Washington State Health Care Authority
Health Technology Assessment

Stereotactic Radiation Surgery & Stereotactic Body Radiation Therapy

Scheduled Presentations

	Name / Representing
1	John Rieke, MD American Society of Radiation Oncology
2	Trent Tredway, MD Washington State Association of Neurological Surgeons
3	Sandra Vermeulen, MD Executive Director Swedish Radiosurgery Center
4	Li-Ming Christine Fang, MD / Lia Halasz, MD / Ed Y. Kim, MD / George E. Laramore, MD, PhD / Shilpen Patel, MD / Jason Rockhill, MD, PhD / University of Washington School of Medicine, Department of Radiation Oncology

Washington State Health Care Authority
Health Technology Assessment

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Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		✓
2.	Equity interests such as stocks, stock options or other ownership interests.		✓
3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.		✓

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: If representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	✓	

If yes to #7, provide name and funding Sources: American Society of Radiation Oncology (ASTRO). Funding is from dues. I am receiving no compensation or travel expenses to participate. I am a volunteer.

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X _____ 8/28/12 John W Ricke, MD
Signature *Date* *Print Name*

For questions contact: Christine Masters
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Disclosure

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4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.		✓

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Synmes - Teaching Honoraria; Medtronic - Teaching Honoraria; Aesculap - Teaching Honoraria

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X _____ 10/30/12 Trent L. Tedway, MD

Signature *Date* *Print Name*

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Trent L. Tredway, MD

- Associate Professor of Neurological Surgery
- Joint-Appointed Associate Professor of Orthopedic Surgery
- Director, Minimally Invasive Spine Surgery
- Fellowship Director, Spinal Neurosurgery
- Department of Neurological Surgery
- University of Washington Medical Center

- American Association of Neurological Surgeons (AANS)
- Congress of Neurological Surgeons (CNS)
- Washington State Association of Neurological Surgeons (WSANS), Vice-President

Definition of Stereotactic Radiosurgery

Stereotactic Radiosurgery is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate (a) defined target(s) in the head or spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist.

Stereotactic Radiosurgery (SRS) typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five.

Technologies that are used to perform SRS include linear accelerators, particle beam accelerators, and multisource Cobalt 60 units. In order to enhance precision, various devices may incorporate robotics and real time imaging.

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

SRSBackground

From a strict evidence based medicine standpoint, most of the evidence regarding stereotactic radiosurgery (SRS) is level III or higher.

The majority of level I evidence for SRS exists for brain metastasis and glioblastomas.

SRS was introduced more than 40 years ago, an era in which evidence based approaches were less of a priority.

Today, if a prospective trial of patients with small to moderately sized meningiomas was designed to randomize patients to SRS, EBRT, and microsurgical resection, it would be unlikely to accrue secondary to clinical equipoise issues.

While it may seem humbling that the majority of the practice of SRS is supported by class III evidence and a small amount of class I and II data, evidence based methodologies are useful to organize existing literature and to see if there is truly objective data to answer specific questions.

However, there is overwhelming evidence derived from a broad array of institutions and hundreds of thousands of patients treated over more than 40 years to support the clinical benefits, cost effectiveness, and safety of SRS in patients who may be eligible for SRS, EBRT, and/or microsurgery.

The clinical efficacy and safety of SRS and, to a lesser extent, the cost effectiveness and quality of life benefits of it compared to EBRT or resection are well documented by the report prepared by the Center for Evidenced-Based Policy at the Oregon Health & Science University.

Patient Quality of Life Issues

From a quality of life standpoint, there is prospective evidence to support the use of stereotactic radiosurgery for patients with brain metastasis, acoustic neuromas, meningiomas, and pituitary adenomas.

In a randomized, prospective trial of patients with brain metastasis, Chang and colleagues found significant benefit in terms of neurocognition in patients treated with SRS alone over SRS plus whole brain radiation therapy (WBRT) (Chang et al., 2009).

In a study constituting level II evidence, radiosurgery afforded a higher quality of life for vestibular schwannoma patients as compared to microsurgery (Pollock et al., 2006).

In a case controlled study of patients with small to medium sized meningiomas, SRS was also demonstrated to provide better neurological preservation than surgical resection for patients with small to moderately size meningiomas (Pollock et al., 2003).

In a nonrandomized, prospective study of pituitary adenoma patients, SRS afforded neurocognitive preservation as compared to patients undergoing external beam radiotherapy (EBRT) or being left untreated for their pituitary adenoma (Tooze et al., 2012).

With regard to spinal metastases patients, spinal radiosurgery has been demonstrated in a recently published phase 1-2 study to lead to significant reductions in pain and other symptoms and provide a high rate of progression free survival while at the same time resulting in a low rate of spinal cord toxicity (Wang et al., 2012).

Cost Effective Analysis

From an economic standpoint, SRS has been shown to be very cost-effective for multiple indications including brain metastases, acoustic neuromas, meningiomas, arteriovenous malformations, trigeminal neuralgia, and spinal metastases (Tarricone et al., 2008; Wellis et al., 2003, van Roijen et al., 1997).

In a comparison of surgical and follow up costs associated with vestibular schwannoma patients, radiosurgery was shown to be less expensive than microsurgery even when factoring in long-term follow up expenses (Banerjee et al., 2008).

In a cost-effectiveness analysis of the Chang et al. study (Lancet Oncology, 2009), SRS alone had a higher average effectiveness than when added to WBRT (Lal et al., 2012). This finding of a high cost-effectiveness of SRS for brain metastases patients is consistent with prior publications (Lee et al., 2009; Mehta et al., 1997).

SRS has also been shown to be more cost effective than resection for patients with brain metastases (Vuong et al., 2012; Rutigliano et al., 1995).

Cho et al. (2006) evaluated the socioeconomic costs of open surgery and SRS for 174 patients with benign skull based tumors. They found shorten hospital stays, reduced complications, improvements in return to work, and an overall better cost-effectiveness with SRS over resection for comparable groups of patients.

Cost Effective Analysis (Continued)

- It is also well accepted, as noted in recent meta-analyses, that radiosurgery provides a faster rate of endocrine remission compared to EBRT for patients with functioning pituitary adenomas thereby allowing radiosurgery patients to be removed from costly antisecretory medications much more quickly than comparable patients treated with EBRT (Loeffler et al., 2011; Sheehan et al., 2005).
- In an analysis of the cost-effectiveness of SRS for patients with spinal metastasis, spinal radiosurgery was found to be superior to conventional EBRT for appropriately selected patients (Papatheofanis et al., 2009).

Summary

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

Conclusion

- SRS remains one of the safest and most effective approaches in neurosurgery and radiation oncology.
- SRS technologies have resulted in a major paradigm shift in the use of both alternative surgical and radiation therapy techniques for a broad array of well-defined clinical indications.
- During the last 40 years more than 6,000 SRS publications provide this evidence in great detail.
- The cost effectiveness and quality of life benefits are also well documented.
- We thank you again for the opportunity to present our (AANS/CNS) views and are eager to answer any questions the panel may have about the use of SRS by neurosurgeons.

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WA HCA/HTA Program Update: Public Comments for November Public Meeting

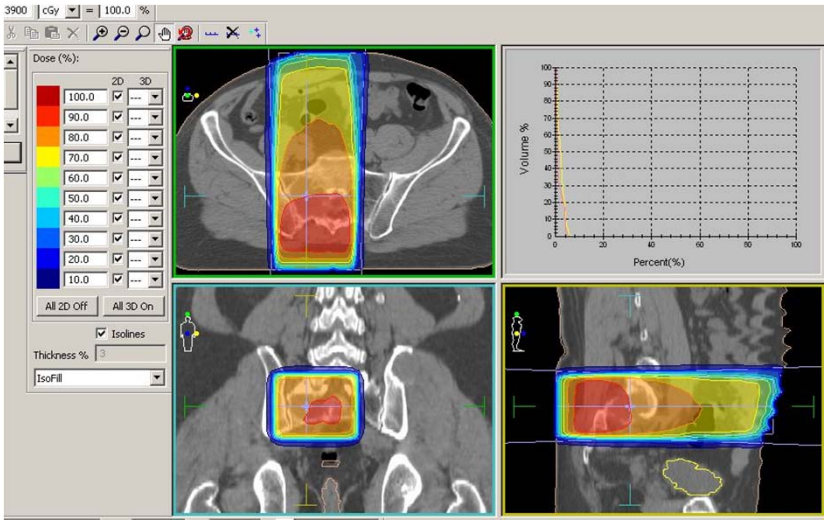
Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy

