summary KQ4. • Lack of clinical literature which compares the cost of radiation therapies • Three cost-effectiveness studies provided	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*
	Summary Conclusion • SRS/SBRT is the standard of care available to cancer patients. SRS/SBRT can treat patients with brain, spine, lung, liver, pancreas, and prostate cancer • Urges Washington State Health Care Authority to add codes G0339 and G0340 as covered benefit for Medicaid patients in the State of Washington	*Thank you for your comment.* *No changes to Key Questions.*
ELEKTA		
Todd Howard, MBA	• Submitted four articles for consideration	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*
Eleckta Dossier	Summary KQ1 • Provided conclusions from recent guidelines from the American Society of Therapeutic Radiation Oncology, the American Association of Neurological Sugeons, and the Congress of Neurological Surgeons Summary KQ2 • Discusses the benefits of Gamma Knife and provides supporting references Summary KQ3 • Discusses a proposed grading to provide detailed prognostic information for radiosurgery	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*

Reviewer	Comment	Disposition
	• Discusses the efficacy and safety of Gamma Knife Summary KQ4 • Suggests a cost advantage for SRS followed by surveillance in terms of quality adjusted life years	
INTERNATIONAL RADIOSURGERY ASSOCIATION (IRSA)		
	Summary KQ1 • Discusses patient factors to consider based on IRSA Radiosurgery Guidelines for the conditions of o Acoustic neuroma o Intracranial arteriovenous malformations (AVM) o Metastatic brain tumors o Trigeminal neuralgia refractory to medical treatment o Pituitary adenomas	*Thank you for your comments. We are aware that, for some tumor types such as acoustic neuroma, SBRT has been compared to treatments other than EBRT (including surgery, observation, chemotherapy, intensity modulated radiation therapy [IMRT]). EBRT may or may not be the optimal or most appropriate comparator in these instances. The scope of this technology assessment report is to evaluate SBRT where radiation therapy is an appropriate treatment choice. The purpose of the report is not to evaluate the most effective treatments for various tumors, but to evaluate whether there is a role for SBRT compared to EBRT. A description of the therapies used for each tumor type will be included in the body of the report.* *Guidelines were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*
	Summary KQ2 • Discusses benefits of SBRT over EBRT	*Thank you for your comment.* *Guidelines were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*

Reviewer	Comment	Disposition
	Summary KQ3 • Discusses harms of EBRT compared to SRS and SBRT • Discusses use of EBRT in pediatric population	*Thank you for your comment.* *Guidelines were forwarded to TAC for consideration in the review process.*
	Summary KQ4 • Provides cost information for SRS, SRS/SBRT, and EBRT	*Thank you for your comment.* *Guidelines were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*
NANCY LANG		
	"I am a 70 year old woman with ovarian cancer. My first diagnosis was in December 2004 with surgery and complete hysterectomy, followed in January 2005 by chemotherapy, a combination of carboplatin and taxol. My cancer returned in 2007 with a duplication of the previous chemotherapy and, in 2010 another round of chemotherapy with an addition of Avastin. In 2011, after a reaction to the carbo and taxol, I continued on a different treatment option of cisplatin and gemsidibine while waiting for approval for CyberKnife radiosurgery. I selected to go with CyberKnife because a new tumor, detected in a November 2010 PET –CT showed the location in the *periportal region*. Surgery in this area is not a good option. After receiving marker fiducials my CyberKnife treatment began the end of February over a period of five treatments. I had neither pain nor any negative reaction during or after my treatment. A November 2011 follow-up PET-CT displayed a recurrence in *aortocaval lymph nodes*, requiring additional treatment. After three medical opinions clearly stating that, because of the location of the recurrence, surgery was not an option and chemo was taking a toll on my body, CyberKnife would be the best treatment. With my health insurance approval we started treatment January 3, 2012 for five	*Thank you for your comment.* *No changes to Key Questions.*

Reviewer	Comment	Disposition
	days. I walked daily, after each treatment, and continue to do so. I felt nothing during the treatment, maybe one slow day when I felt a little tired but, in general I feel perfectly normal." With my experience, I can highly vouch for the value of CyberKnife treatment process and recommend it be funded by all health care programs."	
L. DADE LUNSFORD (UNIVERSITY OF PITTSBURG PHYSICIANS, DEPARTMENT OF NEUROLOGICAL SURGERY)		
	"Stereotactic radiosurgery is an integral part of the field of neurosurgery with collegial interaction with the field of radiation oncology. At our center, more than 11,300 patients have undergone Gamma Knife stereotactic radiosurgery over the last 25 years since we placed the first Leksell Gamma Knife in North America." "Stereotactic radiosurgery is used for approximately 20% of all brain indications for intervention at our center with an increasing role in the management of metastatic cancer, arteriovenous malformations, chronic pain especially related to trigeminal neuralgia, glial neoplasms, and a wide variety of skull-based tumors including pituitary tumors." "In the last 25 years, more than 500 outcome studies have been published related to Gamma Knife radiosurgery, and it is approved for use by all insurance providers. This type of technique has been a radical transformation in the management of patients with a wide variety of otherwise frequently fatal brain conditions. Because of its superior technology and minimally invasive nature, patients are often done as an outpatient and can retu+rn to regular activities on the following day. Therefore, quality assessment, comparative outcomes research, and cost effectiveness research have substantiated the role of this technology in a wide variety of indications."	*Thank you for your comment.* *No changes to Key Questions.*
BERIT L. MADSEN, MD, R. ALEX HIS, MD, AND HEATH R. FOXLEE, MD (PENINSULA CANCER CENTER)		
	"We have received copies of the letters that Dr. Todd Barnett and his associates at the Swedish Cancer Institute have written in support of Intensity Modulated Radiotherapy (IMRT) and Stereotactic Radiotherapy (SRT), currently under review by	*Thank you for your comment.* *No changes to Key Questions.*

Reviewer	Comment	Disposition
	your board. We have reviewed their letters and supportive documents and applaud their work and endorse their recommendations that IMRT and SRT/SBRT are important treatment techniques that benefit cancer patients while being safe and cost effective. IMRT and stereotactic radiotherapy are techniques that have been in common use in most radiation therapy centers for greater than 10 years; it would be impossible to think of not utilizing these advanced techniques for patients with conditions that warrant such treatment. We are hopeful that your review will support the continued utilization of these beneficial treatment techniques."	
DEAN G. MASTRAS, MD AND RANDY D. SORUM, MD (TACOMA/VALLEY RADIATION ONCOLOGY CENTERS)		
	"These technologies are currently available in many places in the State of Washington and are quickly becoming standard of care for many treatment sites throughout the nation. As clearly stated in the summary, these technologies are more expensive than conventional radiation. The trade off, however, is very significant when it comes to not only improvements in outcomes but they are vastly superior in reduction in side effects and toxicity. We are also able to treat specific tumor locations that we never were able to accomplish in the past with minimal morbidity and harm to the patient. There is no question that radiation can be extremely harmful to living tissue. My 20+ year career can certainly attest to that. When I explain these new modalities to patients, one of the very first comments I make is that I wish I'd had these technologies available to me during the early days of my career. The number of patients treated with significant radiation morbidity, both short term and long term, in the form of bowel damage, bladder damage, lung damage, soft and bony structure damage as well as even brain damage, could have been reduced and outright avoided if I'd had these technologies available in the past. These newer modalities allow us to target tissues at risk and greatly reduce surrounding tissues that do not need to be radiated. Not only do these technologies allow us to target the cancer and spare the surrounding normal tissue, but they allow us to give even higher doses of radiation to the cancer, thus improving outcomes. Nowhere has this become more evident than in treatment of cancer of the prostate. The concept of increasing the dose of radiation (known as dose	*Thank you for your comment.* *No change to Key Questions.*

Reviewer	Comment	Disposition
	escalation) to prostate cancer has been verified in numerous clinical trials. In the past we were unable to deliver high doses of radiation to the prostate because the organ is "sandwiched" between the bowel and the bladder. " "Stereotactic body (SBRT) and stereotactic radiosurgery (SRS) are again technologies that allow us with pin-point accuracy to deliver very toxic doses of radiation therapy to cancers and eliminate surrounding tissue. One only needs to see a patient who is trying to live with radiation damage of the brain from old conventional treatments to realize the significance of these new technologies. We are now able to treat patients non-surgically for aneurysms, tremors, brain metastases and even gliomas. Patients are alive and function today because of these technologies. They certainly can be treated by more conventional means but the price is higher in side effects and long-term complications. I have seen patients harmed by conventional radiation to a much greater extent. "	
JAMES F. RAYMOND (RADIANTCARE RADIATION ONCOLOGY)		
	"We share your concerns pertaining to patient safety, effectiveness, efficiency and the rising cost of contemporary radiation treatment modalities. We have instituted a group designed to address these issues as they relate to the treatment of the patients of RadiantCare. SRS and SBRT are both extremely precise treatment modalities which can be delivered with a Linear Accelerator, Gamma Knife, or Cyberknife system. These systems are designed to precisely target tumor regions with millimeter accuracy. These treatments require intense quality assurance, measurements and monitoring during treatment since the entire dose is delivered through 1-5 treatments. This requires a significant amount of medical physicist support to ensure accuracy. We believe that the initial increased cost associated with IMRT, SBRT, and SBRT is outweighed by their long term savings due to lower costs associated with lower risk of side effects and increased clinical outcomes." • Summary KQ1 – references studies supporting role of SRS and SBRT for various cancers • Summary KQ2 – Discusses benefits of SRS and SBRT	*Thank you for comments.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	• Summary KQ3 – Discusses SRS and SBRT as beneficial options to treat an array of cancers • Summary KQ 4 – Discusses aspects of quantifying the cost effectiveness of EBRT and SRS/SBRT	
ERIC TAYLOR (EVERGREEN RADIATION ONCOLOGY)		
	"Stereotactic Radiosurgery has been used for certain brain malignancy situations as well as for some benign diseases. The clinical experience is well and heavily reported in the literature. My main concern for overuse of SRS is in the patient with brain metastases. The National Comprehensive Cancer Network guidelines (nccn.org) are clear that this technique is appropriate for patients with 1-3 brain metastases and with disease reasonably controlled or stable elsewhere...so that the cost of such treatment could be justified in well selected patients. Unfortunately, I think that there is OVERUSE of SRS and IMRT for patients with multiple brain metastases whose ultimate outcomes and lives are unfortunately very limited. The use of Stereotactic Body Radiation Therapy (SBRT) or Stereotactic Ablative Radiation Therapy (SABR) are becoming of increasing usefulness and benefit. The Japanese data for early lung cancer treatment with SBRT is excellent and from an outcome perspective is competitive with surgery. There is a current randomized trial sponsored by the American College of Surgeons and the Radiation Therapy Oncology Group comparing SBRT/SABR versus surgery. Depending on the outcomes of this study, this might support increased use of SBRT in the future. Currently, SBRT is the standard of care (National Comprehensive Cancer Network Guidelines at nccn.org) for early lung cancers in the patient that is medically inoperable. If well planned and delivered, patients tolerate this therapy very well with excellent reports from the current literature (Japan, UT Southwestern, Indiana and others)."	*Thank you for your comment.*
TUMOR INSTITUTE RADIATION ONCOLOGY GROUP		
	"As experts in the field of Radiation Oncology, we embrace your concerns regarding safety, efficacy, and cost of contemporary radiation modalities. Technologies such as IMRT, SRS, and SBRT have broken new ground in their capability to control cancer	*Thank you for your comment.* *No change to Key Questions.*

Reviewer	Comment	Disposition
	and minimize side effects. Our goal is to help educate health providers and healthcare payers, as well as government, business, and other professionals as to the patients for whom use of these newer technologies can mean a world of difference in regard to cancer control and a decreased risk of treatment related side effects. The utility of IMRT, SRS, and SBRT in many circumstances is very specifically dependent on a patient's cancer, their anatomy, the proximity of critical structures, and prior radiation dose delivered. The key aspects that all these modalities have in common is better dose distributions: escalated doses to tumors, lower doses (and lower resultant toxicity) to normal tissue. Using IMRT, SRS, and SBRT, it is now potentially feasible to deliver safe curative or safe palliative treatment to many patients where treatment was not even an option with conventional external beam radiation therapy. For example, in cases where tumors recur in a previously irradiated field, re-irradiation with IMRT, SRS, or SBRT may deliver a long term cure that was not previously possible. We realize that a circumstance such as this is not one in which a comparative trial could be conducted, for most of these patients simply would not be a candidate for treatment with a conventional external beam radiation therapy approach. We believe that it is imperative to be able to offer these treatments to patients in an expedient time frame when indicated. We remain readily available and encourage an open dialogue on these topics. We have tried our best given the short comment period to address your questions regard SBRT and SRS. Although there are increased costs associated with newer technologies such as IMRT, SRS, and SBRT, their effectiveness and lower risk for side effects demonstrates long term cost savings. As well, the relevant key comparison is often IMRT, SRS, or SBRT in comparison to other different modalities of treatment, such as surgery, or radiofrequency ablation (rather than to conventional external beam irradiation). For example, there was a publication a few months ago comparing the cost effectiveness, quality of life and safety for medically inoperable lung cancer patients. The study compared conventional radiation, SBRT, and radiofrequency ablation. SBRT was by far the most effective and cost effective treatment, even though it may	

Reviewer	Comment	Disposition
	have the highest upfront direct cost (reference: [1] Sher, Wee and Punglia, **Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer**. Journal/Int J Radiat Oncol Biol Phys, 81, e767-74, 2011). Given the extraordinarily short time period for comment, we have done our best to summarize responses to the four key questions of the Washington State Healthcare Authority with regard to SRS, and SBRT in comparison to conventional (conformal) external beam therapy (EBRT). We must emphasize, though, while there are many well done peer reviewed studies from top academic institutions pertinent to IMRT, SRS and SBRT, and in some cases there are head-to-head comparisons which demonstrate the benefits of this technology, the short response timeframe created by your March 6th deadline, which apparently is not negotiable, does not allow adequate time to research. Therefore, we want to be sure the Washington State Healthcare Authority and its staff are advised that we believe the key questions posed for SRS, SBRT and IMRT are extensive and a more complete level of detail is not possible to produce within the time frame allotted."	
	Summary – KQ 1 • Discusses the use of IMRT and SBRT for the treatment of prostate cancer • Discusses use of SRS/SBRT for the treatment of head and neck cancer • Discusses use of SRS/SBRT for the treatment of central nervous system/spine cancer • Discusses the use of SBRT for the treatment of gastrointestinal/pancreatic cancers • Discusses the use of SBRT for gastrointestinal/liver metastases • Discusses the use of SBRT for gastrointestinal/primary liver cancers • Discusses the use of SBRT for lung cancers • Discusses the effectiveness and safety of SBRT for re-irradiation Summary – KQ2 • Discusses the safety and harms of SRS and SBRT	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*

Reviewer	Comment	Disposition
	Summary – KQ3 • Refers to KQ1 and KQ2 Summary – KQ4 • Discusses the cost and cost-effectiveness of SRS, SBRT, IMRT, and EBRT	
UNIVERSITY OF WASHINGTON MEDICINE / SEATTLE CANCER CARE ALLIANCE DEPARTMENT OF RADIATION ONCOLOGY AND UW DEPARTMENT OF NEUROLOGICAL SURGERY		
	Summary KQ1. • Provides an overview of the effectiveness of stereotactic radiosurgery • Discusses the benefit of SRS/SBRT for a range of cancers Summary KQ2. • Discusses the risks of permanent neurological deficit in using SRS/SBRT for a range of cancers Summary KQ3. • Discusses the safety and efficacy concerns for SRS/SBRT Summary KQ4. • Discusses cost and cost-effectiveness of SRS/SBRT compared with conventional surgery, resection, and EBRT	*Thank you for your comment.* *All references forwared to TAC.* *These studies provide evidence. No changes to Key Questions.*
US TOO INTERNATIONAL		
Pamela Barrett	"In response to your recent request to concerned stakeholders to submit comments as part of your upcoming review of stereotactic radiosurgery and stereotactic body radiation therapy (SBRT), we prostate cancer survivors in the Us TOO International Prostate Cancer Education & Support Network encourage the Washington State Health Care Authority add prostate cancer as a diagnosis that is eligible for coverage under its SBRT policy."	*Thank you for your comment.* *No changes to Key Questions.*

Reviewer	Comment	Disposition
Thomas N. Kirk	"We believe that men who happen to live in Washington state and have Medicare medical coverage should not be denied access to SBRT (stereotactic body radiation therapy) treatment. We feel that it is Medicare's obligation to provide coverage for all medical treatments that have shown to improve the lives of prostate cancer patients. SBRT, a more recent form of radiation therapy, has been used to treat prostate cancer since 2001. Data suggests that this treatment is as effective as conventional treatments such as HDR brachytherapy, alternative external beam radiation techniques, and surgery. Due to the unique nature of prostate cancer, we do not believe there is not a "one size fits all" treatment for this disease. However, it is our opinion that patients should be afforded the opportunity to select a therapy that both he and his health care provider feel will provide the best possible outcomes. This requires that all clinically appropriate treatment options be eligible for coverage under the Medicare program. We request that the Washington State Health Care Authority add prostate cancer as a diagnosis that is eligible for coverage under its SBRT policy. By providing coverage for this treatment, the state of Washington will provide hope to thousands of men and their families who suffer from this disease."	*Thank you for your comment.* *The Washington Health Technology Assessment program addresses health care services provided by state government, not Medicare, which is a federal program.* *No changes to Key Questions.*
VARIAN MEDICAL SYSTEMS		
	Summary KQ1. • Summarized evidence supporting the effectiveness of SRS and SBRT Summary KQ2. • Summarized evidence supporting the benefits, safety, and efficacy of SRS and SBRT Summary KQ4. • Summarized studies discussing the cost-effectiveness of SRS and SBRT	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*

Reviewer	Comment	Disposition
SANDRA VERNEULEN (SWEDISH RADIOSURGERY CENTER)		
	Summary – Acoustic Neuroma • Provided a summary of clinical results from Gamma Knife radiosurgery in relation to tumor growth control, hearing preservation, facial nerve and trigeminal nerve preservation, neurofibromatosis 2, and clinical algorithm for decision making. Summary – Trigeminal Neuralgia • Discusses the efficacy of Gamma Knife stereotactic radiosurgery for trigeminal neuralgia, and provides factors to consider in making a recommendation for Gamma Knife stereotactic radiosurgery. Summary – Pituitary Adenoma • Discusses the applicability of stereotactic radiosurgery for pituitary adenoma and tumor growth control after radiosurgery for this condition • Discusses the function effect of radiosurgery (e.g., growth hormone secreting adenomas (acromegaly), ACTH secreting adenomas, prolactin secreating adenomas), radiation tolerance of functioning pituitary tissue, complications of pituitary radiosurgery, clinical algorithms for decision making, and fractionated radiation theraby (EBRT) Summary – Intra-cranial Ateriovenous Malformations • Discusses the use of stereotactic radiosurgery for patients with unresectable AVMs including the probability of AVM obliteration with radiosurgery, early adverse effects of radiosurgery, late complication after AVM radiosurgery, and factors to be considered in making a recommendation for stereotactic radiosurgery for AVM Summary – Brain Metastases • Discusses the role of radiosurgery for brain metastases including retrospective studies showing support for SRS, local tumor control, survival, the role of SRS for multiple brain metastases, indications for radiosurgery, and a clinical decision making algorithm that includes tumor size and patient preference. Summary – Meningiomas	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*

Reviewer	Comment	Disposition
	• Discusses long-term outcomes of meningioma after radiosurgery, the use of radiosurgery for malignant meningioma, the use of radiosurgery with cavernous sinus meningiomas, and early complication of radiosurgery for meningiomas. Summary – SRS Thalamotomy for Tremor • Discusses radiofrequency and radiosurgical thalamotomy to treat tremors Summary – Gliomas • Discusses the use of EBRT and Gamma Knife for patients with gliomas	
VIRGINIA MASON MEDICAL CENTER		
	Summary – Stereotactic Radiosurgery / Stereotactic Radiation Therapy • Discusses the evidence for the effectiveness, safety, modes of delivery. of stereotactic radiosurgery • Discusses the use of SRS for specific conditions such as AVMs, acoustic neuromas, meningiomas, brain metastases, nonfunctioning pituitary adenomas, malignant gliomas, and trigeminal neuralgia. • Discusses the effectiveness of stereotactic body radiation therapy • Discusses the uses for SBRT for specific conditions including small peripheral lung cancers, early stage prostate cancer, spine/vertebral body tumors, and liver tumors.	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to Key Questions*

Full Public Comments

AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS (AANS) AND THE CONGRESS OF NEUROLOGICAL SURGEONS (CNS)

AMERICAN ASSOCIATION OF
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American Association of Neurological Surgeons

CONGRESS OF
NEUROLOGICAL SURGEONS
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President
CHRISTOPHER E. WOLFLA, MD
Milwaukee, Wisconsin

July 2, 2012

Josh Morse, MPH
Program Director, Health Technology Assessment
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712
E-Mail: Josh.Morse@hca.wa.gov

Subject: Revised Key Questions for Health Technology Assessment of Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiotherapy (SBRT)

Dear Mr. Morse,

The American Association of Neurological Surgeons (AANS), and the Congress of Neurological Surgeons (CNS), would like to thank you and the Washington State Health Care Authority for the opportunity to provide comment on the revised technology assessment questions for the Washington State Health Care Authority Health Technology Clinical Committee consideration of Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiotherapy (SBRT). The AANS and CNS have been actively involved in policy issues surrounding SRS and are eager to work with you to provide appropriate guidance and evidence assessment regarding the efficacy, safety, and cost effectiveness of SRS for selected patients with brain and spine disorders. Neurosurgeons have extensive experience and literature from over 40 years, since a neurosurgeon first introduced SRS care in the United States.

We are concerned that some of the key questions in the *"DRAFT Key Questions and Background Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy"* are very general and we are eager to provide more specific details in response to the draft technical assessment expected on July 6, 2012.

KQ1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy compared to conventional external beam radiation therapy (EBRT) for the following patients:

a. Patients with central nervous system (CNS) tumors;

   AANS/CNS Comment: Stereotactic radiosurgery (SRS) has been shown to offer a high rate of tumor control and an excellent chance of neurological preservation for many patients with select primary central nervous system tumors, vascular malformations, and functional disorders. Levels of evidence range from Class II to Class V (references below).

b. Patients with non-central nervous system cancers?
   AANS/CNS Comment: The same is true for SRS for non-CNS tumors that have spread to the brain. In particular, SRS has been used Class I through Class V evidence for the safe and effective treatment of patients with brain metastases (references below).

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KATIE O. ORRICO, *Director*
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KQ2: What are the potential harms of SRS and SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.

AANS/CNS Comment: SRS and EBRT are forms of ionizing radiation, and share the potential for a similar range of side effects. In appropriately selected patients and with careful delivery of SRS, the incidence of serious and irreversible side effects for most indications is under 5%. When weighed against treatment alternatives for benign and malignant CNS tumors, functional disorders, and vascular malformations, the risks of SRS are typically lower than that of other options and certainly of progression or persistence of the CNS pathology. In particular for brain metastases and skull base tumors, SRS has been shown to offer a better chance of neurological and neurocognitive preservation than external beam radiotherapy (EBRT) or surgical resection for select cohorts of patients (Chang et al., 2009; Tooze et al., 2011; Ivan et al., 2011).

KQ3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in sub populations? Including consideration of:

a. Gender

AANS/CNS Comment: There is no appreciable effect of gender on SRS outcomes (references below).

b. Age

AANS/CNS Comment: Age has been shown to be a factor in survival of brain metastasis patients after SRS. Age is an important factor in RPA, GPA, and disease specific GPA indices for brain metastases patient outcomes after SRS (Sperduto et al.., 2008; Andrews et al., 2004). For nonmalignant pathologies SRS indications, age can be a favorable prognostic factor for SRS outcomes compared to open surgery or EBRT (Regis et al., 2006; Williams et al., 2011; Dewas et al., 2011).

c. Site and type of cancer; and
d. Stage and grade of cancer

AANS/CNS Comment: Parts c. and d. of Key question 3 are more relevant to body SBRT, and are not considered a significant factor in the evidence of CNS disease.

e. Setting, provider characteristics, equipment, quality assurance standards and procedures.

AANS/CNS Comment: This is a difficult question to answer. In general, outcomes with SRS have not been shown to be device specific. However, they are likely related to SRS team experience, neurosurgeon's technique, and volume (Koga et al., 2011; Kondziolka et al., 1999).

KQ4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

AANS/CNS Comment: When appropriately indicated, SRS has been found to be cost effective for patients with brain metastases, spinal metastases, and skull base tumors (Haley et al., 2011; Lal et al., 2012; Banerjee et al., 2008; Rutigliano et al., 1995; Park et al., 2011).

Again, thank you for this opportunity to comment and we look forward to the release of the draft report. If you have any questions, please feel free to contact us.

Sincerely,

Joseph Cheng, MD, Chair
AANS/CNS Joint Section Joint Section on Disorders of the Spine and Peripheral Nerves
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References

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AMERICAN COLLEGE OF RADIATION ONCOLOGY (ACRO)

From: Jason Mckitrick
To: HCA ST Health Tech Assessment Prog
Cc: Andrew Woods; Morse, Josiah (HCA)
Subject: ACRO Comment Letter to Mr. Josh Morse (WSHCA HTA) Regarding Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy, and Intensity Modulated Radiation Therapy Technology Assessment Key Questions
Date: Tuesday, March 06, 2012 12:26:38 PM
Attachments: Comment Letter to Mr. Josh Morse (WSHCA Health Technology Assessment) 3-6-2012.pdf
Importance: High

Dear Mr. Morse,

Attached please find the comment letter submitted on behalf of the American College of Radiation Oncology for **Stereotactic Radiation Surgery, Stereotactic Body Radiation Therapy, and Intensity Modulated Radiation Therapy Technology Assessment Key Questions**.

Please let me know if you have any questions.

Thank you.
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March 6, 2012

Josh Morse, MPH
Program Director
Washington State Health Care Authority
Health Technology Assessment
P.O. Box 42712
Olympia, Washington 98504-2712

Re: Stereotactic Radiation Surgery, Stereotactic Body Radiation Therapy, and Intensity Modulated Radiation Therapy Technology Assessment Key Questions

Dear Mr. Morse:

The American College of Radiation Oncology (ACRO) appreciates the opportunity to offer its comments to the Washington State Health Care Authority (WSHCA) draft Technology Assessment Key Questions on the topics of Stereotactic Radiation Surgery (SRS), Stereotactic Body Radiation Therapy (SBRT), and Intensity Modulated Radiation Therapy (IMRT). ACRO represents radiation oncologists in the socioeconomic and political arenas. With a current membership of approximately 1,000, ACRO is dedicated to fostering radiation oncology education and science; improving patient care services; studying the socioeconomic aspects of the practice of radiation oncology; and encouraging education in radiation oncology.

ACRO received notice of the key questions on February 22, 2012 and we understand the deadline for comments is March 6, 2012. Full and appropriate comments to these questions requires months of preparation. Unfortunately, the short time frame within which to answer these questions does not allow for a direct detailed, and fully documented response.

However, ACRO can provide the following more general comments within the allotted time frame:

- The issues surrounding choices of radiation-emitting modalities, (e.g. IMRT) are usually based on physical (physics) data and empirical observations, rather than randomized controlled clinical trials. The US Food and Drug Administration does not require such Level I data for device approval, and once devices are approved and marketed, there is little ability to complete those trials. Proposals to payers to assist in implementing trials, as with *Coverage with Evidence Development*, have been shunned, and patients (and IRBs) will rarely if ever accept randomization to trials where the only presumed differences are related to morbidity.

- As a delivery system widely available since 1998 (when the CPT© codes and RVUs were established), IMRT has been shown in every and innumerable instances measured, to reduce morbidity to the adjacent organs at risk in proximity to target tumor volumes. In instances where this morbidity-reduction has been used to permit an increase in radiation dose to tumors (e.g. prostate, head/neck, central nervous system, liver, etc.), a concomitant increase in local control has also been demonstrated. Regrettably, in radiation oncology, unlike drug development, since long-term control or cure is often the determinant end-point, years may be required to define the parameters, so physical data and morbidity reduction MUST be used as surrogates. Randomized device trials also require a large installed base of the devices, which is also impractical. Alternatively, drug studies may provide actionable (albeit often non-clinically relevant) information in weeks to months, at minimal cost, since the primary end-points are more often simply measurement of some surrogate tumor marker or interval free from progression..

- There is clear and increasing evidence that in certain circumstances, SBRT and SRS may be equivalent and/or preferable to conventional fractionated and protracted radiation. SBRT and SRS, unlike IMRT, relate to "biology" and not "technology," in that they merely represent the delivery of high-dose, short-course radiation (5 or fewer treatments, rather than daily, protracted, lower-dose, longer-course therapies). Evidence mounts that numerous sites, including brain, spinal cord, liver, and lung, as well as other emerging indications, are appropriately treated by SRS (for central nervous system) and SBRT (for non-central nervous system).

We understand that the American Society for Radiation Oncology (ASTRO) has included its own model coverage policies on SRS, SBRT and IMRT for your review that outline specific technology of each treatment, clinical indications, coding considerations and references. ACRO supports your review of these materials and their conclusions. We also are aware that physicians with the Swedish Medical Center are submitting information regarding studies that have been performed relating to SRS, SBRT and IMRT. We would encourage the committee to review these in detail.

We appreciate your consideration of our comments and look forward to reviewing the WSHCA's draft report. Should you have any questions, please contact Jason McKitrick, ACRO Economics Committee consultant, at (202) 442-3754.

Sincerely,

Sheila Rege, MD, FASTRO, FACRO
Chair, Economics Committee
American College of Radiation Oncology
5272 River Road
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AMERICAN SOCIETY OF RADIATION ONCOLOGY (ASTRO)

From: Marsha Kaufman
To: HCA ST Health Tech Assessment Prog
Cc: Patton, Gregory A (Gregory.Patton@USOncology.com); Michael Dzeda; Thomas Eichler, M.D. (thomas.eichler@hcahealthcare.com); Joel Cherlow, M.D., Ph.D. (jcherlow@memorialcare.org); Najeeb Mohideen; Brian Kavanagh, M.D. (brian.kavanagh@uchsc.edu); Daneen Grooms; Crystal Carter
Subject: ASTRO comment letter - SRS, SBRT and IMRT Key Questions
Date: Monday, March 05, 2012 9:43:14 AM
Attachments: SRS-SBRT-IMRT KeyQCommentLtr FINAL3-5-12.pdf
SRSModelPolicyFINAL 7-25-11.pdf
SBRT2010 FINAL 11-17-10.pdf
ASTRO IMRT Model FINAL 05.09.07-with disclaimer.pdf

Good afternoon Mr. Morse. Please find attached the American Society for Radiation Oncology's (ASTRO) comment letter on the key questions related to the technologies of Stereotactic Radiation Surgery (SRS), Stereotactic Body Radiation Therapy (SBRT) and Intensity Modulated RadiationTherapy (IMRT). As indicated in our letter, attached are copies of the ASTRO Model Policies on SRS, SBRT and IMRT.

Thank you for your consideration and please do not hesitate to contact me should you have any questions.

Regards,
Marsha Kaufman
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ASTRO

TARGETING CANCER CARE

March 5, 2012

Josh Morse, MPH
Program Director
Washington State Health Care Authority
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P.O. Box 42712
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BY ELECTRONIC SUBMISSION to shtap@hca.wa.gov

Re: Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy, and Intensity Modulated Radiation Therapy Technology Assessment Key Questions

Dear Mr. Morse:

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 draft Technology Assessment Key Questions on the topics of Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT), and Intensity Modulated Radiation Therapy (IMRT). ASTRO received notice of the Key Questions on February 22, 2012 and we understand the deadline for comments is March 6, 2012. The Key Questions posed for SRS, SBRT and IMRT are extensive and ask for a level of detail that we cannot produce within the time frame allotted. The information requested for all three technologies, specifically comparisons to external beam radiation therapy (benefits and harms), and differential efficacy or safety issues in subpopulations including consideration of gender, age, site and type of cancer, stage and grade of cancer and setting, provider characteristics, equipment, quality assurance standards and procedures, constitutes a full research study that would take many months to produce. While ASTRO believes these technologies offer clear benefits to many of the cancer patients our members treat, we would require significantly more time to adequately address the important issues raised in the Key Questions.

ASTRO plans on reviewing the draft report that will be produced as a result of the public comment period and we look forward to reviewing this report in early July. We have noted that the Health Technology Clinical Committee that will be reviewing the technology assessment reports and making coverage decisions does not include a radiation oncologist and we strongly recommend that a radiation oncologist be added to this committee.

In anticipation of the more detailed comments that we will submit in response to the draft report, we offer a general observation relating to the fundamental basis of some of our positions about IMRT in particular. During the past two decades, an abundant number of clinical studies have characterized the relationship between the dose given to various normal tissues using 3D EBRT

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and the risk of toxicity to those tissues. There are recognized dose thresholds known to relate to the risk of toxicity for bowel, bladder, spinal cord, and other important organs. Whereas IMRT offers the capacity to avoid exceeding those recognized thresholds for toxicity, it is considered an appropriate standard for numerous indications as a result of this property. The field of radiation oncology has not considered it ethical or resource-efficient to conduct head-to-head comparisons of 3D EBRT vs. IMRT in all settings where a clear improvement in a surrogate measure of toxicity risk is easily demonstrated.

We have included ASTRO's model coverage policies on SRS, SBRT and IMRT for your review that outline the specific technology of each treatment, clinical indications, coding considerations and references.

We appreciate your consideration of this material and look forward to the draft report. Should you have any questions please contact Marsha Kaufman, Director of Health Policy, at 703-839-7374 or marshak@astro.org.

Sincerely,

Gregory Patton, MD
Chair, Regulatory Committee

Michael Dzeda, MD
Vice Chair, Regulatory Committee

Enclosure: ASTRO SRS Model Policy
ASTRO SBRT Model Policy
ASTRO IMRT Model Policy

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

JEANNE R. BERRY

From: jrberry719@aol.com
To: HCA ST Health Tech Assessment Prog; JRBerry719@aol.com
Subject: Prostate Cancer SRS/SBRT patient information
Date: Saturday, March 03, 2012 5:28:09 PM
Attachments: Cyberknife testimony (Autosaved).docx

My husband is "down under" traveling for a month, so he asked me to share our story with his journey through Prostate Cancer. I will join him next week. We believe it is important for anyone that is making decisions regarding treatment to hear the journey of "real folks" who have had treatment.

If there is any other information needed, I can be texted at 206 793 3200 or will be back in the country 4/3.

Thanks for your kind attention.

Jeanne R. Berry

March, 2012

To Whom It May Concern,

As the Mayor of a town in Washington State for 8 years, I know the importance of our government getting information from the public about decisions that are being faced. I hope to share my journey to let you know why SRS/SBRT needs to be supported by my government. Usually comments from the end users (no pun intended) are important for decision makers.

Last fall, my husband of 37 years needed to have ankle replacement surgery. During his presurgery checkup, he was given a complete physical review. At 68 years of age, he was in excellent health, and has been very active in his retirement of five years, though he had an orthopedic challenge.

The physical performed found his PSA abnormal, so he was referred to his Urologist, who immediately performed a biopsy. We soon got some difficult news ,my husband had Prostate Cancer, his Gleeson score was six, yet was scheduled for the ankle replacement surgery the very next week. We learned that his cancer was slow growing, so while his ankle was healing for 5 months, we turned our energies turned to understanding all we could about Prostate cancer.

For 62 years, I was a WA resident, now retired and living in central Oregon , so being far from major medical support was a challenge. We researched the entire West Coast, for information about Prostate Cancer treatments. Our myriad layers of concern and confusion were significant, but information about cancer treatments was essential.

There is very little that frighten me more that “your husband has cancer”, followed by the words “right now all we can do is watchful waiting”. For the next few months healing from ankle replacement, my highly educated scientist husband began a research inquiry process that was second to none. The side effects he studied about Prostate Cancer treatments involving surgery, proton therapy, cryogenic therapy, and external beam, and IMRT were clearly going to limit the life style that we had shared. We could not find any data on SRS/SBRT on the internet. Bear in mind, husband is a man who had snowboarded one million vertical miles in 70 trips to the mountains the previous winter. Incontinence, rectal bleeding, lack of sexual function were certainly not in his retirement plan. We are folks in charge of our health, and take all precautions to enjoy a long and healthy retirement. My knowledge of “Man Land” increased exponentially.

As his ankle healed, my husband continued his research. We flew to Seattle and interviewed the physicians at Swedish Hospital, we interviewed in depth with the team at Loma Linda in CA, and other oncologists and urologist and Oncologists at U of WA hospital. We talked with Urologists in Portland, at Stanford, and went to myriad websites worldwide.

Then, a friend of his mentioned that he had completed treatment with Cyberknife (or SRS/SBRT) for Prostate Cancer in Seattle. My husband poured over all the studies and research on Cyberknife (SRS/SBRT), and found the five days of treatment to be compelling, and so much more humane. Also, the accuracy this form of treatment was so clearly evident with all the data and literature, and the ability to correct the appropriate direction of radiation at the cancer in real time seemed much more appropriate than other methods that may miss the area needed to get rid of cancer. If we had gone to CA for their protocol at Loma Linda (proton therapy), we would have had to move to California, and two months living in another state is challenging to a fixed income, so we ruled out Loma Linda. Our primary oncologist walked us through the entire process, and is maintaining health checkups in central Oregon.

We decided to undertake the 5 day, one hour treatments with the most positive outcomes and that was at Swedish Hospital in Seattle. Finally, we had clear direction, and renewed hope that his cancer might be eliminated.

Our trip to Seattle, in late January 2011, for the Cyberknife SRS/SBRT treatment, was exactly as outlined by the Swedish Oncology team. My husband went through the process with **no** unexpected side effects from the Prostate Cancer treatment, though he had a short time (10 day) challenge of urinary flow, which did not affect his daily activities, post procedure. He experienced no sexual challenges, or rectal problems. In a short time, he was on the golf course and at the gym working out, doing spin classes and weight lifting 10 times a week. In the past year, his PSA is back down to a low level, and he has had absolutely no complications.

We have been so impressed with the SRS/SBRT treatment process, that we invited his Oncologis to come to Central Oregon to speak about the research to interested people . Thinking that a half dozen folks would appear, we were surprised to have 100 attend on a Thursday night with only word of mouth advertising. The men and women were deeply interested in the Cyberknife SRS/SBRT therapy. Attending this seminar were many physicians, health care professional s and just normal folks trying to understand treatment options for Prostate Cancer, which are complex and highly confusing. Prostate cancer is on the minds of so many folks we know, and my husband is asked weekly about his treatment process.

In my mind, limiting access to Cyberknife SRS/SBRT due to government intervention is terribly short sighted, and would be very economically bad. Why should anyone be afforded less than the best therapy? My husband inquired about how much each therapy would cost, and Cyberknife SRS/SBRT was the cheapest, least invasive and quickest process, so that is what we chose this treatment. If an arbitrary decision to take away this absolutely positive procedure was enacted, we still would have had the SRS/SBRT treatment that we underwent. The benefits are excellent, the outcome positive. To us, all other choices were archaic and outdated in comparison. After supporting our government with both of us working and paying into the Medicare system for five decades, it would have been criminal to be denied access to appropriate treatment. To have our government fund much more expensive machinery and process is exactly the wrong direction for the leadership of Medicare to follow, especially in a 10 state area, where it has been supported by Medicare funding previously. My analogy would be “I have a smart phone that makes life work very well for me…why should I accept the “BRICK” as a phone because a government agency made an arbitrary administrative decision”? We need the support of Medicare for prostate cancer. Thank you for your kind attention, Jeanne R. Berry

From: Carlson, Thomas MD
To: HCA ST Health Tech Assessment Prog
Subject: Public Comment for: Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy
Date: Monday, March 05, 2012 11:22:53 AM

Members of the Health Technology Committee,

I appreciate the work you do in recognizing the need to evaluate new technologies and the implementation of these technologies in the health care sector.
I am concerned with respect to the path we have been going down regarding the complexity of reimbursement evaluation. We seem to be reimbursing physicians based on the tools they are using to accomplish a task as opposed to the task itself. In the case of IMRT, Stereotactic Radiosurgery (in the brain or body) or brachytherapy, we are reimbursing based on the tool. Do we reimburse a surgeon for using one scalpel blade over another? No. The surgeon chooses what's most appropriate for the situation and is paid for the job. I believe a tremendous amount of waste could be removed from the system if a case rate reimbursement model was initiated.

Thomas Carlson, MD
Department of Radiation Oncology
Wenatchee Valley Medical Center

SUBJECT: Comments regarding SRS and SBRT
FROM: John.Rieke@multicare.org
TO: shtap@hca.wa.gov
CC: John.Rieke@multicare.org
SENT: Mon 05 Mar 2012 22:30:54 PST
EXPIRES: Fri 04 May 2012 22:30:54 PDT

I am pleased to offer these comments regarding SBRT and SRS per your request. A letter is attached. Please feel free to call with questions anytime; my office phone is 253-403-4994, and my cell phone is 206-920-3469.

I was asked to review the material you received from Dr. Barnett of TIROG in Seattle regarding IMRT. I support the submittal completely. I think it represents mainstream thinking of radiation oncologists across the state.

I understand there will be a chance to discuss your report due out later this year, at a meeting September 21, 2012. Please add me to relevant mailing list. I have been asked to represent the ASTRO, our national radiation oncology/biology/physics professional society in your proceedings.

Best wishes,

John W. Rieke, MD, FACR
Medical Director
MultiCare Regional Cancer Center
Tacoma, WA

_____

MULTICARE'S SHARED VALUES | Respect | Integrity | Stewardship | Excellence | Collaboration | Kindness

Mailgate1.multicare.org made the following annotations

CYBERKNIFE®
CKC
COALITION

March 6, 2012

The CyberKnife© Coalition (CKC) writes in response to the call for public comments on the Washington State Health Care Authority, HTA Program, "Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy" Health Technology Assessment.

About the CyberKnife Coalition

Formed in 2003 and incorporated in 2005, the CKC is a non-profit association of hospitals and freestanding centers across the United States committed to improving patient access to image-guided robotic stereotactic radiosurgery as a treatment option for cancer patients. In addition to the numerous community hospitals and clinics that belong to the CKC, our membership also includes major academic institutions and premiere cancer centers such as Stanford Hospital and Clinics, Georgetown University Medical Center, Baylor Healthcare System, and University Hospitals-Case Medical Center. All of our members offer image-guided robotic stereotactic radiosurgery to treat malignant and benign tumors and other select disorders with high dose, precisely targeted radiation.

Since 2003, the CKC has supported efforts to collect and develop data demonstrating the therapeutic, quality of life, and economic benefits of CyberKnife treatments and has worked collaboratively with payers to ensure appropriate patient access. Over 100,000 patients worldwide have been treated with CyberKnife since it received approval in 1996 in Japan and in 1999 from the United States Food and Drug Administration (FDA).

Background information:

For more than 30 years, traditional radiosurgery (e.g. Gamma Knife) has been used primarily to destroy brain tumors. While the Gamma Knife is an extremely effective neurosurgery device, it is limited in its clinical application to only treat intracranial and upper spinal lesions. This limitation is due to its inability to track for motion, which necessitated application of a rigid head frame screwed into the patient's skull for immobilization.

The CyberKnife Robotic Radiosurgery System built on the principles of Gamma Knife radiosurgery and was developed to extend radiosurgical treatments to lesions and tumors anywhere in the body. When used to treat intracranial and upper spinal lesions, the CyberKnife and Gamma Knife are similar in that they deliver non-coplanar treatment – meaning they are able to deliver beams from multiple angles to converge or "cross fire" on tumors and ablate them. Both are excellent tools for delivering single fraction radiosurgical treatments. However, unlike the Gamma Knife which is only able to deliver treatment in a single session, or "fraction", to tumors inside the skull or upper spine, the CyberKnife is able to deliver treatment over multiple sessions and can treat tumors throughout the body. This makes the CyberKnife a more useful device in terms of clinical application and utility.

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Whether used for intracranial or extracranial radiosurgery, the CyberKnife differs from other linear accelerators in that it is the only **robotic** radiosurgery system in existence today. The use of the word "robotic" in "image-guided robotic stereotactic radiosurgery" refers to a non-gantry based[3] autonomous device that has the ability to sense its own environment, evaluate it, and take independent action based on the results of its analysis. The CyberKnife does this by combining a compact linear accelerator, mounted on a robotic arm, with a high speed computer to process *continuous* X-ray images and then uses that information to *continuously* respond to changes in tumor and patient movement by correcting its position and then delivering the radiation to the new target location. Due to its robotic mobility and real-time image guidance capabilities, the CyberKnife System is able ensure the safe and extremely accurate delivery of hundreds of radiation beams, delivered from as many as 1,600 unique angles. In other words, the treatment is multi-dimensionally delivered from any point in space based on information it obtains on an ongoing basis. All of these characteristics result in precise delivery of radiation with little exposure to healthy surrounding tissue.

Treatment with CyberKnife is non-invasive, does not require anesthesia, and, unlike other forms of external beam radiation treatment, is a potentially curative treatment option for operable and inoperable patients alike. Due to its pinpoint treatment accuracy, CyberKnife can safely deliver extremely high doses of radiation to the tumor, facilitating a significantly shorter course of treatment than other forms of radiation treatment, while sparing surrounding healthy tissue. For cancer patients who cannot be cured and for whom prolonged courses of radiation treatment are not feasible or practical, the CyberKnife may be used to improve local control rates and quality of life.

In contrast, *non-robotic*, gantry-based systems (e.g. C-arm systems) can be used to deliver radiosurgical doses, but can only deliver radiation along a single plane. This is due to their fixed position that allows the linear accelerator to only be tilted left or right on a fixed pivot. If image-guidance is used, it is used to guide patient set-up but is not generally done during treatment. If it is used during treatment (e.g. through the use of beacons) a therapist has to stop treatment as the targeted area moves away from the radiation beam and reposition the patient, which is an inefficient approach compared to robotic radiosurgery. For patients whose tumors move widely, a therapist might program a larger threshold for movement (e.g. tumor moving from 2 mm to 4 cm) to limit the number of times the treatment must be stopped to reposition the patient (otherwise the treatment would be very prolonged). This results in less accurate delivery of the radiation to the target and increases the exposure to healthy surrounding tissue and critical structures.

From a patient perspective, the CyberKnife provides an option for treatment that is significantly shorter (≤ 5 treatments compared to 20-45 treatments depending on the indication), thus allowing patients to spend more time with family, with less interruption on work schedules, and resume their normal daily lives as quickly as possible.

Key questions

KQ1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy compared to conventional external beam radiation therapy (EBRT) for the following patients:

a. Patients with central nervous system (CNS) tumors?

b. Patients with non-central nervous system cancers?

a. CyberKnife is commonly used to treat patients diagnosed with well demarcated central nervous system (CNS) tumors, generally 5 cm or less in volume – in both the brain and in the spine. Examples of the types of tumors appropriate for CyberKnife radiosurgery include primary central nervous system malignancies, primary and secondary tumors involving the brain or spine parenchyma, meninges/dura, meningiomas, pituitary adenomas, pineal cytomas, cranial arteriovenous malformations, hemangiomas, and movement disorders (e.g. essential tremor) that are refractory to conventional therapy, including trigeminal neuralgia. CyberKnife is also extremely well suited to treat tumors that require "fractionated treatment" (dividing the dose into two or more treatment sessions) such as those located near the optic chasm or inner ear which benefit from a more gentle approach than what can be delivered via the highly destructive single session SRS of the Gamma Knife. A fractionated approach, using the

[3] CMS Robotic Definition: Transmittal 1139 of the CMS Manual System Pub 100-04 Medicare Claims Processing (12/22/2006)

CyberKnife to treat acoustic neuromas and tumors around the optic chasm, is extremely important for the preservation of hearing and sight. Clinical data have demonstrated a substantial benefit to patients using this approach.[4]

External beam radiation therapy (EBRT) is appropriate for the treatment of different patient population including patients with widespread disease and ill defined tumors with microscopic extension. Such as patients are not candidates for SRS and are typically treated with whole brain irradiation. Therefore it is not appropriate to compare SRS with EBRT for most indications as the patient populations are different. As we have pointed out, because CyberKnife and EBRT are used to treat different types of brain tumors, it is difficult to produce a true "apples to apples" comparison for intracranial tumors. For extracranial, spinal tumors, however, data do exist since prior the advent of CyberKnife, radiosurgery was not physically possible in this patient population due to limitations of the rigid frame that was affixed to patient's skulls for Gamma Knife radiosurgery.

The table below shows comparative data of CyberKnife SRS for spinal tumors vs. EBRT. As the table illustrates, significant clinical benefit is achieved with CyberKnife radiosurgery for all three measures of local control, acute toxicity, and survival.

According to Martin et al (2010)[5], conventional EBRT is used in the management of spinal metastases, for local control, palliation of pain, and treatment of spinal cord compression. However, the EBRT prescribed doses are limited by radiation tolerance of the spinal cord and spinal nerves. The steep dose falloff seen with CyberKnife SRS allows the delivery of a higher, more effective cell killing dose to the tumor, while staying within cord tolerance. Compared to EBRT, CyberKnife treatment results in significant improvements in long-term tumor control, acute toxicity, and survival (noted in table below). CyberKnife is also an excellent tool for the management of debilitating spinal pain.

Gerszten PC, Burton SA, Ozhasoglu C, et al. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. Spine 2007;32:193-199. **Comparison of Conventional EBRT vs. CyberKnife Clinical Outcomes for Spine**[6]		
Conventional EBRT		***CyberKnife***
Local control	65%	92-100%
Acute toxicity	56%	39%
2-year survival	17%	56%
Long-term pain relief	N/A	86%

b. While the CyberKnife has been used interchangeably by many neurosurgeons and radiation oncologists for years to perform SRS on intracranial tumors, it is the unique motion management,
tracking, and real-time adjustment capabilities that gave rise to the adoption of CyberKnife radiosurgery in 2001 for the treatment of extracranial tumors beyond those in the spine. This is because CyberKnife was, and still remains, the only technology that can compensate for motion (e.g., breathing, digestion, patient movement, peristalsis, etc.) and adjust the beam during treatment, always following the target. It is no accident that for many clinical indications (e.g. prostate) the CyberKnife is used virtually exclusively, as it can deliver high doses of radiation (SBRT) and avoid extremely sensitive tissues and organs, (e.g. rectum, and bladder) reducing toxicity and improving outcomes. Below we will highlight the evidence of CyberKnife SBRT compared to conventional EBRT for extracranial tumors.

4 Sources:
Bianciotto C, Shields CL, Lally SE, et al. CyberKnife radiosurgery for the treatment of intraocular and periocular lymphoma. Arch Ophthalmol 2010;128(12):1561-1567.
Zorlu F, Selek U, Kiratli. Initial results of fractionated CyberKnife radiosurgery for uveal melanoma. J Neuro Oncol 2009;94:111-117.
Adler JR, Gibbs IC, Puataweepong P, et al. Visual field preservation after multisession CyberKnife radiosurgery for perioptic lesions. Neurosurgery 2008;62:733-743.
5 Martin A & Gaya A. Stereotactic body radiotherapy: a review. Clin Oncol 2010;22(3):157-172.
6 Sources:
Gagnon GJ, Nasr NM, Liao JJ, et al. Treatment of Spinal Tumors Using CyberKnife Fractionated Stereotactic Radiosurgery: Pain and Quality-of-Life Assessment after Treatment in 200 Patients. Neurosurg 2009;64(2)1-10.
Sahgal A, Ames C, Chou D, et al. Stereotactic body radiotherapy is effective salvage therapy for patients with prior radiation of spinal metastases. Int J Radiat Oncol Biol Phys 2009;74:723-731.
Gerszten PC, Burton SA, Ozhasoglu C, et al. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. Spine 2007;32:193-199.

Non-small cell lung cancer

SBRT is well accepted for the treatment of non-small cell lung cancer (NSCLC), which biologically has been shown to respond better to hypofractionated treatment (e.g. larger doses in fewer fractions) than conventionally fractionated therapy (EBRT). Because CyberKnife SBRT can deliver hundreds of radiation beams while continuously tracking and compensating for respiratory motion (up to 4 cm), it is able to safely deliver ablative doses to regions of the lung located next to critical organs including the spinal cord, left ventricle, esophagus, main bronchus, trachea, and aorta. Conventional EBRT has been used for inoperable tumors, in patients who refuse surgery, or in patients (due to comorbid conditions) are not surgical candidates. However, the total dose is limited by lung tolerance for peripheral tumors, and mediastinal tolerance for central tumors[7]. SBRT has improved local control and survival rates for these patients compared to conventional EBRT. CyberKnife provides clinicians with an enhanced ability to deliver highly conformal treatments and dose escalate, to achieve maximum cell killing effect in the tumor while avoiding critical structures. The ability of the CyberKnife to track and adjust for motion during treatment allows clinicians to safely and effectively treat extremely sick patients with many comborid conditions such as emphysema, and COPD who may have difficulty holding their breath during treatment, which is required for all other devices. The table below highlights the improved clinical outcomes of CyberKnife SBRT compared to conventional EBRT for non-small cell lung cancer.

Comparison of Conventional EBRT vs. CyberKnife Clinical Outcomes for Non-Small Cell Lung[8]		
	Conventional EBRT	***SBRT***
5-year local control	<50%	73-92%
5-year survival	10-30%	63-72%
Late toxicity ≥ grade 3	17%	5-9%

Liver Cancer

Radiation dosing to healthy liver tissue for the treatment of liver cancer can cause radiation induced liver disease (RILD). Unfortunately, the treatment options for RILD are limited, and in severe cases, liver failure and death can occur. CyberKnife SBRT is widely used for patients who are not surgical candidates or cannot be treated with other methods. Given the shortened life expectancy of patients with metastatic liver cancer, CyberKnife SBRT offers a more patient friendly option – CyberKnife SBRT is 3-5 treatments versus 20-30 treatments for conventional EBRT. CyberKnife SBRT provides patients with liver metastases an option that nearly doubles survival time, drastically decreases toxicity, and greatly improves quality of life. The shorter treatment time of CyberKnife SBRT for these incredibly sick patients allows them to avoid weeks of travel back and forth to the hospital (required for conventional treatment), and avoid additional financial hardship (e.g. lost wages, gas, and sometimes lodging expenses). For the Medicaid population, in particular, with limited means, these are not insignificant issues. The reduced treatment time may also have a positive impact on treatment compliance.

Comparison of Conventional EBRT vs. CyberKnife Clinical Outcomes for Liver Metastases[9]

[7] Martin A & Gaya A. Stereotactic body radiotherapy: a review. Clin Oncol 2010;22(3):157-172.

[8] Sources:
van der Voort van Zyp NC, Prevost JB, van der Holt B, et al. Quality of life after stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2010;77:31-37.
Collins BT, Vahdat S, Erickson K, et al. Radical cyberknife radiosurgery with tumor tracking: an effective treatment for inoperable small peripheral stage I non-small cell lung cancer. J Hematol Oncol 2009;2:1.
Brown WT, Wu X, Fayad F, et al. Application of robotic stereotactic radiotherapy to peripheral stage I non-small cell lung cancer with curative intent. Clin Oncol (R Coll Radiol) 2009;21:623-631.
Fakiris AJ, McGarry RC, et al. Stereotactic Body Radiation Therapy for Early-Stage Non-Small-Cell Lung Carcinoma: Four-Year Results of a Prospective Phase II Study. Int J Radiat Oncol Biol Phys 2009;75(3):677-682.
Onishi H, Shirato H, Nagata Y, et al. Stereotactic Body Radiotherapy (SBRT) for Operable Stage I Non-Small Cell Lung Cancer: Can SBRT be Comparable to Surgery? Int J Radiat Oncol Biol Phys 2010.

[9] Sources:
Stintzing S, Hoffmann RT, Heinemann V, et al. Radiosurgery of Liver Tumors: Value of Robotic Radiosurgical Device to Treat Liver Tumors. Ann Surg Oncol 2010;17:2877-2883.

	Conventional EBRT	***CyberKnife***
Median survival	11-15 months	10-25 months
Late toxicity ≥ grade 3	30%	0-4%
2-year survival	18-47%	32-62%

Prostate

It is important to note that SBRT to treat prostate cancer is not a novel concept. Researchers in the United Kingdom first began to experiment with hypofractionation techniques to treat prostate cancer in the 1980's. The best current explanation of the effect of radiation on cancerous tumors is derived from a linear quadratic model (α/β ratio), which calculates biologically effective dose using number of fractions, and dose per fraction. This model shows that slow growing tumor cells, such as those in the prostate, are more sensitive to higher doses of radiation given in a smaller number of fractions.

The radiobiology of prostate cancer, which shows improved outcomes from high doses per fraction, has been demonstrated by practitioners of high dose rate (HDR) brachytherapy, for which there are comparable data, in terms of long-term follow-up. Trials with HDR prostate brachytherapy have shown excellent biochemical disease free survival, with low levels of toxicity. In clinical practice, SBRT is frequently performed to treat prostate cancer in patients who would otherwise be treated with HDR brachytherapy. Unfortunately, HDR brachytherapy is a technically challenging and highly invasive procedure, which requires general anesthesia and an inpatient hospital stay, adding to patient discomfort and inconvenience.

In 2000, the first prostate cancer patients in the United States were treated with SBRT. Since that time, just under 10,000 patients worldwide have received SBRT to treat their prostate cancer, with the vast majority of these patients being treated (approx 8,000) with the CyberKnife. The rapid adoption of SBRT stems from the fact that prostate cancer is biologically distinct from most other cancers. Researchers at Stanford University (Xie et al 2008) noted that intrafractional organ motion (up to 1 cm) of the prostate has long been recognized as one of the major limiting factors of prostate dose escalation in conformal radiation therapy. The same publication notes the importance of real-time image guidance and motion-compensation techniques that are employed by the CyberKnife robotic system to deliver extremely precise hypofractionated prostate radiation treatment. Given the magnitude and random nature of prostate motion, as well as recent technical advancements in various related fields, real-time monitoring of prostate position to compensate for the motion is critical to ensure adequate dose coverage of the target while maintaining adequate sparing of the adjacent structures. A UCSF study (Jabbari et al., 2011) noted the following about CyberKnife SBRT, *"…the prostate gland's intrafractional motion and minimal PTV expansions required for safe HDR brachytherapy-like dosimetry may preclude the use of linac-based systems for prostate SBRT without a real-time target tracking and beam-correction system to account for intra-fraction motion."*

The table below highlights the improved clinical outcomes of CyberKnife SBRT compared to conventional EBRT for prostate cancer. It is important to note that the vast majority of prostate SBRT is being performed with the CyberKnife because it can track for the random motion of the prostate and adjust the beam in real-time based this motion, which is critically important when delivering dose to the area around the rectum and bladder, to reduce complications such as incontinence, ED, and rectal bleeding. Since the vast majority of SBRT is performed utilizing the CyberKnife, the majority (> 90%) of the SBRT clinical literature available is based on results from the CyberKnife. The table below highlights the improved clinical outcomes of SBRT compared to conventional EBRT.

Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009;27:1572-1578

Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008;26:657-664.

Wulf J, Guckenberger M, Haedinger U, et al. Stereotactic Radiotherapy of Primary Liver Cancer and Hepatic Metastases. Acta Oncologica 2006;45:838-847.

Wulf J, Hadinger U, Oppitz U, et al. Stereotactic Radiotherapy of Targets in the Lung and Liver. Strahlenther Onkol 2001;177:645-655. Herfarth KK, Debus J, Lohr F, et al. Stereotactic Single-Dose Radiation Therapy of Liver Tumors: Results of a Phase I/II Trial. J Clin Onc 2001;19(1):164-170.

Dawood O, Mahadevan A, Goodman K. Stereotactic Body Radiation Therapy for Liver Metastases. Eur J Cancer 2009;45(17)2947-2959.

Comparison of Conventional EBRT vs. CyberKnife Clinical Outcomes for Prostate Cancer[8][10]		
	Conventional EBRT	***SBRT***
Late toxicity	4-6%	0-2%
Biochemical disease free survival	84% (5-year)	93% (5-year)

Pancreas

For those patients who are no longer surgical candidates, radiation therapy in addition to chemotherapy presents the best treatment option. Conventional EBRT along with chemotherapy results in high rates of local failure for patients diagnosed with pancreatic cancer[11]. Conventional EBRT requires significantly longer treatment times, which can take a substantial amount of time from pancreatic patients with limited life expectancy. In addition, the toxicity and side effects from conventional EBRT are significant. A Beth Israel Deaconess Medical Center study (Mahadevan et al. 2010) noted the following about the importance of abbreviated treatment (vs. EBRT) using the CyberKnife SBRT for the treatment of pancreatic cancer, *"Hypofractionated SBRT can be delivered safely and quickly to potentially benefit patients with locally advanced unresectable pancreatic cancer. Our results have shown that three-fraction SBRT, given on 3 consecutive days, can be performed safely with minimal side effects, allowing rapid initiation of chemotherapy. The toxicity and outcomes appeared comparable to, or more favorable than, those of conventional chemoradiotherapy."*[12]

In addition, a University of Pittsburgh study indicated the following about the shorter course of treatment with SBRT versus conventional radiation therapy, *"…SBRT was completed in 1 to 2 days compared with typical 4 or more weeks required to complete external beam radiotherapy, which serves to further expedite chemotherapy in these patients. An additional benefit of SBRT is pain relief, which was achieved in 81.3% of those who presented with pain prior to SBRT."*[13]

The following table below notes the significantly improved clinical outcomes of CyberKnife SBRT +/- chemotherapy compared to conventional EBRT +/- chemotherapy.

[10] Sources:
Engineer R, Bhutani R, Mahantshetty U, et al. From 2-dimensional to three-dimensional conformal radiotherapy in prostate cancer: an Indian experience. Ind J Cancer 2010;47(3):332-338.
Kupelian P, Kuban D, Thames H, et al. Improved Biochemical Relapse-Free Survival with increased External Radiation Doses in Patients with Localized Prostate Cancer: The Combined Experience of Nine Institutions Treated in 1994 and 1994. Int J Radiat Oncol Biol Phys 2005;61(2):415-419.
Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of Conventional-Dose vs. High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate: A Randomized Clinical Trial. JAMA 2005;294(10):1233-1239.
Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. Radiat Oncol 2010;6:3. King CR, Brooks JD, Gill H, et al. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. Int J Radiat Oncol Biol Phys 2012;82(2):877-882.
Friedland JL, Freeman DE, Masterson-McGary ME, et al. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. Technol Cancer Res Treat 2009;8:387-392.
Katz AJ, Santoro M, Ashley R, et al. Stereotactic body radiotherapy for organ-confined prostate cancer. BMC Urol 2010;10:1.

[11] Martin A & Gaya A. Stereotactic body radiotherapy: a review. Clin Oncol 2010;22(3):157-172.

[12] Mahadevan A, Jain S, Goldstein M, et al. Stereotactic Body Radiotherapy and Gemcitabine for Locally Advanced Pancreatic Cancer. Int J Rad Oncol Biol Phys 2010;78:735-742.

[13] Rwigema JM, Parikh SD, Heron DE, et al. Stereotactic Body Radiotherapy in the Treatment of Advanced Adenocarcinoma of the Pancreas. Amer J Clin Oncol 2011;34:63-69.

Comparison of Conventional EBRT vs. CyberKnife Clinical Outcomes for Pancreatic Cancer[14]		
	***Conventional EBRT* +/- chemotherapy**	***CyberKnife SBRT* +/- chemotherapy**
Treatment times	6 weeks	< 1 week
Median overall survival	5.3-11.4 months	8-18.6 months
Local progression free survival	42-62%	91.7%

KQ2: What are the potential harms of SRS and SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.

The tables in section KQ1 provide details of the significantly reduced toxicity levels of treatment with SRS/SBRT compared to conventional EBRT.

SRS and SBRT treatments deliver much higher doses of radiation in far fewer treatments compared to EBRT (although the overall biological equivalent dose per treatment is similar). Higher doses per treatment can potentially harm patients, necessitating a treatment plan with steep dose falloff and the ability to track and adjust for motion. The CyberKnife's robotically enhanced ability to deliver beams from over 1600 unique beam angles achieves the dose falloff and tighter treatment margins, by tracking and compensating for movement throughout the treatment. This is accomplished by moving to and with the patient, and tracking and adjusting for movement and tumor deformation during beam on. EBRT systems image before but not during "beam on", therefore clinician must attempt to compensate for movement by controlling the patient movement instead of adjusting dose delivery with the natural patient movement. One way clinicians using non-robotic, EBRT systems attempt to compensate for movement is by a procedure called respiratory gating. For gating to work properly a) the patient's respiratory cycle must be periodic and maintained during treatment, b) the movement of the target must be related to the respiratory cycle, and c) the gating window is set sufficiently large to minimize overall treatment time. Even if all these requirements are met, contouring should still account for the tumor residual motion, setup uncertainty, and deviation from the expected respiratory cycle during treatment. These requirements result in a significantly larger treatment margin, increasing the chance of irradiating healthy tissue and critical structures. In other treatment areas where movement is random, the only solution for EBRT systems is to increase the margin irradiating the entire area of movement the tumor may travel. The CyberKnife's robotic delivery, which moves beams to and with the patient during treatment, significantly reduces irradiation of healthy tissue and organs at risk.

Coding

The unique codes CMS created for Robotic Stereotactic Radiosurgery are G0339 and G0340. While the majority of fractionated SRS and SBRT in the United States are performed with the CyberKnife, curiously G0339 and G0340 are not listed on the Washington Medicaid Fee Schedule, and the codes for gantry-based SRS and SBRT (G0251 and G0173) are. Below we provide information on SRS and SBRT codes, which have been in effect since January of 2003. G0339 and G0340 are well accepted and recognized codes by Medicare and private payers alike. CMS offers the following direction when coding claims for robotic and non-robotic/gantry-based systems:

Transmittal 1139 of the CMS Manual System Pub 100-04 Medicare Claims Processing (12/22/2006), defines SRS and the associated coding this way: *"There are two basic methods in which SRS can be delivered to patients, linear accelerator-based treatment and multi-source photon-based treatment (often referred to as Cobalt 60). Advances in technology have further distinguished linear accelerator-based SRS therapy into two types: gantry-based systems and image-guided robotic SRS systems. These two types of linear accelerator-based SRS therapies may be delivered in a complete session or in a fractionated course of therapy up to a maximum of five sessions."*

[14] Sources:
Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2010;78:735-742.
Didolkar MS, Coleman CW, Brenner MJ, et al. Image-guided stereotactic radiosurgery for locally advanced pancreatic adenocarcinoma results of first 85 patients. J Gastrointest Surg 2010;14:1547-1559.

Linear Accelerator-Based Robotic Image-Guided SRS	
Planning	Use existing CPT codes
Delivery	G0339 (Complete course of therapy in one session or first session of fractionated treatment) G0340 (Second through fifth sessions, maximum five sessions per course of treatment)

Linear Accelerator-Based Non-Robotic/Gantry Image-Guided SRS	
Planning	Use existing CPT codes
Delivery	G0173 (Complete course of treatment in one session) G0251 (All lesions, maximum 5 session per course of treatment)

KQ3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in sub populations? Including consideration of: a) gender b) age c) site and type of cancer d) stage and grade of cancer e) setting, provider characteristics, equipment, quality assurance standards and procedures

SRS/SBRT are used to treat a wide variety of patients and demographics.

The CyberKnife received FDA clearance to *provide treatment planning and image-guided stereotactic radiosurgery and precision radiotherapy for lesions, tumors and conditions of the brain, base of skull and cervico-thoracic spine (CTS), head and neck in 1999 (FDA 510(k) # K984563).* In 2001, the CyberKnife received FDA clearance *to provide treatment planning and image-guided stereotactic radiosurgery and precision radiotherapy for lesions, tumors and conditions anywhere in the body when radiation treatment is indicated (FDA 510(k) # K011024).* Unlike frame-based radiosurgery systems, which are generally limited to treating brain tumors, CyberKnife radiosurgery is being used to treat to tumors throughout the entire body.

Aetna's national SRBT policy which has been in place since 2008 (most recent update 1/26/2012) states the following: *"Stereotactic body radiation therapy (SBRT) with a gamma knife, Cyberknife, or linear accelerator (LINAC) is considered medically necessary for localized malignant conditions within the body where highly precise application of high dose radiotherapy is required…",* allowing the physician and patient to determine the correct treatment option for the patient.

SRS/SBRT treatment can be delivered in the hospital and physician office setting by well qualified and trained physicians. The multi-specialty treatment team should include, Radiation Oncologists, Physicists, Radiation Therapists, additional Physician Specialists (depending on the treatment area), and support staff. All staff should be trained on the SBRT system being used.

KQ4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

Unfortunately, there is a lack of clinical literature which compares the cost of radiation therapies across the board. However, the data that have been published demonstrate a significant cost effectiveness advantage of SBRT over 3D conformal radiation, which we believe supports its use for the other indications for which clinical outcomes are shown by the literature to be improved using SBRT over 3D conformal radiation. The table provided as an appendix, provides information about the three clinical publications that note the cost differential between SBRT and conventional EBRT for medically inoperable non-small cell lung cancer and pancreatic cancer.

Conclusion
As outlined above, SRS/SBRT has become a standard of care and a clinical option that is available to cancer patients throughout the United States. SRS/SBRT can treat patients with brain, spine, lung, liver, pancreas, and prostate cancer (and other lesions with a documented necessity to treat using a high dose per fraction of radiation). Given the positive SRS/SBRT clinical outcomes compared to conventional EBRT, we urge the Washington State Health Care Authority to add G0339 and G0340 as a covered benefit for Medicaid patients in the state of Washington.

The CKC thanks the Washington State Health Care Authority for this opportunity to provide comments regarding CyberKnife SRS/SBRT. Our member institutions, including those in Washington State, would be delighted to meet with you in person to answer any further questions or concerns. In addition, please feel free to contact us at the numbers below if we can be of any assistance as your organization continues to evaluate this topic.
Sincerely,

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Publication	Comparators	Summary
Lanni TB, Grills IS, Kestin LL, et al. **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.** Amer J Clin Oncol 2011;34(5)494-498.	• SBRT • 3D-CRT	• 3D-CRT: n=39; SBRT: n=44 • Median follow-up: 36 months • SBRT was significantly less expensive ($13,639 EBRT vs. $10,616 SBRT, P < 0.01) based on 2010 hospital-based Medicare reimbursement (technical + professional) • Superior 36-month overall survival using SBRT, 71% vs. 42% for EBRT (P<0.05) • SBRT reduced local failure by nearly 3 times compared with EBRT (12% vs. 34%, P = 0.10)
Sher DJ, Wee JO, Punglia RS. **Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable early-stage non-small cell lung cancer.** Int J Rad Oncol Biol Phys 2011;81(5):e767-774.	• SBRT • 3D-CRT	• Study developed a Markov model for 65-year old men with medically inoperable NSCLC • Incremental cost-effectiveness ratio (ICER) for SBRT over 3D-CRT was $6,000/QALY • Model predicted 3-year local recurrence, regional recurrence, and distant metastasis rates: SBRT – 10.5%, 9%, 9%;

Publication	Comparators	Summary
		3D-CRT – 34%,7%,7%; "In comparison to 3D-CRT, SBRT was the most cost-effective treatment for medically inoperable NSCLC…" • "On the basis of efficacy and cost, SBRT should be the primary treatment for this disease."
Murphy JD, Chang DT, Abelson J, et al. **Cost-effectiveness of modern radiotherapy techniques in locally advanced pancreatic cancer**. Cancer 2012;118(4):1119-1129.	• Gemcitabine alone • Gemcitabine plus conventional radiotherapy • Gemcitabine plus intensity-modulated radiotherapy (IMRT) • Gemcitabine with SBRT	• SBRT increased life expectancy by 0.20 quality-adjusted life years (QALY) at an increased cost of $13,700 compared with gemcitabine along • SBRT was more effective and less costly than conventional radiotherapy and IMRT • Current results indicate that IMRT in locally advanced pancreatic cancer exceeds what society considers cost-effective • In contrast, combining gemcitabine with SBRT increased clinical effectiveness beyond that of gemcitabine alone at a cost potentially acceptable by today's standards

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From: Howard, Todd
To: HCA ST Health Tech Assessment Prog
Cc: Gilmore-Lawless, Catherine C; Howard, Todd
Subject: Public Comment for: Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy
Date: Friday, March 02, 2012 12:26:27 PM
Attachments: Washington State Health Care Authority Dossier V 1.0 3.2.2012.pdf
Addendum D - Apparatus Dependent Brain Mets.pdf
Addendum A - ASTRO Brain mets guideline.pdf
Addendum B - Neuro Guidelines.pdf
Addendum C - Saghaletal Meta-Analysis.pdf
Importance: High

To whom it may concern:
Elekta, the manufacturer of the Leksell Gamma Knife® and a comprehensive array of oncology solutions including linear accelerators, treatment planning and electronic medical records software, sincerely appreciates the opportunity provided by the Washington State Health Care Authority to comment on the topic of *Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy*. We hope you find the facts in this document to be beneficial to your assessment. Additionally, we would be more than willing to meet in person with you as a follow-up or coordinate a meeting with one of the Gamma Knife centers in the State of Washington to address any additional questions or data needs that you may have during this process.

Best regards,

Todd Howard

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Note: The following articles were attached to this email as PDFs

Linskey, M.E., Andrews, D.W., Asher, A.L., Burri, S.H., Kondziolka, D., Robinson, P.D., Ammirati, M., Cobbs, C.S., Gaspar, L.E., Loeffler, J.S., McDermott, M., Mehta, M.T., Mikkelsen, T., Olson, J.J., Paleologos, N.A., Patchell, R.A., Ryken, T.C., & Kalkanis, S.N. (2010). The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline. *Journal of Neurooncology, 96*, 45-68.

Ma, L., Petti, P., Wang, B., Descovich, M., Chuang, C., Barani, I.J., Kunwar, S., Shrieve, D.C., Sahgal, A., & Larson, D.A. (2011). Apparatus dependence of normal brain tissue dose in stereotactic radiosurgery for multiple brain metastases. *Journal of Neurosurgery, 114*(6), 1580-4..

Tsao, M.N., Rades, D., Wirth, A., Lo, S.S., Danielson, B.L., Gaspar, L.E., Sperduto, P.W., Vogelbaum, M.A., Radawski, J.D., Wang, J.Z., Gillin, M.T., Mohideen, N., Hahn, C.A., & Chang, E.L. (2012). Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. *Practical Radiation Oncology.* [Article in Press].

Tsao, M.N., Xu, W., & Sahgal, A. (2011). A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer.* [ePub ahead of print]

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Leksell Gamma Knife®

Comments on Stereotactic Radiation Surgery
For: Washington State Health Care Authority

Prepared by: *Catherine Gilmore-Lawless, Vice President, Clinical Intelligence*
Todd Howard, Director of Business Development
Elekta, Inc.
Date: *March 2, 2012*

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Introduction

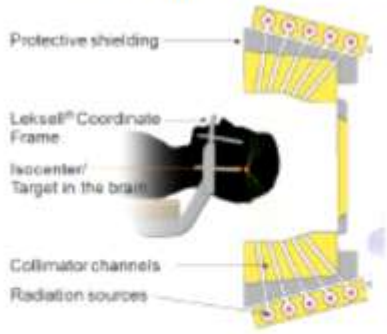
Elekta, the manufacturer of the Leksell Gamma Knife® and a comprehensive array of oncology solutions including linear accelerators, treatment planning and electronic medical records software, sincerely appreciates the opportunity provided by the Washington State Health Care Authority to comment on the topic of *Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy*. We hope you find the facts in this document to be beneficial to your assessment. Additionally, we would be more than willing to meet in person with you as a follow-up or coordinate a meeting with one of the Gamma Knife centers in the State of Washington to address any additional questions or data needs that you may have during this process.

Stereotactic Radiosurgery

Elekta was founded in 1972 by the late Lars Leksell, Professor of Neurosurgery at the Karolinska Institute in Stockholm, Sweden. His pioneering work led to the development of the technique: Stereotactic Radiosurgery which he defined as the "delivery of a single, high dose of irradiation to a small and critically located intra-cranial volume through the intact skull." The technique differs markedly from conventional radiation therapy (RT), which involves exposing large areas of tissue to relatively broad fields of radiation over a number of sessions. Originally used to treat just "inoperable" brain tumors and vascular malformations, the technique of stereotactic radiosurgery has become an indispensable alternative and adjunct to conventional techniques such as surgery (craniotomy) or conventional radiation therapy for a wide array of intracranial indications. Patients benefit from this fast, painless treatment, usually conducted in an outpatient setting without the need for general anesthesia, inpatient hospitalization or even convalescence. The benefits of this non-invasive approach include high clinical efficacy, low mortality and morbidity, high patient satisfaction and cost effectiveness.

The Gamma Knife

The Leksell Gamma Knife® was developed specifically to perform stereotactic radiosurgery of the brain. Recognizing the enormous need for accuracy and precision, given neuroanatomy and the potential toxicity of high doses of radiation, the Gamma Knife was designed to be as accurate and precise as possible; its hallmark design principle is that the target (isocenter) and sources of radiation are in a fixed relationship during treatment. With no moving parts during treatment, the Gamma Knife is guaranteed to deliver radiation with sub-millimetric accuracy. Its hemispheric source array and dose distributions allow for extremely conformal and selective treatments, resulting in very high clinical efficacy and minimal morbidity.



Unlike other linear accelerator-based technologies such as CyberKnife or Tomotherapy which are used most frequently for stereotactic body radiation therapy (SBRT), the Gamma Knife is dedicated to, and used exclusively for, the treatment of brain disorders.