Presenter
Dr Sandra Vermeulen, MD
Providence/Swedish Medical Center
Seattle

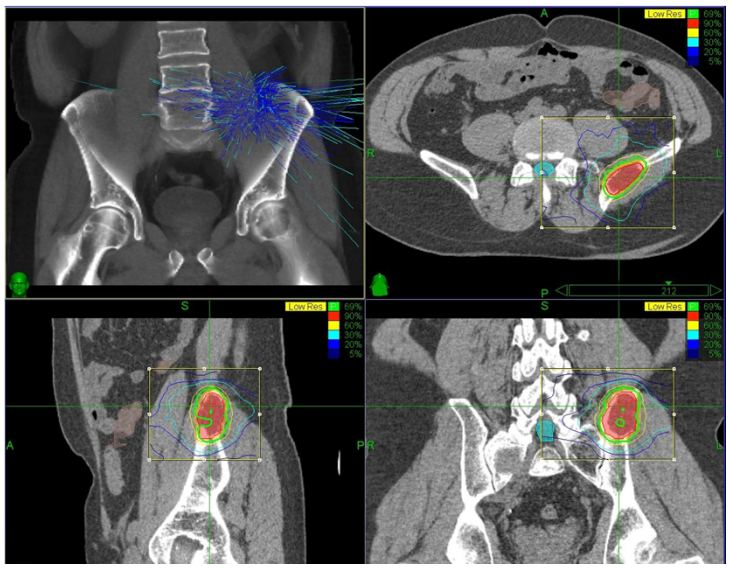
Stereotactic Radiosurgery

- Multiple beams of radiation converging in three dimensions onto a target
- millimeter accuracy
- 1-5 treatment sessions
- Control rates similar to surgery
  - 40+ years of experience
  - Over 8,000 SRS/SBRT peer review articles

Conventional RT Dose Cloud



SBRT Dose Cloud



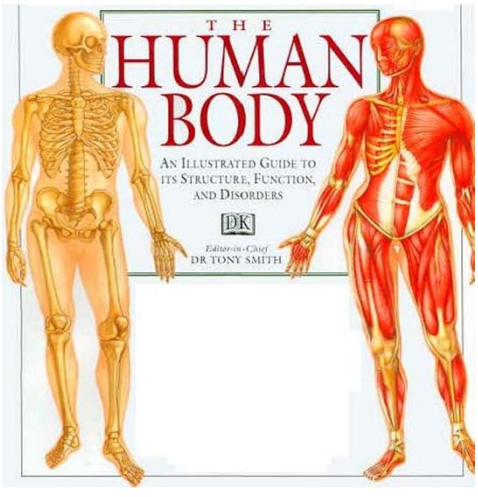
SRS/SBRT Advantages over Conventional RT/IMRT

- Less normal tissue toxicity
- Short overall length of treatment
- Greater accuracy and conformality
  - Spare critical or sensitive stuctures
  - Can be used if prior conventional radiation has been given
- Higher radiation doses can be delivered
  - Better response rates
  - Response more durable

Tumors Appropriate for SRS/SBRT

- Intracranial
  - Level I evidence/metastases
    - Chang et al., 2000
    - Aoyama et al, 2008
    - RTOG 95-08
- Head and Neck
- Lung
  - SBRT standard of care for stage I
  - Timmerman, RTOG 0238
- Liver
- Pancreas
- Prostate
- Breast
  - Swedish, Georgetown U, Winthrop U, UT Southwestern Medical Center
- Previously irradiated areas
  - Spine, pelvis, lung

Compared with conventional RT/IMRT
Cost effective
Better controls
Less toxicity



Intra-cranial Indications for SRS

- Functional disorders
  - Trigeminal neuralgia
  - Essential tremors
- Well circumscribed lesions
  - AVM's
  - Benign (Meningiomas, Pituitary Tumors, AN)
  - Malignant (Mets, Gliomas)
- Minimal brainstem compromise
- Surgical lesion:
  - Residual after surgery
  - Recurrent after surgery
  - Surgical approach difficult or impossible
  - Medical co-morbidities
  - Previous radiation
  - Radioresistant tumor

SRS Intra-cranial response rates Gamma Knife (#, control, comment) IRSA: Practice Guidelines

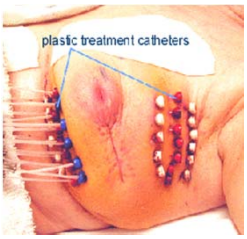
- **Acoustic Neuroma:** >45,000, 94%
- **Meningiomas**: > 60,000, 90%
- **Brain Mets**: >300,000, 70+%,
  - total volume matters, number may not
  - Medicare/Noridian registry for multiple BM
- **Pituitary tumors**:>40,000, 90%NS
- **AVM**: >50,000, 73%

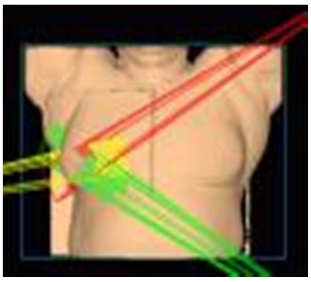
SBRT for Stage I-II Prostate CA: Literature Summary

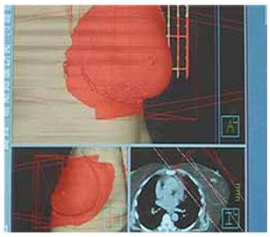
Type of Evidence	Institution	# pts f/u	Conclusion	Reference
Prospective single-institution	Stanford	67 2.7 yrs	"current evidence supports … stereotactic body radiotherapy among the therapeutic options for localized prostate cancer."	King IJROBP 82:877 (2012)
Prospective single-institution	Winthrop Hospital	304 2 yrs	"rectal and sexual QOL following SBRT may be comparable, if not better than… EBRT, BT and RP. SBRT is less costly…than IMRT "	Katz BMC Urology 10:1 (2010)
Pooled prospective 2 institutions	Naples Hospital & UCLA	41 5 yrs	"biochemical disease control is comparable to other available therapies, with equal to or better toxicity profiles."	Freeman Radiat Oncol 6:3 (2011)
Controlled phase II 21 institutions	Swedish & Harvard (Beth Israel)	129 3 yrs	"progression-free survival rate of 99.2%", "acute and late toxicities… minimal", "urinary, bowel and sexual function… favorable compared to other…modalities"	Meier IJROBP 84:S148 (2012)
Pooled prospectiv e	UCLA, Harvard, George	1,101 3 yrs	"excellent efficacy was demonstrated at 5 years… these results compare favorably with other modalities"	Katz IJROBP 84:S147

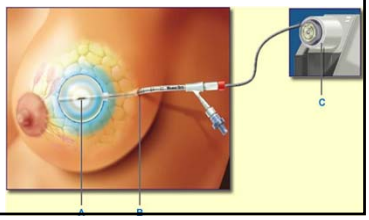
NSABP B-39/RTOG 0143
Whole Breast vs Partial Breast RT

- 3D-CRT
- Single catheter brachytherapy
- Multi-catheter brachytherapy









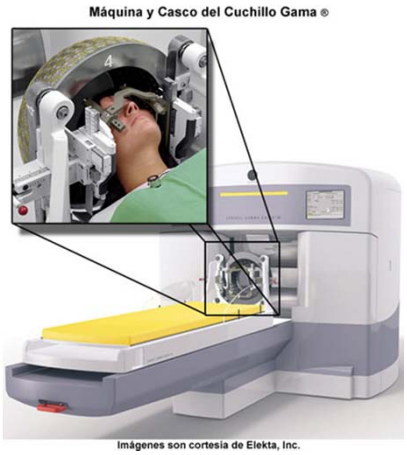
Differences between Partial Breast Treatments

- IMRT: Jagsi/Univ of Michigan reports unacceptable cosmesis when V50>46% and V100> 23%
- 3D-CRT: Hepel/Tufts Univ suggests the NSABP/RTOG trial can lead to an unacceptable high number of patient with subcutaneous fibrosis
- Both authors (Jagis/Hepel) call for stricter normal tissue dose constraints
- Patel et al. showed the V100 and V50 to be significantly larger for patients receiving 3DCRT vs an interstitial implant
  - 26% vs **12%** and 52% VS **24%**
  - **CONTRAST** SBRT CK SWEDISH HOSPITAL SERIES
    - **11%** AND **26%.**

What Lesions? Which Modality?