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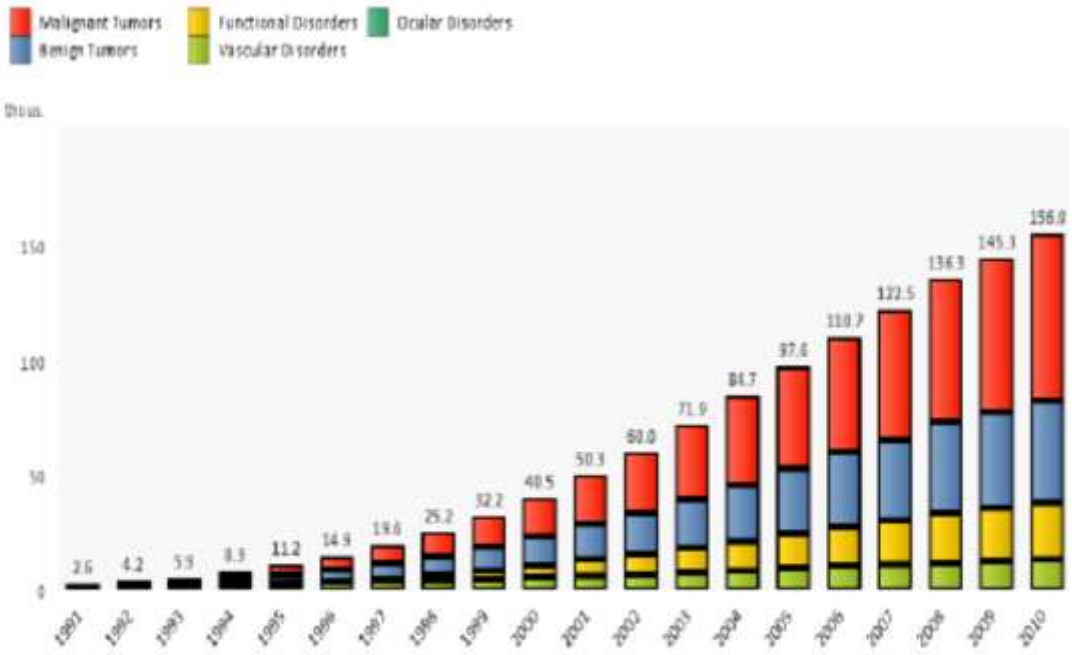
With more than 440 Leksell Gamma Knife® systems, Elekta has the largest installed base of dedicated *intracranial* stereotactic radiosurgery systems in the world, including 128 units in North America, four (4) of which are located in Washington State at:

- Harborview, University of Washington, Seattle
- Spokane Gamma Knife Center, Spokane
- Swedish Hospital, Seattle
- South Sound Gamma Knife at St. Joseph, Tacoma

These centers serve the State of Washington but also treat patients from surrounding geographies including Idaho, Montana, Alaska and Canada.

Indications Overview

According to the Leksell Gamma Knife Society[1], over 156,000 patients have been treated in the U.S. since the first Gamma Knife was installed in August, 1987 with approximately 11,000 patients receiving Gamma Knife surgery each year. The corresponding global numbers are 610,000 and 60,000, respectively.



PATIENTS TREATED WITH THE GAMMA KNIFE IN THE U.S. 1897-2010

[1] The International Leksell Gamma Knife® Society was formed in 1989 to further validate and expand the role of Gamma Knife surgery in the treatment of intracranial disorders and foster a commitment to the highest standards of research and technical achievement while stimulating multi-center trials and cross-site collaboration. The Society conducts an annual survey of all Gamma Knife sites to track the total treatment volume, clinical trends and regional differences. Not all sites report.

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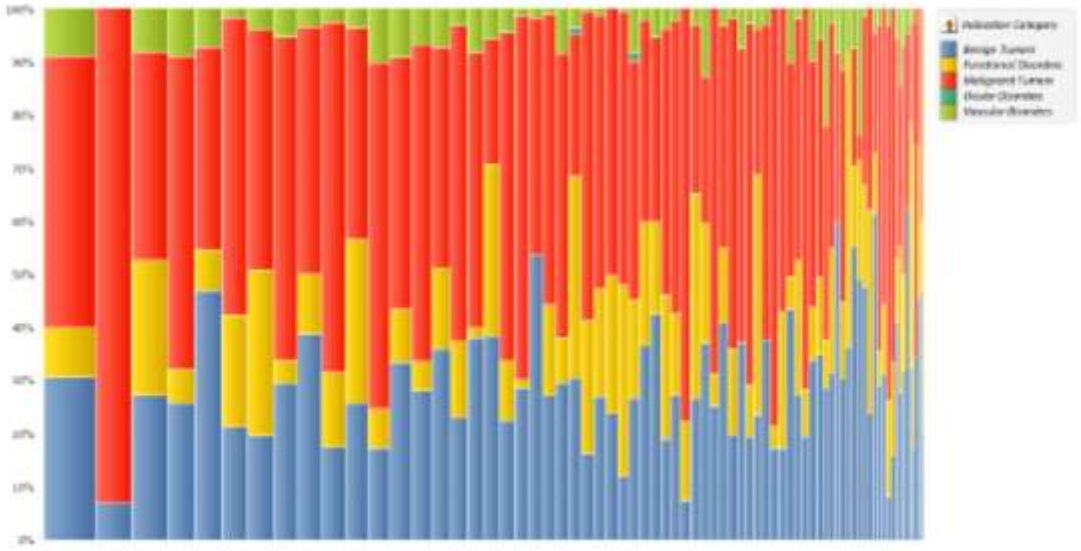
The Gamma Knife is used for neoplastic and vascular anomalies of the brain and upper cervical spine (usually to C2). It has also been used for the treatment of facial pain and movement disorders such as essential tremor. The ICD-9 codes currently applicable to Gamma Knife surgery are as follows:

Gamma Knife Relevant Disease Indications	
ICD-9 Code	**Disease**
191.0-191.9	Malignant neoplasm of brain
192.0	Malignant neoplasm of Cranial Nerves
192.1	Cerebral Meninges
192.3	Spinal Meninges
194.3-194.4	Malignant Neoplasm (pituitary/pineal)
198.3-198.4	Metastatic neoplasm to brain/meninges
225.0-225.2	Benign Neoplasms-brain/nerve/meninges
227.3-4, 237.0	Pituitary/craniopharyngeal neoplasm
237.0-1	Neoplasms of uncertain behavior
227.6	Glomus jugulare
237.3	Glomus neoplasm
747.81	AVM of cerebral vessels
350.1	Trigeminal Neuralgia
332.1	Essential Tremor

The Gamma Knife case mix has evolved over time. Originally, vascular malformations and benign brain tumors were the most common indications. Today, as indicated in the chart below, malignant tumors (red bars), specifically metastases, are the most common indication treated, followed by trigeminal neuralgia.



2010 CASE MIX BY U.S. SITE[1]

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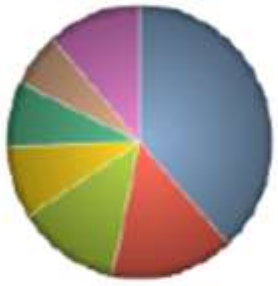
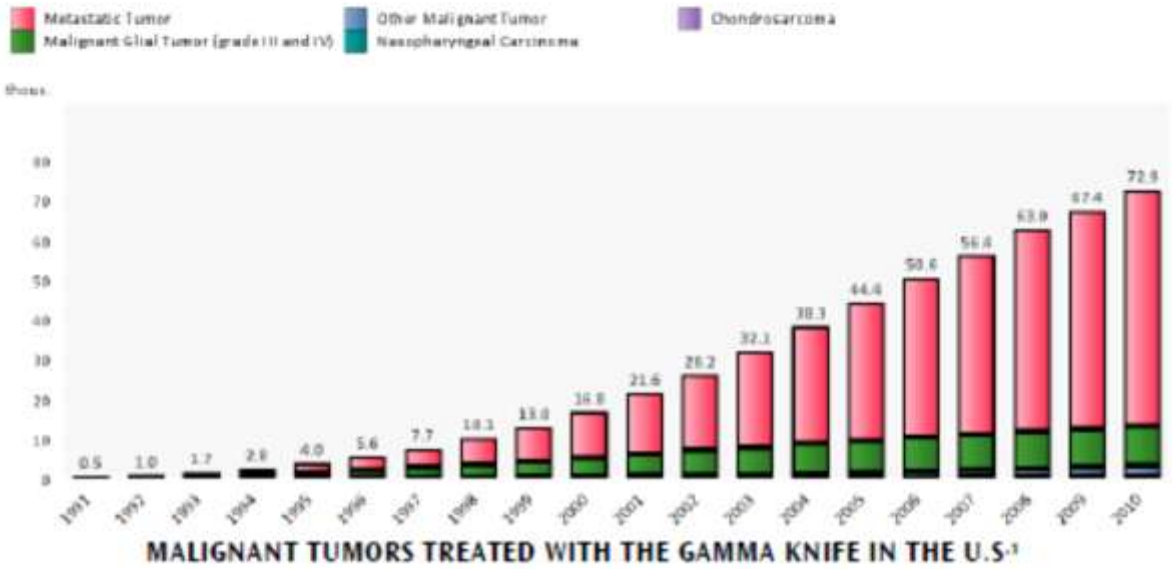
Over 60,000 metastatic brain tumor patients have been treated with the Gamma Knife in the U.S. Additionally, over 10,000 primary malignant tumor patients have been treated, usually in a recurrent setting.



Indication	
Metastatic Tumor	59,797
Trigeminal Neuralgia	23,485
Meningioma	19,553
Vestibular Schwannoma	13,168
AVM	12,199
Malignant Glial Tumor (grade III a...	9,937
Others	17,871

Further detail of the types of malignant brain conditions treated over time with the Gamma Knife is illustrated in the chart below:



MALIGNANT TUMORS TREATED WITH THE GAMMA KNIFE IN THE U.S.[1]

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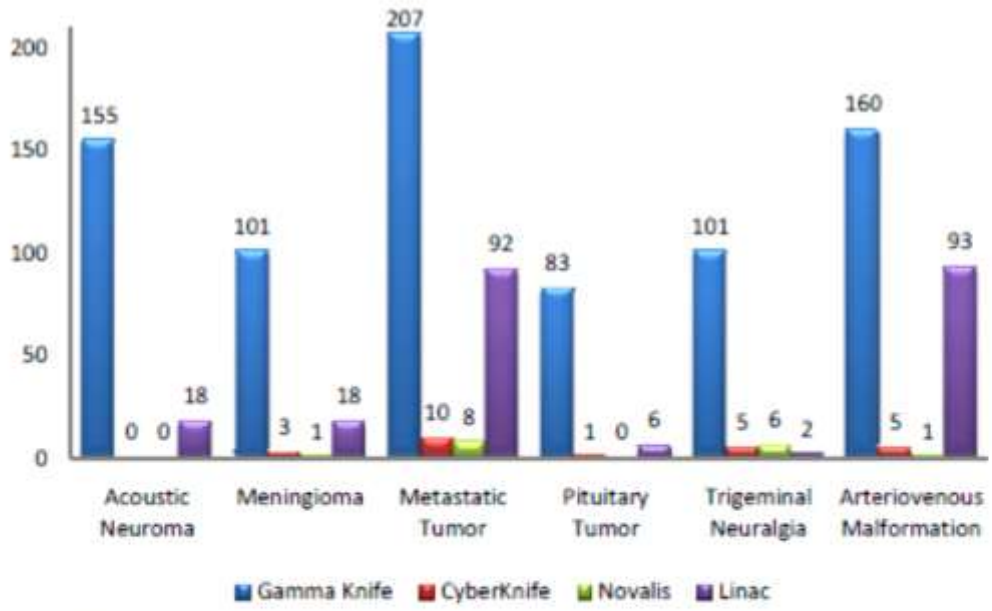
Clinical Evidence Overview

Because the Gamma Knife was designed and is dedicated for the brain, Gamma Knife centers tend to be located in neuroscience and oncologic centers of excellence or centers with a major focus on cranial conditions. Gamma Knife sites tend to be recipients of a larger number of referrals both from physicians and patients themselves and the average case volume is typically three times that of centers using other technology for radiosurgery, allowing centers to build significant expertise. Robust clinical activity, a relatively homogenous treatment technique (even globally) and a strong interest and commitment to scientific excellence have resulted in a large number of presentations and publications. The Gamma Knife has an impressive and unparalleled scientific track record with over 3,000 peer-reviewed articles. No other radiosurgery technology approaches the Gamma Knife in terms of clinical documentation for brain radiosurgery as indicated in the following chart which reflects the number of (single session) stereotactic radiosurgery papers reporting series of 30 patients or more.

RADIOSURGERY PAPERS REPORTING MORE THAN 30 PATIENTS THROUGH FEBRUARY 2012



Source: Elekta Clinical Database (using PubMed)

Elekta maintains a comprehensive database of articles and would be happy to provide references upon request. A Reference List of articles concerning the use of the Gamma Knife in the treatment of metastatic and primary malignant tumors may be found in the Addendum.

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The remainder of this document will address the following topics and specific questions as outlined in the Health Care Authority assessment on "Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy."

- (KQ1) – What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy compared to conventional external beam radiation therapy (EBRT) for the following patients:
    - Patients with central nervous system (CNS) tumors
    - Patients with non-central nervous system cancers?
- (KQ2) - What are the potential harms of SRS and SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatments in unnecessary or inappropriate ways.
- (KQ3) – What is the evidence that SRS and SBRT have differential efficacy or safety issues in sub populations? Including consideration of:
    - Gender
    - Age
    - Site and type of cancer
    - Stage and grade of cancer
    - Setting, provider characteristics, equipment, quality assurance standards and procedures.
- (KQ4) – What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

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Key Question #1 – Washington State Health Care Authority

What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy compared to conventional external beam radiation therapy (EBRT) for the following patients:

- *Patients with central nervous system (CNS) tumors*
- *Patients with non-central nervous system cancers?*

In responding to Key Question #1, we will limit our comments to central nervous system (CNS) tumors only as the Gamma Knife is only used for intracranial conditions. We will also limit our comments to malignant disease only. Please let us know if you would like additional commentary on benign disease.

Brain metastases are the most common intracranial solid tumor. The incidence is increasing because of advances in diagnostic imaging and ubiquitous screening, an aging population and longer survival due to effective targeted systemic therapies. The current purpose of brain metastasis management is no longer restricted to palliation; goals include extended survival, and importantly preservation of quality of life. To meet these requirements, SRS and in particular, the Gamma Knife, has become a very important tool in the management of these patients. With the increased utilization of SRS, significant effort has been put forth by clinicians, and researchers to identify the ideal treatment paradigm; these efforts are aligned with the questions appropriately posed by the Washington State Health Care Authority.

Two sets of guidelines have been recently released by the professional associations of radiation oncologists and neurosurgeons and are provided in the Addendum to this comment. The most recent guidelines from the American Society of Therapeutic Radiation Oncology (ASTRO) were released in early February, 2012 and are currently in press. They conducted an extensive review of the available evidence to address a number of important metastatic brain tumor issues including two areas germane to the WSHA Key Question #1, namely:

- "is there a survival or brain control difference in patients treated with WBRT and radiosurgery boost versus WBRT alone?
- is there a difference in survival, brain control or neurocognitive outcomes in patients treated with radiosurgery alone versus WBRT and radiosurgery?"

They found that "In selected patients with single brain metastasis, **radiosurgery or surgery has been found to improve survival and locally treated metastasis control (compared with WBRT alone).**" ASTRO additionally provided the following guidelines for patients with good prognosis (expected to live longer than three months):

- "For single metastasis less than 3 to 4 cm, radiosurgery alone or WBRT and radiosurgery or WBRT and surgery (all based on level 1 evidence) should be considered. Another alternative is surgery and radiosurgery or radiation boost to the resection cavity (level 3).

- For single brain metastasis (less than 3 to 4 cm) that is not resectable or incompletely resected, WBRT and radiosurgery, or radiosurgery alone should be considered (level 1).
- For patients with multiple brain metastases (all less than 3 to 4 cm), radiosurgery alone, WBRT and radiosurgery, or WBRT alone should be considered, based on level 1 evidence. Safe resection of a brain metastasis or metastases causing significant mass effect and postoperative WBRT may also be considered (level 3)."

These more recent guidelines are essentially congruent with the earlier guidelines published by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons in the December 2009 issue of the *Journal of Clinical Oncology*. In specifically addressing the role of SRS and EBRT, they concluded:

SRS plus WBRT vs. WBRT alone
Level 1 Single-dose SRS along with WBRT leads to significantly longer patient survival compared with WBRT alone for patients with single metastatic brain tumors who have a KPS ≥70.

Level 2 Single-dose SRS along with WBRT is superior in terms of local tumor control and maintaining functional status when compared to WBRT alone for patients with 1–4 metastatic brain tumors who have a KPS≥70.

Level 3 Single-dose SRS along with WBRT may lead to significantly longer patient survival than WBRT alone for patients with 2–3 metastatic brain tumors.

Level 4 There is class III evidence demonstrating that single-dose SRS along with WBRT is superior to WBRT alone for improving patient survival for patients with single or multiple brain metastases and a KPS < 70.

SRS plus WBRT vs. SRS alone
Level 2 Single-dose SRS alone may provide an equivalent survival advantage for patients with brain metastases compared with WBRT? single-dose SRS. There is conflicting class I and II evidence regarding the risk of both local and distant recurrence when SRS is used in isolation and class I evidence demonstrates a lower risk of distant recurrence with WBRT; thus, regular careful surveillance is warranted for patients treated with SRS alone in order to provide early identification of local and distant recurrences so that salvage therapy can be initiated at the soonest possible time.

Surgical Resection plus WBRT vs. SRS ± WBRT
Level 2 Surgical resection plus WBRT, vs. SRS plus WBRT, both represent effective treatment strategies, resulting in relatively equal survival rates. SRS has not been assessed from an evidence-based standpoint for larger lesions (> 3 cm) or for those causing significant mass effect (>1 cm midline shift). Level 3: Underpowered class I evidence along with the preponderance of conflicting class II evidence suggests that SRS alone may provide equivalent functional and survival outcomes compared with resection + WBRT for patients with single brain metastases, so long as ready detection of distant site failure and salvage SRS are possible.

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SRS alone vs. WBRT alone

Level 3 While both single-dose SRS and WBRT are effective for treating patients with brain metastases, single dose SRS alone appears to be superior to WBRT alone for patients with up to three metastatic brain tumors in terms of patient survival advantage

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Key Question #2 – Washington State Health Care Authority

What are the potential harms of SRS and SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatments in unnecessary or inappropriate ways.

It is Elekta's opinion that the Gamma Knife provides significant clinical advantages over EBRT for the treatment of brain metastases, rather than the reverse. The addition of SRS to EBRT extends survival. The addition of EBRT to SRS has been found to produce neurocognitive decline. A paper In Lancet by Eric Chang of MD Anderson *(Chang, E.L., et al., Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol, 2009. 10(11): p. 1037-44)* reported on a randomized controlled trial which was actually stopped early as it was apparent that patients treated with "SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone." Dr. Chang concluded that in the case of newly diagnosed brain metastases, "Initial treatment with a combination of SRS and close clinical monitoring is recommended as the preferred treatment strategy to better preserve learning and memory in patients".

A recent metaanalysis conducted by Tsao et al *(Tsao, M., W. Xu, and A. Sahgal, A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. Cancer, 2011.)* concluded "for selected patients with up to 4 brain metastases eligible for SRS, our meta-analysis concludes no OS benefit for WBRT plus SRS boost compared with SRS alone despite significant gains in both local and distant brain tumor control with WBRT. SRS alone may allow patients to optimally retain their neurocognitive function, experience fewer serious late side effects, and are not at adverse risk with respect to maintaining performance status. Therefore, we conclude that SRS alone with frequent magnetic resonance imaging (MRI)-based follow-ups in order to salvage recurrent brain metastases before symptomatic manifestations, should be routinely offered to selected patients as a treatment option to consider.

Other research which discusses the relative benefit of omitting whole brain radiation due to its morbidity includes:

- *Rush, S.E., R. E.; Morsi, A.; Mehta, N.; Spriet, J.; Narayana, A.; Donahue, B.; Parker, E. C.; Golfinos, J. G., Incidence, timing, and treatment of new brain metastases after Gamma Knife surgery for limited brain disease: the case for reducing the use of whole-brain radiation therapy. Journal of Neurosurgery, 2011. 115(1): p. 37-48.*
- Serizawa, T.Y., M.; Sato, Y.; Higuchi, Y.; Nagano, O.; Kawabe, T.; Matsuda, S.; Ono, J.; Saeki, N.; Hatano, M.; Hirai, T., *Gamma Knife surgery as sole treatment for multiple brain metastases: 2-center retrospective review of 1508 cases meeting the inclusion criteria of the JLGK0901 multi-institutional prospective study.* Journal of Neurosurgery, 2010. 113 Suppl: p. 48-52.
- *Sneed, P.K.L., K. R.; Forstner, J. M.; McDermott, M. W.; Chang, S.; Park, E.; Gutin, P. H.; Phillips, T. L.; Wara, W. M.; Larson, D. A., Radiosurgery for brain metastases: is*

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Key Question #3 – Washington State Health Care Authority

What is the evidence that SRS and SBRT have differential efficacy or safety issues in sub populations? Including consideration of:

- *Gender*
- *Age*
- *Site and type of cancer*
- *Stage and grade of cancer*
- *Setting, provider characteristics, equipment, quality assurance standards and procedures.*

There has been increasing focus on developing a more tailored approach to using radiosurgery based on the patients' specific characteristics including genetic subtype. The most extensive work of this kind has been undertaken under the leadership of Dr. Paul Sperduto. His recent article on this subject (*Sperduto, P.W.K., N.; Roberge, D.; Xu, Z.; Shanley, R.; Luo, X.; Sneed, P. K.; Chao, S. T.; Weil, R. J.; Suh, J.; Bhatt, A.; Jensen, A. W.; Brown, P. D.; Shih, H. A.; Kirkpatrick, J.; Gaspar, L. E.; Fiveash, J. B.; Chiang, V.; Knisely, J. P.; Sperduto, C. M.; Lin, N.; Mehta, M., Summary Report on the Graded Prognostic Assessment: An Accurate and Facile Diagnosis-Specific Tool to Estimate Survival for Patients With Brain Metastases. Journal of Clinical Oncology, 2011*) details a sophisticated grading scheme to provide detailed prognostic information. Through analysis of over 3,000 cases from multiple institutions, it was concluded that prognosis varies by histology. The report found that "for lung cancer, prognostic factors were Karnofsky performance score, age, presence of extracranial metastases, and number of brain metastases" while "For melanoma and renal cell cancer, prognostic factors were Karnofsky performance score and the number of brain metastases. For breast cancer, prognostic factors were tumor subtype, Karnofsky performance score, and age. For GI cancer, the only prognostic factor was the Karnofsky performance score."

With regard to 'differential efficacy and safety of equipment', Elekta believes that the Gamma Knife is superior to other forms of delivering stereotactic radiosurgery. As described previously, the Gamma Knife has been designed specifically for the purpose of brain radiosurgery. Its long term accuracy is guaranteed by the manufacturer. It provides more conformal treatment than other devices with lower dose to normal brain and to the body. In support of this statement, is the article: *Ma, L.P., P.; Wang, B.; Descovich, M.; Chuang, C.; Barani, I. J.; Kunwar, S.; Shrieve, D. C.; Sahgal, A.; Larson, D. A., Apparatus dependence of normal brain tissue dose in stereotactic radiosurgery for multiple brain metastases. Journal of Neurosurgery, 2011.* ***114****(6): p. 1580-4* which assesses the relative differences of equipment (CyberKnife, Novalis and Gamma Knife) in the treatment of metastatic tumors specifically, and concludes that "The dose delivered to normal brain is strongly dependent on the radiosurgery platform", with the dose to normal brain typically 2-3 times lower for the Gamma Knife when compared to other equipment. This difference is illustrated in the following dose distribution profiles for 3, 6, 9 and 12 metastatic targets.

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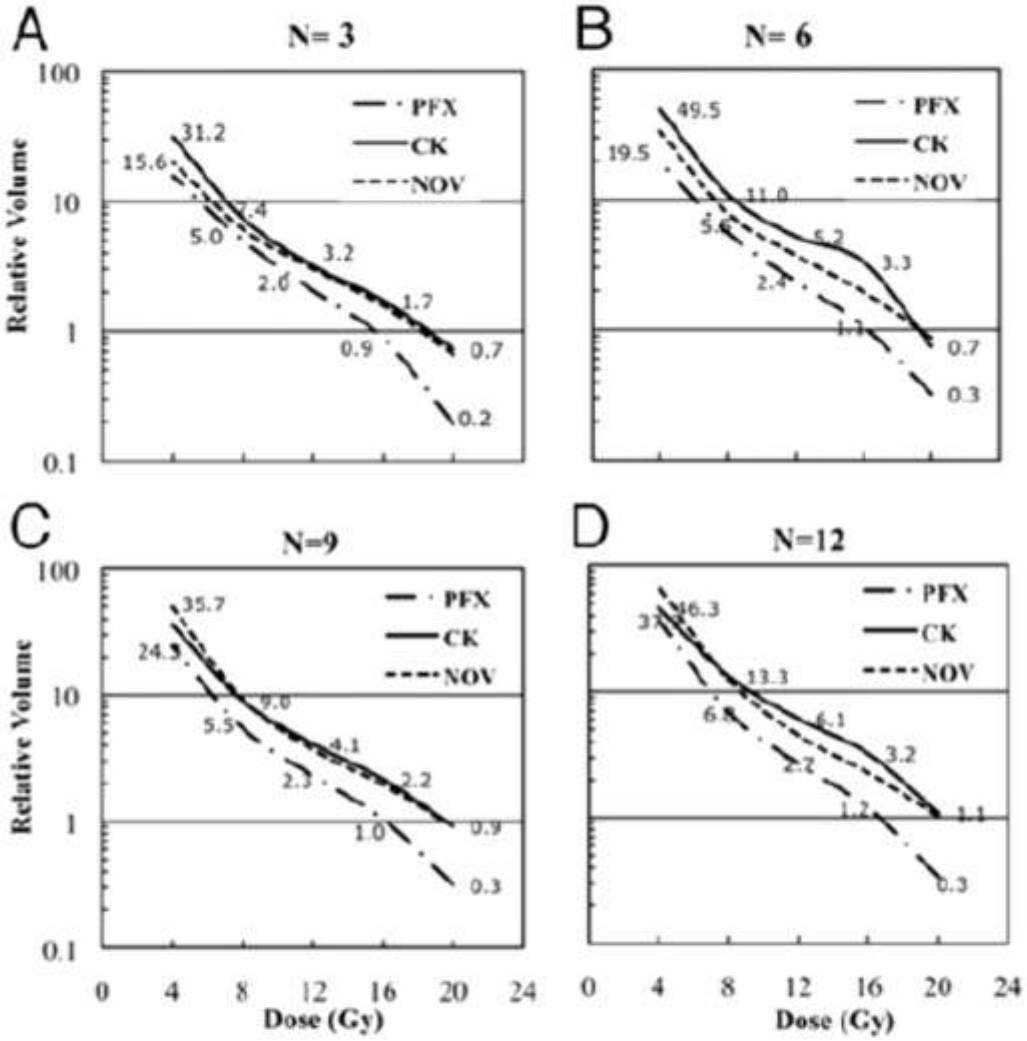

Fig. 4. Apparatus dependence of normal brain isodose volumes for multitarget treatment plans with 3 (**A**), 6 (**B**), 9 (**C**), and 12 (**D**) targets. The numbers on the curves are the normalized total target volumes for Perfexion and CyberKnife for 4, 8, 12, 16, and 20 Gy, respectively.

*Ma, L.P., P.; Wang, B.; Descovich, M.; Chuang, C.; Barani, I. J.; Kunwar, S.; Shrieve, D. C.; Sahgal, A.; Larson, D. A., Apparatus dependence of normal brain tissue dose in stereotactic radiosurgery for multiple brain metastases. Journal of Neurosurgery, 2011. **114**(6): p. 1580-4*

As described previously, the evidence base for the Gamma Knife far exceeds that for other equipment including the CyberKnife, Novalis, Tomotherapy and generic linear accelerator both with respect to number of patients treated and peer-reviewed publications.

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Key Question #4 – Washington State Health Care Authority

What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

Elekta contends that because of enhanced quality of life resulting from less whole brain radiation, the quality adjusted life years provide a cost advantage for SRS followed by surveillance.

There are a number of papers which have compared the cost effectiveness of SRS and EBRT to EBRT alone. They include:

- *Lal, L.S., et al., Cost-effectiveness Analysis of a Randomized Study Comparing Radiosurgery With Radiosurgery and Whole Brain Radiation Therapy in Patients With 1 to 3 Brain Metastases. American Journal of Clinical Oncology, 2011.*

- *Lal, L.S., et al., Economic impact of stereotactic radiosurgery for malignant intracranial brain tumors. Expert Rev Pharmacoecon Outcomes Res, 2011.* ***11****(2): p. 195-204.*

The papers conclude that " Compared with other interventions in the $50,000 to $100,000/QALY cost-effectiveness range, the application of SRS and observation, with subsequent neurosurgical management of recurrences, is shown to be a reasonable treatment modality for brain metastases."

One paper: *Lee, W.Y., et al., Outcomes and cost-effectiveness of gamma knife radiosurgery and whole brain radiotherapy for multiple metastatic brain tumors. J Clin Neurosci, 2009.* ***16****(5): p. 630-4* specifically addressed the issue of multiple brain metastases and concluded that for 2-5 tumors "GKRS results in a better post-treatment KPS score, QALY, and higher cost-effectiveness than WBRT for treating multiple metastatic brain tumors."

Reference List: The Gamma Knife and the Treatment of Metastatic Brain Tumors (1989-2/2012)

1. Yamamoto, M., T. Kawabe, and B.E. Barfod, How many metastases can be treated with radiosurgery? Prog Neurol Surg, 2012. 25: p. 261-72.

2. Patel, T.R., et al., Implications of Identifying Additional Cerebral Metastases during Gamma Knife Radiosurgery. Int J Surg Oncol, 2012. 2012: p. 748284.

3. Kondziolka, D., et al., Gamma knife radiosurgery of other brain metastases. Prog Neurol Surg, 2012. 25: p. 190-200.

4. Chung, H.T. and D.G. Kim, Modern radiosurgery equipment for treating brain metastases. Prog Neurol Surg, 2012. 25: p. 236-47.

5. Yoo, T.W.P., E. S.; Kwon do, H.; Kim, C. J., Gamma knife radiosurgery for brainstem metastasis. J Korean Neurosurg Soc, 2011. 50(4): p. 299-303.

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Addendum A – ASTRO Brain Mets Guidelines

See separate attachment.

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Special Article

Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline

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Addendum B – Neuro Guidelines

See separate attachment.

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INVITED MANUSCRIPT

The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline

Mark E. Linskey · David W. Andrews · Anthony L. Asher · Stuart H. Burri · Douglas Kondziolka · Paula D. Robinson · Mario Ammirati · Charles S. Cobbs · Laurie E. Gaspar · Jay S. Loeffler · Michael McDermott · Minesh P. Mehta · Tom Mikkelsen · Jeffrey J. Olson · Nina A. Paleologos · Roy A. Patchell · Timothy C. Ryken · Steven N. Kalkanis

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Abstract

Question

Should patients with newly-diagnosed metastatic brain tumors undergo stereotactic radiosurgery (SRS) compared with other treatment modalities?

Target population

These recommendations apply to adults with newly diagnosed solid brain metastases amenable to SRS; lesions amenable to SRS are typically defined as measuring less than 3 cm in maximum diameter and producing minimal (less than 1 cm of midline shift) mass effect.

Recommendations

SRS plus WBRT vs. WBRT alone

Level 1 Single-dose SRS along with WBRT leads to significantly longer patient survival compared with WBRT alone for patients with single metastatic brain tumors who have a KPS > 70.

Level 2 Single-dose SRS along with WBRT is superior in terms of local tumor control and maintaining functional status when compared to WBRT alone for patients with 1–4 metastatic brain tumors who have a KPS > 70.

Level 3 Single-dose SRS along with WBRT may lead to significantly longer patient survival than WBRT alone for patients with 2–3 metastatic brain tumors.

Level 4 There is class III evidence demonstrating that single dose SRS along with WBRT is superior to WBRT alone for improving patient survival for patients with single or multiple brain metastases and a KPS < 70.

SRS plus WBRT vs. SRS alone

Level 2 Single-dose SRS alone may provide an equivalent survival advantage for patients with brain metastases compared with WBRT + single-dose SRS. There is conflicting class I and II evidence regarding the risk of both local and distant recurrence when SRS is used in isolation, and class I evidence demonstrates a lower risk of distant recurrence with WBRT; thus, regular careful surveillance is warranted for patients treated with SRS alone in order to provide early identification of local and distant recurrences so that salvage therapy can be initiated at the soonest possible time.

Surgical Resection plus WBRT vs. SRS ± WBRT

Level 2 Surgical resection plus WBRT, vs. SRS plus WBRT, both represent effective treatment strategies, resulting in relatively equal survival rates. SRS has not been assessed from an evidence-based standpoint for larger lesions (>3 cm) or for those causing significant mass effect (>1 cm midline shift). Level 3, Underpowered class I evidence along with the preponderance of conflicting class II evidence suggests that SRS alone may provide equivalent functional and survival outcomes compared with resection + WBRT for patients with single brain metastases, so long as ready detection of distant site failure and salvage SRS are possible.

SRS alone vs. WBRT alone

Level 3 While both single-dose SRS and WBRT are effective for treating patients with brain metastases, single dose SRS alone appears to be superior to WBRT alone for patients with up to three metastatic brain tumors in terms of patient survival advantage.

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Addendum C – Tsao, M., W. Xu, and A. Sahgal, A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. Cancer, 2011.

See separate attachment.

Original Article

A Meta-Analysis Evaluating Stereotactic Radiosurgery, Whole-Brain Radiotherapy, or Both for Patients Presenting with a Limited Number of Brain Metastases

May Tsao, MD[1], Wei Xu, PhD[2], and Arjun Sahgal, MD[3,4]

BACKGROUND: To perform a meta-analysis on newly diagnosed brain metastases patients treated with whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) boost versus WBRT alone, or in patients treated with SRS alone versus WBRT and SRS boost. **METHODS:** The meta-analysis primary outcomes were overall survival (OS), local control (LC), and distant brain control (DBC); secondary outcomes were neurocognition, quality of life (QOL), and toxicity. Using published Kaplan-Meier curves, results were pooled using hazard ratios (HR). **RESULTS:** Two RCTs reported on WBRT and SRS boost versus WBRT alone. For multiple brain metastases (2-4 tumors) we conclude no difference in OS, and LC significantly favored WBRT plus SRS boost. Three RCTs reported on SRS alone versus WBRT plus SRS boost (1-4 tumors). There was no difference in OS despite both LC and DBC significantly favoring WBRT plus SRS boost. Although secondary endpoints could not be pooled for meta-analysis, those RCTs evaluating SRS alone conclude better neurocognition using the validated Hopkins Verbal Learning Test, no advantage in deteriorating Mini-Mental Status Exam scores or in maintaining performance status, and fewer late toxicities. We conclude insufficient data for QOL outcomes. **CONCLUSIONS:** For selected patients, we conclude no OS benefit for WBRT plus SRS boost compared with SRS alone. Although additional WBRT improves DBC and LC, SRS alone should be considered a routine treatment option due to favorable neurocognitive outcomes, less risk of late side effects, and does not adversely affect the patient's performance status. **Cancer 2011;000:000–000.** © 2011 American Cancer Society.

KEYWORDS: brain metastases, stereotactic radiosurgery, whole brain radiotherapy, meta-analysis, neurocognition.

INTRODUCTION

Treatment options for selected patients with good prognosis (eg, Karnofsky performance status [KPS] at least 70% or World Health Organization (WHO) performance status of 0–2 and controlled or quiescent extracranial disease[1,2]) have evolved over the last few decades. Whole brain radiation (WBRT)[3] and steroids were the standard of care before the development of stereotactic radiosurgery (SRS). As SRS developed into a safe and focal high dose treatment for brain metastasis[4] to optimize local control, the first question to be tested was the use of SRS as a "boost" to WBRT.[5,6] Two randomized controlled trials (RCTs) were conducted and concluded significant improvements in local control secondary to boost SRS,[5,6] and 1 study reported a modest overall survival (OS) benefit for patients with only a single brain metastasis.[5]

The question then evolved to test SRS alone with the intent to spare patients the side effects of WBRT, notably neurocognition. The landmark RCT was reported in 2006 by Aoyama et al,[7] where patients with 1 to 4 brain metastases were randomized to SRS alone or WBRT and SRS boost. Although WBRT and SRS boost resulted in a modest gain in local control and a lower incidence of new brain metastases, no OS difference was observed (this trial was initially powered for OS; however, halted at the interim analysis with sufficient power to detect a significant difference in brain tumor recurrence rate). It is only recently that 2 RCTs[8,9] have been reported comparing SRS alone to WBRT and SRS boost to further our understanding of the treatment options and expand our knowledge beyond the Aoyama study.[7] However, these 2

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Addendum D – Apparatus dependence of normal brain tissue dose in stereotactic radiosurgery for multiple brain metastases

See separate attachment.

See the corresponding editorial. DOI: 10.3171/2010.11.JNS102024.

DOI: 10.3171/2011.1.JNS101696

Apparatus dependence of normal brain tissue dose in stereotactic radiosurgery for multiple brain metastases

Technical note

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Object. Technical improvements in commercially available radiosurgery platforms have made it practical to treat a large number of intracranial targets. The goal of this study was to investigate whether the dose to normal brain when planning radiosurgery to multiple targets is apparatus dependent.

Methods. The authors selected a single case involving a patient with 12 metastatic lesions widely distributed throughout the brain as visualized on contrast-enhanced CT. Target volumes and critical normal structures were delineated with Leksell Gamma Knife Perfexion software. The imaging studies including the delineated contours were digitally exported into the CyberKnife and Novalis multileaf collimator–based planning systems for treatment planning using identical target dose goals and dose volume constraints. Subsets of target combinations (2, 6, 9, or 12 targets) were planned separately to investigate the relationship of number of targets and radiosurgery platform to the dose to normal brain.

Results. Despite similar target dose coverage and dose to normal structures, the dose to normal brain was strongly apparatus dependent. A nonlinear increase in dose to normal brain volumes with increasing number of targets was also noted.

Conclusions. The dose delivered to normal brain is strongly dependent on the radiosurgery platform. How general this conclusion is and whether apparatus dependent differences are related to differences in hardware design or differences in dose planning algorithms deserve further investigation. (DOI: 10.3171/2011.1.JNS101696)

Key Words • **Gamma Knife** • **CyberKnife** • **Novalis** • **stereotactic radiosurgery** • **treatment planning** • **brain metastasis**

Stereotactic radiosurgery, with or without WBRT, is commonly used in the treatment of patients with a limited number of metastatic brain tumors. The clinical role of radiosurgery in patients with more than 4 or 5 brain metastases has not been established. Nevertheless, given the technical developments in SRS apparatuses in recent years, it is now practical to treat such patients with SRS with any of several various radiosurgery platforms, including Leksell Gamma Knife Perfexion (Elekta), CyberKnife (Accuray), and Novalis (BrainLAB AG).

Perfexion uses a new tecrot-based collimator design with collimators that can be activated rapidly to permit a large combination of beam apertures at the isocenter, resulting in reduced procedure times and highly conformal dose distributions for both individual and multiple targets.[5,10] The CyberKnife and Novalis multileaf collimator–based systems have had marked technical improvements applicable to the treatment of multiple targets.[4,9,17] In particular, there has been a several-fold increase in machine output and the speed of changing beam directions (CyberKnife) or individual multileaf-collimator leaf motions (Novalis). For treatment of a large number of brain lesions these technical features can be particularly beneficial.

For each of these technologies, there has been clinical concern regarding the dose to normal brain. For example, some studies have reported a possible relationship between normal brain volumes, such as the 10- or 12-Gy volume, and treatment-related toxicity,[3,7] and we have previously reported the possible need for target dose reductions in patients with multiple metastases treated with

Abbreviations used in this paper: SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

Addendum E – Excerpt from Regence BCBS Medical Policy on Stereotactic Radiosurgery

(http://blue.regence.com/trgmedpol/surgery/sur16.html)

Medical Policy

Introduction · Table of Contents · Recent Updates · Contact Medical Policy Staff

Surgery Section - Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

Topic: Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy
Section: Surgery
Effective Date: 01/01/2012

Date of Origin: 01/1996
Policy No: 16

POLICY/CRITERIA

I. Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) using Gamma Knife®, LINAC, Cyberknife®, BrainLAB Novalis®, or TomoTherapy® units may be considered **medically necessary** for the following indications:
   - A. Intracranial arteriovenous malformations
   - B. Acoustic neuromas (also known as Vestibular Schwannomas)
   - C. Pituitary adenomas
   - D. Non-resectable, residual, or recurrent meningiomas
   - E. Solitary or multiple brain metastases in patients who meet both of the following:
     1. Karnofsky performance score ≥70 (or an ECOG score ≤2); AND
     2. Life expectancy >6 months.
   - F. Primary malignancies of the CNS, including but not limited to high-grade gliomas (initial treatment or treatment of recurrence)
   - G. Spinal or vertebral body tumors (metastatic or primary) in patients who have received prior radiation therapy
   - H. Trigeminal neuralgia (also known as tic douloureux) refractory to medical management
   - I. Stage 1 non-small cell lung cancer (NSCLC) when the patient is an unsuitable candidate for surgical resection.
     1. Stage 1 NSCLC is defined by the following clinical stage groupings: [1]
        - a. T1, N0, M0
        - b. T2, N0, M0
   - J. Lung metastases when all of the following criteria are met:
     1. Life expectancy >6 months
     2. Karnofsky performance score ≥70
     3. Adequate lung function
     4. Locally controlled primary tumor
     5. ≤3 metastatic lung lesions (oligometastases)
     6. Targeted tumor diameter ≤5cm
     7. Clinical records from a cardiothoracic surgeon document at least one of the following:
        - a. The tumor is not resectable; or
        - b. The patient is not a good surgical candidate.
     8. No other metastatic disease
II. Stereotactic radiosurgery and stereotactic body radiation therapy are considered **investigational** for all other indications including but not limited to:
   - A. Functional disorders other than trigeminal neuralgia
   - B. Epilepsy
   - C. Chronic pain
   - D. Treatment of extracranial sites (e.g. prostate, ovaries), except for the cases of spinal tumors, stage 1 non-small cell lung cancer, and lung metastases as noted above
   - E. Refractory symptoms of essential tremor or Parkinson's disease

INTERNATIONAL RADIOSURGERY ASSOCIATION (IRSA)

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June 25, 2012

RE: WA Health Technology Assessment SRS and SBRT

To whom it may concern:

IRSA (International RadioSurgery Association) appreciates the opportunity to provide comments on the assessment of Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT). IRSA has operated since 1995 as an association which represents, among others, the gamma and linear accelerator stereotactic radiosurgery unit's installation base. Installations of this type are primarily hospital based and specialize in treating both brain tumors and brain disorders. The Association's mission is to provide education and guidance on radiosurgery to governments, regulatory agencies, insurers, patients and referring physicians. This is accomplished through providing practice guidelines, position statements, general literature, and comments on issues affecting operations or patient safety.

Until the late 2000s, Stereotactic Radiosurgery, by definition, was a single surgical procedure that takes advantage of an energy source that can be focused through tissue without incising it. Since then, 'short' fractions of generally five (5) or less utilizing high level technology (CyberKnife,® BrainLab, Novalis® and others) have commonly been accepted as part of the SRS definition. Radiosurgery may be gamma or linear accelerator based. Radiosurgery occurs in lieu of or as an adjunct to open skull surgery and is normally limited to intracranial locations. A multi-disciplinary team normally makes the decision whether to offer SRS. The team usually consists of a neurosurgeon, a radiation oncologist and a physicist.

IRSA's comments will be directed at SRS (defined as one-session or short fractions) and CNS tumors (intracranial lesions and disorders) at this time. We have no information or comments on SBRT or non-CNS tumors.

KQ1:
Stereotactic Radiosurgery has over 2,500 scientific articles supporting its use with CNS tumors and disorders over the use of external beam radiation therapy (EBRT), which in general may result in up to 30 fractions of radiation targeted over healthy brain tissue. These articles attest to significant outcomes when SRS is compared to EBRT for CNS tumors and disorders. We direct your attention to the selection of *evidence based* Radiosurgery Guidelines which are a part of this document. Each evidence based guideline was drafted and reviewed by a panel of committee members that consisted of both physicians who provide SRS and those who do not provide SRS. Each committee was composed of multidisciplinary specialties including neurosurgeons, radiation oncologists, physicists, and other medical specialties where appropriate (neurologists, endocrinologists and neurotologists, among others). We have included the patient related criteria to be considered when deciding whether SRS is appropriate and an algorithm for each diagnosis.

Acoustic Neuroma (Research References—110):
Patient factors to consider:

- Age and symptoms
- Tumor anatomy (intracanalicular)
- Brain stem compression and/or hydrocephalus
- Hearing status
- Current neurological status
- Medical condition
- Presence or absence of Neurofibromatosis 2
- Presence or absence of prior procedures
- Concern and risk tolerance for hearing, facial and trigeminal nerve function

The associated clinical algorithm suggests *microsurgery (open skull surgery), SRS and observation* dependent on the patient and his/her associated criteria. You will note that EBRT is not an option in this algorithm because EBRT would not be appropriate for the diagnosis.

Intracranial Arteriovenous Malformations (AVM) (Research References—84):
Patient factors to consider:

- Patient's medical condition
- Previous bleed(s)
- Prior procedures
- Volume of AVM
- Location of AVM
- Presenting symptoms

The associated clinical algorithm suggests *microsurgery (open skull surgery), embolization and SRS* dependent on the patient and his/her associated criteria. You will note that EBRT is not an option in this algorithm because EBRT would not be appropriate for the diagnosis.

Metastatic Brain Tumors (Research References—135):
Patient factors to consider:

- Patient's age and symptoms
- Status of systemic disease
- Patient's current neurological status
- Patient's medical condition and functioning level
- Presence or absence of other organ metastases
- History of prior whole brain radiation therapy (WBRT)
- History of prior brain procedures
- Patient's concern and risk tolerance for neuro-cognitive functions

The associated clinical algorithms suggest *biopsy, microsurgery (open skull surgery), SRS and EBRT (singly or in combination). EBRT in this algorithm is defined as WBRT or XRT. Whether to utilize SRS or EBRT radiation is highly dependent on the patient and his/her associated criteria.* EBRT may be utilized to momentarily delay the formation of new CNS metastases, but will not provide quality of life or extended survival for the patient.

Trigeminal Neuralgia Refractory to Medical Treatment (Research References—62):
Patient factors to consider:

- Patient's age
- Patient's medical condition
- Presence or absence of multiple sclerosis
- Presence or absence of vascular contact and/or compression on thin section MRI

- Presence or absence of prior procedure
- The type of prior procedure and its response
- Severity of pain and how long the patient can reasonably wait for pain relief

The associated clinical algorithm suggests *retro-mastoid craniotomy, microvascular decompression, percutaneous retrogasserian rhizotomy (by glycerol, radiofrequency or balloon compression) and/or SRS* dependent on the patient and his/her associated criteria. These procedures are for patients in which medications have not provided relief. EBRT is not appropriate to treat the diagnosis of Trigeminal Neuralgia and is not supported by research.

Pituitary Adenomas (Research References—70):
Patient factors to consider:

- Patient's age
- Hormonal status of the adenoma (secretory or non-secretory)
- Presenting symptoms and neurological status (vision) of the patient
- Patient's medical condition (comorbidities)
- Previous tumor resection (via trans-sphenoidal approach or craniotomy) history
- Prior radiation exposure
- Volume of the tumor
- Proximity to the optic apparatus
- Response to medical management

The associated clinical algorithm suggests *open skull surgery, adrenalectomy, dopamine agonists, octreotide, GH receptor antagonists, other medical interventions, and SRS* dependent on the patient and his/her associated criteria. When the patient is unsuitable for both surgery and SRS, then EBRT (preferably IMRT which is more focused) may be an option.

We encourage this technology board to review the complete and full narrative guideline for each indication which can be found at http://irsa.org/guidelines.html and on the National Guideline Clearinghouse website (NGC.gov). In this response to the questions we have only included parts of each guideline that were specifically addressed in the key questions. IRSA is currently updating all guidelines and preparing new ones for Essential Tremor, Meningiomas, and Gliomas. We are proud to state that many insurers utilize our guidelines in their coverage policies for their covered lives.

KQ2:
Unlike EBRT, SRS restricts the radiation of healthy tissue by restricting the targeting of the radiation to the tumor bed with negligible overlap to healthy tissue. Therefore by definition, EBRT is more harmful than SRS.

SRS and SBRT have been shown in research to provide the following positive effects over EBRT:

- Better local tumor control
- Extended survival
- Stable and improved functioning score (Karnofsky)
- Fewer complications
- Better quality of life
- Immediate return to work
- Easier procedure times by weeks
- Less burden on family to provide access and travel for EBRT versus a one session procedure
- Less staff and resource utilization by hospitals (1–5 procedures versus 30 procedures)
- No issues with fatigue, nausea or other effects of EBRT
- EBRT may result in more progression of disease or be simply inappropriate for CNS indications
- EBRT has been shown to rarely result in new tumors and reduce intellect where children are concerned

- There is also evidence that EBRT may cause permanent 'brain fog' in CNS patients, thus lowering their survival quality of life
- EBRT within the brain will only work to limit the progression of existing 'seeding' of tumors to the brain or spine. Within a few months after EBRT treatment, new tumors can appear from seeding of the systemic cancer. At that time, EBRT can usually not be repeated and SRS and SBRT are the only procedures available to the patient.

KQ3:
Please review our guidelines and answers to KQ1. Patient criteria for utilization of SRS are clearly provided. Except with CNS metastases or malignant tumors, EBRT may be totally inappropriate for benign brain tumors and CNS disorders. In children, EBRT can result in permanent intellectual issues. It should be noted that EBRT can be utilized only once with CNS tumors. Since SRS does not spread radiation throughout the brain and is focused, it can be utilized more than one time and after EBRT has failed.

The CNS system can be damaged by EBRT. Acute and subacute transient symptoms may develop early but progressive, permanent, often disabling nervous system damage may not appear for months to years. The total radiation dose, size of the fractions, duration of therapy, and volume of [healthy brain] nervous tissue irradiated influence the likelihood of injury. Considerable variation in individual susceptibility complicates the effort to predict safe radiation doses.

Acute reactions occur during or immediately after radiation. They are normally caused by swelling and can be easily controlled with medications. Delayed or late reactions are normally permanent and can be progressive. They can vary from mild to severe and may include decreased intellect, memory impairment, confusion, personality changes and more. All symptoms would be dependent on the amount of healthy tissue targeted with radiation.

Oncogenesis, the development of another tumor caused by radiation treatment to the brain, is now a recognized, although rare, possible long-term side effect of EBRT to the brain.

EBRT may target wide areas of the brain resulting in more neurotoxicity. Significant neurotoxicity has been reported with the use of EBRT. Acute effects include hair loss (alopecia), nausea, vomiting, lethargy, otitis media and severe cerebral edema. Though some of these effects can be transient, dermatitis, alopecia, and otitis media can persist for months after irradiation. Chronic effects are even more serious, and these include atrophy, leukoencephalopathy, radiation necrosis, neurological deterioration and dementia.

Reports of development of severe radiation induced dementia have varied between 11% in one-year survivors to 50% in those surviving two years. The time involved in this therapeutic intervention frequently is two to six weeks, in itself a burden to many patients.

We now know that new tumors may again 'seed' to the brain within a few months of having completed whole brain radiation. Thus the treatment may only help for one point in time. Unlike radiosurgery or conformal radiotherapy, there is a limit to how much whole brain radiation therapy a person may have. This is usually 6000 gray.

EBRT is the most damaging of all types of radiation treatments and causes the most severe side effects in the long run to patients. In the past, patients who were candidates for whole brain radiation were selected because they were thought to have limited survival times of less than 1–2 years and other technology did not exist. Patients in good survival status (more than 18 months) may need to question the use of EBRT as a first line of defense when one-session radiosurgery or multi-session stereotactic radiotherapy can be repeated for original tumors or used for additional tumors with little or no side effects from radiation to

healthy tissues. Major studies and research have shown that the benefits of radiosurgery and stereotactic radiotherapy are more effective than EBRT, without the side effects.

KQ4A: Costs

IRSA surveyed its member hospitals regarding the CPT codes they use for SRS, SBRT and EBRT. We have provided the information for each of these procedures. In our analysis we used the codes which more than 50% of members reported using for a service. While there was some variation, we noted that differences would not have changed the overall ranking and results. We applied Medicare reimbursement amounts to each CPT code, so that the services for SRS, SBRT, and EBRT would be comparable. Medicare determines what it deems to be costs by utilizing the Hospital Medicare Cost Report to determine a rate that approaches cost. With this method there are no differences in the cost results of the analysis, whether the procedure is intracranial or a body treatment. We found the following results for a complete course of treatment for each method and have provided the detailed analysis for your review:

SRS Intracranial Only Technical Costs, 1 Session Cobalt Gamma Knife®	$ 9,385
SRS/SBRT Image Guided Robotic Technical Costs, 1 Session Linac	$ 9,269
SRS/SBRT Image Guided Robotic Technical Costs, 5 Fractions Linac	$19,456
EBRT 10 Sessions Technical Costs (Becoming more Common)	$11,533
EBRT 15 Sessions Technical Costs (Most Common)	$14,103
EBRT 30 Sessions Technical Costs (Not as Common)	$21,603

We submit to the Technology Assessment group that the costs above are only the facility/technical costs and do not include professional costs. EBRT would have the highest professional costs over the one or five sessions SRS/SBRT when the resources of the physicians for EBRT (which is given over days and weeks) are added to the facility costs above.

KQ4B: Cost Effectiveness

Our association believes it is clear that SRS/SBRT is less costly than EBRT both in monetary figures and in damage to the patient. SRS and SBRT have been shown in research to provide the following positive effects over EBRT:

- Better local tumor control
- Extended survival time
- Stable and improved functioning score (Karnofsky)
- Fewer complications
- Better quality of life
- Minimal cognitive impairment
- Immediate return to work
- Shorter procedure times by weeks
- Less burden on family to provide access to and travel for a one session procedure versus EBRT
- Less staff and resource utilization by hospitals (1–5 procedures versus 30 procedures)
- No issues with fatigue, nausea or other effects of EBRT
- EBRT may result in more progression of disease or be simply inappropriate for CNS indications
- EBRT has been shown to rarely result in new tumors and reduce intellect in children
- There is also evidence that EBRT may cause permanent 'brain fog' in CNS patients, thus lowering their survival quality of life
- EBRT within the brain will only work to limit the progression of existing 'seeding' of tumors to the brain or spine. Within a few months after EBRT treatment, new tumors can appear from seeding of the systemic cancer. At that time, EBRT can usually not be repeated and SRS and SBRT (which can be utilized several times because of the sparing of healthy tissue) are the only procedures available to the patient.

SRS Intracranial/Technical Costs for 1 Session Delivery [Cobalt]

Gamma Knife® RadioSurgery

Note: Does not include Professional Fees

Medicare reimbursement is used as a comparator to costs. Medicare does not seek to reward treatments but to reimburse for the costs of the procedure. (Source: Member Centers 20+)

Total Medicare Reimbursement for one session Cobalt (Gamma Knife®)

	No. Times	MC Rate	Total
77295	1	$955	$955
77334	3	200	600
77470	1	395	395
77300	1	107	107
77370	1	107	107
77371	1	107	7221

TOTAL for One Session Cobalt ***$9,385***

The Hospital's Specific Wage Base is added to the above number.

SRS Intracranial Procedure Facility Costs for One Session & Five Sessions

Image Guided Robotic RadioSurgery -- Linac

CyberKnife®, Novalis®, Rapid Arc®, Synergy® and others

Note: Does not include Professional Fees

Each provider treats each patient on a case by case basis and the following may vary. Medicare reimbursement is used as a comparator to costs. Medicare does not seek to reward treatments but to reimburse for most of the cost. (Source: Survey of 15 member sites,)

		Times			
Pre Treatment Simulation for EBRT					
77401	CT for placment of fields	1	955	$955	
77290	Complex Simulation	1	264	264	
77334	Immobilizaton frame/body fixatio	4	200	800	
77333	Bite Block Custom	2	200	400	
77470	Special TX Procedure	1	395	395	
Pre Treatment review of above films and software					
77295	3-D Planning	1	955	955	
77301	Inverse Planning	1	955	955	
77370	Physics Consult	1	107	107	
First Session Day					
77290	Verify Day of Treatment	1	264	264	
77334	Beam Modification Devices Verfie	4	200	800	
G0339	Treatment Delivery Single Fraction	1	3374	3374	
	TOTAL for One Session				***$9,269***
2nd through 5th Session Day					
G0340	Robotic Delivery 2-5 day	4	2520	10080	
77336	On-going Physics	1	107	107	
	Total for 2nd through 5th Fractions				**$10,187**
	TOTAL for 5 Fractions				***$19,456***

The Hospital's Specific Wage Base is added into the above number.

EBRT Facility/Technical Costs Treatments

Note: Does not include Professional Fees

Each provider treats each patient on a case by case basis and the following may vary. While EBRT may be done over 30 treatments, there is growing information that 15 treatments to 30 gy is becoming the norm. Therefore we have utilized a 15 day treatment. Medicare reimbursement is used as a comparator to costs. Medicare does not seek to reward treatments but to reimburse for most of the cost. (Source: Survey of 12 member sites,)

Pre Treatment Simulation for EBRT

77401	CT for placment of fields	Multiple
77290	Complex Simulation	
77334	Immobilizaton frame/body fixation	Multiple
77333	Bite Block Custom	Multiple
77470	Special TX Procedure	

Pre Treatment review of above films and software

77295	3-D Planning	
77300	Dose Calculations	Multiple
77370	Physics Consult	

First Treatment Day through last Treatment Day		**15 days**
77290	Verify Day of Treatment	Weekly and Pre Tx
77334	Beam Modification Devices Verfied daily	Daily
77336	On-going Physics Billed weekly	Weekly
77305-315	Teletherapy Isodose Plans	Daily
77401-77416	Treatment Delivery by complexity and voltage	Daily

Total Medicare Reimbursement assuming 15 days of EBRT:

	No. Times	MC Rate	Total	
77295	1	$955	$955	
77290	5	264	1320	
77334	16	200	3200	
77310	16	107	1712	
77333	4	200	800	
77401	3	99	297	
77470	1	395	395	
77300	8	107	856	
77370	1	107	107	
77336	3	107	321	
77305-315	15	107	1605	
77408*	15	169	2535	
TOTAL for 15 Sessions EBRT			***$14,103***	***EBRT 15 Sessions***
TOTAL for 10 Sessions EBRT			***$11,533***	***EBRT 10 Sessions***
Estimated TOTAL for 30 Sessions			***$21,603***	***EBRT 30 Sessions***

The Hospital's Specific Wage Base is added into the above number.

* 77408 Treatment Delivery: Intermediate -- 2 separate treatment areas. Three or more ports to each area, multiple non-complex devices For 6-10 MeV machines.

Summary:
As documented by the evidence based guidelines IRSA developed for intracranial diagnoses, SRS, SBRT and EBRT **all** have a place in the treatment of these formidable diseases and conditions. Only by assessing the patient's condition, functioning level, prior procedures, location of the offending tumor or disorder, can an assessment be made as to what procedure(s) and when are best for the patient. As we have tried to note here, there are disease processes where EBRT is clearly not a choice and SRS and SBRT are. We should not forget that patients also have the right to choose and decide what is best for themselves and their quality of life, as well as their survival time. We would like to stress, there is little difference from our analysis of these techniques for intracranial diagnoses and for body diagnoses.

While all can benefit from SRS and SBRT, it is of great concern to our Association that the elderly and the working poor have the opportunity to avail themselves of one or few session SRS and SBRT procedures. These two groups have much to gain from these procedures.

We hope this information will be useful to you in the assessment of SRS, SBRT and EBRT. We would be pleased to ask one of our Board members that works in the State of Washington to speak to your panel if it would be beneficial. Please take the time to obtain our full guidelines which contain formerly written narratives of the evidenced based research supporting our algorithm(s) in the guidelines.

Yours Sincerely,

Rebecca L Emerick/e-sign

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Partial Guideline Attachments

DISEASE/CONDITION: *Vestibular Schwannoma (acoustic neuroma)*

Radiosurgery[1] Practice Guideline Report # 4-06

GROUP COMPOSITION:

This radiosurgery guidelines group is comprised of neurosurgeons, neurotologists, and radiation oncologists.

Names of Group Members: L. Dade Lunsford, M.D., Neurosurgeon, Chair; Ajay Niranjan, M.B.B.S., M.Ch., Neurosurgeon; Georg Norén, M.D., Neurosurgeon; Jay Loeffler, M.D., Radiation Oncologist; Alain de Lotbinière, M.D., Neurosurgeon; Jordan Grabel, M.D., Neurosurgeon; Douglas Kondziolka, M.D., Neurosurgeon; Jean Régis, M.D., Neurosurgeon; Pierre-Hughes Roche, M.D., Neurosurgeon; Robert Smee, M.D., Radiation Oncologist; Neurosurgeon; Burton Speiser, M.D., Radiation Oncologist; Mark Alden, M.D., Radiation Oncologist; Sandra Vermeulen, M.D., Radiation Oncologist; William F. Regine, M.D., Radiation Oncologist; Barry Hirsch, M.D., Neurotologist; Tonya K. Ledbetter, M.S., M.F.S., Editor; Rebecca L. Emerick, M.S., M.B.A., C.P.A., ex officio.

NUMBER OF REFERENCES: 110

Clinical Algorithm

A number of patient related factors are considered in making a recommendation. These factors include:

- Patient desires
- Tumor size and anatomy
- Current impairment
- Patient's decision after informed consent

Preoperative Hearing Level

Opinions vary considerably about what constitutes useful hearing. The 50/50 rule is frequently quoted. The rule suggests that individuals with a pure-tone average greater than 50 dB and speech discrimination less than 50% do not have useful hearing.

Tumor Anatomy

Radiosurgery can be performed for intracanalicular tumors and small to medium size tumors without brainstem compression and without signs of hydrocephalus. If hydrocephalus is present in old or infirm patients, a shunting procedure should be considered in addition to radiosurgery. There is no broadly accepted classification of tumor volumes. In addition to tumor diameter, Koos classification[46] is useful because it takes into account the mass effect of the tumor on the brainstem. Koos IV tumors (large tumors with brain shift) with a main diameter less than 3 cm should be offered microsurgery as first management. For intracanalicular tumors, hearing level may influence the decision.[7] Some authors believe that for tumors with a predominant cystic component microsurgery may be more suitable.

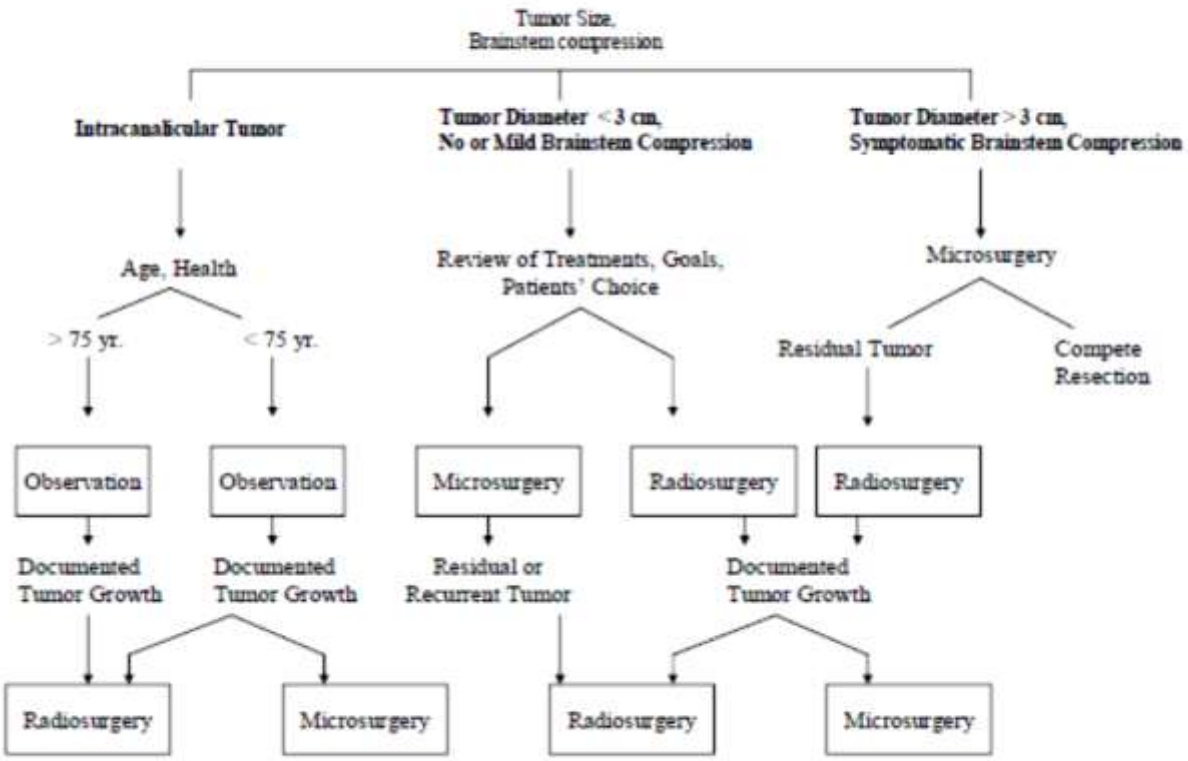
Patient Preference

Patients' preference is also considered in selecting a management approach. Some patients prefer tumor removal rather than tumor stabilization. Some patients are willing to sacrifice good hearing if doing so even slightly enhances the possibility of complete tumor removal. For these patients tumor resection is an obvious choice. Many patients prefer effective non-invasive management techniques like radiosurgery. Some patients insist on hearing conservation even when the treating physician is quite convinced that the patient's preoperative hearing is non-serviceable.

Neurofibromatosis 2

Considerations in NF2 patients may be different and additional parameters such as contralateral hearing, previous treatment, lip reading acquisition and additional tumors should be taken into account.

Management Algorithm for Acoustic Tumors



Go to www. IRSA.org/guidelines for a full copy of the guideline and references

[1] Radiosurgery is defined as one session or short fractions of 5 or less.

DISEASE/CONDITION: *Intracranial Arteriovenous Malformations (AVM)*
Radiosurgery[1] Practice Guideline Report #2-03

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

The radiosurgery guidelines group is comprised of neurosurgeons, radiation oncologists and physicists. Community representatives did not participate in the development of this guideline.

Committee Members: L. Dade Lunsford, M.D., Neurosurgeon, Chair; Douglas Kondziolka, M.D., Neurosurgeon; Ajay Niranjan, M.B.B.S., M.Ch., Neurosurgeon; Christer Lindquist, M.D., Neurosurgeon; Jay Loeffler, M.D., Radiation Oncologist; Michael McDermott, M.D., Neurosurgeon; Michael Sisti, M.D., Neurosurgeon; John C. Flickinger, M.D., Radiation Oncologist; Ann Maitz, M.S., Medical Physicist; Michael Horowitz, M.D., Neurosurgeon and Interventional Radiologist; Tonya K. Ledbetter, M.S., M.F.S., Editor; Rebecca L. Emerick, M.S., M.B.A., C.P.A., ex officio.

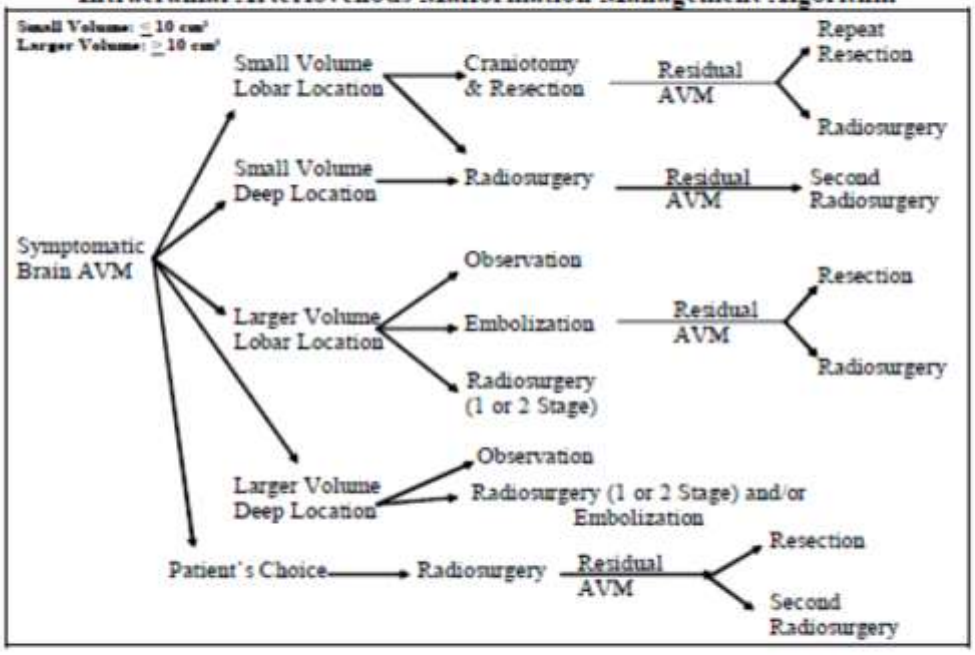
References: 84

Clinical Algorithm

A number of factors are considered in making a recommendation. These factors include:

- Patient's age
- Patient's medical condition
- Previous bleed
- Prior procedures
- Volume of AVM
- Location of AVM
- Presenting symptoms

Intracranial Arteriovenous Malformation Management Algorithm



Go to www.IRSA.org/guidelines for a full copy of the guideline and references

[1] Radiosurgery is defined as one session or short fractions of 5 or less.

Radiosurgery[1] Practice Guideline Report # 5-08

Group Composition

The radiosurgery guidelines group is comprised of neurosurgeons, neuro-oncologists, radiation and medical oncologists and physicists. Community representatives did not participate in the development of this guideline.

Names of Group Members: Ajay Niranjan, M.B.B.S., M.Ch., Neurosurgeon, Chair; L. Dade Lunsford, M.D., Neurosurgeon; Richard L. Weiner, M.D., Neurosurgeon; Gail L. Rosseau, M.D., Neurosurgeon; Gene H. Barnett, M.D., F.A.C.S., Neurosurgeon; Massaki Yamamoto, M.D. Neurosurgeon; Lawrence S. Chin, M.D., F.A.C.S., Neurosurgeon; Paul J. Miller, M.D., Radiation Oncologist; Andrew E. Sloan, M.D., Neurosurgeon; Burton L. Speiser, M.D., Radiation Oncologist; Sandra S. Vermeulen, M.D., Radiation Oncologist; Harish Thakrar, M.D., Radiation Oncologist; Frank Lieberman, M.D., Neuro-Oncologist; David Schiff, M.D., Neuro-Oncologist; Sammie R. Coy, Ph.D., Medical Physicist; Tonya K. Ledbetter, M.S., M.F.S., Editor; Rebecca L. Emerick, M.S., M.B.A., C.P.A., ex officio.

References: 135

Clinical Algorithm

Several factors are considered in making a recommendation. These factors include:

- Patient's age
- Patient's symptoms
- Status of systemic disease
- Patient's current neurological status
- Patient's medical condition
- Presence or absence of other organ metastases
- History of prior WBRT
- History of prior brain procedures
- Patient's concern and risk tolerance for neuro-cognitive functions
- Patient's wishes

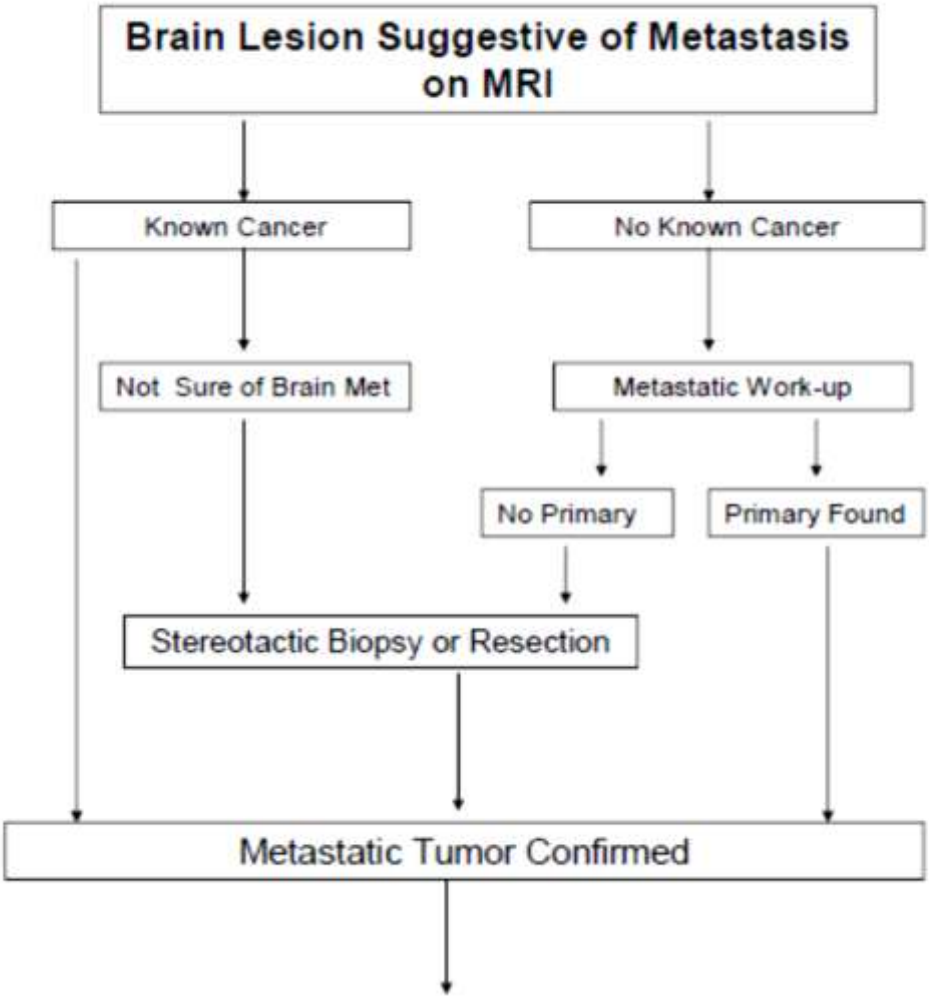
Tumor Size

Radiosurgery can be performed for tumors up to 4 cm in maximum diameter. However, tumor volume, dose and location are more important variables.

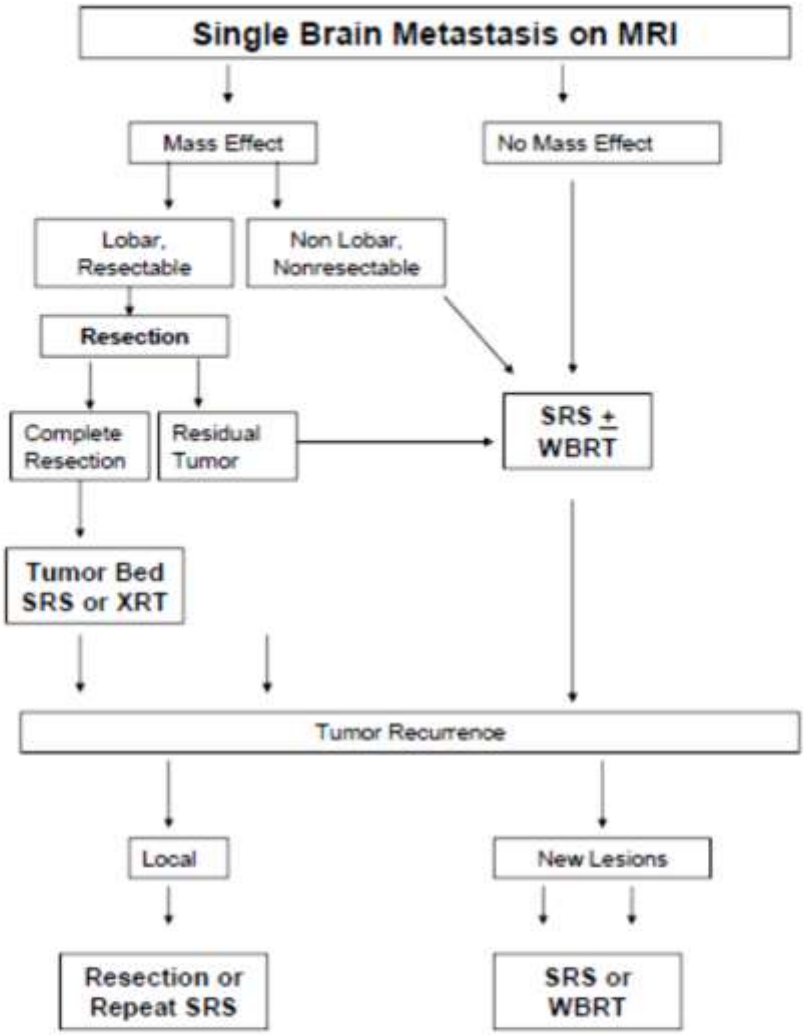
Patient Preference

Patients' preferences are also considered in selecting a management approach.