Gamma Knife

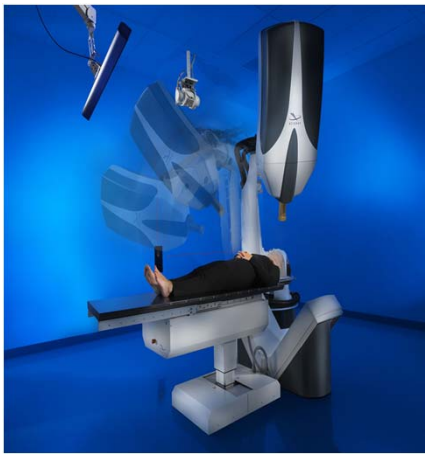
- Manufactured in Sweden
- 40+ years of experience
- >700,000 patients
- 280+ center
- Intracranial targets only
- Approximately 200 beams
- Fixation frame required
- Single fraction/time 4 hrs
  - Ideal target <4.0 cm
  - Dose limited by critical structure
    - Optic apparatus
    - cochlea
- Exceptional control rates



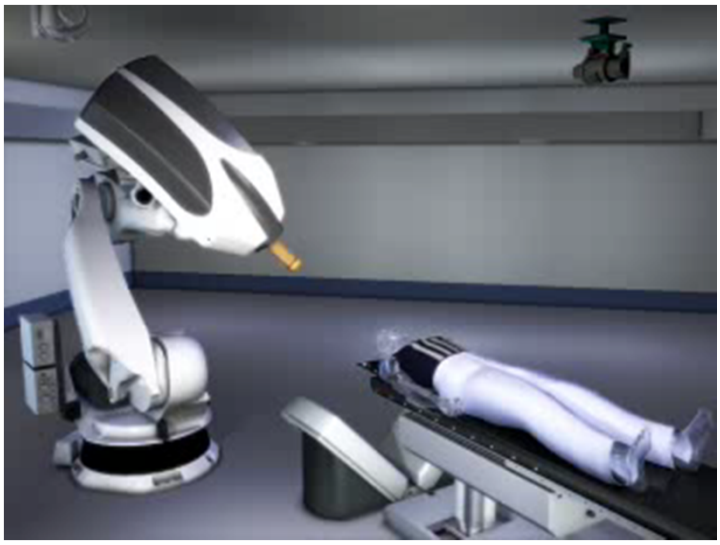
Cyberknife

- Infinite beam number
- 1-5 session
- Treatment time
  - <1 hour
- No fixation frame
- Real time imaging
- Motion tracking

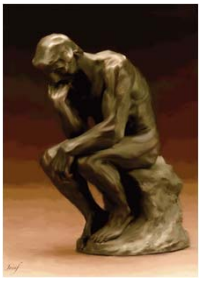
FDA approved 2002
>100,000 patients treated
240+ center worldwide



Cyberknife



When is one SRS modality better suited for treatment than the other?



- GK planning system best for AVM's
- Multiple targets (greater than 4)
  - Integral brain dose higher with CK than GK
- Functional targets (?)
- Fractionate targets close to critical structures
  - Optic apparatus
  - Cochlea
  - Brain stem, spinal cord

SRS/SBRT CONCLUSIONS

- 1-1.5 mm target accuracy
- Offers greater dose delivery to tumors and less dose to surrounding normal tissues than conventional radiation
  - greater tumor control, less toxicity
- Acceptable control rates when compared to surgical

Thank you

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4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

#2 - My professional group, TMOC, is in a joint venture with Swedish Hospital and has a 50% ownership in a Gamma Knife / Cyberknife

#3 - I am on the Cyberknife Society Board, ASTRO

	Potential Conflict Type	Yes	No
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X _____ 10/25/12 Susan Kramer

Signature *Date* *Print Name*

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If yes to #7, provide name and funding Sources: University of Washington / UW Medicine

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3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.	X	

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I am a clinical provider of gamma knife radiosurgery at the Harborview Medical Center Gamma Knife Center.

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources: _____

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X _____ _____
Signature *Date*

Lia Halasz MD
Print Name

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		✓
2.	Equity interests such as stocks, stock options or other ownership interests.		✓
3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.		

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	✓	

If yes to #7, provide name and funding Sources: UNIVERSITY OF WASHINGTON
UW Medicine

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X Edward Kim — *Signature*
10/19/12 — *Date*
EDWARD KIM — *Print Name*

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Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		✓

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

(1) I am Chairman of the Department of Radiation Oncology at the University of Washington

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources: _____

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X [signature] 10/22/2012 GEORGE E. LARAMORE PhD, MD

Signature *Date* *Print Name*

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Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		X
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	X	

If yes to #7, provide name and funding Sources: University of Washington

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X _____ 10/22/12 Shilpen Patel

Signature *Date* *Print Name*

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		X
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	X	

If yes to #7, provide name and funding Sources: University of Washington / UW Medicine

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X _____ 10/28/22 _____ Jason Bartlett

Signature *Date* *Print Name*

For questions contact: Christine Masters
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360-725-5126

SRS: Brain metastases

- Background
  - Historically, patients had poor median survival and were treated with whole brain radiation therapy
    - Currently certain subgroups of patients with brain metastases have median survival of up to 15 months*
  - Development of SRS over the past 25 years allows for pinpoint radiation that ablates metastases while avoiding the rest of the brain

** Sperduto PW et al 2010*

SRS: Brain metastases

- A randomized trial showed that SRS added to whole brain RT improves overall survival for patients with single metastasis and good KPS*
- SRS alone spares side effects of whole brain RT without compromising survival
  - Whole brain RT side effects include fatigue, hair loss, neurocognitive decline, headaches, and nausea
  - MD Anderson trial showed patients had increased neurocognitive decline at 4 months following whole brain RT**

**Andrews et al 2004*
***Chang EL et al 2009*

SRS: Benign brain tumors

- Background
  - Although meningiomas, acoustic schwannomas, pituitary adenomas, and glomus tumors are benign, they can cause serious morbidity and mortality due to their location in the central nervous system
  - SRS has been developed over the past 50 years as an important alternative to surgical resection

SRS: Benign brain tumors

- Meningioma
  - Multiple studies with 10+ year follow-up
  - Recent study of 4565 patients from Europe
    - 5y local control rate of **92.5%***
- Vestibular Schwannoma
  - Multiple studies with 10+ year follow-up
  - Recent study of 829 patients
    - 10y local control rate of **97%****

**Santacroce A et al. 2012*
***Lunsford LD et al. 2005*

SRS: Benign brain tumors

- Glomus tumors
  - Rare tumor, but recent series of 132 patients
    - 5y local control of **88%***
    - Cranial nerve deficit **15%**
  - Surgery has higher risk of cranial nerve deficits and real risk of bleeding/stroke
- Pituitary tumors
  - Multiple series with local control rates ≥ 90%

**Sheehan J et al. 2012*

SRS: Benign brain tumors

- Randomized trials of SRS vs. EBRT would compromise patient care
  - Dosimetric studies comparing SRS and EBRT have not been performed given clear avoidance of normal tissue with SRS
  - SRS has equivalent local control to EBRT in multiple series
  - Long term EBRT adverse effects include neurocognitive decline, second malignancy, and pituitary dysfunction
  - EBRT requires 5-6 weeks versus one day for SRS

SRS: Gliomas

- Background
  - For select patients, SRS can be used for recurrent glioma
- Though a randomized trial* did not show survival benefit of upfront SRS for glioblastoma multiforme, multiple series suggest a role for SRS in recurrent gliomas**

**Souhami L et al. 2004*
***Kong DS et al. 2006*

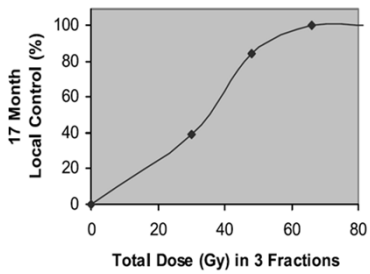
Stereotactic Body Radiation Therapy

Stereotactic Body Radiation Therapy

- Ultra-high doses of radiation per fraction
- Single or limited number of fractions i.e. hypofractionated regimen
- Target is localized stereotactically i.e. in reference to an existing 3-D coordinate system
- Target is discrete and margins are small

Biological Equivalent Dose

$$BED = n \cdot d \left[1 + d / (\alpha/\beta)\right]$$



TOTAL DOSE (Gy)	*# FRACTIONS*	*BED (Gy_{10})*
Conventional Fractionation		
60	30	72
70	35	84
SBRT Fractionation		
60	12	90
50	5	100
48	4	104
60	5	132
60	3	180