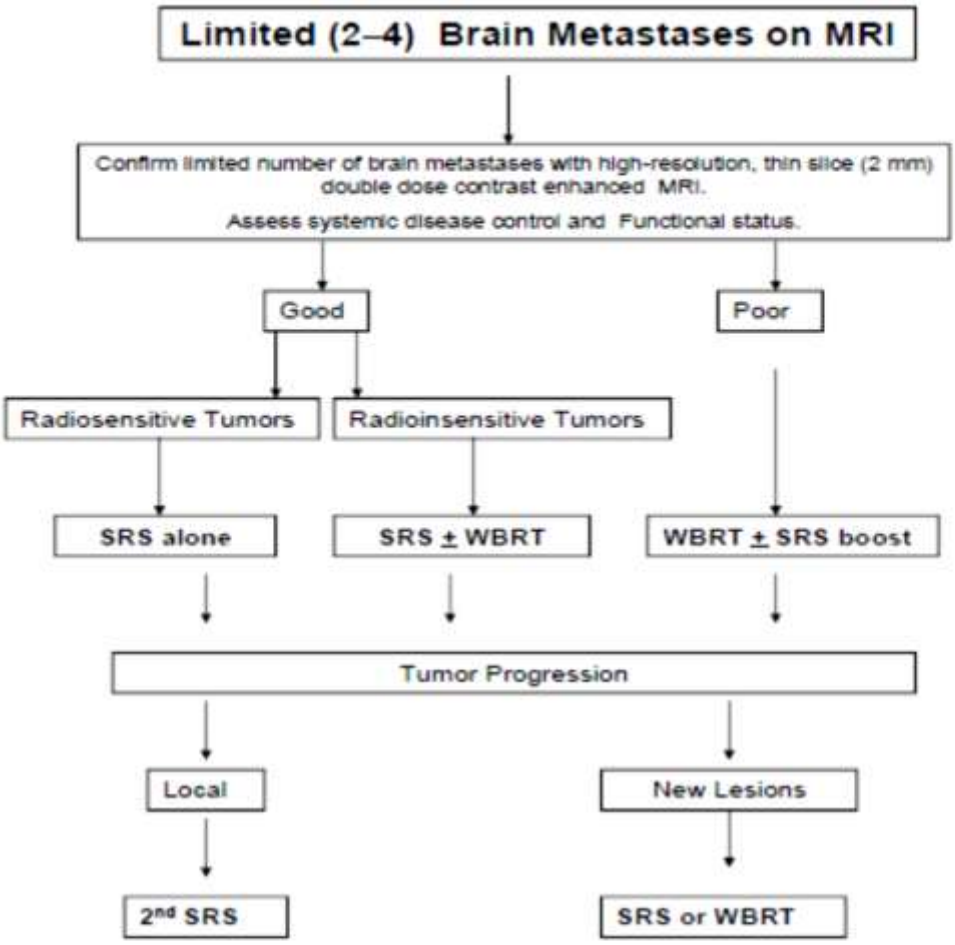
A broad outline of brain metastases diagnostic work-up and management algorithms for single tumor, limited brain disease (2–4 tumors) and multiple metastases are shown. However, the final recommendation is usually influenced by the recommending surgeon's, radiation oncologist's and neuro-oncologist's experiences along with patient preference.

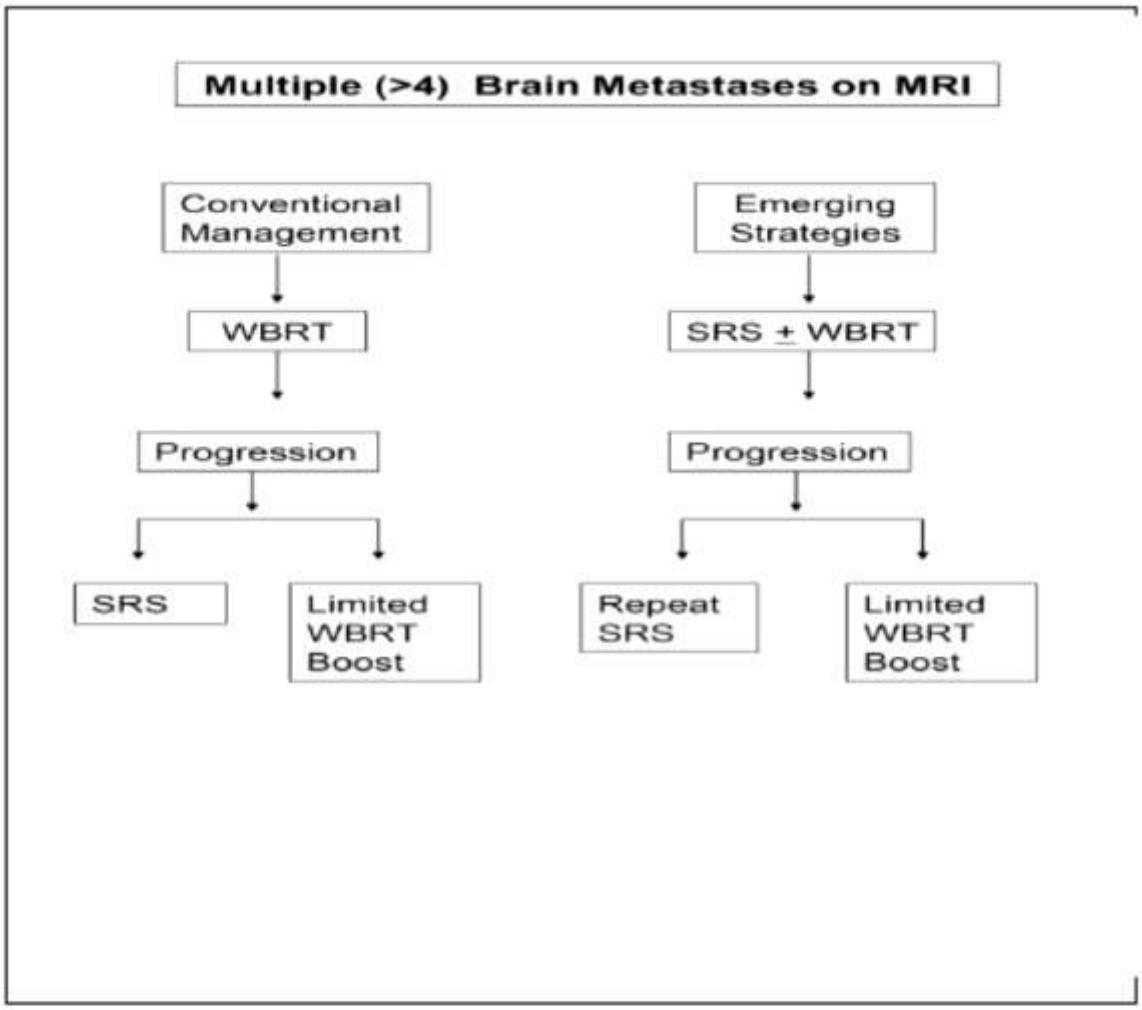


1. Discuss roles of SRS, WBRT, Resection and Chemotherapy at different stages in treatment.
2. Assess systemic disease (status of primary and metastases in other organ systems).
3. Address concerns regarding cognitive effects, local and distant tumor control.
4. Help patient choose appropriate management option.
5. Start treatment with patient's first choice of management.


Single Brain Metastasis on MRI
Mass Effect
No Mass Effect
Lobar, Resectable
Non Lobar, Nonresectable
Resection
Complete Resection
Residual Tumor
SRS ± WBRT
Tumor Bed SRS or XRT
Tumor Recurrence
Local
New Lesions
Resection or Repeat SRS
SRS or WBRT

Metastatic Brain Tumors Continued





Go to www. IRSA.org/guidelines for a full copy of the guideline and references

1 Radiosurgery is defined as one session or short fractions of 5 or less.
2 WBRT is defined as external beam radiation therapy in up to 30 fractions.

DISEASE/CONDITION: *Intractable Typical Trigeminal Neuralgia who have failed Medical Management*

Radiosurgery[1] Practice Guideline Report #1-03

Group Composition:
The radiosurgery guidelines group is comprised of neurosurgeons, radiation oncologists and physicists. Community representatives did not participate in the development of this guideline but will in future updates.

Names of group members: Drs. L. Dade Lunsford, M.D., Neurosurgeon, Chair; Ajay Niranjan, M.B.B.S., M.Ch., Neurosurgeon; Ron Young, M.D., Neurosurgeon; Ronald Brisman, M.D., Neurosurgeon; David Cunningham, M.D., Neurosurgeon; Christer Lindquist, M.D., Neurosurgeon; David Newell, M.D., Neurosurgeon; John C. Flickinger, M.D., Radiation Oncologist; Ann Maitz, M.S., Medical Physicist; Rebecca L. Emerick, M.S., M.B.A., C.P.A., "ex officio."

References: 62

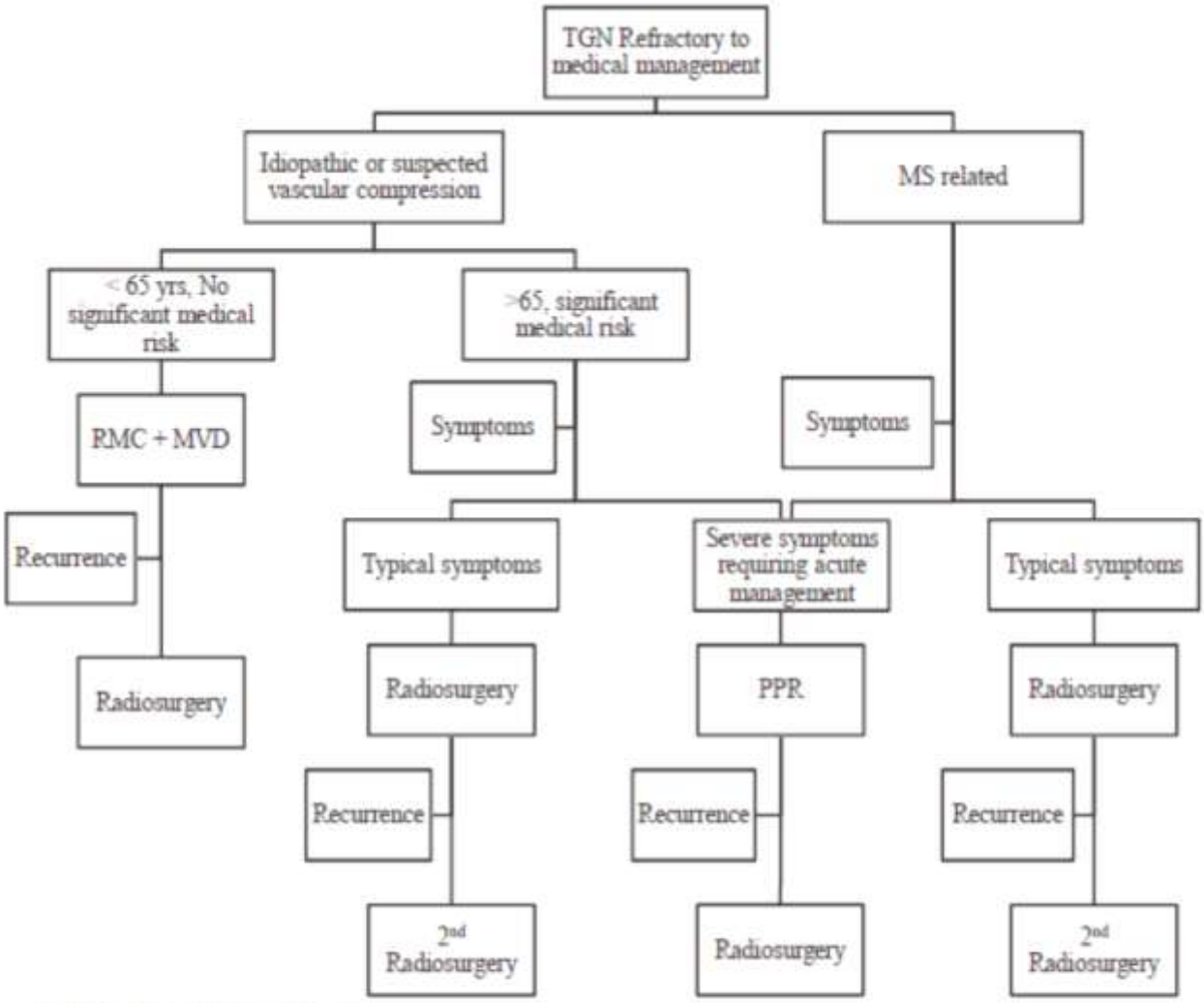
CLINICAL ALGORITHM(S):

A number of factors are considered in making a recommendation. These factors include:

- Patient's age
- Patient's medical condition
- Presence or absence of multiple sclerosis
- Presence or absence of vascular contact and/or compression on thin section MRI
- Presence or absence of prior procedures
- The type of prior procedure and its response
- Severity of pain and how long the patient can reasonably wait for pain relief
- Patient's concern and risk tolerance for dysesthesias, recurrence, or complications from surgery

A broad outline of management algorithm is shown below, however, the final recommendation is usually influenced by the recommending neurosurgeon's experience.

Intractable Typical Trigeminal Neuralgia Continued



RMC = Retro-Mastoid Craniotomy,
MVD = Microvascular decompression,
PRR = Percutaneous Retrogassarian Rhizotomy (Glycerol / Radiofrequency / Balloon compression)

Go to www. IRSA.org/guidelines for a full copy of the guideline and references

Radiosurgery/SRS = Defined as one session, short fractions are not supported by research at this time.

DISEASE/CONDITION: *Pituitary Adenomas*

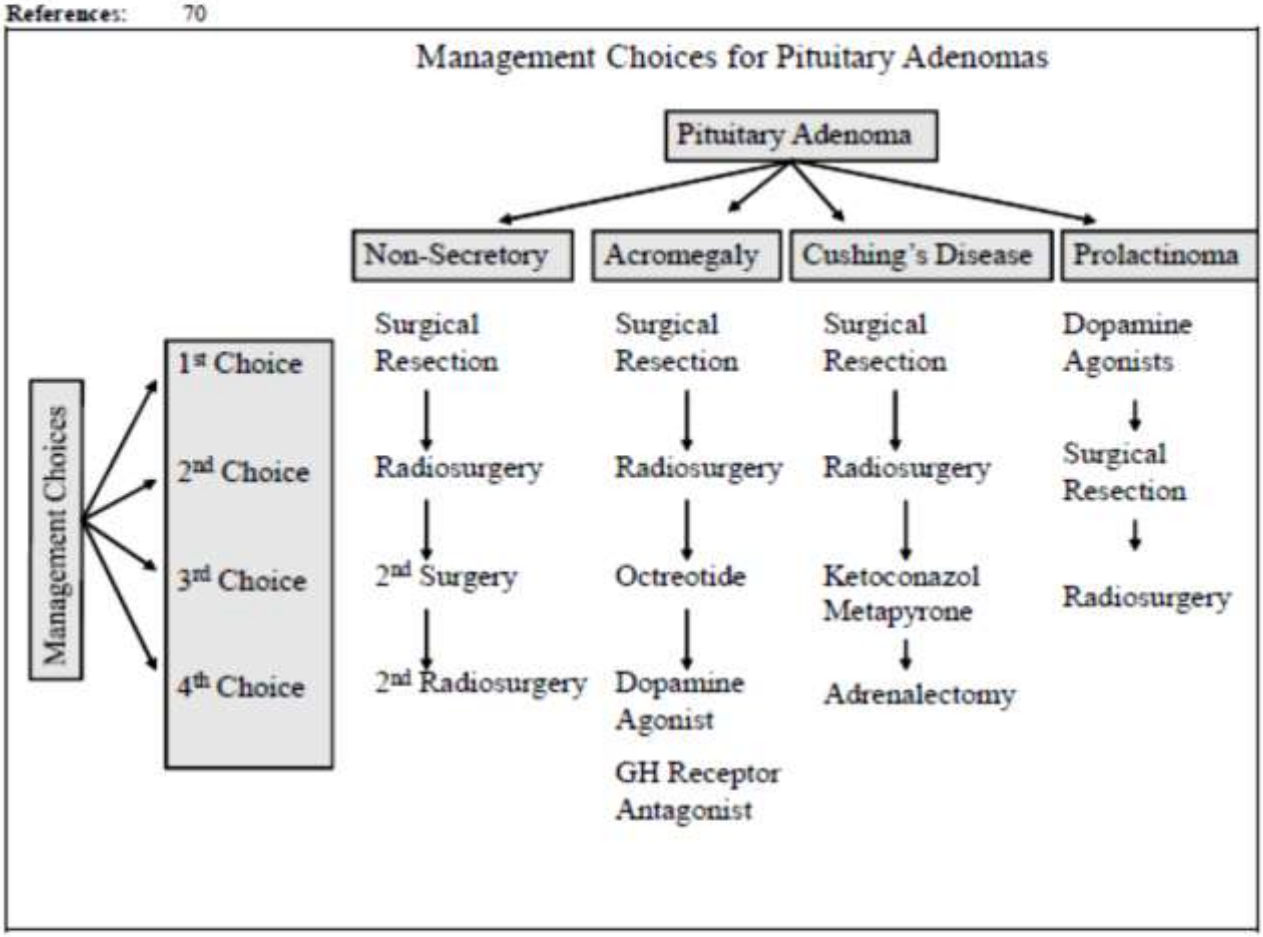
Radiosurgery[1] Practice Guideline Report #3-04

Group Composition

The Radiosurgery Guidelines Committee is comprised of neurological surgeons, radiation oncologists, physicians, endocrinologists and medical physicists.

Names of Group Members: L. Dade Lunsford, M.D., Neurosurgeon, Chair; Ajay Niranjan, M.B.B.S., M.Ch., Neurosurgeon; Tatsuya Kobayashi, M.D., Ph.D., Neurosurgeon; Mark Linskey, M.D., Neurosurgeon; Thomas Witt, M.D., Neurosurgeon; Alex Landolt, M.D., Neurosurgeon; Roman Liscak, M.D., Neurosurgeon; Edward R. Laws Jr., M.D., Neurosurgeon; Mary Lee Vance, M.D., Endocrinologist; John Buatti, M.D., Radiation Oncologist; Jonathan Knisely, M.D., Radiation Oncologist; Paul Sperduto, M.D., Radiation Oncologist; Sammie Coy, Ph.D., Medical Physicist; Tonya K. Ledbetter, M.S., M.F.S., Editor; Rebecca L. Emerick, M.S., M.B.A., C.P.A., ex officio.

References: 70



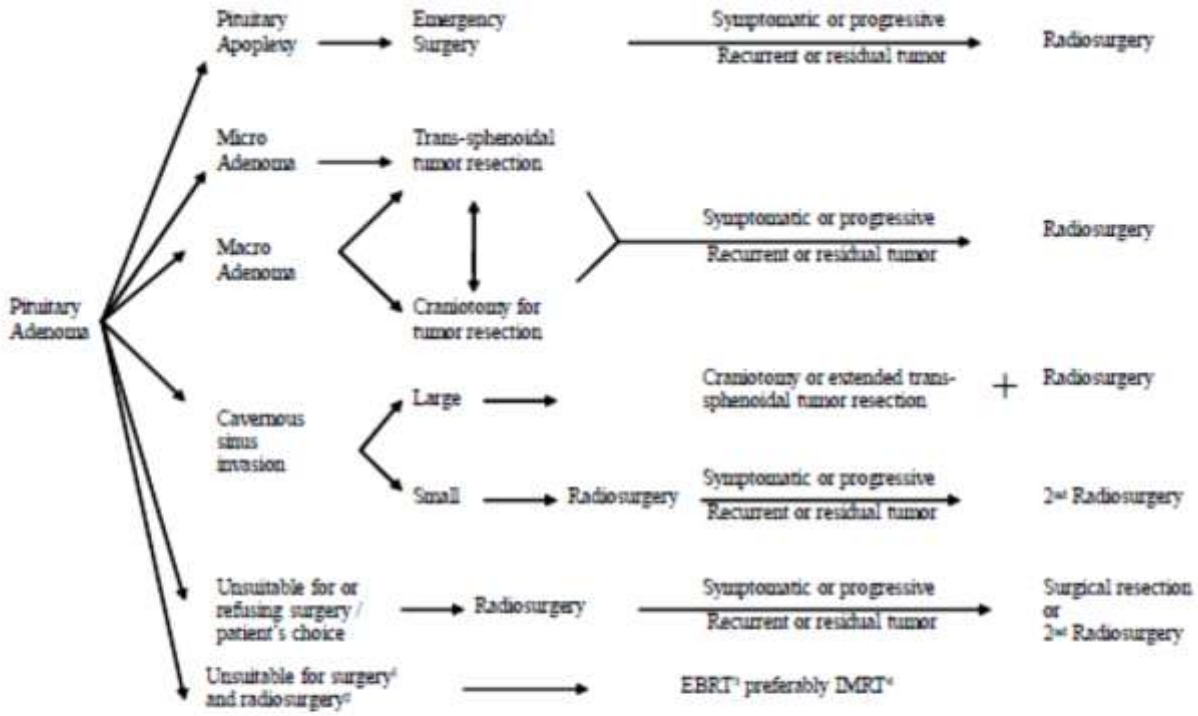
Pituitary Adenomas Continued

Management considerations

A number of factors are considered in making a recommendation regarding management of Pituitary Adenomas. These factors include:

- Patient's age
- Hormonal status of the adenoma (secretory or non-secretory)
- Presenting symptoms and neurological status (vision) of the patient
- Patient's medical condition (comorbidities)
- Previous tumor resection (via trans-sphenoidal approach or craniotomy) history
- Prior radiation exposure
- Volume of the tumor
- Proximity to the optic apparatus
- Response to medical management

Pituitary Adenoma Management Algorithm



[1] High risk for general anesthesia. [2] Tumor too large. [3] External Beam Radiation Therapy. [4] Intensity Modulated Radiation Therapy

Radiosurgery/SRS = Defined as one session. Short fractions are not supported by research at this time.

Go to www. IRSA.org/guidelines for a complete copy of the guideline, which includes a discussion of the research and a listing of all references

NANCY LANG

From: Nancy Lang

To: HCA ST Health Tech Assessment Prog
Cc: cbonetti@accuray.com
Subject: CyberKnife radiosurgery safety and funding comments
Date: Friday, March 02, 2012 4:45:40 PM

2 March 2012

I am a 70 year old woman with ovarian cancer. My first diagnosis was in December 2004 with surgery and complete hysterectomy, followed in January 2005 by chemotherapy, a combination of carboplatin and taxol. My cancer returned in 2007 with a duplication of the previous chemotherapy and, in 2010 another round of chemotherapy with an addition of Avastin.

In 2011, after a reaction to the carbo and taxol, I continued on a different treatment option of cisplatin and gemsidibine while waiting for approval for CyberKnife radiosurgery. I selected to go with CyberKnife because a new tumor, detected in a November 2010 PET –CT showed the location in the *periportal region*. Surgery in this area is not a good option.

After receiving marker fiducials my CyberKnife treatment began the end of February over a period of five treatments. I had neither pain nor any negative reaction during or after my treatment.

A November 2011 follow-up PET-CT displayed a recurrence in *aortocaval lymph nodes*, requiring additional treatment. After three medical opinions clearly stating that, because of the location of the recurrence, surgery was not an option and chemo was taking a toll on my body, CyberKnife would be the best treatment.

With my health insurance approval we started treatment January 3, 2012 for five days. I walked daily, after each treatment, and continue to do so. I felt nothing during the treatment, maybe one slow day when I felt a little tired but, in general I feel perfectly normal.

With my experience, I can highly vouch for the value of CyberKnife treatment process and recommend it be funded by all health care programs.
Sincerely,

Nancy Lang
808 Golf Course Road
Port Angeles, WA 98362
(360) 452-4348
nancyplang@yahoo.com

L. DADE LUNSFORD (UNIVERSITY OF PITTSBURG PHYSICIANS, DEPARTMENT OF NEUROLOGICAL SURGERY)

UPMC | University of Pittsburgh Medical Center

University of Pittsburgh Physicians
Department of Neurological Surgery

February 26, 2012

School of Medicine

L. Dade Lunsford, MD, FACS
Lars Leksell Professor
University of Pittsburgh
Residency Director
Director
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412-647-6781
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Washington State Healthcare Authority
Health Technology Assessment
Email: shtap@hca.wa.gov

RE: Stereotactic Radiosurgery

Dear Sirs:

It gives me pleasure to be able to comment directly upon the current evaluation under your auspices related to stereotactic radiosurgery. I serve as chair of the Technology Assessment Committee for UPMC (a 9 billion dollar integrated delivery system in Western Pennsylvania), chair of the Medical Advisory Board of the International Radiosurgery Association (IRA) and chair of the North American Gamma Knife Consortium. As an individual, I have spent a large part of my academic career in the field of minimally invasive surgery. I would like to provide the following data:

1. Stereotactic radiosurgery is an integral part of the field of neurosurgery with collegial interaction with the field of radiation oncology. At our center, more than 11,300 patients have undergone Gamma Knife stereotactic radiosurgery over the last 25 years since we placed the first Leksell Gamma Knife in North America.

2. Stereotactic radiosurgery is used for approximately 20% of all brain indications for intervention at our center with an increasing role in the management of metastatic cancer, arteriovenous malformations, chronic pain especially related to trigeminal neuralgia, glial neoplasms, and a wide variety of skull-based tumors including pituitary tumors.

3. In the last 25 years, more than 5000 outcome studies have been published related to Gamma Knife radiosurgery, and it is approved for use by all insurance providers. This type of technique has been a radical transformation in the management of patients with a wide variety of otherwise frequently fatal brain conditions. Because of its superior technology and minimally invasive nature, patients are often done as an outpatient and can return to regular activities on the following day. Therefore, quality assessment, comparative outcomes research, and cost effectiveness research have substantiated the role of this technology in a wide variety of indications.

I hope this information will be useful to you in the assessment of this technology which has resulted in radical improvements in healthcare delivery across the world.

Yours sincerely,

L. Dade Lunsford, M.D.

LDL/jt #155162

BERIT L. MADSEN, MD, R. ALEX HIS, MD, AND HEATH R. FOXLEE, MD (PENINSULA CANCER CENTER)

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Poulsbo, WA 98370
(360) 697-8000
www.peninsulacancercenter.com

3/5/12

Mr. Josh Morse, MPH, Program Director and the
Health Technology Assessment Program Board & Staff
Washington State Health Care Authority
P.O. Box 42712
Olympia, Washington 98504-2712

Dear Mr. Morse and Members of the Board and Staff:

We have received copies of the letters that Dr. Todd Barnett and his associates at the Swedish Cancer Institute have written in support of Intensity Modulated Radiotherapy (IMRT) and Stereotactic Radiotherapy (SRT), currently under review by your board. We have reviewed their letters and supportive documents and applaud their work and endorse their recommendations that IMRT and SRT/SBRT are important treatment techniques that benefit cancer patients while being safe and cost effective. IMRT and stereotactic radiotherapy are techniques that have been in common use in most radiation therapy centers for greater than 10 years; it would be impossible to think of not utilizing these advanced techniques for patients with conditions that warrant such treatment. We are hopeful that your review will support the continued utilization of these beneficial treatment techniques.

Please do not hesitate to contact us for more information or questions.

Respectfully,

Berit L. Madsen, MD, FACR
Clinic Director
R. Alex Hsi, MD
Heath R. Foxlee, MD

DEAN G. MASTRAS, MD AND RANDY D. SORUM, MD (TACOMA/VALLEY RADIATION ONCOLOGY CENTERS)

From: Zemanek, Julie
To: HCA ST Health Tech Assessment Prog
Cc: Willis, Brett; "James.Dingels@swedish.org"
Subject: HTA Program Response
Date: Monday, March 05, 2012 2:56:14 PM
Attachments: 2012 0305 DGM RDS Letter to State.docx
120304 Vermeulen Letter to the State CNS Tumors 2-29-12.doc
2012 03 MPH Supporting Doc IMRT.docx

Thank you for allowing Tacoma/Valley Radiation Oncology Centers the opportunity to provide responses to Key Questions, which are attached.

Should you have any questions, please feel free to contact me.

Julie J. Zemanek | Practice Manager
253.627.6172 (main) | 253.779.6328 (direct) | 253.627.5967 (fax)
Jackson Hall Medical Center

March 5, 2012

Mr. Josh Morse, MPH, Program Director
Health Technology Assessment Program Board & Staff
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712

Dear Mr. Morse, Members of the Board and Staff:

I am writing this letter as part of a public response to the state regarding the healthcare technology program (HTA) policies that are currently being drafted.

I am a radiation oncologist who is in a large multicenter practice that covers most of the south sound. We are free standing and independent cancer centers. We are very familiar with the technologies of Intensity Modulated Radiation Therapy (IMRT), stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) that the healthcare technology program is now looking at. I can speak from a position of complete familiarity with these treatment modalities.

These technologies are currently available in many places in the State of Washington and are quickly becoming standard of care for many treatment sites throughout the nation. As clearly stated in the summary, these technologies are more expensive than conventional radiation. The trade off, however, is very significant when it comes to not only improvements in outcomes but they are vastly superior in reduction in side effects and toxicity. We are also able to treat specific tumor locations that we never were able to accomplish in the past with minimal morbidity and harm to the patient. There is no question that radiation can be extremely harmful to living tissue. My 20+ year career can certainly attest to that. When I explain these new modalities to patients, one of the very first comments I make is that I wish I'd had these technologies available to me during the early days of my career. The number of patients treated with significant radiation morbidity, both short term and long term, in the form of bowel damage, bladder damage, lung damage, soft and bony structure damage as well as even brain damage, could have been reduced and outright avoided if I'd had these technologies available in the past. These newer modalities allow us to target tissues at risk and

greatly reduce surrounding tissues that do not need to be radiated. Not only do these technologies allow us to target the cancer and spare the surrounding normal tissue, but they allow us to give even higher doses of radiation to the cancer, thus improving outcomes. Nowhere has this become more evident than in treatment of cancer of the prostate. The concept of increasing the dose of radiation (known as dose escalation) to prostate cancer has been verified in numerous clinical trials. In the past we were unable to deliver high doses of radiation to the prostate because the organ is "sandwiched" between the bowel and the bladder.

The use of IMRT actually allows us to bend the radiation around these crucial structures, therefore allowing us not only to spare these normal tissues but allowing us to give more radiation to the prostate, thus improving the outcomes in the long term and ultimately curing the patient of his cancer. IMRT has become standard of care for most tumor sites.

I sit down on a day to day basis and explain the treatment course to a patient which is often combined with very extensive chemotherapy. I am now able, with confidence, to say to patients that they will make it through treatment with greatly minimized side effects that we have seen in the past. Above all, as stated in the Hippocratic Oath, is to "do no harm." All cancer therapy walks a fine line between trying to eradicate the patient's malignancy without destroying normal tissue. IMRT and other related technologies have allowed us to increase the "therapeutic window" to accomplish that goal, increasing radiation and decreasing side effects. Until the so-called "Magic Bullet" is invented for cancer therapy, this is one of the most significant breakthroughs in radiation therapy in the 20th century. To simply say that we can treat cancers using standard therapy brings us back to the 1980s, a time when we only dreamed about having the ability to eradicate tumors without eradicating the patient in the process.

Stereotactic body (SBRT) and stereotactic radiosurgery (SRS) are again technologies that allow us with pin-point accuracy to deliver very toxic doses of radiation therapy to cancers and eliminate surrounding tissue. One only needs to see a patient who is trying to live with radiation damage of the brain from old conventional treatments to realize the significance of these new technologies. We are now able to treat patients non-surgically for aneurysms, tremors, brain metastases and even gliomas. Patients are alive and function today because of these technologies. They certainly can be treated by more conventional means but the price is higher in side effects and long-term complications. I have seen patients harmed by conventional radiation to a much greater extent.

I have another patient whom I am currently treating as I write this letter. She is not a surgical candidate. She has a large metastasis to her liver. She is unable to go through a big procedure. There is no other means of treating this metastasis. Her options are either to fight her disease or simply let nature take its course. If faced with that situation, I would do the same thing and fight for my survival. IMRT and stereotactic

body radiosurgery offer the chance of fighting cancer. I cannot pass judgment on whether or not these treatments are useful unless faced with that same situation.

It is very difficult from this letter or from reading the literature to pass judgment on any of this unless you come in and experience it for yourself.

I welcome anyone involved in reviewing this information to please visit our center. I would be more than happy to sit down for as long as needed to explain the differences between conventional radiation therapy and modern technologies of Intensity Modulated Radiation Therapy and the others listed above. I can show you examples and even have you talk to patients. We can search the literature together and find you examples of their utility. I would be more than happy to sit on any review committee and assist anyone in the field currently, gathering data and researching the information. I am available any time you should require.

Our free-standing cancer center's goal is to give the best possible treatment to our patients. Our mission statement is precisely that. Utilizing these technologies allows us to accomplish that mission statement. There is no question that these modern technologies are expensive. As a free-standing center, we can keep our costs to a minimum.

Sincerely,

Dean G. Mastras, MD

President

Randy D. Sorum, MD

JAMES F. RAYMOND (RADIANTCARE RADIATION ONCOLOGY)

RadiantCare

March 5, 2012

Mr. Josh Morse, MPH, Program Director and the Health Technology Assessment
Program Board and Staff
Washington State Health Care Authority
P.O. Box 42712
Olympia, Washington, 98504-2712

Dear Mr. Morse and Members of the Board and Staff:

Thank you for allowing us to comment on the Key Questions that where raised pertaining to Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT). I will be speaking for all members of RadiantCare Radiation Oncology in the following correspondence. Due to the short time frame allowed to comment we have chosen to collaborate with the Tumor Institute Radiation Oncology Group (TIROG) in our response.

We share your concerns pertaining to patient safety, effectiveness, efficiency and the rising cost of contemporary radiation treatment modalities. We have instituted a group designated to address these issues as they relate to the treatment of the patients of RadiantCare.

SRS and SBRT are both extremely precise treatment modalities which can be delivered with a Linear Accelerator, Gamma Knife or Cyberknife system. These systems are designed to precisely target tumor regions with millimeter accuracy. These treatments require intense quality assurance, measurements and monitoring during treatment since the entire dose is delivered through 1-5 treatments. This requires a significant amount of medical physicist support to ensure accuracy.

We believe that the initial increased cost associated with IMRT, SRS and SBRT is outweighed by their long term savings due to lower costs associated with lower risk of side effects and increased clinical outcomes.

KQ1; What is the effectiveness for SRS and SBRT compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer.

There is extensive documentation in the literature to support the role of SRS and SBRT. There are studies showing support for CNS/spine, prostate, head and neck, gastrointestinal, liver, pancreas, and lung cancers to name a few. These studies include primary, metastatic, boost and previous irradiated areas. If you would like us to provide you with an extensive list of the citations please let us know.

KQ2: What are the potential harms of SRS/SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.

Highly conformalized treatment is needed when treating an area that has been previously irradiated. Tissue that has been previously treated is less tolerant to radiation and the normal tissues must be minimized to reduce unnecessary side effects. The rapid dose fall of SRS or SBRT is a perfect option in this setting. The exhaustive patient positioning, planning and delivery process are required to ensure that the procedure is done correctly.

KQ3: What is the evidence that SRS/SBRT has differential efficacy or safety issues in subpopulations? Including consideration of:

a. Gender
b. Age
c. Site and type of cancer
d. Stage and grade of cancer
e. Setting, provider characteristics, equipment, quality assurance standards, and procedures.

SRS/SBRT is capable of treating a vast array of cancers in a variety of locations, for both genders and all ages. These modalities are utilized in freestanding centers and hospitals which allows access to patients everywhere. In some instances, one of these two treatments may be the only options available to the patient due to the tumor location and circumstances. Advanced quality assurance standards and measurements are published to perform SRS/SBRT.

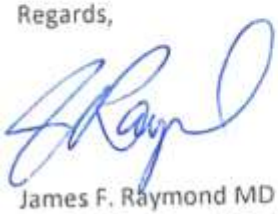
KQ4: What is the evidence of cost and cost-effectiveness of SRS/SBRT/ IMRT compared to EBRT?

Cost effectiveness between EBRT and SRS/SBRT is a very difficult study to quantify due to the quality of life that is being compared. Conventional EBRT is delivered over an average of 2-6 weeks while SRS/SBRT is delivered over 1-5 treatments. Cost and cost effectiveness can be measured in loss of work, cost of treatment, cost of side effect management (acute and long term), or indirect costs but these indirect savings can be difficult to accurately compare.

As is always the case, we choose the most appropriate treatment modality for each patient's specific case. We evaluate all of our treatment options and determine which will offer the patient the best clinical outcome with the least amount of side effects.

We encourage any questions you may have about this topic. Please feel free to contact any of us.

Regards,



James F. Raymond MD
Clinical Director of Radiosurgery
RadiantCare Radiation Oncology

ERIC TAYLOR (EVERGREEN RADIATION ONCOLOGY)

From: Eric W. Taylor, MD
To: HCA ST Health Tech Assessment Prog
Cc: Eric W. Taylor, MD
Subject: Public Comment for: Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy
Date: Sunday, February 26, 2012 3:29:15 PM

Thank you for the opportunity to comment.
Stereotactic Radiosurgery has been used for certain brain malignancy situations as well as for some benign diseases. The clinical experience is well and heavily reported in the literature. My main concern for overuse of SRS is in the patient with brain metastases. The National Comprehensive Cancer Network guidelines (nccn.org) are clear that this technique is appropriate for patients with 1-3 brain metastases and with disease reasonably controlled or stable elsewhere...so that the cost of such treatment could be justified in well selected patients. Unfortunately, I think that there is OVERUSE of SRS and IMRT for patients with multiple brain metastases whose ultimate outcomes and lives are unfortunately very limited.

The use of Stereotactic Body Radiation Therapy (SBRT) or Stereotactic Ablative Radiation Therapy (SABR) are becoming of increasing usefulness and benefit. The Japanese data for early lung cancer treatment with SBRT is excellent and from an outcome perspective is competitive with surgery. There is a current randomized trial sponsored by the American College of Surgeons and the Radiation Therapy Oncology Group comparing SBRT/SABR versus surgery. Depending on the outcomes of this study, this might support increased use of SBRT in the future. Currently, SBRT is the standard of care (National Comprehensive Cancer Network Guidelines at nccn.org) for early lung cancers in the patient that is medically inoperable. If well planned and delivered, patients tolerate this therapy very well with excellent reports from the current literature (Japan, UT Southwestern, Indiana and others).

Respectfully submitted,

Eric Taylor MD, FACR, FACRO
Evergreen Radiation Oncology
Evergreen Healthcare
Kirkland, Wa

Sent from my iPad

DISCLAIMER:

TUMOR INSTITUTE RADIATION ONCOLOGY GROUP

Submitted from the Tumor Institute Radiation Oncology Group:

Stereotactic Radiosurgery (SRS), Stereotactic Body Radiation Therapy (SBRT) and Key Question 4 IMRT Reimbursement Information

Thank you for the opportunity to comment on questions regarding Intensity Modulated Radiation Therapy (IMRT), Stereotactic Radiosurgery (SRS), and Stereotactic Body Radiation Therapy (SBRT). We recognize that approximately half of all cancer patients receive some form of radiation therapy, and that radiation dose delivery techniques and practices have rapidly evolved over the last decade.