Timmerman JTO 2007

Natural History of ESLC

- Even in those with stage I NSCLC, high rate of cancer specific death in untreated patients
  - California Registry Study – 1,432 patients who did not undergo therapy for NSCLC
    - 9% OS and 23% CSS for stage I pts
  - Indiana University Study
    - 14 month MS in Stage I-II patients
    - Over 50% died of cancer

Raz et al. Chest 2007
McGarry et al. Chest 2002

Conventional Radiation Therapy

- With 60-66 Gy:

–15% long term survivors

- 25% death from intercurrent illness
- 30% death from metastatic disease
- 30% death from local failure only

Sibley, Cancer 1998

Conventional Radiation Therapy

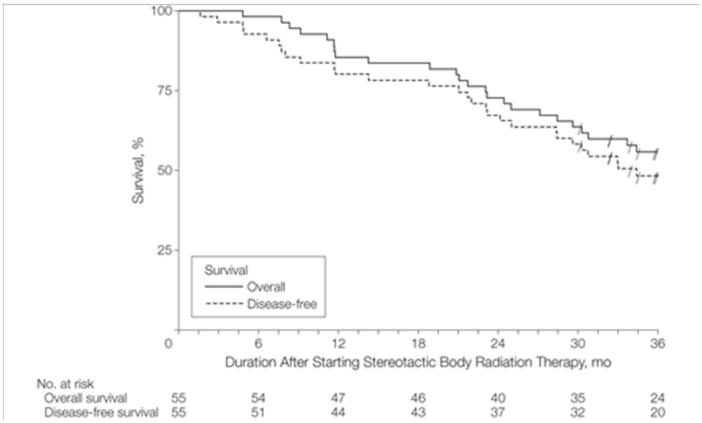
- What is the influence of dose?
  - Retrospective studies show local and distant failures decrease with increasing dose <65 Gy vs ≥ 65 Gy in Stage I patients
  - In a prospective dose-escalation study, doses ≥ 80 Gy resulted in improved local control and overall survival in stage I/II patients
- So increased dose may IMPROVE SURVIVAL

Kaskowitz L et al. IJROBP 1993
Dosoretz D et al. IJROBP 1992
Sibley G et al. IJROBP 1998
Rosenzweig et al. Cancer 2005

SBRT Results – Local Control

Author	*# pts*	*Dose/Fx*	*2 yr (%)*	*3 yr (%)*	*5 yr (%)*
Timmerman	70	60-66/3	95	-	-
Xia	43	50/10	-	95	-
Onishi (multi-inst)	300	18-75/1-22	-	-	80
Uematsu	50	50-60/5-10	-	94	-
Nagata	45	48/4	-	98	-
RTOG 0238	59	54/3	-	98	-
Nyman	45	45/15	-	-	80

RTOG 0236 Phase II



- Median follow-up = 34 months
- Three year local control = 98%
- Median Overall Survival = 48 months

Timmerman et al JAMA 2010

Conclusions

- SBRT is safe and efficacious in the short term
- Wide variety of regimens but dose and planning is important
- The treatment of choice for medically inoperable patients
- Long term toxicity data is good thus far
- Determining local control is important

Washington State Health Care Authority

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000		x
2.	Equity interests such as stocks, stock options or other ownership interests		x
3.	Status of position as an officer, board member, trustee, owner		x
4.	Loan or intellectual property rights		x
5.	Research funding	x	
6.	Any other relationship		x

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

___Varian Medical Systems_____

___Brainlab_____

_____

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		x

7. If yes, Provide Name and Funding Sources: _____

_____

_____

_____

	Potential Conflict Type	Yes	No
8.	Travel: if an organization or company has financially paid your travel accommodations (e.g. airfare, hotel, meals, private vehicle mileage, etc).		x

8. If yes, Provide Name of Organization / Company and Disclose Travel Accommodations:

_____Varian Medical Systems_____

_____

_____

Washington State Health Care Authority

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may ***attach additional sheets*** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X	9/6/12	Martin Fuss
Signature	*Date*	*Print Name*

FOR QUESTIONS: Denise Santoyo, Health Care Authority, 360-923-2742,
PO Box 42712, Olympia, WA 98504-2712

Last update: March 2012

CURRICULUM VITAE

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DOB: 10/03/1963 in Mannheim, Germany

Current address: 7179 SW Arranmore Way
Portland, OR 97223

Education:
1970-1974 Friedrich-Ebert-Schule, Eppelheim
1974-1983 Kurfürst-Friedrich-Gymnasium, Heidelberg
1983 Matura
1983-1985 Armed Forces (Bundeswehr), Degree: Lieutenant
1985-1986 University of Heidelberg, Study of German Language and History
1986-1994 University of Heidelberg, Medical School
1992-1993 Final year in the Departments of Radiation Oncology and Medical Oncology, Internal Medicine, and Surgery

Magna cum laude Ph.D. thesis: Blood volume changes in normal brain tissue and low-grade astrocytoma following radiation therapy.
Accepted by the Senate of the University of Heidelberg in June 1998

Affiliations

7/94-6/00	Residency: Dept. of Radiation Oncology and Medical Oncology, Univ. of Heidelberg and Dept. of Radiological Diagnostic and Therapy, German Cancer Research Center (dkfz), Heidelberg
8/98-7/99	Research Fellow: Loma Linda University Medical Center, Proton Radiation Therapy, Loma Linda, CA
7/00-6/01	Research Fellow: Dept. of Radiation Oncology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas

7/01-11/03	Assistant Professor, Dept. of Radiation Oncology, University of Texas Health Science Center at San Antonio, San Antonio, Texas
10/01-7/06	Member of the Graduate Faculty, Division of Radiological Sciences, University of Texas Health Science Center at San Antonio, San Antonio, Texas
10/03-7/06	Head of Radiation Techniques Research, Cancer Therapy & Research Center, San Antonio, Texas
12/03-7/06	Associate Professor, Dept. of Radiation Oncology, University of Texas Health Science Center at San Antonio, San Antonio, Texas
8/06-	Professor (adjunct), Director Program in Image-guided Radiation Therapy, Dept. of Radiation Medicine, Oregon Health & Science University, Portland, Oregon
8/06-	Joint Professor, Dept. of Computer Science & Electrical Engineering, Oregon Graduate Institute (OGI) School of Science & Engineering, Portland, OR
7/07	Professor, Dept. of Radiation Medicine, Oregon Health & Science University, Portland, Oregon
8/08	Professor, Dept. of Nuclear Engineering and Radiation Health Physics, Oregon State University, Corvallis, OR
10/08	Vice Chair, Dept. of Radiation Medicine, Oregon Health & Science University, Portland, Oregon
10/10	Graduate Faculty, School of Medicine, Oregon Health & Science University, Portland, Oregon

Member

DEGRO (German Society of Radiation Oncology)
ASTRO (American Society for Therapeutic Radiation Oncology)
ESTRO (European Society for Therapeutic Radiation Oncology)
ISRS (International Stereotactic Radiosurgery Society)
PROS (Pediatric Radiation Oncology Society)

Committee participation

Member of the MD/PhD committee at OHSU, 3 year terms (July 2008 – 2011 and 2012-)
OHSU Knight Cancer Institute Clinical Research Review Committee (2011-)
Member of the Agency for Healthcare Research and Quality (AHRQ) Oregon Evidence-based Practice Center (EPC) Technical Expert Group: Comparative Effectiveness Review (CER) on Intensity-modulated Radiation Therapy, since 2007

Protocol Review and Monitoring System Committee, San Antonio Cancer Institute (SACI, NCI designated Comprehensive Cancer Center), 2 year term (2001-2003)
Institutional Review Board (IRB 3), The University of Texas Health Science Center at San Antonio (UTHSCSA), San Antonio, Texas, 3 year term (2003-2006)
Radiation Safety Committee, The University of Texas Health Science Center at San Antonio (UTHSCSA), San Antonio, TX, 2001-2006
Membership committee, American Society for Therapeutic Radiation Oncology (ASTRO), since 2003. Committee vice-chair 2007.
Search committee for the Director of Medical Physics, Cancer Therapy & Research Center, San Antonio, TX, 2005
Search committee for the Associate Director for Business Development, Knight Cancer Institute, OHSU, 2011