As experts in the field of Radiation Oncology, we embrace your concerns regarding safety, efficacy, and cost of contemporary radiation modalities. Technologies such as IMRT, SRS, and SBRT have broken new ground in their capability to control cancer and minimize side effects. Our goal is to help educate health providers and healthcare payers, as well as government, business, and other professionals as to the patients for whom use of these newer technologies can mean a world of difference in regard to cancer control and a decreased risk of treatment related side effects.

The utility of IMRT, SRS, and SBRT in many circumstances is very specifically dependent on a patient's cancer, their anatomy, the proximity of critical structures, and prior radiation dose delivered. The key aspects that all these modalities have in common is better dose distributions: escalated doses to tumors, lower doses (and lower resultant toxicity) to normal tissue. Using IMRT, SRS, and SBRT, it is now potentially feasible to deliver safe curative or safe palliative treatment to many patients where treatment was not even an option with conventional external beam radiation therapy. For example, in cases where tumors recur in a previously irradiated field, re-irradiation with IMRT, SRS, or SBRT may deliver a long term cure that was not previously possible. We realize that a circumstance such as this is not one in which a comparative trial could be conducted, for most of these patients simply would not be a candidate for treatment with a conventional external beam radiation therapy approach.

We believe that it is imperative to be able to offer these treatments to patients in an expedient time frame when indicated. We remain readily available and encourage an open dialogue on these topics. We have tried our best given the short comment period to address your questions regard SBRT and SRS.

Although there are increased costs associated with newer technologies such as IMRT, SRS, and SBRT, their effectiveness and lower risk for side effects demonstrates long term cost savings. As well, the relevant key comparison is often IMRT, SRS, or SBRT in comparison to other different modalities of treatment, such as surgery, or radiofrequency ablation (rather than to conventional external beam irradiation). For example, there was a publication a few months ago comparing the cost effectiveness, quality of life and safety for medically inoperable lung cancer patients. The study compared conventional radiation, SBRT, and radiofrequency ablation. SBRT was by far the most effective and cost effective treatment, even though it may have the highest upfront direct cost (reference: [1] Sher, Wee and Punglia, **Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer**. Journal/Int J Radiat Oncol Biol Phys, 81, e767-74, 2011).

Given the extraordinarily short time period for comment, we have done our best to summarize responses to the four key questions of the Washington State Healthcare Authority with regard to SRS, and SBRT in comparison to conventional (conformal) external beam therapy (EBRT). We must emphasize, though, while there are many well done peer reviewed studies from top academic institutions pertinent to IMRT, SRS and SBRT, and in some cases there are head-to-head comparisons which demonstrate the benefits of this technology, the short response timeframe created by your March 6th deadline, which apparently is not negotiable, does not allow adequate time to research. Therefore, we want to be sure the Washington State Healthcare Authority and its staff are advised that we believe the key questions posed for SRS, SBRT and IMRT are extensive and a more complete level of detail is not possible to produce within the time frame allotted.

KQ1: What is the effectiveness for SRS and SBRT compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer.

RESPONSE:

Prostate – SBRT

A conventional radiotherapeutic treatment for prostate cancer consists of 8-9 weeks of daily external beam radiotherapy (EBRT) – such treatment is typically implemented with IMRT and daily image guidance, which helps align the patient prior to delivering each fraction of treatment. An alternative approach is prostate brachytherapy – using either a high dose rate (HDR) delivery system, or the implantation of approximately 100 permanent radioactive seeds. These procedures require anesthesia, and for HDR brachytherapy, hospitalization. Often brachytherapy is combined with a five week course of IMRT.

A newer method of delivering radiotherapy is called "stereotactic body radiotherapy" (SBRT); this differs from conventional radiotherapy in several important ways. First, SBRT uses new technology to deliver radiotherapy with extreme precision. Second, the target is treated from numerous different beam angles, which concentrates dose to the target and minimizes dose to surrounding organs. By contrast, EBRT/IMRT commonly uses 4-7 beam angles, treating from a single rotational plane. Finally, the extreme accuracy and rapid dose fall-off of SBRT allows very high doses of radiation to be safely delivered to the cancer in 1-5 fractions. The CyberKnife is an SBRT platform that uses robotic technology to adjust in real-time for patient and organ motion, thus treating with an accuracy of less than 1mm.

In order to account for prostate motion during EBRT/IMRT treatment delivery, the prostate plus a 5-10mm margin around it is treated. This gives unnecessary radiation to surrounding organs. The CyberKnife is capable of tracking motion of the prostate during treatment delivery, while still treating with sub-mm accuracy (Xie et al., 2008). This exceptional accuracy minimizes radiation exposure to surrounding normal tissues (e.g., rectum and bladder). The Cyberknife can duplicate the radiation delivered with HDR brachytherapy (Fuller et al., 2007) while avoiding anesthesia, hospitalization, and trauma from numerous need punctures. Like HDR, the CyberKnife delivers dose in only a few (five) fractions.

The feasibility of CyberKnife for treating early-stage prostate cancer was first described in 2003 (King et al.), and the first clinical outcomes from Stanford University were published in 2009 (King et al.). Later that year, Friedland reported on a series of 112 prostate cancer patients treated with SBRT. In 2010, Katz published a report of 304 CyberKnife SBRT prostate patients. These publications showed exceptionally good PSA response rates, low relapse rates, acceptable toxicity, and excellent quality of life outcomes. Early results from a large multi-institutional study (Meier et. 2010) employing Cyberknife for prostate cancer recently reported acceptable toxicity and favorable PSA responses. The first 5-year SBRT outcomes have now been reported by Freeman and

King (2011): toxicity was low and the rate of cancer remission was similar to other radiation modalities. Finally, the long-term outcomes of prostate SBRT at Stanford University conclude "The current evidence supports consideration of stereotactic body radiotherapy among the therapeutic options for localized prostate cancer" (King and Brooks, 2011). Thus multiple peer-review studies, including mature 5-year outcomes, have confirmed that CyberKnife SBRT is safe and effective in treating early-stage prostate cancer.

Selected reference(s):

- Xie Y, Djajaputra D. Intrafractional Motion of the Prostate During Hypofractionated Radiotherapy*. International Journal of Radiation Oncology, Biology, Physics.* 72(1), 236-246, 2008
- Fuller DB, Naitoh J et al. Virtual HDR CyberKnife Treatment for Localized Prostatic Carcinoma: Dosimetry Comparison With HDR Brachytherapy and Preliminary Clinical Observation. *International Journal of Radiation Oncology Biology Physics* 70(5),1588-97, 2007
- King CR, Lehmann J, Adler JR, Hai J. CyberKnife radiotherapy for localized prostate cancer: Rationale and technical feasibility. *Tech Can Res Treat*: 2003; 2: 25-29.
- King C, Brooks, et al. Stereotactic Body Radiotherapy for Localized Prostate Cancer: Interim Results of a Prospective Phase II Clinical Trial. *International Journal of Radiation Oncology Biology Physics*, 73(4):1043-1048 (2009).
- Friedland J, Freeman D, et al. Stereotactic Body Radiotherapy: An Emerging Treatment Approach for Localized Prostate Cancer. *Technology in Cancer Research and Treatment,* 8(5): 387-392 (2009)
- Katz A, Santor M et al. Stereotactic body radiotherapy for organ confined prostate cancer. BMC Urology, 10(1):2010
- Meier R, Beckman A et al. Stereotactic Radiotherapy for Organ-confined Prostate Cancer: Early Toxicity and Quality of Life Outcomes from a Multi-institutional Trial. *International Journal of Radiation Oncology Biology Physics*. 78(3):S57 (2010)
- Freeman D, King C. Radiation Oncology. 6(3):2011

- King CR, Brooks JD et al. Long-term outcomes for a prospective trail of stereotactic body radiotherapy for low-risk prostate cancer. *International Journal of Radiation Oncology Biology Physics*, in press (2011).

Head and Neck Cancer – SRS/SBRT

SRS and SBRT in Head and Neck cancer play a critical role in patients with locally advanced disease in the region of the skull base in multiple settings. These patients represent a small subgroup of patients for whom SRS/SBRT offer a potentially curative treatment with potentially very low risk in a situation in which historically conventional EBRT simply was not a treatment option.

Head and Neck patients for whom making access to this treatment is critical are

- Patients with recurrent cancer in a previously irradiated field.

Selected reference(s):

[2] Unger, Lominska, Deeken, Davidson, Newkirk, Gagnon, Hwang, Slack, Noone and Harter, **Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer**. Journal/Int J Radiat Oncol Biol Phys, 77, 1411-9, 2010

- Patients with skull base invasion at the time of presentation. For these patients, a combined approach of IMRT and a radiosurgical boost with SRS or SBRT can be curative with minimal morbidity.

Selected Reference(s):

[3] Uno, Isobe, Ueno, Fukuda, Sudo, Shirotori, Kitahara, Fukushima and Ito, **Fractionated stereotactic radiotherapy as a boost treatment for tumors in the head and neck region**. Journal/J Radiat Res (Tokyo), 51, 449-54, 2010

[4] Chen, Tsai, Wang, Wu, Hsueh, Yang, Yeh and Lin, **Experience in fractionated stereotactic body radiation therapy boost for newly diagnosed nasopharyngeal carcinoma**. Journal/Int J Radiat Oncol Biol Phys, 66, 1408-14, 2006

[5] Ahn, Lee, Kim, Huh, Yeo, Lim, Kim, Shin, Park and Chang, **Fractionated stereotactic radiation therapy for extracranial head and neck tumors**. Journal/Int J Radiat Oncol Biol Phys, 48, 501-5, 2000

Central Nervous System – SRS/SBRT/IMRT

Please refer to the separate letter and commentary of Dr. Sandra Vermeulen.

CNS/Spine – SRS/SBRT

SBRT plays and increasing role in the management of patients with spinal tumors in three key settings:

- Re-irradiation of the spine.
  For patients that have undergone prior radiation therapy for spine metastases that have progression of spine disease, SBRT offers dramatic control of tumor, protection of neurologic function, and pain control

Selected reference(s):

[6] Garg, Wang, Shiu, Allen, Yang, McAleer, Azeem, Rhines and Chang, **Prospective evaluation of spinal reirradiation by using stereotactic body radiation therapy: The University of Texas MD Anderson Cancer Center experience**. Journal/Cancer, 117, 3509-16, 2011

- Treatment of radioresistant histologies.
  For patients with radioresistant cancers such as renal cell carcinoma and melanoma, conventional external beam radiation therapy offered poor durability of cancer control. With SBRT, cancer control rates are dramatically improved. With SBRT, long term pain improvement and cancer control is 75 to 100% for classically radioresistant cancers. Traditional radiation therapy offered control on average for only 1 to 3 months for radioresistant histologies.

Selected reference(s):

[7] Gerszten, Burton, Ozhasoglu and Welch, **Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution**. Journal/Spine (Phila Pa 1976), 32, 193-9, 2007

- Treatment of radioresistant tumors after decompressive surgery.
  Increasingly, patients with advanced spine disease are undergoing less invasive surgery. As demonstrated in the article cited below from Memorial Sloan Kettering, patients treated with minimal surgery followed by stereotactic radiosurgery for radioresistant tumors

[8] Moulding, Elder, Lis, Lovelock, Zhang, Yamada and Bilsky, **Local disease control after decompressive surgery and adjuvant high-dose single-fraction radiosurgery for spine metastases**. Journal/J Neurosurg Spine, 13, 87-93, 2010

Gastrointestinal/Pancreas – SBRT

For patients with unresectable pancreatic cancer, the strategy of chemotherapy and stereotactic radiosurgery has been shown to yield excellent local cancer control with low morbidity. Across these studies, tumor control ranges 85 to 95%, and late grade 3 or greater late toxicities occurred in 5 to 10% of patients. Utilizing chemotherapy and stereotactic radiosurgery, long term overall survival is approximately 20%.

Selected reference(s):

[9] Mahadevan, Miksad, Goldstein, Sullivan, Bullock, Buchbinder, Pleskow, Sawhney, Kent, Vollmer and Callery, **Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer**. Journal/Int J Radiat Oncol Biol Phys, 81, e615-22, 2011

[10] Schellenberg, Kim, Christman-Skieller, Chun, Columbo, Ford, Fisher, Kunz, Van Dam, Quon, Desser, Norton, Hsu, Maxim, Xing, Goodman, Chang and Koong, **Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer**. Journal/Int J Radiat Oncol Biol Phys, 81, 181-8, 2011

[11] Chang, Schellenberg, Shen, Kim, Goodman, Fisher, Ford, Desser, Quon and Koong, **Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas**. Journal/Cancer, 115, 665-72, 2009

Gastrointestinal/Liver Metastases

Based on prior experience at this institution and other major medical centers in the United States, Europe and Asia, stereotactic body radiotherapy (SBRT) for liver metastases is effective and safe. Initial reports of phase I/II data for stereotactic body radiation to the liver metastases have been published (Schefter and Colleagues, IJROBP 2005; Kavanagh and colleagues, Acta Oncol 2006). Investigators at the University of Colorado/Denver have demonstrated 92% control of liver lesions at 2 years when treating up to 3 liver lesions. For liver tumors < 3cm, 2 year control was 100%. For this mixed population of cancer patients, median survival was 20.5 months (Rusthoven et al, JCO 2009).

More recently, data from Stanford University (Chang et al, Cancer 2011), detailed a pooled analysis on liver metastases from colorectal primary tumors similarly showing that this treatment is effective and well tolerated. On multivariate analysis, it was found that sustained local control through use of SBRT is closely correlated with overall survival. This was true even for patients heavily pretreated with chemotherapy.

SBRT for liver metastases has been best studied in "oligometastatic situations" (≤4 liver metastases). Extensive published literature exists showing that surgical resection of limited metastatic liver disease is associated with favorable outcome (Gayowski et al, Surgery 1994; Rosen et al, Ann Surg 1992; Nordlinger et al, Ann Surg 1987; Fong et al, JCO, 1997; Singletary et al, Oncologist 2003). Even in a noncurative situation, patients who do not fit this criterion can also safely derive palliative benefit from SBRT by undergoing treatment to symptomatic metastases as detailed above.

Selected reference(s):

[12] Schefter, Kavanagh, Timmerman, Cardenes, Baron and Gaspar, **A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases**. Journal/Int J Radiat Oncol Biol Phys, 62, 1371-8, 2005

[13] Kavanagh, Schefter, Cardenes, Stieber, Raben, Timmerman, McCarter, Burri, Nedzi, Sawyer and Gaspar, **Interim analysis of a prospective phase I/II trial of SBRT for liver metastases**. Journal/Acta Oncol, 45, 848-55, 2006

[14] Rusthoven, Kavanagh, Cardenes, Stieber, Burri, Feigenberg, Chidel, Pugh, Franklin, Kane, Gaspar and Schefter, **Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases**. Journal/J Clin Oncol, 27, 1572-8, 2009

[15] Chang, Swaminath, Kozak, Weintraub, Koong, Kim, Dinniwell, Brierley, Kavanagh, Dawson and Schefter, **Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis**. Journal/Cancer, 117, 4060-9, 2011

Gastrointestinal/Primary Liver Cancers

For primary liver lesions such as hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), SBRT can also play an important role as a local ablative therapy. A multicenter report published this year (Ibarra et al, Acta Oncol, 2012) showed median time to local progression of 6.3 mo for HCC and 4.2 mo for ICC, better than historical averages for these respective diseases. 1 year survival rates were 87% and 45% for HCC and ICC, respectively. Similar data are reported in a publication by Indiana University (Andolino, IJROBP, 2011). In a separate publication by this same institution, nearly 75% of patients responded to SBRT treatment with the majority of these patients showing complete nonenhancement on followup imaging (Price et al, Cancer 2011).

For primary tumors such as HCC, the data suggests safe, effective treatment for smaller lesions such as those < 6 cm in size (Andolino, IJROBP 2011; Takeda et al, Radiother Oncol, 2012).

Selected reference(s):

[16] Ibarra, Rojas, Snyder, Yao, Fabien, Milano, Katz, Goodman, Stephans, El-Gazzaz, Aucejo, Miller, Fung, Lo, Machtay and Sanabria, **Multicenter results of stereotactic body radiotherapy (SBRT) for non-resectable primary liver tumors**. Journal/Acta Oncol, 2012

[17] Andolino, Johnson, Maluccio, Kwo, Tector, Zook, Johnstone and Cardenes, **Stereotactic body radiotherapy for primary hepatocellular carcinoma**. Journal/Int J Radiat Oncol Biol Phys, 81, e447-53, 2011

[18] Price, Perkins, Sandrasegaran, Henderson, Maluccio, Zook, Tector, Vianna, Johnstone and Cardenes, **Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma**. Journal/Cancer, 2011

Lung – SBRT

Stereotactic body radiation therapy for lung cancer in medically inoperable patients has dramatically improved local control and survival for patients with early stage lung cancers. Historic local control of early stage, medically inoperable lung cancer was approximately 50%. In the SBRT era, cancer control rates range 85 to 98%.

In a multi institution trial, RTOG 0236 demonstrated 3 year local control of 90% in patients with medically inoperable T1-T2 lung cancer (Timmerman, JAMA, 2010). Similarly excellent results have been reiterated in multiple single institution studies in the US, as well as internationally.

As well, in the case of lung SBRT, direct comparisons to conventional radiation therapy have demonstrated superior cost effectiveness of SBRT (Sher, 2011)

Selected references:

[19] Timmerman, Paulus, Galvin, Michalski, Straube, Bradley, Fakiris, Bezjak, Videtic, Johnstone, Fowler, Gore and Choy, **Stereotactic body radiation therapy for inoperable early stage lung cancer**. Journal/JAMA, 303, 1070-6, 2010

[20] Fakiris, McGarry, Yiannoutsos, Papiez, Williams, Henderson and Timmerman, **Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma:**

four-year results of a prospective phase II study. Journal/Int J Radiat Oncol Biol Phys, 75, 677-82, 2009

[21] Zimmermann, Wulf, Lax, Nagata, Timmerman, Stojkovski and Jeremic, **Stereotactic body radiation therapy for early non-small cell lung cancer**. Journal/Front Radiat Ther Oncol, 42, 94-114, 2010

[1] Sher, Wee and Punglia, **Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer**. Journal/Int J Radiat Oncol Biol Phys, 81, e767-74, 2011

CNS - SRS/SBRT/IMRT

Please refer to the separate letter and commentary of Dr. Sandra Vermeulen.

Re-irradiation – SRS/SBRT

Multiple lines of evidence exist showing the effectiveness and safety of using stereotactic body radiotherapy (SBRT) for re-irradiation (either for salvage or palliation).

1) Cengiz et al, IJROBP, 2010. Salvage reirradiation with stereotactic body radiotherapy for locally recurrent hand and neck tumors

2) Comet et al, IJROBP, 2012. Salvage stereotactic reirradiation with or without cetuximab for locally recurrent head and neck cancer.

3) Dworzecki et al, Noeplasma 2012. Stereotactic radiotherapy as sole or salvage therapy in non small cell lung cancer patients.

4) Heron et al, IJROBP, 2009. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck.

5) Kunos et al, Technol Cancer Res Treat, 2008. Cyberknife radiosurgery for squamous cell carcinoma of vulva after prior pelvic radiation therapy.

6) Thariat et al, Br J Radiol, 2010. Innovative image guided Cyberknife stereotactic radiotherapy for bladder cancer. (Includes previously irradiated bladder cancer patient data).

KQ2: What are the potential harms of SRS/SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.

SRS/SBRT have been shown in multiple studies to be safe as primary treatment and in cases of re-irradiation. Specific toxicities and risks for harm vary across cancer sites and depend on the specific cancer scenarios, prior radiation dose, and anatomy as well as proximity of normal organs.

After an initial course of radiation, normal adjacent tissue has decreased tolerance to additional radiation delivered over the same region. In many cases, surgery and chemotherapy are not viable treatment options. In these situations, a highly conformal technique with the most rapid dose falloff within adjacent normal tissue is necessary to minimize side effects. SRS, and SBRT techniques can safely provide good salvage or palliative results.

For example, for gastrointestinal/liver tumors, side effects related to radiation therapy can include adjacent soft tissue and bony necrosis (including abdominal wall, surrounding liver, and kidney), skin reaction, fatigue, nausea/vomiting, bowel adhesions, and secondary malignancies. However, when the appropriate constraints are used in terms of total adjacent tissue dose, the incidence of high grade toxicity in SBRT is relatively low due to the much higher degree of conformality and steeper dose falloff in tissue outside the target. Multi-institutional trial data show that only 2% of patients treated for liver metastases had greater than grade 2 toxicity and none had grade 4 or higher toxicity (Rusthoven, JCO 2009).

Given the short time period allowed for comment, it is not possible to organize a comprehensive site related characterization of potential toxicities related to SRS/SBRT. However, we remain available at any time to answer and site or technology specific questions.

Additional References:

1) Cengiz et al, IJROBP, 2010. Salvage reirradiation with stereotactic body radiotherapy for locally recurrent hand and neck tumors

2) Comet et al, IJROBP, 2012. Salvage stereotactic reirradiation with or without cetuximab for locally recurrent head and neck cancer.

3) Dworzecki et al, Noeplasma 2012. Stereotactic radiotherapy as sole or salvage therapy in non small cell lung cancer patients.

4) Heron et al, IJROBP, 2009. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck.

5) Kunos et al, Technol Cancer Res Treat, 2008. Cyberknife radiosurgery for squamous cell carcinoma of vulva after prior pelvic radiation therapy.

6) Thariat et al, Br J Radiol, 2010. Innovative image guided Cyberknife stereotactic radiotherapy for bladder cancer. (Includes previously irradiated bladder cancer patient data).

7) Barney et al, Am J Clin Oncol, 2011. Clinical outcomes and dosimetric considerations using SBRT for abdominopelvic tumors.

8) Peulen et al, Radiother Oncol 2011. Toxicity after reirradiation of pulmonary tumors with SBRT.

9) Scorsetti et al, Strahlenther Onkol, 2011. SBRT for adrenal metastases: a feasibility study of advanced techniques with modulated photons and protons.

10) Rwigema et al, 2011 The impact of tumor volume and radiotherapy dose on outcome in previously irradiated recurrent squamous cell carcinoma of the head and neck treated with SBRT.

KQ3: What is the evidence that SRS/SBRT has differential efficacy or safety issues in subpopulations? Including consideration of:

a. **Gender**
b. **Age**
c. **Site and type of cancer**
d. **Stage and grade of cancer**
e. **Setting, provider characteristics, equipment, quality assurance standards, and procedures.**

The above discussion applies to nearly all patient subpopulations as evidenced by the wide range of anatomical subsites, patient demographics, and tumor characteristics described in the studies listed above.

KQ4: What is the evidence of cost and cost-effectiveness of SRS/SBRT/IMRT compared to EBRT?

Our ability to uncover cost and cost-effectiveness comparisons between these modalities has been significantly affected by the time frame allotted for responding. Except for studies of medically inoperable, early-stage non-small cell lung cancer which were readily available, our response is limited to generalizing our own clinical

experience. Further, when determining the true, total "cost" and "cost-effectiveness" of each of these treatment alternatives, one needs to quantify the less obvious, indirect costs and benefits of these alternative therapeutic options. For example, how does one quantify the quality of life improvement for patients cured of head and neck cancers with IMRT? What dollar value do we assign to the improved long-term dental health of the patient who is able to receive IMRT instead of EBRT? Or as a second example, what is the financial cost/benefit dollar value assigned to the longer life expectancy of the SRS/SBRT patient receiving a potentially curative treatment with potentially very low risk rather than not having a treatment option since EBRT is not able to be used as a treatment option? Our analysis does NOT address these less obvious, indirect cost/benefit factors so if anything, the benefits of the appropriate use of SRS, SBRT and IMRT are understated in our own clinical experience generalizations.

Sher, Wee and Punglia in "Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer". (Journal/Int J Radiat Oncol Biol Phys, 81, e767-74, 2011) in a comparison of 3-D EBRT, RFA and SBRT concluded that "SBRT was the most cost-effective treatment for medically inoperable NSCLS over a wide range of treatment and disease assumptions. On the basis of efficacy and cost, SBRT should be the primary treatment approach for this disease".

This is consistent with an earlier study by Lanni, Grills, Kestin and Robertson in "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". (American Journal of Clinical Oncology, 34(5):494-498, October 2011) which concluded that "SBRT was found to be less expensive than standard fractionated EBRT, with the cost savings highly dependent on the number of SBRT fractions and EBRT technique (3-D conformal RT vs. IMRT). SBRT was also associated with superior local control and overall survival."

Most radiation oncologists in Washington State (this group included) do not own the linear accelerators that deliver therapeutic radiation. They are typically owned by the hospitals who charge separately for their use. For linear accelerator based IMRT and 3D treatments, we are paid according to the applicable professional services fee schedule. The actual physician time and work effort involved is vastly greater for IMRT than for 3D yet despite this we are most often paid less for IMRT (in part due to bundling of charges). When we as physicians recommend IMRT over 3D we do so knowing we will spend three to four times more effort on the case and get paid less. Clearly our incentive for doing so is to provide the very best care and treatment for our patients.

UNIVERSITY OF WASHINGTON MEDICINE / SEATTLE CANCER CARE ALLIANCE
DEPARTMENT OF RADIATION ONCOLOGY AND UW DEPARTMENT OF NEUROLOGICAL SURGERY

From: JASON K. ROCKHILL [jkrock@u.washington.edu]
Sent: Tuesday, March 06, 2012 4:20 PM
To: HCA ST Health Tech Assessment Prog
Cc: mail=jkrock@uw.edu
Subject: Comments on SRS and SBRT from UW Medicine
Attachments: UW Medicine Response SRS_SBRT Final.docx

Please see the attached comments on the use of SRS and SBRT. Thank you - Dr. Jason Rockhill

March 6, 2012

To: Washington State Health Care Authority, HTA Program

Please see attached comments below from the UW Medicine/Seattle Cancer Care Alliance Department of Radiation Oncology and UW Medicine Department of Neurological Surgery regarding the Health Technology Assessment for Stereotactic Radiosurgery / Stereotactic Body Radiotherapy.

Anthony Avellino MD MBA
Professor, Department of Neurological Surgery

Michael Brown MD
Assistant Professor of Radiation Oncology

Ralph Ermoian MD
Assistant Professor of Radiation Oncology

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Ken Russell MD
Professor of Radiation Oncology

George Sandison PhD FCCPM
Professor, Clinical Director of Medical Physics

KQ1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy compared to conventional external beam radiation therapy (EBRT) for the following patients:

a. Patients with central nervous system (CNS) tumors

There are well over 10,000 articles spanning more than 30 years of use detailing the effectiveness of stereotactic radiosurgery (1 treatment - SRS) and stereotactic radiotherapy (2-5 treatments – SBRT) for tumors of the central nervous system including the skull base region as well as tumors involving the head and neck region. The benefit of SRS and SBRT has been show for all of the following:

1. Brain metastases
2. Primary brain tumors both initial treatment and recurrent
3. Meningiomas
4. Vestibular Schwanomas/Acoustic Neuromas
5. Pituitary tumors
6. Craniopharyngiomas
7. Paragangliomas
8. Salivary Gland Tumors in conjugation with Fast Neutron Radiotherapy
9. Recurrent Head and Neck tumors
10. Arteriovenous Malformations

A majority of these disease processes are not common and there is limited Level 1 evidence from randomized controlled trials comparing SRS to EBRT. Treatment decisions are based mainly on historical reports from institutional series in addition to the limited level 1 evidence. This is true even if looking at the data for conventional EBRT. A recent meta-analysis published in the Journal of Neurooncology (Pannullo *et. al*. J Neurooncol (2011) 103:1-17) summarized the effectiveness of SRS for a number of disease sites. For vestibular schwanomas and meningiomas, SRS led to control rates of approximately 90%. This reported control rate for meningiomas is further supported by a large retrospective series from Europe following 4565 benign meningiomas treated with SRS (Santacroce *et al.* Journal of Neurosurgery Vol 70:1 Jan 2012). For recurrent high grade primary brain tumors, patients who received SRS had improved survival of 9.5–26 months beyond expected. This is a particularly challenging group given that limited salvage options exist after initial treatment.

The treatment of brain metastases has become very controversial. Multiple randomized trials have failed to end the international debate on the optimal management of brain metastases, which can include supportive care, surgery, whole brain irradiation, SRS/SBRT or some combination of these treatments. At the center of the debate is preserving quality of life for patients who have a short life expectancy. Overtreatment with conventional radiation therapy carries the risk of long term neurocognitive toxicities in those patients who do better than average. Even in the short term, SRS/SBRT has the advantage of less acute toxicity, including fatigue and neurocognitive changes (Chang *et al. Lancet Oncol 2009; 10: 1037–44,)*. Reported control rates of SRS/SBRT for brain metastases have been approximately 80-90%. In addition,

SRS/SBRT has been reported to improve local control of tumors that have been traditionally considered "radiation resistant," such as melanoma, renal cell, and sarcomas, when compared to standard whole brain irradiation. SRS also offers the benefit of minimizing interruption of chemotherapy, whereas whole brain radiotherapy typically requires patients to discontinue chemotherapy for 3-4 weeks while receiving treatment to avoid synergistic toxicities.

b. Patients with non-central nervous system cancers?

Stereotactic body radiation therapy (SBRT) has been shown to be very effective therapy for prostate, lung, spine, and liver as described below:

Prostate:

For prostate, Kang et al (*Tumori 97: 43-48, 2011*) show biochemical local control at 5 years of 100% for low and intermediate risk disease and 90.8% for high risk disease with Cyberknife (a specific device for SBRT). King et al (*Int J Radiat Oncol Biol Phys 82: 877-882, 2012*) show a 4 year biochemical local control rate of 94% for 67 low risk prostate cancer patients treated at Stanford with Cyberknife.

Lung tumors:

SBRT has improved survival and local control in patients with inoperable early-stage lung cancer, as noted in a study published in the March 17, 2010 issue of the Journal of the American Medical Association. (*Timmerman, et al. JAMA 2010, 303 (11), 1070-6*.) The phase 2 single-group study, which had 55 evaluable patients, demonstrated a 3-year disease-free survival of 48.3% and an overall survival of 55.8%. These findings represent a remarkable improvement over treatment with standard fractionated radiotherapy (EBRT) for patients with early-stage medically inoperable lung cancer. Previous studies reporting results from similar patient groups showed 2- to 3-year survival rates in the range of 25% to 35%. (*Armstrong JG, et al. Cancer Treat Rev. 1989;16(4):247–255; Kaskowitz L, et al. Int J Radiat Oncol Biol Phys. 1993;27(3):517–523*) In lung tumors, there is convincing evidence from United States, Japan and Europe that SBRT may be as effective as surgery for early stage lung cancer.(*Nagata Y, et al. Int J Radiat Oncol Biol Phys. 2005;63(5):1427–1431.; Fakiris AJ, et al. Int J Radiat Oncol Biol Phys. 2009;75(3):677–682*) It is certainly the treatment modality of choice for patients who cannot undergo surgery to remove their tumors from either a medical or technical perspective.

Liver tumors:

Radiation has historically had a minor role in the management of primary or metastatic liver tumors due to the poor tolerance of the entire liver to radiotherapy. Recent advances in treatment planning techniques have allowed delivery of highly focused doses of radiotherapy to portions of the liver while leaving remaining normal liver intact. These stereotactic radiosurgical and stereotactic radiotherapy techniques have allowed successful treatment of primary and metastatic liver tumors either as an alternative to surgery or for patients with medically inoperable disease.

In 2001, the University of Wurzburg published a promising early series of 23 patients who received SBRT for liver tumors with a 2 yr local control rate of 61%. (*Wulf J, et al, Strahlenther Onkol 2001, 177:645-655*) Several years later, the University of Colorado published a phase I/II trial of SBRT for liver metastases treating patients to a higher radiotherapeutic dose with a 93% local control rate at 18 months. (*Kavanaugh et al. Acta oncologica 2006, 45, 848-55*) A multi-

institutional phase I/II trial of SBRT for liver tumors showed a 2 year local control rate of 92% and median overall survival of 20.5 months.(*Rusthoven, et al. J Clin Oncol 2009, April 1, (11), 1572-8*) Andolino et al (*Int J Radiat Oncol Biol Phys 81: e447-3453, 2011*) reported on 60 patients with hepatocellular carcinomas treated at Indiana University and concluded that SBRT was a safe and effective option for tumors < 6 cm in greatest diameter. A Taiwanese group performed a matched-pair analysis of SBRT vs other/no treatments for 36 patients with recurrent hepatocellular cancer. Patients treated with SBRT had a 2 year survival of 72.6% vs 42.3% for other patients (p = 0.013). Toxicities were minimal.*(Huang et al. Int J Radiat Oncol Biol Phys 2012, PMID 22342300)*

By way of comparison to results with EBRT, the University of Michigan has performed dose escalation studies of 3D conformal external beam radiotherapy for patients with liver tumors with concurrent chemotherapy and reported a median survival of 15.2 months with a 30% incidence of grade 3-4 toxicity and 4% incidence of radiation induced liver disease. (*Dawson et al. Cancer Radiotherapie 2008, Mar;12:96-101*)

Aggressive treatment of liver metastases is of particular importance in patients with colorectal cancer, as ~20% of patients with liver-only metastases may achieve long term survival (> 10 years) or cure with successful control of their liver disease. (*Tomlinson JS, et al. J Clin Oncol 2007, 25, 4575-80)* In this group of patients, control of liver disease does not just palliate metastases, but can lead to cure. A pooled analysis of patients with colorectal liver metastases treated with SBRT at 3 different institutions showed sustained local control of disease was strongly correlated with overall survival. (*Chang et al. Cancer 2011, Sep 117, 4060-9*)

Spinal radiosurgery:
There is also evidence supporting the use of SBRT for the treatment of spine metastases. This is a similar situation to SRS/SBRT for brain metastases in that these patients likely have a short survival. Local control based on imaging and/or pain control indicates high rates of local control around 80% (Sahgal *et al*. J Neurosurg Spine 14:151-166, 2011.) This is particularly important given one usual indication for treatment is for palliation of pain. Conventional treatment over 10 fractions can be very challenging to patients due to the pain issue. SBRT can be administered as primary treatment or as salvage after failure of prior radiotherapy. In this clinical setting, the primary purpose of treatment is palliation of symptoms for the longest duration of benefit, prevention/reduction of morbidity from tumor progression into the spinal canal, and reduction of treatment-related toxicity. Mayo Clinic published a series of 85 patients with a 1 year local control rate of 83% for patients who were treated for salvage and 91% for patients treated with radiosurgery alone. (*Ahmed et al. Int J Radiat Oncol Biol Phys 2012 -epub ahead of print- PMID 22330988*)

Other disease sites:
Because of its non-invasive but ablative approach, SBRT has been investigated as a means of treating patient populations for which surgical metastatectomy has previously demonstrated benefit (i.e. colorectal cancer, sarcoma). A Korean group has published 3 year local control and overall survival rates of 64% and 60% for patients treated with SBRT to oligometastases from colorectal cancer in lymph nodes, liver, and lung. *(Bae et al. J Surg Oncol 2012, PMID 22297789)* The University of Colorado has also published a series showing 2 yr local control

rates of 96% and medial survival of 19 months for patients with lung metastases treated with SBRT. (*Rusthoven et al. J Clin Oncol 2009, 27, 1579-84*)

Radiation-resistant tumors:
Certain tumors, such as melanoma and renal cell cancer, are resistant to radiation damage with conventionally fractionated doses of radiotherapy. The ablative doses used in SBRT are able to overcome this radiation resistance. In these clinical scenarios, SBRT's benefit is less likely to be measured in improvements in overall survival, but in palliation of symptoms, and prevention of morbidity from local progression of disease at a symptomatic site. The University of Colorado has published a series of patients with melanoma or renal cell carcinoma with local control of 88% at 18 months with tumor control probability modeling predicting > 90% local control with doses equivalent to 48 Gy or higher. *(Stinauer et al. Radiat Oncol 2011, Apr,6, 34*). This exceeds

KQ2: What are the potential harms of SRS and SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.

SRS/SBRT is well tolerated due to the treatment of smaller fields. The acute and long-term toxicity of SRS/SBRT for brain metastases is generally dependent on the size of lesions treated. In the series by Elliott *et al.,* the risk of permanent neurological deficit was less than 3.3% for lesions less than 2 cm in eloquent areas to 0% in lesions in non-eloquent areas (J Neurosurg 113:53–64, 2010). In the meta-analysis by Pannullo *et al.* the rate of complications following SRS was less than 7% for vestibular schwanomas and meningiomas. This rate is higher than most modern series due to inclusion of older series when higher doses were used for benign diseases. In the prostate study above, Grade 3 or greater bladder toxicities were only 3%, there were no grade 3 or greater rectal toxicities. In the JAMA study mentioned above for lung patients, seven patients (12.7%) experienced grade 3 and 2 patients (3.6%) experienced grade 4 protocol-specified adverse events. These events included hypoxia, hypocalcemia, pneumonitis, and decreased pulmonary function tests. However, the study has also led to better guidelines regarding patients suitable for lung SBRT, including decreasing the dose for patients with more central tumors. In general, patients must be carefully selected by an experienced radiation oncologist.

KQ3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in sub populations? Including consideration of:
a. Gender
b. Age
c. Site and type of cancer
d. Stage and grade of cancer
e. Setting, provider characteristics, equipment, quality assurance standards and procedures

There has been no evidence that SRS/SBRT use would have different efficacy or safety issues based on gender. There is a least a theoretical advantage that SRS/SBRT in younger patients might reduce the long-term complication of radiation due to the smaller volume of normal tissue that receives a therapeutic dose.

Many cancers occur adjacent to organs that are more radiation sensitive such as the optic nerves, optic chiasm, cranial nerves, and spinal cord. The challenge is to obtain the optimal therapeutic dose for a good chance of tumor control without exceeding normal tissue tolerance. Many times the tumor may be adjacent to an organ that tolerates radiation reasonable well, however higher doses or dose escalation would allow for better tumor control. For low grade tumors or early stage cancers the concern is that these patients are likely going to survive for a long time and have to deal with the long-term effects of large field EBRT. SRS/SBRT with smaller fields and less dose to normal tissue reduces the risk of long-term complications if delivered appropriately. At the other end of the spectrum, patients with aggressive cancers or advanced stage have a poor prognosis where survival is limited and their time is best not taken up by protracted trips to the clinic for 4-8 weeks of EBRT.

The equipment used for SRS/SBRT is fairly equivalent but with subtle differences. An important component to optimal efficacy and improved safety is having a team with adequate experience, procedural acumen and quality assurance protocols in place (including medical physics support).