Reviewer

International Journal of Radiation Oncology Biology Physics
Radiology
Radiotherapy & Oncology
Cancer
British Journal of Cancer
Acta Oncologica
Future Oncology
Pancreatology
Cancer Therapy
Technology in Cancer Research and Therapy
Journal of Applied Clinical Medical Physics
Physics in Medicine and Biology
Southern Medical Journal
Expert Opinion on Drug Delivery
European Commission, 6th Framework Program (FP6)
2010 and 2011 Collaborative Health Research Projects competition, Natural Sciences and Engineering Research Council (NSERC) and the Canadian Institutes of Health Research (CIHR)

Awards:

Varian poster prize: Pitfalls in inverse treatment planning: sometimes the physician is the problem. DEGRO annual meeting June 2002, Berlin, Germany

Publications:

1. Tanyi JA, Kato CM, Chen Y, Chen Z, Fuss M. Impact of the high-definition multileaf collimator on linear accelerator-based intracranial stereotactic radiosurgery. Br J Radiol. 2011 Jul;84(1003):629-38
2. Fuss M. Strategies of assessing and quantifying radiation treatment metabolic tumor response using F18 FDG Positron Emission Tomography (PET). Acta Oncol. 2010 Oct;49(7):948-55.
3. Tanyi JA, He T, Summers PA, Mburu RG, Kato CM, Rhodes SM, Hung AY, Fuss M. Assessment of Planning Target Volume Margins for Intensity-Modulated Radiotherapy of the Prostate Gland: Role of Daily Inter- and Intrafraction Motion. Int J Radiat Oncol Biol Phys. 2010 Dec 1;78(5):1579-85
4. Achanta P, Fuss M, Martinez JL Jr. Ionizing radiation impairs the formation of trace fear memories and reduces hippocampal neurogenesis. Behav Neurosci 2009 Oct 123(5):1036-45.
5. Tanyi JA, Summers PA, McCracken CL, Chen Y, Ku LC, Fuss M. Implications of a high-definition multileaf collimator (HD-MLC) on treatment planning techniques for stereotactic body radiation therapy (SBRT): a planning study. Radiat Oncol. 2009 Jul 10;4:22.
6. Lin L, Shi C, Eng T, Swanson G, Fuss M, Papanikolaou N. Evaluation of inter-fractional setup shifts for site-specific helical tomotherapy treatments. Technol Cancer Res Treat. 2009 Apr;8(2):115-22.Fuller CD, Dang ND, Wang SJ, Desai P, Choi M, Thomas CR Jr, Fuss M. Image-guided intensity-modulated radiotherapy (IG-IMRT) for biliary adenocarcinomas: Initial clinical results. Radiother Oncol. 2009 Aug;92(2):249-54.
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10. Tanyi JA, Fuss M. Volumetric image-guidance: Does routine usage prompt adaptive re-planning? An institutional review. Acta Oncol. 2008 Jul 25:1-10.
11. Siddiqui F, Shi C, Papanikolaou N, Fuss M. Image-guidance protocol comparison: Supine and prone set-up accuracy for pelvic radiation therapy. Acta Oncol. 2008 Jul 29:1-7.

12. Fuller CD, Schillerstrom JE, Jones WE 3rd, Boersma M, Royall DR, Fuss M. Prospective Evaluation of Pretreatment Executive Cognitive Impairment and Depression in Patients Referred for Radiotherapy. Int J Radiat Oncol Biol Phys. 2008 Oct 1;72(2):529-3.
13. Zhang J, Xu G, Shi C, Fuss M. Development of a geometry-based respiratory motion–simulating patient model for radiation treatment dosimetry. J Appl Clin Med Phys. 2008;9:16-28.
14. Tanyi JA, Krafft SP, Hagio T, Fuss M, Salter BJ. MOSFET sensitivity dependence on integrated dose from high-energy photon beams. Med Phys. 2008 Jan;35(1):39-47.
15. Boda-Heggemann J, Köhler FM, De Meerleer G, De Neve W, Fuss M, Lohr F, Wenz F. Image-guided radiation therapy: many roads lead to Rome? Int J Radiat Oncol Biol Phys. 2008 Feb 1;70(2):646-7 (letter to the editor)
16. Rassiah-Szegedi P, Fuss M, Sheikh-Bagheri D, Szegedi M, Stathakis S, Lancaster J, Papanikolaou N, Salter B. Dosimetric evaluation of a Monte Carlo IMRT treatment planning system incorporating the MIMiC. Phys. Med. Biol. 2007;52:6931-41
17. Fuller CD, Forthuber B, Choi M, Rajagiriyil, Slater BJ, Fuss M. Standard fractionation intensity-modulated radiation therapy (IMRT) for primary and recurrent glioblastoma multiforme. Radiation Oncology 2007;2(26):1-7.
18. Wang SJ, Choi M, Fuller CD, Salter BJ, Fuss M. Intensity-Modulated Radiosurgery for Patients with Brain Metastases: A Mature Outcomes Analysis. TCRT 2007;6:161-168.
19. Fuss M, Salter BJ. Intensity-modulated radiosurgery: improving dose gradients and maximum dose using post inverse-optimization interactive dose shaping. TCRT 2007;6:197-204.
20. Fuss M, Boda-Heggemann J, Papanikolaou N, Salter BJ. Image-guidance for Stereotactic Body Radiation Therapy. Medical Dosimetry 2007;32(2):102-10.
21. Achanta P, Thompson KJ, Fuss M, Martinez JL. Gene Expression Changes in the Rodent Hippocampus Following Whole Brain Irradiation. Neuroscience Letters 2007;418(2):143-7.
22. Tanyi JA, Fuss M, Varchena V, Lancaster JL, and Salter BJ. Phantom investigation of three-dimensional motion-dependent volume aliasing during computed tomography simulation for radiation therapy planning. Radiation Oncology 2007;2:1-15.
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25. Fuss M, Shi, C, Papanikolaou N. Tomotherapeutic Stereotactic Body Radiation Therapy: Techniques and Comparison between Modalities. Acta Oncologica 2006;45(7);953-960.
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27. Rassiah P. Salter BJ, Fuller D, Blough M, Papanikolaou N, Fuss M. Monte Carlo Characterization of Target Doses in Stereotactic Body Radiation Therapy (SBRT). Acta Oncologica 2006;45(7);989-994.
28. Fuller CD, Thomas CR Jr., Salter BJ, Herman TS, Fuss M. Preliminary endpoint analysis of daily ultrasound-based image-guided IMRT in the treatment of cancers of the gallbladder. Radiotherapy Oncology 2006;81:65-72.
29. Yang G, Wagner T, Fuss M, Thomas CR Jr. Multimodality Approaches for Pancreatic Cancer. CA A Cancer Journal for Clinicians 2005;55(6):352-367.
30. Cavanaugh SX, Fuller CD, Kupelian PA, Reddy C, Bradshaw P, Pollock BH, Fuss M. Time and PSA Threshold Model Predicts Long-Term Overall and Disease Specific Survival in Prostate Cancer Patients as Early as Three Months after External Beam Radiation Therapy. Prostate Cancer and Prostatic Diseases 2005;8(4):353-358.
31. Fuss M, Salter BJ, Caron JL, Vollmer DG, Herman TS. Intensity-modulated radiosurgery for childhood arteriovenous malformations. Acta Neurochirurgica 2005;147(11):1141-1150.
32. Cheek D, Holder A, Fuss M, Salter BJ. The relationship between the number of shots and the quality of Gamma Knife radiosurgeries. Optimization and Engineering 2005;6(4):449-462.
33. Salter BJ, Fuss M. The Song, Kavanagh, Benedict, et al. article reviewed. Oncology 2004;18(11):1435-1436.
34. Fuss M, Salter BJ, Herman TS, Thomas CR Jr. External beam radiation therapy for hepatocellular carcinoma: Potential of intensity-modulated and image-guided radiation therapy. Gastroenterology 2004;127(5 Suppl 2):S206-17.
35. Fuss M, Salter BJ, Cavanaugh SX, Fuss C, Sadeghi A, Fuller CD, Ameduri A, Hevezi JM, Herman TS, Thomas CR Jr. Daily ultrasound-based image-guided targeting for radiotherapy of upper abdominal malignancies. Int J Radiat Oncol Biol Phys 2004;59(4):1245-1256.
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Publications accepted (in press):

Publications submitted for peer review:

Contribution to critical summaries of published research

Mike Martin. How Do You Track Lung Tumor Motion? A Critical Question with Competing Answers. JNCI 2009 101(20):1372-74.