KQ4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

When comparing the cost and cost-effectiveness of SRS/SBRT, the comparison is not only to external beam radiotherapy but also conventional surgery. From the patient's out-of-pocket expenses, the fact that the treatment is much shorter significantly reduces cost. In addition, with fewer side effects, patients are able to return to work faster. Chao et al. found that 84% of patients returned to work in a median of 4 days following SRS treatment for a variety of disease processes (Technol Cancer Res Treat. 2012 Apr;11(2):117-22).

Mehta and colleagues performed a cost analysis of radiosurgery versus resection for single brain metastases. Though they found that both resection and radiosurgery yielded superior survival and functional independence, compared to whole brain radiotherapy alone. Resection resulted in a 1.8-fold increase in cost when compared to radiosurgery. (Int J Radiat Oncol Biol Phys 1997; 39(2):445-54. Lal *et al*. found that SRS with observation had a higher average cost when compared to whole brain plus SRS. They also found that SRS with observation was associated also with higher average life years saved (0.6 for WBI + SRS versus 1.64 for SRS + observation) (American Journal of Clinical Oncology 35:1 Feb 2012). Part of the reason for the higher average cost in the SRS + observation arm was that those who did progress after SRS alone where generally salvaged with surgery thus contributing to the overall cost.

SRS/SBRT is generally less expensive than conventional surgery. The Mayo group found that for vestibular schwanomas the mean cost was $23,788 for the microsurgery group compared with $16,143 for the radiosurgical group (Banerjee et al., J. Neurosurg 108:1220-1224, 2008).

Direct comparisons between EBRT and SRS/SBRT are limited. Haley *et al*., found that patients who underwent SBRT for spine metastases had the higher total gross charge but that depending on the technique, EBRT could approach 71% of the SBRT charge (J Neurosurgery Spine 14:537-

542, 2011). Furthermore patients treated using EBRT had more acute toxicities, and required further intervention at the initial treated level. Papatheofanis *et al.* found that the cost of SBRT for spine metastases with Cyberknife was $1933 less than EBRT for comparable effectiveness (Neurosurgery 64:2, Feb 2009 Supplement.) Lastly, Sher *et al*., found the SBRT was cost effective over a wide range of conditions when compared to EBRT or RFA for medically inoperable non-small cell lung cancer. (Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 5, pp. e767–e774, 2011).

Washington University published a cost-comparison analysis of surgical intervention vs SBRT for early stage lung tumors in high risk patients. In that analysis, SBRT was less costly than surgical intervention. (*Puri et al. J Thorac Cardiovasc Surg. 2012, 143(2), 428-36.; Crabtree TD, et al. J Thorac Cardiovasc Surg. 2010 Aug;140(2):377-86)*

William Beaumont Hospital published a cost comparison for SBRT and EBRT demonstrating lower expenses with SBRT for stage I non-small cell lung cancer patients. *(Lanni et al. Am J Clin Oncol 2011, 34(5): 494-8)*

US TOO INTERNATIONAL

From: Pamela Barrett
To: HCA ST Health Tech Assessment Prog
Cc: jimkiefert@aol.com; Jack7474Sr@aol.com; raf0444@comcast.net
Subject: Us TOO International, prostate cancer patient comments on SBRT coverage in WA state
Date: Tuesday, March 06, 2012 10:38:40 AM
Attachments: WA state health care authority Us TOO LOR Mar 2012.pdf
Importance: High

Dear Washington State Health Care Authority Health Technology Assessment Team,

In response to your recent request to concerned stakeholders to submit comments as part of your upcoming review of stereotactic radiosurgery and stereotactic body radiation therapy (SBRT), we prostate cancer survivors in the Us TOO International Prostate Cancer Education & Support Network encourage the Washington State Health Care Authority add prostate cancer as a diagnosis that is eligible for coverage under its SBRT policy.

Please find attached our letter of support from our President and CEO, Tom Kirk.

We are happy to answer any questions you may have.

Thank you for taking into consideration the lives of all the men and their families battling a prostate cancer diagnosis in Washington state.

All the best,
Pam

Pam Barrett, Director of Development
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www.ustoo.org | facebook.com/UsTOOInternational
Us TOO makes list of Top 10 Health Charities -- read our reviews here

March 6, 2012

Someone to talk to... who understands!

Washington State Health Care Authority
Health Technology Assessment Team
626 8th Avenue SE
Olympia, WA 98501

Dear Health Technology Assessment Team,

Us TOO International is a 21-year old Chicagoland-based, 501c3 non-profit, grassroots prostate cancer education and support network made up of 325 support group/chapters worldwide. We are the largest global survivor and volunteer-based organization for prostate cancer, and we are a source of peer-to-peer support and free materials for men and their families to make informed choices on prostate cancer detection, treatment options and coping with ongoing survivorship. In addition to providing education and support programs, Us TOO is an active advocate for patients.

Medicare coverage issues have been brought to our attention by patients and their care givers over the years, and we are concerned with ongoing patient access issues. We believe that men who happen to live in Washington state and have Medicare medical coverage should not be denied access to SBRT (stereotactic body radiation therapy) treatment.

We feel that it is Medicare's obligation to provide coverage for all medical treatments that have shown to improve the lives of prostate cancer patients. SBRT, a more recent form of radiation therapy, has been used to treat prostate cancer since 2001. Data suggest that this treatment is as effective as conventional treatments such as HDR brachytherapy, alternate external beam radiation techniques, and surgery. Due to the unique nature of prostate cancer, we do not believe there is not a "one size fits all" treatment for this disease. We do not make any recommendations on which type of therapy is best for a patient. However, it is our opinion that patients should be afforded the opportunity to select a therapy that both he and his health care provider feel will provide the best possible outcomes. This requires that all clinically appropriate treatment options be eligible for coverage under the Medicare program.

In conclusion, we request that the Washington State Health Care Authority add prostate cancer as a diagnosis that is eligible for coverage under its SBRT policy. By providing coverage for this treatment, the state of Washington will provide hope to thousands of men and their families who suffer from this disease.

Thank you in advance for your thoughtful consideration of this matter.

Sincerely,

Thomas N. Kirk
President & CEO
tom@ustoo.org

Member since 2005
Standards of Excellence® Certification Program

Us TOO is a 501(c)3 non-profit organization founded in 1990 by prostate cancer survivors and their families.

Us TOO International
Prostate Cancer Education & Support Network

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VARIAN MEDICAL SYSTEMS

From: Sarah Svoboda
To: HCA ST Health Tech Assessment Prog
Cc: Andy Whitman
Subject: 2012 Washington HTA Review of SRS and SBRT: Varian Comments and Clinical Evidence
Date: Tuesday, March 06, 2012 3:01:55 PM
Attachments: SRS SBRT Review by Washington HTA- Varian Comments 6 March 2012.pdf
Enclosure 1- Varian Cover Letter and SRS SBRT Bibliography Jan 17 2011.pdf
Importance: High

Dear Mr. Morse,
Please find attached Varian Medical Systems' submittal of clinical evidence and answers to the Key Questions in regards to the Washington Health Tech Assessment's 2012 review of Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy with related enclosure. Thank you and please let me know if you have any questions regarding these materials.

Sincerely,

Sarah Svoboda

Sarah Svoboda
Government Affairs Associate
Varian Medical Systems
525 9th St NW, Suite 450
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Phone: (202) 629-3441
Mobile: (408) 314-4199
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Delivered via E-mail

January 14, 2011

Denise Santoyo
Program Coordinator
Washington Health Technology Assessment
P.O. Box 42712
Olympia, WA 98504-2712
shtap@hca.wa.gov

Dear Ms. Santoyo:

Attached please find information compiled by Varian Medical Systems that may be useful in your evaluation of stereotactic radiosurgery for the 2011 Washington Health Technology Assessment Program.

The information is a bibliography of clinical and technical journal publications from the time period January 2000 through December 2010, where Varian LINACs were used for Radiosurgery (SRS) or Stereotactic Body Radiotherapy (SBRT) or Varian users developed enabling techniques that are applied in the clinical practice of SRS and SBRT.

The bibliography is organized such that the first portion is the relevant journal papers, grouped by anatomical organ system. The second section is a collection of journal papers that are broad assessments or reviews. The third section details technical aspects of the delivery of SRS and SBRT.

Please feel free to contact me if you have any questions regarding the materials submitted.

Sincerely yours,

Calvin J. Huntzinger
Senior Director, Varian Surgical Sciences

VARIAN medical systems | A partner for life

Varian Medical Systems, Inc
525 9th Street NW, Suite 450
Washington, DC 20004
Telephone: 202.629.3459
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March 6, 2012

Mr. Josiah Morse, MPH
Program Director
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712
shtap@hca.wa.gov

Dear Mr. Morse:

Thank you for the opportunity to submit clinical evidence to answer the Key Questions for your upcoming review of Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT). In addition to the data below, I have also included our previous comment letter that provides numerous studies on this topic that may be helpful. Please feel free to contact me with any questions at (202) 629 3441.

Sincerely yours,

Andrew M. Whitman
Vice President, Government Affairs

Enclosures (1)

KQ1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy compared to conventional external beam radiation therapy (EBRT) for the following patients:

The research cited below is categorized by disease-site studies highlighting the benefits of SRS and/or SBRT. For example, the research shows that SRS and SBRT have improved accuracy and tumor control rates, and effective symptom alleviation. The research also demonstrates that there is a potential improvement in quality of life as well as the ability to treat medically inoperable tumors with this non-invasive treatment.

a. Patients with central nervous system (CNS) tumors

Evidence/Quotation	Reference
The delivered radiation dose does appear to make a difference. With image-guided treatment verification, errors can be minimized to within 2 mm. This level of accuracy has enabled the delivery of high-dose, single-fraction RT within close proximity to the spinal cord without toxicity. IMRT is ideally suited to creation of the concave dose distributions necessary for cord-sparing treatment plans. Image-guided verification provides a mechanism to minimize the uncertainties associated with traditional RT. The coupling of IMRT and image-guided techniques takes full advantage of the extremely conformal potential of IMRT to provide high-dose RT with low normal tissue exposure and a high degree of confidence. The experience reported for high-dose, single-fraction image-guided RT is proof of principle that improved treatment accuracy has resulted in improved outcomes, with minimal serious morbidity.	Yamada, Y., Bilsky, M.H., Lovelock, D.M., Venkatraman, E.S., Toner, S., Johnson, J., … Fuks, Z.,(2008), High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. International journal of radiation oncology biology physics, 71(2), 484-490. doi: 10.1016/j.ijrobp.2007.11.046
"Both conventional and stereotactic radiosurgery are important treatment methods for the management of solid tumors metastatic to the spine. Both methods are well tolerated and provide effective tumor control and symptom palliation." Led here by SBRT symposium summary which quotes the authors of this study saying "We are able to deliver these treatments safely, and significant complications are rare. The literature consistently shows local control rates of up to 85 percent for those patients, and they often experience near complete pain relief. The majority of patients feel a significant improvement in pain within about 10 days of radiosurgery."	Gerszten PC, Mendel E, Yamada Y. Radiotherapy and radiosurgery for metastatic spine disease: what are the options, indications, and outcomes? Spine. 2009:34(suppl):S78-92.

b. Patients with non-central nervous system cancers

Evidence/Quotation	Reference
"The main finding in this prospective study was the high rate of primary tumor control (97.6% at 3 years). Primary tumor control is an essential requirement for the cure of lung cancer... Stereotactic body radiation therapy as delivered in [one study] provided more than double the rate of primary tumor control than reports describing conventional radiotherapy... Series reporting results from conventional radiotherapy for similar patient groups report	Timmerman R, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010;303:1070–1076

Evidence/Quotation	Reference
2-3 year OS in the 20-35% range, considerably lower than the 55.8% rate at 3 years in this report."	
Indeed, for both T1 and T2 malignancies, SBRT was still the most cost-effective treatment modality over many assumptions. Furthermore, if SBRT is not available, RFA would be the most cost-effective therapy for small cancers, whereas 3D-CRT would be the preferred modality for larger lesions. The implications of this study could affect a significant number of patients, because an estimated 25% to 35% of early-stage lung cancer patients are not medically fit for lobar resection, and thus alternative therapies must be implemented 24... As we have shown, the superb control rates with SBRT overwhelm almost any increase in cost... If SBRT is available, conventional fractionated radiotherapy no longer appears to be a viable treatment approach for peripheral, early-stage lung cancers, based either on efficacy or on cost outcomes.	Sher, D.J., Wee, J.O., & Punglia, R.S. (2011). Cost-Effectiveness Analysis Of Stereotactic Body Radiotherapy And Radiofrequency Ablation For Medically Inoperable, Early-Stage Non–Small Cell Lung Cancer. International journal of radiation oncology, biology, physics, in press. doi: 10.1016/j.ijrobp.2010.10.074
Continuous hyperfractionated and accelerated radiotherapy "was found to yield better overall survival than conventional irradiation...with a 22% reduction in the relative risk of death..."	Chouaid, C., Atsou, K., Hejblum, G., & Vergnenegre, A.. (2009). Economics of Treatments for Non-Small Cell Lung Cancer. PharmacoEconomics, 27(2), 113-25. Retrieved September 6, 2011, from Alumni - ABI/INFORM Complete. (Document ID: 1692754451).
"The results of the present study have confirmed single-dose RT as a powerful clinical approach for achieving long-term local control of human tumors." "The experience reported for high-dose, single-fraction image-guided RT is proof of principle that improved treatment accuracy has resulted in improved outcomes, with minimal serious morbidity."	Yamada, Yoshiya, et al. (2008). High-Dose, Single-Fraction Image-Guided Intensity-Modulated Radiotherapy for Metastatic Spinal Lessons. International Journal of Radiation Oncology, Biology, and Physics, Vol 71:2, 484-490.
"The delivery of SBRT as described in this report offers excellent local control for medically inoperable patients with Stage I lung cancer, and results in an overall survival rate that is superior to outcomes reported for similar patients treated with conventionally fractionated RT." "Timmerman et al. reported a 95% local tumor control rate at 24 months in their Phase II study of SBRT in 70 medically inoperable lung cancer patients." "In conclusion, IMRT-based SBRT for medically inoperable Stage I [non-small cell lung cancer]...provides excellent local control and survival without undue toxicity."	Videtic G, et al. Intensity-modulated radiotherapy-based stereotactic body radiotherapy for medically inoperable early-stage lung cancer: excellent local control. Int J Radiat Oncol Biol Phys. 2010; 77:344–349.

KQ2: What are the potential harms of SRS and SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.

The peer-reviewed studies listed below highlight that the use of SRS and SBRT can improve outcomes for patients. The research also shows that these types of treatment techniques are safe and effective.

Evidence/Quotation	Reference
The delivered radiation dose does appear to make a difference. With image-guided treatment verification, errors can be minimized to within 2 mm. This level of accuracy has enabled the delivery of high-dose, single-fraction RT within close proximity to the spinal cord without toxicity. IMRT is ideally suited to creation of the concave dose distributions necessary for cord-sparing treatment plans. Image-guided verification provides a mechanism to minimize the uncertainties associated with traditional RT. The coupling of IMRT and image-guided techniques takes full advantage of the extremely conformal potential of IMRT to provide high-dose RT with low normal tissue exposure and a high degree of confidence. The experience reported for high-dose, single-fraction image-guided RT is proof of principle that improved treatment accuracy has resulted in improved outcomes, with minimal serious morbidity.	Yamada, Y., Bilsky, M.H., Lovelock, D.M., Venkatraman, E.S., Toner, S., Johnson, J., … Fuks, Z.,(2008), High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. International journal of radiation oncology biology physics, 71(2), 484-490. doi: 10.1016/j.ijrobp.2007.11.046
Figures on page 1189-90 on symptom reduction post RT--decreased fatigue, pain, disturbed sleep, drowsiness, and distress, with less symptom interference affecting genera; activity, mood, normal work, relations, walking ability, and enjoyment of life.	Nguyen, QN, et al. Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys. 2010;76:1185–1192
"Both conventional and stereotactic radiosurgery are important treatment methods for the management of solid tumors metastatic to the spine. Both methods are well tolerated and provide effective tumor control and symptom palliation." Led here by SBRT symposium summary which quotes the authors of this study saying "We are able to deliver these treatments safely, and significant complications are rare. The literature consistently shows local control rates of up to 85 percent for those patients, and they often experience near complete pain relief. The majority of patients feel a significant improvement in pain within about 10 days of radiosurgery."	Gerszten PC, Mendel E, Yamada Y. Radiotherapy and radiosurgery for metastatic spine disease: what are the options, indications, and outcomes? Spine. 2009:34(suppl):S78-92

KQ4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

The studies listed below show that an investment in technology that can perform radiosurgery (SRS/SBRT) can be beneficial given the wide array of treatments that can be performed using a single medical device. In comparison to other treatment techniques for cancer, radiosurgery may be the most cost-effective.

Evidence/Quotation	Reference
Subsequent sensitivity analyses showed that SRS and observation was always cost effective compared with SRS and WBRT with ICERs in the range of $50,000 to $100,000/QALY. Therefore, from a resource allocation perspective, SRS and observation for brain metastases is a cost-effective treatment option within a WTP (willingness-to-pay) threshold of $100,000/QALY	Lal, L.S., Byfield, S.D., Chang, E.L., Franzini, L., Miller, L.A., Arbuckle, R., … Swint, J.M. (2011). Cost-effectiveness Analysis of a Randomized Study Comparing Radiosurgery With Radiosurgery and Whole Brain Radiation Therapy in Patients With 1 to 3 Brain Metastases. American journal of clinical oncology, 0, 0. doi: 10.1097/COC.0b013e3182005a8f
Indeed, for both T1 and T2 malignancies, SBRT was still the most cost-effective treatment modality over many assumptions. Furthermore, if SBRT is not available, RFA would be the most cost-effective therapy for small cancers, whereas 3D-CRT would be the preferred modality for larger lesions. The implications of this study could affect a significant number of patients, because an estimated 25% to 35% of early-stage lung cancer patients are not medically fit for lobar resection, and thus alternative therapies must be implemented 24... As we have shown, the superb control rates with SBRT overwhelm almost any increase in cost... If SBRT is available, conventional fractionated radiotherapy no longer appears to be a viable treatment approach for peripheral, early-stage lung cancers, based either on efficacy or on cost outcomes.	Sher, D.J., Wee, J.O., & Punglia, R.S. (2011). Cost-Effectiveness Analysis Of Stereotactic Body Radiotherapy And Radiofrequency Ablation For Medically Inoperable, Early-Stage Non–Small Cell Lung Cancer. International journal of radiation oncology, biology, physics, in press. doi: 10.1016/j.ijrobp.2010.10.074
The incremental cost-effectiveness ratio for SBRT over 3D-CRT was $6,000/quality-adjusted life-year, and the incremental cost-effectiveness ratio for SBRT over RFA was $14,100/quality-adjusted life-year. One-way sensitivity analysis showed that the results were robust across a range of tumor sizes, patient utility values, and costs. ...In comparison to 3D-CRT and RFA, SBRT was the most cost-effective treatment for medically inoperable NSCLC over a wide range of treatment and disease assumptions. On the basis of efficacy and cost, SBRT should be the primary treatment approach for this disease	Sher, D.J., Wee, J.O., & Punglia, R.S. (2011). Cost-Effectiveness Analysis Of Stereotactic Body Radiotherapy And Radiofrequency Ablation For Medically Inoperable, Early-Stage Non–Small Cell Lung Cancer. International journal of radiation oncology, biology, physics, in press. doi: 10.1016/j.ijrobp.2010.10.074
For inoperable stage I NSCLC, carbon-ion therapy costed euro 67.257 per quality-adjusted-life-year gained compared to SBRT. Both treatments dominated protons and CRT. Considerable uncertainty surrounded these results, resulting in a high EVPI. For operable stage I NSCLC SBRT dominated carbon-ion therapy.	Grutters, J.P.C., Pijls-Johannesma, M., De Ruysscher, D., Peeters, A., Reimoser, S., Severens, J.L., … Joore, M.A. (2010). The cost-effectiveness of particle therapy in non-small cell lung cancer: Exploring decision uncertainty and areas for future research. Cancer Treatment Reviews, 36(6), 468-476. doi: 10.1016/j.ctrv.2010.02.018

Evidence/Quotation	Reference
The cost-effectiveness per unit of QALY was better for the GKRS treatment (US$10,381/QALY) than in the WBRT treatment (US$17,622/QALY), $p<0.05$. The cost-effectiveness per KPS score was also higher for the GKRS treatment (US$139/KPS score) than for WBRT (US$229/KPS score), $p<0.01$. Thus, the mortality rate for multiple metastatic brain tumors treated by GKRS is significantly better with a good initial KPS score and when the tumor number is 2-5. GKRS results in a better post-treatment KPS score, QALY, and higher cost-effectiveness than WBRT for treating multiple metastatic brain tumors.	Lee, W.Y., Cho, D.Y., Lee, H.C., Chuang, H.C., Chen, C.C., Liu, J.L., … Ho, L.H. (2009). Outcomes and cost-effectiveness of gamma knife radiosurgery and whole brain radiotherapy for multiple metastatic brain tumors. Journal of Clinical Neuroscience,(5), 630-634. doi: 10.1016/j.jocn.2008.06.021

SRS AND SBRT BIBLIOGRAPHY

CLINICAL AND TECHNICAL JOURNAL PUBLICATIONS 2000 THROUGH DECEMBER 2010

WHERE VARIAN LINACS WERE USED FOR SRS & SBRT OR VARIAN USER'S-DEVELOPED ENABLING TECHNIQUES ARE USED IN SRS & SBRT

BRAIN TUMORS – BENIGN

Benign Meningioma & Other Benign Tumors [20]

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*

Golanov AV, Cherekaev VA, Serova NK, Pronin IN, Gorlachev GE, Kotel'nikova TM, Podoprigora AE, Kudriavtseva PA, Galkin MV [Linear accelerator-based stereotactic radiation treatment of patients with medial middle fossa meningiomas] *Zh Vopr Neirokhir Im N N Burdenko*. 2010 Jan-Mar;(1):13-8. Russian.

Anker CJ, Shrieve DC. Basic principles of radiobiology applied to radiosurgery and radiotherapy of benign skull base tumors. *Otolaryngol Clin North Am.* 2009 Aug;42(4):601-21. *University of Utah, Salt Lake City*

Kimball MM, Friedman WA, Foote KD, Bova FJ, Chi YY. Linear Accelerator Radiosurgery for Cavernous Sinus Meningiomas. *Stereotact Funct Neurosurg.* 2009 Feb 27;87(2):120-127. *University of Florida, Gainsville*

Fogliata A, Clivio A, Nicolini G, Vanetti E, Cozzi L. Intensity modulation with photons for benign intracranial tumours: a planning comparison of volumetric single arc, helical arc and fixed gantry techniques. *Radiother Oncol.* 2008 Dec;89(3):254-62. *Oncology Institute of Southern Switzerland, Bellinzona, Switzerland.*

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BRAIN TUMORS – BENIGN

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Metastatic Disease [37]

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BRAIN – FUNCTIONAL DISEASE

BRAIN – Seizure Treatment: Thalamotomy & Corpus Callosotomy [4]

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SPINE

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

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LUNG

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H&N-EENT & Skull Base

Non-CNS Tumors of the Orbt and Head & Neck

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February 29, 2012

To whom it may concern,

As a member of the IRSA (International Radiosurgery Association) Board of Directors, my colleagues and I spent years developing consensus-based radiosurgery practice guidelines for the radiosurgical treatment of conditions as well as for numerous benign and malignant tumor diagnoses in the brain. These areas included the radiosurgical treatment of **Acoustic Neuromas**, **Trigeminal Neuralgia, Pituitary Adenomas**, **AVM (Aterio-Venous Malformations) and Brain Metastases**. Our aim was to improve outcomes for these diagnoses by assisting physicians in applying research evidence to clinical decisions while promoting the responsible use of health care resources. I have attached the link to these documents below. Guidelines from ISRA are pending for the following tumors and conditions **Meningiomas, Essential Tremor and Gliomas.** Nevertheless, the rational to treat them with SRS are included in this letter.

Acoustic Neuroma

http://www.irsa.org/AN%20Guideline.pdf

KQ1 and KQ2:

Gamma Knife Radiosurgery: Clinical Results

Tumor Growth Control

Long-term results of Gamma Knife® radiosurgery for vestibular schwannomas have been documented.[14,22,32,42,45,55] Recent reports suggest a tumor control rate of 93–100% after radiosurgery.[14,16,21-24,31,32,34,36,37,42-45,50-52,54,55,61,67,68] Kondziolka et al studied 5 to 10-year outcomes in 162 vestibular schwannoma patients who had radiosurgery at the University of Pittsburgh.[44] In this study a long-term 98% tumor control rate was reported. Sixty-two percent of tumors became smaller, 33% remained unchanged, and 6% became slightly larger. Some tumors initially enlarged 1–2 mm during the first 6 to 12 months after radiosurgery as they lost their central contrast enhancement. Such tumors generally regressed in volume compared to their pre-radiosurgery size. Only 2% of patients required tumor resection after radiosurgery. Norén, in his 28-year experience with vestibular schwannoma radiosurgery, reported a 95% long-term tumor control rate. Litvack et al reported a 98% tumor control rate at a mean follow-up of 31 months after radiosurgery using a 12 Gy margin dose.[53] Niranjan et al analyzed the outcome of intracanalicular tumor radiosurgery performed at the University of Pittsburgh.[65] All patients (100%) had imaging-documented tumor growth control. Flickinger et al performed an outcome analysis of acoustic neuroma patients treated between August 1992 and August 1997 at the University of Pittsburgh. The actuarial 5-year clinical tumor control rate (no

requirement for surgical intervention) was 99.4 + 0.6%.[21,22] The long-term (10–15 year) outcome of benign tumor radiosurgery has been evaluated. In a study which included 157 patients with vestibular schwannomas**,** the median follow-up for the patients still living at the time of the study (n=136) was 10.2 years. Serial imaging studies after radiosurgery (n=157) showed a decrease in tumor size in 114 patients (73%), no change in 40 patients (25.5%), and an increase in three patients who later had resection (1.9%).[45] No patient developed a radiation associated malignant or benign tumor (defined as a histologically confirmed and distinct neoplasm arising in the initial radiation field after at least two years have passed).

Hearing Preservation

Pre-radiosurgery hearing can now be preserved in 60–70% of patients, with higher preservation rates found for smaller tumors. In a long-term (5–10 year follow-up) study conducted at the University of Pittsburgh, 51% of patients had no change in hearing ability.[21,44] All patients (100%) who were treated with a margin dose of 14 Gy or less maintained a serviceable level of hearing after intracanalicular tumor radiosurgery.[65] Among patients treated after 1992, the 5-year actuarial rates of hearing level preservation and speech preservation were 75.2% and 89.2%, respectively, for patients (n=89) treated with a 13 Gy tumor margin dose. The 5-year actuarial rates of hearing level preservation and speech preservation were 68.8% and 86.3%, respectively, for patients (n=103) treated with >14 Gy as the tumor margin dose.[22] Unlike microsurgery, immediate hearing loss is uncommon after radiosurgery. If hearing impairment is noted, it occurs gradually over 6 to 24 months. Early hearing loss after radiosurgery (within three months) is rare and may result from neural edema or demyelination. The exact mechanism of delayed hearing loss after radiosurgery is still unclear. Perhaps gradual obliteration of microvessels or even direct radiation axonal or cochlear injury is implicated. The effect of radiation on normal microvessels supplying the cochlear nerve or cochlea itself is not known. However, with doses as low as 12–13 Gy (which are sufficient to halt the tumor growth) vascular obliteration of normal vessels seems less likely. This dose probably does not adversely affect the vessels as well as the axons. Although with current imaging techniques the cochlear nerve cannot be well visualized, efforts should be made to achieve high conformality at anterior and inferior margin of the tumor. Conformal dose planning using 4 mm collimators for the intracanalicular portion of the tumor may prevent further injury to the cochlear nerve. It is likewise important to avoid radiation of the cochlea.[70]

Facial Nerve and Trigeminal Nerve Preservation

Facial and trigeminal nerve function can now be preserved in the majority of patients (>95%). In the early experience at University of Pittsburgh normal facial function was preserved in 79% of patients after five years and normal trigeminal nerve function was preserved in 73%. These facial and trigeminal nerve preservation rates reflected the higher tumor margin dose of 18–20 Gy used during the CT based planning era before 1991. In a recent study using MR based dose planning, a 13 Gy tumor margin dose was associated with 0% risk of new facial weakness and 3.1% risk of facial numbness (5-year actuarial rates). A margin dose of >14 Gy was associated with a 2.5% risk of new onset facial weakness and a 3.9% risk of facial numbness (5-year actuarial rates).[22] None of the patients who had radiosurgery for intracanalicular tumors developed new facial or trigeminal neuropathies.

Neurofibromatosis 2

Patients with vestibular schwannomas associated with neurofibromatosis 2 represent a special challenge because of the risk of complete deafness. Unlike the solitary sporadic tumors that tend to displace the cochlear nerve, tumors associated with NF2 tend to form nodular clusters that engulf or even infiltrate the cochlear nerve. Complete resection may not always be possible. Radiosurgery has been performed for patients with NF2. Subach et al studied 40 patients (with 45 tumors) who were treated with radiosurgery for NF2. Serviceable hearing was preserved in 6 of 14 patients (43%), and this rate improved to 67% after modifications made to the technique in 1992. The tumor control rate was 98%.[98] Only one patient showed imaging documented growth. Normal facial nerve function and trigeminal nerve function was preserved in 81% and 94% of patients, respectively. In two recent series,[78,80] serviceable hearing was preserved in only 30%[78] and 40%[80] of cases, respectively. The tumor control rate was respectively 71%[78] and 79%.[80] It now appears that preservation of serviceable hearing in patients with NF2 is an attainable goal with modern

radiosurgery technique, and some centers propose this early treatment when the hearing level is still excellent."

KQ3:

"Clinical Algorithm
A number of patient related factors are considered in making a recommendation. These factors include:
• Age
• Symptoms
• Hearing status
• Current neurological status
• Medical condition
• Presence or absence of NF2
• Presence or absence of prior procedures
• Concern and risk tolerance for hearing, facial and trigeminal nerve function
• Patient desires
• Patient's decision after informed consent"

KQ4:

EBRT is not the standard of care for Acoustic Neuromas

Trigeminal Neuralgia

http://www.irsa.org/TN%20Guideline-UpdatedJan2009.pdf

KQ1 and KQ2:

"Several reports have documented the efficacy of Gamma Knife® stereotactic radiosurgery for TN.[1,3,16,18,20,26,27,29,32,35,39-42,46,50-53,58,62,68] Because radiosurgery is the least invasive procedure for TN, it is a good treatment option for patients with co-morbidities, high-risk medical illness, or pain refractory to prior surgical procedures. Radiosurgery is a good alternative for most patients with medically refractory trigeminal neuralgia, especially those who do not want to accept the greater risk of an MVD for a greater chance of pain relief.

To date, the largest reported series are still characterized by a wide spectrum of success rates after radiosurgery with Grade I outcome in 21–76.8% of patients and Grade II outcome in 65–88% of patients.[6,7,21,29,38,48,52,58,67] Regis et al reported that 87% of patients were initially free of pain in their series of 57 patients treated with a maximum dose of 75–90 Gy.[52,54] In many patients, they used the higher maximum dose of 90 Gy, and their target was placed at a more anterior site (closer to retrogasserian portion). In a series of 441 patients presented at the 2001 meeting of the International Stereotactic Radiosurgery Society, Young et al noted that 87% of patients were free of pain after radiosurgery, with or without medication (median follow-up period, 4.8 years, including repeat procedures). Brisman et al noted vascular contact with trigeminal nerve on thin section MRI in 59% of patients with TN. These authors reported a complete (100%) pain relief without medicines in 22% of patients, 90% or greater relief with or without small doses of medicines in 30% of patients, 75–89% relief in 11% of patients, 50–74% relief in 7% of patients, and less than 50% relief in 8% of patients. Recurrent pain requiring a second procedure occurred in 24% of patients.[7]

In a study, Petit et al. assessed the safety, efficacy and quality of life associated with radiosurgical treatment for TN in 112 patients treated with Gamma Knife® radiosurgery using a standard questionnaire. Ninety-six patients completed questionnaires for a median follow-up of 30 months. Seventy-four patients (77%) reported pain relief at a median of three weeks after the procedure.[44] A decrease in medication usage was noted in 66% of patients. Seven (7.3%) patients reported new or increased trigeminal dysfunction;

however, only 3.1% reported these symptoms as bothersome. Patients with sustained pain relief reported an average of 100% improvement in their quality of life as a direct result of pain relief after radiosurgery, and 100% believed that the procedure was successful. Furthermore, among those patients with temporary pain relief and subsequent recurrence, 65% felt their treatment was a success with an average of 80% improvement in their quality of life.[44] Smith et al. recently published the results of trigeminal neuralgia radiosurgery using a dedicated linear accelerator.[59] These investigators treated 60 patients with central doses of 70–90 Gy delivered to trigeminal nerve root entry zone using a 5-mm collimator. Pain relief was experienced at a mean of 2.7 months. Significant pain relief was obtained in 87.5% of the patients who had essential TN and in 58.3% of the patients who had secondary facial pain. In a recent article, Longhi et al. reported on the results of Gamma Knife® radiosurgery for treatment of medically and, in some instances, surgically refractory TN.[35] These authors found 57% Grade I and 33% Grade II pain control after Gamma Knife® radiosurgery. These favorable results are similar to those reported by Pollock et al.[49] and Kondziolka et al.[28] Recurrence of pain occurred in 18% of patients at a mean interval of 14.2 months after radiosurgery. The side effects of trigeminal paresthesia or hypoesthesia were observed in 9.5% of patients; no cases of anesthesia dolorosa were observed. A higher radiosurgical dose and no previous neurosurgical intervention for TN were positive predictors of a pain-free outcome. The growing body of recent literature suggests that low rates of complications of Gamma Knife® radiosurgery, coupled with high success rates and patient satisfaction, allow it to be increasingly used as primary intervention for trigeminal neuralgia for appropriate patients.[2,12,13,18,20,22,26,34]

KQ3:

"A number of factors are considered in making a recommendation. These factors include:

1. Patient's age
2. Patient's medical condition
3. Presence or absence of multiple sclerosis
4. Presence or absence of vascular contact and/or compression on thin section MRI
5. Presence or absence of prior procedures
6. The type of prior procedure and its response
7. Severity of pain and how long the patient can reasonably wait for pain relief
8. Patient's concern and risk tolerance for dysesthesias, recurrence or complications from surgery"

Pituitary Adenoma

http://www.irsa.org/Pituitary%20Guideline.pdf

KQ1 and KQ2:

Stereotactic Radiosurgery

The endocrine control aims of radiosurgery are no different from those of surgical resection; namely, normalization of any hypersecretory syndrome without new onset hypopituitarism. Unlike surgical resection, which eliminates the tumor on subsequent neuroimaging, the neoplastic goal of stereotactic radiosurgery is permanent tumor control. This means that a tumor, which has been enlarging, is made incapable of further tumor growth, and this control is confirmed through long-term neuroimaging follow-up. While permanent stabilization of tumor size is the desired goal, the majority of tumors will demonstrate varying degrees of tumor shrinkage over time. Thus the goal of pituitary adenoma radiosurgery is to permanently control tumor growth, maintain pituitary function, normalize hormonal secretion in the case of functional adenomas, and preserve neurological function, especially vision. The small risks of late radiation-induced tumorigenesis and of late cerebrovascular accidents from radiation damage to the internal carotid arteries also exist for patients treated with radiosurgery. Delayed complications are less than that of stereotactic radiotherapy.

Tumor Growth Control After Radiosurgery

Non-functioning pituitary adenomas are usually diagnosed late when patients complain of visual dysfunction. Trans-sphenoidal decompression is recommended as the first line of management for these patients. Radiosurgery is often indicated as an adjuvant management after partial resection or later recurrence of pituitary adenomas. However, radiosurgery can be performed as the primary management of nonfunctioning adenomas in carefully selected patients, including those who are high risk for surgery or consciously choose not to undergo resective surgery. Tumor growth control rates of 90–100% have now been confirmed by multiple centers following pituitary radiosurgery (13, 20, 21, 24, 26, 41). The antiproliferative effect of radiosurgery has been reported in nearly all patients who underwent Gamma Knife® radiosurgery (24, 41). Relatively few patients (who usually had received lower margin doses) eventually required additional treatment (12, 46).

Functional Effect of Radiosurgery

Growth Hormone Secreting Adenomas (Acromegaly)

A biochemical remission is defined as GH level suppressed to below 1 μg/L on OGTT and normal age-related serum IGF-1 levels. OGTT remains the gold standard for defining a cure of acromegaly. IGF-1, however, is far more practical. Decrease of random GH to less than 2.5 μg/L is achieved more frequently than the normalization of IGF-1 but it is necessary to obtain the fulfillment of both criteria. Microsurgery results in biochemical remission in 31–80% of patients (1, 5, 19, 53, 59). The suppression of hormonal hyperactivity is more effective when higher doses of radiation are used. Hormonal normalization after radiosurgery was achieved in 29–82% of cases in the published series (3, 4, 11–14, 17, 19, 20, 22, 24, 25, 30, 32, 33, 35, 36, 41, 42, 45, 47–49, 57, 62, 68). Because hormone suppressive medication during radiosurgery may act as a radioprotective agent, this medication should be discontinued at least six to eight weeks prior to radiosurgery (25, 49) and may be resumed after a week. In a study at the University of Pittsburgh, 38% of patients were cured (GH <1 μg/L) and overall, 66% had growth hormone levels <5 μg/L, 3–5 years after radiosurgery (44). An important goal of resective surgery is to achieve an immediate postoperative effect, while the results of radiosurgery have a latency of about 20–28 months (18, 28) that must be sometimes temporized through the temporary use of hormone suppressive medications.

ACTH Secreting Adenomas

Cushing's disease: The results to date achieved by radiosurgery (usually used after failed resective surgery) are slightly inferior to those reported after primary surgical resection in regard to secretory normalization. In addition there is a latency of approximately 14–18 months for maximal therapeutic response (18, 28). Patients with Cushing's disease respond to radiosurgery but more than one procedure may be needed. In various published series 63–98% hormone normalization after radiosurgery has been observed (10, 16, 29, 33, 36, 38, 40, 43, 46, 50, 51, 54, 55, 58, 63). *Nelson's syndrome:* Maintenance of elevated ACTH levels indicates continued biochemical activity of a pituitary adenoma after prior adrenalectomy for Cushing's disease. Strict hormonal normalization is not as important for the treatment of pituitary adenomas associated with Nelson's syndrome as it is for other secretory pituitary adenomas. The most important task of radiosurgery in the case of Nelson's syndrome is to control the growth of the tumor, which has been achieved in the majority of cases (66).

Prolactin Secreting Adenomas

Most prolactinomas can be controlled successfully by medical treatment. Surgery is indicated for cases of intolerance to medical treatment, in cases where women desire to have children, or when patients are dopamine agonist resistant (5–10% of patients). Some patients prefer microsurgery or radiosurgery to the need for life long medical treatment. In published studies of patients treated with radiosurgery, 25–29% showed normalization (26, 49). The possible radioprotective effect of dopaminergic drugs should be taken into account. In one of the studies patients treated with dopamine agonist had lower remission rates. It is therefore recommended that radiosurgery for prolactinoma be performed during a period of drug withdrawal (26).