Book chapters

1. Fuss M, Salter BJ. Case study in liver SBRT: Dose optimization via inverse treatment planning. In: Stereotactic Body Radiation Therapy. Ed. Kavanagh/Timmerman. Lippincott Williams & Wilkins 2005.
2. Herfarth K, Fuss M. SBRT for liver tumors. Ed. Solberg/Slotman. Stereotactic body radiation therapy textbook. Taylor and Francis Books 2006.
3. Salter BJ, Fuss M. Serial Tomotherapeutic Approaches to Stereotactic Body Radiation Therapy. Ed. Solberg/Slotman. Stereotactic body radiation therapy textbook. Taylor and Francis Books 2006.
4. Dawson L, Fuss M. Image-Guided Radiation Therapy and Stereotactic Body Radiation Therapy. Biliary Tract & Gallbladder Cancer: A Multidisciplinary Approach. Demos Medical Publishing 2008.
5. Boda-Heggemann J, Lohr F, Fuss M. Ultrasound-based Image-guided Radiation Therapy. Image-Guided Radiation Therapy: A Clinical Perspective (Mundt AJ, Roeske JC, editors). People's Medical Publishing House - USA 2011.

Presentations (invited talks, CME accredited lectures, grand rounds, session chair)

1. Martin Schneider Memorial Lecture, UTMB, Galveston, TX, March 21, 2012
2. Moderator: "Showdown at La Costa: Early stage liver" debate. SRS/SBRT meeting 2012, La Costa, CA, February 24, 2012

3. Martin Schneider Memorial Visiting Professor, UTMB Galveston, TX, September 20-23, 2011.
4. Faculty and lecturer: SBRT for primary liver tumors and interactive case discussion. VU Medical Center Symposium on Stereotactic Body Radiation Therapy (SBRT). Amsterdam, The Netherlands, January 29, 2011.
5. Program Director, panelist (sessions on SBRT lung, SBRT liver, and SBRT spine), and speaker (SBRT for Primary Liver Tumors – Target Volume Delineation and Image-Guidance Considerations). 5th Novalis Circle Meeting. Munich, Germany June 17-19, 2010.
6. Strategies of assessing and quantifying post-treatment metabolic tumor response. BiGART 2010, Aarhus, Denmark, May 28, 2010
7. Radiation Therapy for primary liver tumors - HCC. 2010 Portland Conference. Progress in the Multidisciplinary Management of Hepatobiliary and Pancreatic Cancer. Portland, OR, April 30, 2010.
8. Radiation Therapy for primary liver tumors – Cholangiocarcinoma. 2010 Portland Conference. Progress in the Multidisciplinary Management of Hepatobiliary and Pancreatic Cancer. Portland, OR, April 30, 2010.
9. Optimizing image-guidance for SBRT. AAPM NW chapter Spring Meeting 2010. Portland, OR, April 30, 2010.
10. SBRT for early stage NSCLC – an update. Roseburg Community Cancer Center Grand Rounds. April 20, 2010.
11. SBRT and motion management for treatment of primary liver tumors SBRT. New Technologies and Applications in SRS/SBRT. April 14, 2010. New York, NY
12. Advances in Stereotactic Body Radiation Therapy (SBRT) planning and delivery. AOCR 2010, Taipei, Taiwan, March 21, 2010.
13. Radiation Therapy for Pituitary Tumors Concepts - Techniques and Outcomes. OHSU Endocrinology Grand Rounds. February 1, 2010.
14. SBRT for early stage NSCLC. OHSU Cardiothoracic Surgery Grand Rounds. January 11, 2010.
15. SBRT using the BrainLAB Novalis Tx. BrainLAB users meeting at ASTRO. Chicago, IL, October 31, 2009.
16. SBRT – new curative treatment options for lung and liver cancer. Oregon Cancer Registrars Association (OCRA) Annual Meeting. Portland, OR, October 16, 2009.
17. Spinal SBRT. OHSU Neurosurgery Grand Rounds. June 15, 2009.
18. SBRT for primary liver tumors. OHSU Gastroenterology Grand Rounds. January 16, 2009.
19. Prostate Cancer Update 2008. Lewis River Rotary Club lecture. November 18, 2008.

20. PET in Radiation Oncology. 33rd Western Region Society of Nuclear Medicine Meeting. Portland, OR, October 16, 2008.
21. Radiation Oncology Grand Rounds. SBRT for primary liver tumors Rationale, technique, and preliminary clinical results. University of Maryland, Baltimore, MD, June 26, 2008.
22. SNM continuing education: Nuclear Medicine in Radiation Therapy Planning – Challenges and Opportunities. Goals and Principles of Image Guided Radiation Therapy. Society of Nuclear Medicine, 55th annual meeting, New Orleans, LA, June 16, 2008.
23. SNM categorical seminar: Molecular Imaging Guided Cancer Therapy: Towards Personalized Treatment – Moving away from 'One Size Fits All' Concept? Personalizing Radiation Therapy – Clinical opportunities and challenges. Society of Nuclear Medicine, 55th annual meeting, New Orleans, LA, June 14, 2008.
24. Session chair. Clinical studies: H&N and brain. Acta Oncologica Symposium, Image-guided and adaptive radiotherapy, Aarhus, Denmark June 7, 2008.
25. Multi-modality imaging in Radiation Oncology. Philips Oncology Symposium. Los Angeles, CA, May 15, 2008.
26. Marquam Hill Lecture Series. Image-Guided Radiation Therapy, Portland, OR, April 17, 2008.
27. Image-guided Radiation Therapy. Oregon Radiation Oncology Society, Portland, OR, November 10, 2007.
28. Panelist, The utility of FDG-PET in Head & Neck Cancer. Oregon Academy of Otolaryngology. Portland, OR, November 9, 2007.
29. Panelist, Rare Neoplasms. Hepatocellular carcinoma. ASTRO 2007, Los Angeles, CA October 28, 2007.
30. Discussant. SBRT for lung tumors. ASTRO 2007, Los Angeles, CA, October 31, 2007.
31. Pancreatic cancer: Is radiotherapy still part of the primary treatment? ICRO/OEGRO 8. Salzburg, Austria, May 2007.
32. Photons or Protons: Prostate cancer. ICRO/OEGRO 8. Salzburg, Austria, May 2007.
33. IMRT and IGRT for H&N Tumors. ENT grand rounds. Oregon Health & Science University, Portland, OR, March 19, 2007.
34. Radiation Therapy for CNS Tumors: GBM and brain metastases. Neurooncology grand rounds. Oregon Health & Science University, Portland, OR, February 26, 2007.
35. Image-guided Radiation Therapy: A look behind the curtain. Marquam Hill Steering Committee. Portland, OR, February 15, 2007.
36. Respiratory Gating Summit at ASTRO, November 6, 2006. Philadelphia, PA.
37. Stereotactic body radiation therapy for early stage lung cancer. Cardiothoracic surgery grand rounds, Oregon Health & Science University, October 16, 2006.

38. An introduction to intensity-modulated radiation therapy (IMRT). Medical Oncology Grand Rounds, Oregon Health & Science University, October 20, 2006
39. Tomotherapeutic Stereotactic Body Radiation Therapy. SBRT2006, Copenhagen, Denmark, June 16, 2006.
40. Stereotactic Body Radiation Therapy (SBRT) for early stage lung cancer. Updates in Lung Cancer Treatment. San Antonio, TX, April 21, 2006.
41. Pre-clinical and Clinical Studies of Radiation-induced CNS Injury. 12th annual Blood Brain Barrier Disruption Consortium Meeting. Sunriver, OR. March 23-25, 2006
42. Intensity-modulated radiation therapy (IMRT) Clinical implications and applications. Northwest AAMD/AAPM meeting. Skamania Lodge, WA. February 24-25, 2006.
43. Image-guided radiation therapy (IGRT) Clinical implications and applications. Northwest AAMD/AAPM meeting. Skamania Lodge, WA. February 24-25, 2006.
44. Radiation therapy for CNS tumors. Department of Rehabilitation Medicine Grand Rounds, UTHSCSA. February, 14, 2006.
45. Stereotactic radiation therapy for spinal and paraspinal tumors. Neurooncology Grand Rounds, Oregon Health & Science University (OHSU), Portland, OR. January 20, 2006.
46. Organ motion and its management. 7th Curso de Education Continua de la Sociedad de Fisica Medica de Nueva Leon. Monterrey, Mexico, December 13, 2005.
47. Stereotactic body radiation therapy. 7th Curso de Education Continua de la Sociedad de Fisica Medica de Nueva Leon. Monterrey, Mexico, December 13, 2005.
48. CNS – review of ASTRO presentations. 5th annual ASTRO review. San Antonio, TX. November 19, 2005.
49. New Technical Developments in external beam radiation oncology. 5th annual ASTRO review. San Antonio, TX. November 19, 2005.
50. Radiation therapy for pituitary adenoma. Endocrinology Grand Rounds. UTHSCSA, San Antonio, TX September 22, 2005.
51. Image-guided intensity-modulated radiation therapy for pancreatic cancer, gallbladder cancer and hepatocellular carcinoma. International Society for Gastrointestinal Oncology. Arlington, VA July 14, 2005.
52. SBRT localization of lung and liver tumors. Stereotactic Body Radiation Therapy: State of the science – Dallas 2005. Dallas, TX May 28, 2005.
53. Patient immobilization – implications for precision radiation therapy. TomoTherapy Users Meeting. Shreveport, LA April 16, 2005.
54. Stereotactic Body Radiation Therapy – the UTHSCSA experience. Tumor Board. UTHSCSA, San Antonio, TX March 31, 2005.
55. Protons, Tomotherapy, Cyberknife for EBRT of prostate cancer. Society of Urologic Oncology/NIH annual meeting. NIH, Bethesda, MD December 3, 2004.