Radiation Tolerance of Functioning Pituitary Tissue

The most important factor influencing post-irradiation hypopituitarism seems to be the mean dose to the hypophysis (pituitary stalk). Vladyka et al. observed some worsening of gonadotropic, corticotropic or thyrotropic functions 12–87 months after radiosurgery and usually 4–5 years after radiosurgery (61). There was no post radiation worsening of gonadotropic and thyrotropic functions when the mean dose to the hypophysis did not exceed 15 Gy. The limiting mean dose to the hypophysis for adrenocorticotropic function was 18 Gy (61). In another study, deterioration in pituitary functions was observed when the pituitary stalk received higher doses (10). The risk for hypopituitarism after stereotactic radiosurgery thus becomes a primary function of the anatomy of the tumor and the dose prescribed. For recurrent tumors primarily involving the cavernous sinus, where the pituitary stalk (and even at times the residual pituitary gland) is separate from the tumor, easily visualized, and can be excluded from the treatment volume, the risk of hypopituitarism is extremely small, even when high doses are utilized for secretory adenomas. For adenomas that cannot be visually separated from the normal gland, particularly if they extend upward to involve or compress the pituitary stalk, the risk is predominantly related to the dose necessary to effectively achieve all treatment goals for the functional status of the tumor (higher for secretory than non-secretory adenomas).

Complications of Pituitary Radiosurgery

Complications of pituitary radiosurgery fall into three categories: hypopituitarism, visual deterioration and hypothalamic damage. The following rates of hypopituitarism have been reported: Levy et al. (32), 33%; Thoren et al. (57), 24%; Rocher et al. (52), 33%; and Lunsford et al. (34), 0%. As discussed in the section above, hypopituitarism risks vary with tumor anatomy relative to the pituitary stalk and gland, and vary with whether the adenoma is secretory or non-secretory (higher dose needed in the former). Stereotactic radiosurgery for residual or recurrent non-secretory adenomas solely involving the cavernous sinus carries the lowest risk of subsequent hypopituitarism, while secretory tumors close to the median eminence or requiring targeting of the whole pituitary gland carry the highest risk. Future studies must stratify for these variables in order to better predict hypopituitarism risk after stereotactic radiosurgery in an individual patient. Levy et al. (32) reported <1% increase in visual deficit in their large series. Lunsford et al. (34) reported one patient with visual compromise. Using LINAC radiosurgery, Rocher et al. reported a 39% incidence of some visual compromise (6% of patients were blinded) (52). The key to avoiding this complication lies in proper patient selection (adequate space between the optic apparatus and the superior edge of the tumor for the radiosurgery technique you are employing), insisting on strictly conformal planning at the critical structure interface, and accurate dose delivery. Lunsford et al. reported one death due to hypothalamic injury in a patient who had multiple operations, prior pituitary apoplexy and prior fractionated radiation therapy (34). Voges et al. reported one patient who developed a severe hypothalamic syndrome (62). Mitsumori et al., using LINAC radiosurgery for tumor invading the cavernous sinus, reported three cases of temporal lobe necrosis (39). As discussed above, there is a theoretical risk of late radiation induced tumorigenesis for patients receiving radiosurgical treatment. A small risk also exists of late cerebrovascular accidents from the effect of the ionizing radiation on the cerebral circulation passing adjacent to the pituitary gland. Fortunately, while the risk of major morbidity or mortality is not zero with radiosurgery, these occurrences appear to be extremely rare.

KQ3:

Clinical Algorithms

"The final recommendation is usually influenced by the cumulative experience of the medical management team. Combinations of different treatments may be necessary and/or desired under certain circumstances. Common examples include patients with cavernous sinus involvement present at diagnosis who undergo first stage microsurgery for the extra-cavernous portion of their tumor followed by second stage radiosurgery for the cavernous sinus component, and patients with secretory adenomas who undergo radiosurgery but are then maintained on their anti-secretory medications during the latency period for hormonal normalization after radiosurgery. The common need for staged or tandem treatments with multiple modalities underscores the importance of the presence of a comprehensive and coordinated multidisciplinary team in the optimal management of pituitary adenoma patients."

KQ4:

"Fractionated Radiation Therapy (EBRT)
Fractionated radiation therapy has been used for the treatment of unresectable pituitary adenomas. Rates of tumor control have been reported to vary from 76% to 97%. Fractionated radiation therapy, however, has been less successful (38–70%) in reducing hypersecretion of hormones by hormonally active tumors. It may take years before the full therapeutic effect is exhibited. The delayed complications of fractionated radiation therapy (2–10 years) include a relatively high risk of hypopituitarism (12–100%) and a low but definite risk of optic neuropathy (1–2%) and secondary tumor formation. Some investigators have reported a higher likelihood of cerebrovascular disease in patients treated with radiation therapy for pituitary tumors. In patients with a benign 3 neoplasm and an otherwise normal expected life span, external beam fractionated radiotherapy (EBRT) leads to exposure of normal surrounding brain to potential long term cognitive effects of radiotherapy. Newer fractioned radiotherapy techniques such as intensity modulated radiotherapy (IMRT) can minimize the amount of normal brain exposed to radiation compared with conventional or standard 3-D conformal techniques. However, the medial temporal lobes on either side, which are intimately involved in memory processing and learning, often remain exposed as the radiation distribution is shifted away from the optic nerves and chiasm. Minimal long-term outcome data exist for IMRT."

Intra-cranial Ateriovenous Malformations:

http://www.irsa.org/AVM%20Guideline.pdf

KQ1, KQ2 and KQ3:

"Stereotactic radiosurgery is considered for patients with unresectable AVMs. Such patients may warrant treatment based on age, location, volume or medical history.[77] Radiation technologies for stereotactic radiosurgery include Gamma Knife® radiosurgery, proton beam radiosurgery, and linear accelerators (LINACs) modified at Centers of Excellence with extensive AVM experience. Multi-modal management teams are essential for proper patient selection and patient care. Because of the delayed obliteration rate of AVMs after radiosurgery, comprehensive long-term management and observational strategies are necessary.

Probability of AVM Obliteration with Radiosurgery
Current studies indicate a success rate between 50–95% at the end of three years of observation after a single radiosurgery procedure.[1,4,5,7–10,17,21,22,33–35,38–43,47,48,51,52,56,57,61–63,66,71,74,76–79,82,84] The long-term (5–14 years) results of Gamma Knife® radiosurgery suggest that the majority of AVM patients (73%) are protected from the risk of future hemorrhage and continue their normal daily activities after radiosurgery.[63]

In a study of rate of AVM obliteration after Gamma Knife® radiosurgery at the University of Pittsburgh, obliteration was documented by angiography in 73% and by MR alone in 86% of patients who refused further angiography.[17] Assuming a 96% accuracy for MR-detected obliteration, the corrected obliteration rate for all patients was 75%.[65] Persistent out-of-field nidus (marginal failure) was identified in 18% of previously embolized versus 5% of non-embolized patients ($p = 0.006$). This was the only significant factor associated with marginal failure. Multivariate analysis correlated in-field obliteration with marginal dose ($p < 0.0001$) and sex (slightly lower in women [$p \leq 0.026$], but overall obliteration was not significantly lower [$p = 0.19$]).

Early Adverse Effects of Radiosurgery
Adverse effects of radiosurgery include short-term problems such as headache from the frame, nausea from pain medication, and perhaps a small increased risk of seizure in patients with cortical lobar AVMs, particularly if a prior history of episodic seizures is present.[14,16,18,65] For this reason we use perioperative anticonvulsants in lobar AVMs.

Late Complications After AVM Radiosurgery
Delayed complications of radiosurgery on AVMs include hemorrhage despite angiographically documented complete obliteration of the AVM, temporary or permanent radiation injury to the brain such

as persistent edema, radiation necrosis, radiation-induced tumors and cyst formation. Cyst formation after AVM radiosurgery was first reported by Japanese investigators who reviewed the outcomes of patients initially treated in Sweden.[24] Jokura et al. 6

KQ3:

A number of factors are considered in making a recommendation. These factors include:

1. Patient's age
2. Patient's medical condition
3. Previous bleed
4. Prior procedures
5. Volume of AVM
6. Location of AVM
7. Presenting symptoms

KQ4:

The standard of care does not include EBRT in the treatment of AVM's.

Brain Metastases

http://www.irsa.org/Metastatic%20Guideline.pdf

KQ1 and KQ2:

"Radiosurgery as the sole initial management or as a boost before or after WBRT has emerged as a widely practiced treatment modality for brain metastases. The goal of radiosurgery without WBRT is to achieve brain control without the possible long term neurotoxic or cognitive side effects of WBRT.[17] The rationale for radiosurgery, when used as a boost after WBRT, is to achieve improved local brain tumor control. Radiosurgery boost improves survival in selected patients in whom the predominant problem is brain disease rather than extracranial disease. Radiosurgery is also used as salvage treatment for progressive intracranial disease after surgery or WBRT. Traditionally radioinsensitive histologies tend to be more responsive to SRS than to conventional fractionated radiation treatment. In addition, SRS causes indirect vascular injury and subsequent sclerosis of blood vessels, and eventual compromise of the blood supply and circulation within the tumor.[121] The overall side effects of SRS are limited but can occasionally be serious. There are very few acute side effects of SRS related to the radiation. Stereotactic radiosurgery may cause mild fatigue and sometimes a temporary patch of hair loss if the tumor is close to the skull and scalp. There is a risk of late side effects that can develop, the most common and serious of which is tumor radionecrosis.[134] Radiation necrosis is damage to the tumor and or adjacent brain in the high-dose area. This can result in edema and additional side effects produced by the mass including seizures and neurological deficits. Radionecrosis can often be managed with corticosteroids. Occasionally surgical intervention is required to reduce the mass effect. The risk of symptomatic radionecrosis is usually less than 5%.[2,5,56] A multicenter phase I RTOG trial involving SRS documented safe SRS in patients previously treated with standard external beam radiation therapy.[111] Early publications showed good control rates and led to further investigation.[24,64,76,120] Retrospective series have consistently revealed local control of the target lesions in the range of 80–85% or even higher with a very acceptable side effect profile.[5,10,20,30,37,51,70] Prospective randomized trials have demonstrated that the one-year local control rate of target lesions with radiosurgery is 73%, which increases to 82–89% with the addition of WBRT.[2,4]

Retrospective Studies for SRS

Patients treated with conventional open surgical resection without WBRT had a 46% risk of failure at the site of the resection in a randomized trial evaluating the role of WBRT after surgical resection.[89] In subsequent studies patients were treated with SRS alone (without WBRT). These studies 8 found excellent local control (70–80% at one year).[21,83] Other published series of patients treated with SRS have

demonstrated a risk of distant brain failure at one year, ranging from 43% to 57%.[22,49,66,117] In general, the risk of new metastasis in patients with solitary tumors is approximately 37% (crude), but the actuarial risk is 50% at one year.[62,89] The histologic features or tumor type may play a role, with melanoma being more likely to be associated with multiple metastases than some other tumor types.[95] Despite a relatively high risk of new metastases outside the radiosurgery volume in patients who have SRS alone, retrospective studies have not confirmed a survival benefit to adjuvant WBRT.[94,117,118] Freedom from local progression in the brain at one year was significantly superior in patients who received both SRS and WBRT compared with SRS alone (28% vs. 69%), although the overall survival rate was not significantly different.[49] A retrospective, multi-institutional study in which patients were treated with SRS alone (n = 268) or SRS + WBRT (n = 301) also reported no significant difference in the overall survival rate.[161] Despite the higher rate of new lesions developing in patients treated with SRS alone, the overall survival appears to be equivalent to SRS + WBRT since salvage therapies are fairly effective and patients' extracranial disease is frequently the cause of death.[117] Only 24% of patients managed initially with radiosurgery alone required salvage WBRT. Pirzkall et al. reported that there was no survival benefit for an overall group of 236 patients with adjuvant WBRT but these authors noted a trend toward improved survival in a subset of patients with no extracranial tumor (15.4 vs. 8.3 months, p = 0.08).[94] Chidel et al. reported on 78 patients managed initially with SRS alone and 57 patients treated with SRS and adjuvant WBRT.[157] Whole-brain radiation therapy did not improve the overall survival rate but was useful in preventing both the local progression and the development of new brain metastases (74% vs. 48%, p = 0.06). These retrospective studies suggest that WBRT will improve local and distant control in the brain, but do not clearly demonstrate a survival advantage.[117]

A multicenter retrospective analysis was performed with 502 patients treated at 10 institutions in which all of the patients were treated with WBRT and SRS. The patients were stratified by the recursive partitioning analysis and compared with similar patients from the RTOG database who had been treated with WBRT alone.[104] The study revealed that patients with higher KPS, controlled primary tumor, absence of extracranial metastases and lower RPA class had statistically superior survival. The addition of an SRS boost resulted in a median survival of 16.1, 10.3 and 8.7 months, respectively, for RPA classes I, II and III. This is in comparison to 7.1, 4.2 and 2.3 months for similar RPA class patients from the RTOG database. This improvement in overall survival, stratified by RPA class with an SRS boost, was statistically significant.[104] In a recent study SRS alone was found to be as effective as resection plus WBRT in the treatment of one or two brain metastases for patients in RPA classes I and II.[98]

Local Tumor Control

In a randomized trial reported in abstract form by Chougule et al.,[23] patients were randomized to Gamma Knife® radiosurgery alone vs. WBRT and Gamma Knife® radiosurgery vs. WBRT alone. The local brain control rate was higher in the two radiosurgery arms: 87% for Gamma Knife® radiosurgery alone and 91% for Gamma Knife® radiosurgery and WBRT, compared with 62% in the WBRT only arm. Another randomized trial compared the use of radiosurgery with WBRT plus radiosurgery as initial therapy in selected patients with brain metastases.[4] Aoyama et al. reported the results of a prospective, multi-institutional, randomized controlled trial comparing WBRT plus SRS vs. SRS alone for patients with limited (defined as < 4) brain metastases with a maximum diameter of 3 cm on contrast-enhanced MRI scan.[4] Patients with metastases from small cell carcinoma, lymphoma, germinoma and multiple myeloma were excluded. Eligible patients had a KPS score of 70 or higher. The WBRT dosage schedule was 30 Gy in 10 fractions over 2–2.5 weeks. Metastases with a maximum diameter of up to 2 cm were treated with SRS doses of 22–25 Gy and those larger than 2 cm were treated with doses of 18–20 Gy. The dose was reduced by 30% when the treatment was combined with WBRT. Local tumor progression was defined as a radiographic increase of 25% or more in the size of a metastatic lesion. The primary end point of the study was overall survival. Secondary end points were cause of death, functional preservation, brain tumor recurrence, salvage treatment and toxic effects of radiation. One hundred thirty-two patients were randomized (65 to WBRT + SRS and 67 to SRS alone). The interim analysis was performed with 122 patients (approximately 60 in each group). The Japanese Radiation Oncology Study Group 99-1 trial[4] reported an actuarial one-year local tumor control rate of 88.7% in the WBRT + SRS group and 72.5% in the SRS-alone group (p = 0.002). The one-year actuarial rate of developing new brain metastases was 41.5% in the WBRT + SRS group and 63.7% in the SRS-alone group (p = 0.003). A prospective, single arm, multi-institutional Eastern Cooperative Oncology Group (ECOG) Phase II study of radiosurgery alone

for "radioresistant" histologies (melanoma, sarcoma, renal cell carcinoma) in patients with one to three brain metastases has also been reported.[69] Inclusion criteria were one to three newly diagnosed brain metastases with a maximum diameter of 4 cm. In patients with multiple lesions and any lesion > 3 cm, all remaining lesions were required to be < 3 cm. Of 36 patients accrued, 31 were eligible and evaluable; 14 had melanoma, 14 had renal cell carcinoma and three had sarcoma. Three of thirty-one patients (10%) had partial response, 10 of 31 (32%) had stable disease, 14 of 31 (42%) had progressive disease, and 4 of 31 (14%) were not evaluable. At six months, 39.2% failed within the radiosurgery volume and 39.4% failed outside the radiosurgery volume. Several retrospective studies[21,94,113,117,128] compared local brain control rates of those patients receiving initial radiosurgery alone with those receiving whole-brain radiation therapy. Chidel et al.[21] found a statistically significant improvement in two-year brain control with the use of WBRT in addition to radiosurgery boost: 80% vs. 52% in patients treated with radiosurgery alone ($p = 0.034$). Pirzkall et al.[94] found one-year local control rates to be inferior with the radiosurgery alone group: 89% vs. 92% in the WBRT and radiosurgery boost group. Shehata et al.[113] reported that patients who had whole-brain radiation therapy had superior local tumor control rates (97%) compared with patients treated with radiosurgery alone (87%; $p = 0.0001$). Sneed et al.[117] reported a statistically significant improvement in one-year brain freedom from progression rate in those patients treated with WBRT + SRS boost (69%) compared with those patients treated with initial radiosurgery only (28%). It was commented that the one-year brain control rate allowing for salvage (using WBRT or serial SRS) at first failure was not statistically different between those treated with initial WBRT + SRS boost (73%) vs. those treated initially with SRS alone (62%). Wang et al.[128] found that the local brain control rate of patients treated with SRS alone was 93.3%, compared with 95.6% in patients treated with WBRT + SRS boost.

Survival

The Japanese trial[4] found no significant survival difference between the groups receiving WBRT + SRS and SRS alone. The median survival time was 7.5 months with WBRT + SRS and 8.0 months with SRS alone. In addition, no significant difference in the frequency of death due to neurologic causes was observed. Death was attributed to neurologic causes in 22.8% in the WBRT + SRS group and in 19.3% in the SRS alone group. In Chougule et al.'s abstract,[23] median survivals were seven, five and nine months for Gamma Knife® radiosurgery alone vs. WBRT and Gamma Knife® radiosurgery vs. WBRT, respectively. Survival was reported as not different among the three arms. The ECOG 12 Phase II trial[69] of radiosurgery alone for radioresistant histologies found median survival to be 8.2 months (95% CI, 7.4–12.2 months) in its cohort of patients. Lutterbach performed a prospective study[66] using radiosurgery alone for the initial management of brain metastases. However, no survival comparisons were made with patients treated with WBRT. Several retrospective studies have reported on the use of radiosurgery alone as initial management of selected patients with brain metastases.[15,21,39,49,53,105,109,113,115,117,118,124,128] Survival outcomes ranged from 8–15 months. Chidel et al.[21] reported the median survival of patients treated with radiosurgery alone as 10.5 months compared with 6.4 months in patients treated with radiosurgery boost and whole-brain radiation therapy (p value not stated). Sneed et al.[117] reported that the median survival of patients treated initially with radiosurgery alone was 11.3 months, which was not statistically different from the survival of patients treated with WBRT + SRS boost (11.1 months). Wang et al.[128] reported a median survival of 15 months in patients treated with SRS alone vs. 20 months in patients treated with WBRT + SRS boost vs. 8.5 months for patients treated with WBRT alone. Pirzkall et al.[94] found no difference in overall survival for patients treated with radiosurgery alone or radiosurgery and WBRT; however, in the subset of patients without extracranial disease, omitting whole-brain radiation therapy resulted in a survival decrement from 15.4 to 8.3 months. Sneed et al.[118] collected data from 10 institutions to compare the survival probabilities of patients with newly diagnosed brain metastases managed initially with SRS alone vs. SRS and WBRT. Of the 569 evaluable patients, 268 had radiosurgery alone initially (24% of these ultimately needed salvage WBRT) and 301 had radiosurgery and up-front WBRT. The median survival times for patients treated with SRS initially vs. SRS + WBRT were 14.0 vs. 15.2 months for RPA Class 1, 8.2 vs. 7.0 months for Class II, and 5.3 vs. 5.5 months for Class III. With adjustment by RPA class, there was no survival difference comparing radiosurgery alone initially with radiosurgery and up-front whole-brain radiation therapy. There is Level I evidence from the recently published Japanese trial[4] and Level II-3 evidence from literature that addition of up-front WBRT does not improve survival in patients treated with up-front radiosurgery. Thus patients with newly diagnosed brain metastases can be treated with up-front SRS alone, reserving WBRT for salvage."

Role of SRS for Multiple Brain Metastases
Stereotactic radiosurgery is an effective treatment for patients with multiple brain metastases. A substantial amount of published literature now supports use of radiosurgery in the treatment of multiple brain metastases. Stereotactic radiosurgery offers a very high control rate with a low risk of serious side effects. The RTOG 95-08 study authors concluded that addition of stereotactic radiosurgery to WBRT improved functional autonomy for all patients; therefore WBRT and stereotactic radiosurgery should be considered for patients with two or three brain metastases. For patients with good performance status up to three brain metastases, SRS with or without the addition to WBRT is reasonable."

Indications for Radiosurgery
• Newly diagnosed single or multiple brain metastases without significant mass effect documented on imaging
• Boost after WBRT for single or multiple brain metastases
• Recurrent brain metastases after WBRT
• Radiosurgery for residual tumor after resection

KQ3:

"Clinical Algorithm

Several factors are considered in making a recommendation. These factors include:

1. Patient's age
2. Patient's symptoms
3. Status of systemic disease
4. Patient's current neurological status
5. Patient's medical condition
6. Presence or absence of other organ metastases
7. History of prior WBRT
8. History of prior brain procedures
9. Patient's concern and risk tolerance for neuro-cognitive functions
10. Patient's wishes

Tumor Size
Radiosurgery can be performed for tumors up to 4 cm in maximum diameter. However, tumor volume, dose and location are more important variables.

Patient Preference
Patients' preferences are also considered in selecting a management approach. A broad outline of brain metastases diagnostic work-up and management algorithms for single tumor, limited brain disease (2–4 tumors) and multiple metastases are shown. However, the final recommendation is usually influenced by the recommending surgeon's, radiation oncologist's and neuro-oncologist's experiences along with patient preference.

Conclusion
There is Level I to Level II-3 evidence that addition of WBRT in patients treated with radiosurgery for 1–3 newly diagnosed brain metastases does not improve survival, compared with radiosurgery alone with WBRT reserved for salvage therapy. There is Level I evidence that omission of WBRT results in decreased tumor control, both at the site of radiosurgery and also in the remaining untreated brain. Level II-1 and Level II-3 evidence further support this observation"

Meningiomas: This information is from an on-line journal (Brain Talk, Volume 6, Number 2).

References are stated below each paragraph

KQ1 and KQ2:

MENINGIOMALONG-TERM OUTCOMES AFTER RADIOSURGERY...
In an effort to determine long-term outcomes of radiosurgery for meningioma, researchers at the University of Pittsburgh followed 99 patients for 5-10 years after radiosurgery Ninety-three percent of the tumors were controlled by radiosurgery. Sixty-three percent of the tumors became smaller, the size of 32% did not change and 5% were enlarged. Three to thirty-one months after radiosurgery, neurological deficits developed in 5% of patients. Fourteen percent of patients reported at least one complication which resolved in nearly half (44%) of these cases. Ninety-six percent of patients completing an outcomes questionnaire 5-10 years after radiosurgery believed it was successful. The authors concluded that long-term tumor control, preservation of neurological function and patient satisfaction were afforded by radiosurgery.
– *from the Journal of Neurosurgery 1999;91(1):44-50.*

RADIOSURGERYFOR MALIGNANT MENINGIOMA...
Twenty-two patients with malignant meningioma were treated with Gamma Knife® radiosurgery. The five-year survival estimate was 40% and the five-year progression-free survival estimate was 26%. Patient age and tumor volume were significant predictors of time to progression and survival. Twenty-three percent of patients developed radiation necrosis. Complications, treatment variables and patient characteristics were unrelated. Greater tumor control after Gamma Knife® radiosurgery was observed in younger patients and in those with smaller tumors. The authors concluded that malignant meningiomas may be treated with Gamma Knife® radiosurgery with acceptable toxicity, and recommended that the relative efficacies of recurrent malignant meningioma therapies be further evaluated.
– *from the Journal of Neurosurgery 2000;93(Suppl.3):62-67.*

CAVERNOUS SINUS MENINGIOMAS AND RADIOSURGERY...
The functional tolerance and tumor control rate of benign cavernous sinus meningiomas treated with Gamma Knife® radiosurgery was evaluated in 80 patients. After radiosurgery, the tumor stabilized in 51 patients, shrank in 25 patients and enlarged in four patients. The five-year progression-free survival was 92.8%. New oculomotor deficits were not observed. Fifty-four patients had existing oculomotor nerve deficits; of these, 15 improved, eight recovered, and one worsened. Thirteen patients had trigeminal neuralgia; of these, four improved, five were unchanged, three recovered and one worsened (coincident with tumor growth). The authors concluded that Gamma Knife® radiosurgery was an effective tool for the low-morbidity treatment of cavernous sinus meningioma. Oculomotor function was restored in a significant number of patients. The authors suggested that Gamma Knife® radiosurgery was an alternative to surgical removal of confined enclosed cavernous sinus meningiomas.
– *from the Journal of Neurosurgery 2000;93(Suppl.3):68-73.*

MENINGIOMAS, RADIOSURGERYAND EARLY COMPLICATIONS...
Complications arising within one year of Gamma Knife® radiosurgery for intracranial meningiomas were assessed in 77 patients. Gamma Knife® radiosurgery followed surgery in 49 patients and was the primary therapy in 28 patients. Fifty patients had basal meningiomas and 27 had non-basal meningiomas. The most common sites were the cerebellopontine angle (14 patients) and parasagittal (23 patients). Five patients experienced seizures and four had increased headaches. Two patients with parasagittal tumors experienced a temporary worsening of hemiparesis. Perilesional edema was observed in nine patients and was symptomatic in six. Six (22%) of the 27 patients with non-basal tumors had edema (all parasagittal); four patients were symptomatic. Three (6%) of the 50 patients with basal meningiomas had edema, and only one patient was symptomatic. Occurrence of edema was not related to radiation received by adjacent brain or tumor volume, margin or maximum dose. Tumor size was reduced in seven patients. The authors concluded that although Gamma Knife® radiosurgery provides good results for selected patients with meningiomas, patients with parasagittal tumors should be treated with caution because of the high incidence of perilesional edema.

– from the Journal of Neurosurgery 2000;93(Suppl.3):57-61.

KQ3 and KQ4

Radiosurgery is considered a standard of care in the treatment of Meningiomas. SRS treats far less normal brain tissue than EBRT which is significant in reducing the long-term side effects in all age groups. These are generally benign tumors and the life expectancy of patients treated is usually not related to this condition. As a result, chronic toxicity from EBRT can present as a life long struggle.

SRS thalamotomy for tremor (Essential and Parkinsons). This information is from an on-line journal (Another Perspective, Volume 4, Number 4) **which was submitted by one of our Neurosurgeons, Dr Ronald Young**

KQ1 and KQ2;

Both radiofrequency and radiosurgical thalamotomy can be expected to relieve tremor in about 85% of patients. In some patients, the tremor is markedly suppressed but not totally relieved and in other patients, the tremor is completely relieved. Examples of a patient's handwriting before and after a thalamotomy was performed with the Gamma Knife® are shown in figures one and two. Virtually all of the treatment of movement disorders using radiosurgery has been with the Gamma Knife®. There is little or no experience in using the other forms of radiosurgery, that is, the linear accelerator or heavy particle beam radiosurgery, to make such lesions for treatment of movement disorders. Therefore, results achieved with Gamma Knife® may not be indicative of results achieved with other types of radiosurgical equipment. The Gamma Knife® is designed to perform this type of treatment. We have performed more than 200 thalamotomies for the relief of tremor over a period of more than eight years. Only two relatively mild side effects have been seen in these 200 patients. Both involve mild weakness or coordination difficulty in the side of the body opposite to the thalamotomy. No other complications of any kind have been seen in any of the other patients. For radiofrequency thalamotomy, the complication rate has been variously estimated from as low as five percent to as high as 20% or 25%. These complications can include paralysis, loss of feeling, difficulties with speech and, in a rare case, severe hemorrhage requiring a major operation (craniotomy) to remove a large blood clot within the brain or on the surface of the brain. It is our belief that radiosurgical thalamotomy with the Gamma Knife® offers the safest method for treatment of tremor. Figure 3 shows a lesion created in the thalamus by radiosurgical thalamotomy.

KQ3 and KQ4

By the end of 1998, it had been reported that 814 patients had received Gamma Knife® treatment for Parkinson's disease at all Gamma Knife® centers throughout the world, and a significant number of additional patients had received treatment for essential tremor and other forms of tremor. The interest in using radiosurgery to treat movement disorders is increasing. It is attractive to patients and their families because of its effectiveness and safety. Many radiosurgical centers perform the procedures on an outpatient basis and, at maximum, an overnight stay is required. Patients are able to return to normal activities immediately without the recovery period generally required after an open skull procedure, such as a radiofrequency thalamotomy or deep brain stimulator implantation.

This procedure is not performed with EBRT.

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Gliomas

KQ1, KQ2, KQ3 and KQ4

Stereotactic Radiosurgery Prolongs Survival

GLIOBLASTOMA MULTIFORME...

Researchers at the University of Maryland examined the results of treating 64 glioblastoma multiforme patients with either external beam radiotherapy (EBRT) alone or EBRT followed by Gamma Knife® radiosurgery. Forty-five and 19 patients had previously undergone craniotomies and stereotactic localization needle biopsies, respectively. Subsequently, 33 patients were treated with EBRT alone, while 31 patients were treated with EBRT and Gamma Knife® within four weeks of EBRT. External beam radiotherapy was delivered in a three-dimensional conformal manner. Median survival for the group with EBRT alone was 13 months from the time of diagnosis, while median survival for the group that received EBRT and a Gamma Knife® boost was 25 months from the time of diagnosis.

- *from Neurosurgery 2002;50(1):41-47.*

ANAPLASTIC ASTROCYTOMA AND GLIOBLASTOMA MULTIFORME...

During an 8 year period, University of Pittsburgh researchers studied the effect of stereotactic radiosurgery with the Gamma Knife on the survival of patients with anaplastic astrocytoma or glioblastoma multiforme. Tumor diagnosis was obtained either through craniotomy or stereotactic biopsy. Sixty-four glioblastoma multiforme patients and 43 anaplastic astrocytoma patients were included in the study. Two year survival time for glioblastoma multiforme patients was 51%, and for anaplastic astrocytoma patients was 67%. The authors concluded that compared to historical controls, radiosurgery provided an improved survival benefit for glioblastoma multiforme and anaplastic astrocytoma patients. Radiosurgery was and is well tolerated with no acute neurological complications after treatment. Further studies with radiosurgery as an adjunct treatment are warranted.

- *from Neurosurgery 1997;41(4):776-785.*

I hope this information will help in your review. Please let me know if I can be of further assistance.

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VIRGINIA MASON MEDICAL CENTER

From: Pham, Huong [Huong.Pham@vmmc.org]
Sent: Tuesday, March 06, 2012 4:22 PM
To: HCA ST Health Tech Assessment Prog
Subject: Public Comment for: Stereotactic Radiation Surgery and Stereotactic Body
Radiation Therapy

We at Virginia Mason Medical center feel strongly that there is good supporting evidence for the Washington State Health Care Authority to cover the services listed below.

Stereotactic radiosurgery/stereotactic radiation therapy
There is high level evidence for the effectiveness of stereotactic radiosurgery (SRS) for many small intracranial lesions such as arteriovenous malformations (AVM), acoustic neuromas, meningiomas, and brain metastases. SRS or SRT may also be useful for pituitary adenomas and recurrent malignant gliomas. SRS has also demonstrated effectiveness for functional disorders such as trigeminal neuralgia and essential tremor from Parkinson's disease. For many of these, SRS offers an alternative to neurosurgery especially when surgery would be associated with significant risks of morbidity or mortality. In contrast to surgery, SRS can be done as an outpatient in a few hours with minimal recovery time. Often, patients can return to work or resume regular daily activities by the next day.

SRS can be delivered with devices such as Gamma Knife or Linear accelerator based technology.
There is most data demonstrating the safety and effectiveness of treatment available with Gamma Knife technology. There is also a fair amount of data for linear accelerator based treatments. Less has been published with Cyberknife and Tomotherapy. Quality assurance standards and procedures are available through American Society of Therapeutic Radiology and Oncology (ASTRO) and American Association of Physicists in Medicine (AAPM). However, currently, there is really no organization or process to ensure that the center or facility performing these procedures have these processes in place. It is reassuring though that if a center is to participitate on any clinical trial through the Radiation Therapy Oncology Group (RTOG), which employs the use of SRS/SRT, they must pass a credentialing process which requires external review of the SRS/SRT process. I think is important for patients (and payors) to be aware of when deciding on where to have treatment

For AVMs, the American Stroke Association recommends that SRS should be considered for small lesions when surgery may be associated with increased risk based on anatomic location or feeding vessel anatomy [1]. The rationale is that the high dose single

fraction treatment causes fibrointimal hyperplasia and ultimately obliteration of the feeding vessel. There is an overall 80 percent obliteration (success) rate by three years occurs with lesions that are 3 cm or smaller. The rate for lesions greater than 3 cm is 30 -70 % depending on dose and size. There is little data regarding the effectiveness of standard external beam radiation therapy (EBRT) for treatment of AVMs. Therefore EBRT is not recommended for the treatment of AVMs.

Acoustic neuromas (vestibular schwannomas) are commonly treated with SRS or stereotactic radiation therapy (SRT) as an alternative to surgery. There are no randomized data but many retrospective studies demonstrate its effectiveness (90% or better control of tumor growth) with few side effects (1-5 % facial or trigeminal neuropathy)[2,3]. In addition, SRS or SRT can help preserve hearing in up 70% of patients who had good hearing prior to treatment which is comparable to most surgical series. SRS or SRT is also used when there is residual disease after surgery or in the setting of recurrence after surgery. Because these tend to be small tumors near the brainstem, high precision with stereotactic approaches are recommended to minimize dose to the brainstem to avoid long term complications. With high focused, precise treatment, it may also be possible to limit dose to the cochlea which has been found to be associated with hearing loss associated with treatment. These are reasons why SRT or SRS are preferred over EBRT.

EBRT is a well established treatment for unresectable and incompletely resected benign meningiomas [4]. The typical course of treatment is 6 weeks of radiation therapy. If the tumors are small, < 3 cm, SRS or SRT may be a good option since this is a 1-5 day treatment compared to a 6 weeks. SRS appears to be as effective as surgery and is an excellent alternative to surgery for these small tumors especially when in the skull base or cavernous sinus regions when there is a high risk of morbidity with surgery. Large series of SRS have demonstrated excellent local control rates in the range of 94-98% at 5 years with low complications rate [5,6,7].

SRS is an important treatment option for patients with small brain metastases (< 3-4 cm). Many studies support its use in patients with favorable prognosis which include patients with Karnofsky performance status 70 or greater and/or controlled primary and stable systemic disease. Studies demonstrate that SRS is more cost effective than surgery for brain mets [8]. It can also be use to treat multiple brain metastases and in locations where surgery is associated with increased morbidity[9]. SRS advantages over EBRT (whole brain radiation therapy, WBRT) include shorter course of therapy(1 fx vs. 10-15 fx), less acute side effects such as hair loss and fatigue, and less late neuro-cognitive effects [10]. The main disadvantages of SRS is a small risk of radiation necrosis of around 5- 10% depending on dose and size of tumor, and the higher risk of additional brain metastases that may require additional treatment with radiosurgery or WBRT [11,12]. Local control rates are dose dependent usually around 90% especially if doses are greater than 14 Gy[13]. In addition to its effectiveness against breast, lung, and

other solid tumors, SRS is also effective in tumors which are traditionally considered to be radioresistant such as renal cell, sarcomas, and melanomas [14] .Overall survival rates are the same or better for SRS vs.WBRT [15]. SRS used as a boost after WBRT has been shown to improve survival in patients with a single brain metastasis[16] SRS is also useful for progression of brain mets after WBRT [17].

SRS has been shown to be as effective as EBRT for residual or recurrent nonfunctioning pituitary adenomas. Advantages are that the treatment is 1 day vs. 5 weeks and there is less risk of pituitary dysfunction by sparing the normal pituitary tissue with the focused precise radiation treatment [18,19]. It can also useful in recurrent secretory adenomas such as for Cushing's disease and acromegaly.

For malignant gliomas, use of SRS or SRT has been reserved primarily for treatment in the recurrent setting when pt. has already received prior EBRT and additional EBRT would be associated with increased risk of morbidity from treatment. SRS or SRT to small recurrent targets offers a relatively safe option. Survival times from SRS/SRT for recurrent gliomas can be up to 1 year[20,21].

For patients with trigeminal neuralgia refractory to medication, it is reasonable to consider surgery, rhizotomy or SRS. The rationale is to deliver very high focused radiation to the proximal nerve root causing axonal degeneration and necrosis and subsequent pain relief. Pain relief is achieved in about 70 % of patients at one year and 50% at 3 years. Often, patients can lower or discontinue their pain medications which could be disabling to the elderly patient [22-24].

In conclusion, SRS/SRT is an effective, safe, and cost effective treatment with definite advantages over EBRT for the disorders listed above.

Stereotactic body radiation therapy

Stereotactic body radiation therapy (SBRT) is similar to SRS/SRT except used for extracranial indications. Treatment is typically 3-5 fractions. There is most evidence for the use of SBRT for early stage lung cancers[25,26]. Typically, patients who are offered this treatment are not felt to be good surgical candidates due to poor lung function or other comorbidities. SBRT offers an excellent alternative as it can be done in the outpatient setting with minimal acute side effects and minimal recovery time. Studies demonstrate local control rates as high as 90% at 3 years which is much higher than can be achieved with standard EBRT which has local control rates in the range of 50-60% and requires daily M-F treatments of 7-8 weeks. Grade 3 or higher toxicities occurred in 15-25% of patients and no patients experienced a lethal toxicity. Majority of the toxicities were pulmonary which is not surprising since the majority of these patients have poor lung function at baseline.

Small peripheral lung tumors or metastasis are also well suited for SBRT due to low acute toxicity and short course therapy. The lung tissue is very sensitive to radiation therapy and therefore minimizing dose to surrounding lung tissue is critical at minimizing risk of lung toxicity. This is a key advantage of SBRT over standard EBRT in this setting.

Other indications for SBRT are under investigation including early stage prostate cancer, spine/vertebral body tumors, and liver tumors. The RTOG currently has 4 studies which involve SBRT. It's crucial that insurance companies pay for the study treatments so that improvements in therapy can be developed.

ASTRO, ACR, and AAPM have put forth guidelines for quality assurance and safety procedures needed in an SBRT program. However, there is no organization monitoring the quality of these programs or facilities. Again, facilities who do participate in RTOG studies which use SBRT do have to go through a credentialing process to have their program approved for SBRT treatment. I think this is important for patients(and payors) to be aware of when deciding on where to have treatment.

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Thank you for your attention and allowing us to comment on this topic.

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