56. Prostate target visualization: EPID is better than ultrasound techniques for target check and visualization for IMRT. Presentation and debate: pro ultrasound. 8th Annual International Conference and Workshop: New and future developments in radiotherapy. San Diego, CA, December 14, 2004.
57. IMRT for prostate cancer: Clinical aspects and treatment planning strategies. 8th Annual International Conference and Workshop: New and future developments in radiotherapy. San Diego, CA, December 14, 2004.
58. Debate: HDR is better than LDR seed and IMRT for treatment of early prostate cancer. Pro IMRT. 8th Annual International Conference and Workshop: New and future developments in radiotherapy. San Diego, CA, December 14, 2004.
59. CNS - Highlights of the 46th ASTRO meeting. 4th ASTRO review. San Antonio, TX, November 12, 2004.
60. Intensity-modulated radiosurgery. Lunch Symposium. ESTRO 2004. Amsterdam, Netherlands October 27, 2004.
61. Imaging for target volume delineation: Chair: M. Fuss/P. Lukas. ESTRO teaching course: Imaging for Radiotherapy: Established and Novel Technologies. Amsterdam, Netherlands October 24, 2004.
62. The use of ultrasound, CT and MRI for planning of prostate treatment. ESTRO teaching course: Imaging for Radiotherapy: Established and Novel Technologies. Amsterdam, Netherlands October 24, 2004.
63. The use of ultrasound for treatment verification. ESTRO teaching course: Imaging for Radiotherapy: Established and Novel Technologies. Amsterdam, Netherlands October 24, 2004.
64. Stereotactic Body Radiation Therapy for liver lesions as a bridge to transplant. Transplant Surgery Grand Rounds. UTHSCSA September 24, 2004.
65. RT-Treatment Planning for Lung Cancer. International Masters Program in Medical Physics. Workshop New Approaches in Radiotherapy of Lung Tumors. Mannheim, Germany September 18, 2004.
66. Stereotactic Body Radiation Therapy. Surgery Grand Rounds. UTHSCSA September 13, 2004.
67. Ultrasound-guided Target Volume Positioning for Prostate: Theoretical Background. Symposium Ultrasound-guided Target Volume Positioning. Innsbruck, Austria September 4, 2004.
68. Organ motion and its management. ABRO/BVRO Residential Seminar 2004. Oudenburg, Belgium. May 14-15, 2004.
69. Daily setup for prostate cancer with echography. ABRO/BVRO Residential Seminar 2004. Oudenburg, Belgium. May 14-15, 2004.

70. Stereotactic Body Radiation Therapy (SBRT). MDACC Orlando. Orlando, FL. May 7th, 2004.
71. IMRT and image-guided targeting. Hepatocellular carcinoma: Screening, diagnosis and management. NIDDK/NIH/NIBIB. Bethesda, MD. April 1-3, 2004.
72. Intensity-modulated hypofractionated extracranial radioablation: Preliminary clinical experience. Radiation Oncology Annual Educational Meeting of the Indiana Radiation Oncology Academy. Indianapolis, IN November, 8, 2003.
73. CNS and SBRT. Highlights of ASTRO. 3rd ASTRO review. San Antonio, TX, November 12, 2004.
74. Extracranial intensity-modulated radioablation - preliminary clinical experience. Extracranial Stereotactic Radioablation: Future Directions. Halifax, NS, Canada June 8-10, 2003.
75. Stereotactic targeting for upper abdominal and pancreatic cancer. Texas Radiological Society 2003 Annual Meeting. April 4th 2003, The Woodlands, TX.
76. Extracranial radioablation for Liver Cancer – UTHSCSA experience. First International Symposium on Extracranial Radiosurgery. March 28-29, 2003. Dearborn, Michigan.
77. Extracranial radioablation for liver metastases. Didactic conference. UTHSCSA, Dept. of Medicine, Division of Gastroenterology and Nutrition. February 6, 2003.
78. Fuss M. Cerebral blood volume changes and cognitive changes following cranial radiation. The effects of radiotherapy on brain and behavior trough the lifespan. Rio Grande, Puerto Rico, December 2002.
79. Radiosurgery, concept and clinical indications. Drug development lecture series. Institute for Drug Development, CTRC/SACI, San Antonio, TX, November, 2002.
80. CNS highlights at ASTRO. 2nd annual ASTRO review. San Antonio, TX, November 1, 2002.
81. Image-guided targeting: current controversies. 2nd annual ASTRO review. San Antonio, TX, November 1, 2002.
82. IMRT for Prostate cancer. Clinical aspects. 6th Annual International Conference and Workshop: New and future developments in radiotherapy. Las Vegas, NV, August 2002.
83. IMRT for Breast cancer. Clinical aspects. 6th Annual International Conference and Workshop: New and future developments in radiotherapy. Las Vegas, NV, August 2002.
84. Extracranial radioablation using a tomotherapeutic IMRT technique. Extracranial Stereotactic Radioablation: Future Directions. Niagara Falls, Ontario, May 10-12, 2002.
85. Stereotactic ultrasound target localization – potential impact on liver target radioablation. Extracranial Stereotactic Radioablation: Future Directions. Niagara Falls, Ontario May 10-12, 2002.

86. Fuss M. BAT. Ultrasound Positioning for Upper Abdominal Target Volumes Undergoing Radiotherapy. SWOG Spring Meeting 2002. Dallas, TX April 19, 2002,
87. Radiation induced intellectual deficits in children. Texas Radiological Society 2002 Annual Meeting. Austin, TX April 12, 2002,
88. Radiosurgery, concept and clinical indications. Drug development lecture series. Institute for Drug Development, CTRC/SACI, San Antonio, TX. January 30, 2002.
89. CNS/Functional Imaging/PET – a summary of ASTRO presenations and discussions. 1st annual ASTRO review, San Antonio, TX November 16-17, 2001.
90. Technical innovations in treatment planning and delivery – an ASTRO summary. 1st annual ASTRO review, San Antonio, TX November 16-17, 2001.
91. Brachytherapy is preferable over IMRT for favorable risk prostate cancer - debate. Fuss M, Orton C, Beyer D, Curren B, Alecu R. Fifth Annual International Conference and Workshop: New and future developments in radiotherapy. Rancho Viecho, TX, October 5-7, 2001.
92. Fuss M. IMRT [for prostate cancer] – Clinical aspects. Fifth Annual International Conference and Workshop: New and future developments in radiotherapy. Rancho Viecho, TX, October 5-7, 2001.

Grants:

Forschungsfoerderungs Kommission der Universitaet Heidelberg. Development of novel external beam stereotactic radiation techniques for uveal melanoma. DM 187,000 for two years (July 1997-June 1999). Closed

Forschungsfoerderungs Kommission der Universitaet Heidelberg. Assessment of cognitive functions after prophylactic and therapeutic whole brain irradiation using neuropsychological testing. DM 234,000 for two years (July 2000-June 2002). Closed

CCRC 02-173, Start-up support for the development of a non-invasive PET imaging assessment of radiation-induced brain tissue damage in rats. Children’s Cancer Research Center, San Antonio, TX, $160,000 (April 2002-March 2004). Closed

RSNA (Radiological Society of North America) Medical Student Departmental Grant #MSD0205, Executive Control Function as a Measure of Cognitive Function in Patients Receiving Cranial Irradiation. $ 15,000 over five years (October 2002–September 2006). Closed

RSNA Leonard B. Holman Resident Research Grant. ^{11}C acetate PET staging in newly diagnosed high-risk prostate cancer patients. Holman Resident and PI: Sean X. Cavanaugh, MD, PhDc. Scientific mentor: Martin Fuss, MD. $30,000 (July 2003-June 2005). Closed

CCC (Cancer Center Council San Antonio at CTRC, San Antonio, TX), Prospective clinical study to assess tumor response of childhood brain tumors following cranial irradiation using positron emission tomography (PET). $20,000 for one year (June 2003-May 2004). Closed

GCRC Bartter Scholars Program. ^{11}C acetate PET staging in newly diagnosed high-risk prostate cancer patients. Medical student: Clifton D. Fuller. Scientific mentor: Martin Fuss, MD. $2,000 (August - September 2003). Closed

SALSI (San Antonio Life Sciences Institute), Radiation-induced changes in hippocampal functioning. $167,000 for one year (June 2004-June 2006). PI's Fuss M (UTHSCSA) and Martinez J (UTSA). Closed

CCC (Cancer Center Counsil San Antonio at CTRC, San Antonio, TX), 11C-acetate PET for prostate cancer. $18,000 for one year (June 2004-May 2005). Closed

Nomos Corp. (Cranberry Township, PA). Unrestricted educational grant. $15,000 for one year (May 2004-April 2005). Closed

Equipment grant from Nomos, Cranberry Township, PA: Corvus inverse treatment planning stations for education and research. PI Fuss M. (2005/2006). Closed

San Antonio Neuroscience Alliance (SANA). Radiation-induced changes in hippocampal functioning. Awardee Pragathi Achanta. UTSA mentor J. Martinez, UTHSCSA mentor M. Fuss. Stipend support (June 2006 to June 2007). Closed

1R01LM009362-01. 4D Visible Human Modeling for Radiation Dosimetry, PI Xu George, Dept. of Mechanical, Aerospace & Nuclear Engineering, Rensselaer, Troy, NY, Fuss M – effort 10%. 4/2007 – 3/2011. Active

Equipment grant from GE Medical System, Milwaukee, WI: 4-dimensional CT imaging for radiation therapy planning and daily image-guidance. PI Fuss M. (2007). Closed

Equipment grant from Imaging3, Burbank, CA: Clinical evaluation of a mobile cone-beam CT unit for radiation therapy image-guidance. PI Fuss M. (2007). Active

Varian Research Grant. Assessment of Stereotactic Body Radiation Therapy (SBRT) induced Lung Ventilation Changes. PI Fuss M (2009-2011). Active

Varian Research Grant. Quality Assurance for Error Analysis of RapidArc Treatment Delivery abnd Investigation of their Significne. PI Wolfram Laub, PhD; Fuss M Co-investigator (2010-2012). Active

Washington State Health Care Authority

Stereotactic Radiosurgery (SRS) &
Stereotactic Body Radiation Therapy (SBRT)

State Agency Utilization & Outcomes

Kerilyn K. Nobuhara MD MHA
Senior Medical Consultant
Health Care Authority
November 16, 2012

Background

Stereotactic Radiosurgery (SRS)

- Developed to treat inoperable brain tumors
- Skeletal fixation device or immobilization device
- Cobalt-60 (Gamma Knife®) or linear accelerator based (CyberKnife®, Axesse™, XKnife™, Novalis Tx™, Synergy®, Trilogy™)
- Gamma Knife® designed to treat intracranial targets
- Single session or hypofractionated

Stereotactic Body Radiation Therapy (SBRT)

- Immobilization device or implanted fiducial markers
- Linear accelerator based
- Hypofractionated

Washington State Health Care Authority

SRS/SBRT

Background

Reasons cited by physicians for adoption of SBRT:

- Allows delivery of higher than conventional radiation doses
- Allows retreatment in select patients
- To perform clinical research
- To gain competitive advantage or remain competitive

☙ *Pain, et al., "**A Survey of Stereotactic Body Radiotherapy Use in the United States**," Cancer 2011; 117:4566-72.*

3

Washington State Health Care Authority

SRS/SBRT

Background

- Started as disruptive technology for neurooncology providers
- Rapidly disseminated to other applications which have become the accepted "standard of care" in many institutions
- Widespread adoption without adequate comparative clinical trials to other radiotherapies or surgical resection
- No consensus with respect to the number of radiation fractions, radiation dose per fraction, or maximum number/size of lesions to be treated
- No comparative effectiveness studies of SBRT vs. IMRT
  - Therapeutic ratio is unknown
  - Early stage prostate cancer and cervical cancer areas of controversy
  - Hypofractionated regimens more convenient for patient

4

Washington State Health Care Authority

SRS/SBRT

HTA Workgroup Perspective

Primary Criteria Ranking

Safety = Medium
Efficacy = High
Cost = High

5

Washington State Health Care Authority

SRS/SBRT

Current State Policy

PEB

- Medically necessary for: intracranial AVM, acoustic neuromas, pituitary adenomas, non-resectable/residual/recurrent meningiomas, craniopharyngiomas, glomus jugulare tumors, solitary or multiple brain metastases with Karnofsky performance score ≥ 70 AND life expectancy > 6 months
- Primary malignancies of CNS, including but not limited to, high grade gliomas
- Spinal or vertebral body tumors in patients who have received prior radiation therapy
- Trigeminal neuralgia
- Stage 1 NSCLC when patient is an unsuitable candidate for surgical resection
- Lung metastases when: life expectancy > 6 months, Karnofsky performance score ≥ 70, adequate lung function, locally controlled primary tumor, ≤ 3 metastatic lung lesions, targeted tumor diameter < 5 cm, tumor either non-resectable or patient medically inoperable, no other metastatic disease

Washington State Health Care Authority

SRS/SBRT

Current State Policy

Medicaid
- Hayes, NCCN guidelines, LCD draft

Labor and Industries
- No published criteria

Department of Corrections
- Follows NCCN guidelines

Washington State Health Care Authority

SRS/SBRT

Medicare Coverage Decisions

National Coverage Determination
- None

Local Coverage Determination: SBRT
- L28366 Wisconsin Physicians Service Insurance Corporation
- For lung, liver, kidney and pancreas neoplasms: Covered with conditions
  - When other forms of radiotherapy cannot be safely or effectively utilized
- For prostate neoplasms: Covered with conditions
  - Low risk and low/intermediate risk as monotherapy
  - When other forms of radiotherapy cannot be safely or effectively utilized

Washington State Health Care Authority

SRS/SBRT

Medicare Coverage Decisions

Local Coverage Decision: Cranial SRS

- L30318 Wisconsin Physicians Service Insurance Corporation
- Intracranial lesions under the following conditions:
  - Lesion has an image-distinct margin
  - Karnofsky Performance Scale is greater than 50% or ECOG performance status is two or less
  - Specific indications include: neuromas of the cranial nerves including acoustic, trigeminal, etc.
    - Intracranial unresectable meningioma and/or residual meningioma where the patient's medical condition precludes surgery; and where, because of the location of the tumor, surgery would result in devastating neurodeficits.

Washington State Health Care Authority

SRS/SBRT

Medicare Coverage Decisions

Local Coverage Decision: Cranial SRS

- Coverage for treatment of metastatic brain lesions under the following conditions:
  - Patients have essentially stable disease
  - Lesion margins are radiographically distinct
  - Number of lesions does not exceed five
- As a boost treatment for larger cranial lesions that have been treated initially with external beam radiation therapy or surgery: (i.e. grade III and IV gliomas: pilocytic astrocytoma, oligodendrogliomas, sarcomas, chordomas)
- Trigeminal neuralgia refractory to medical treatment
- Essential tremor: patients who cannot be controlled with medication, have major systemic disease or coagulopathy, and are unwilling or unsuited for open surgery. Coverage further limited to unilateral thalamotomy. Gamma Knife pallidotomy remains non-covered.

Washington State Health Care Authority

SRS/SBRT

Medicare Coverage Decisions

Local Coverage Decision: Cranial SRS

- AV Malformations
- Acoustic neuromas
- Pituitary adenoma
- Craniopharyngiomas
- Glomus jugulare tumors

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Washington State Health Care Authority

SRS/SBRT

Medicare Coverage Decisions

Local Coverage Decision: Cranial SRT

Cover with conditions:

- AV Malformations
- Pituitary Adenoma
- Vestibular schwannoma
- Meningioma
- Benign neoplasms previously treated with conventional radiotherapy
- Malignant lesions:
  - Within 5 mm of the optic nerves or chiasms
  - Recurrent malignant gliomas
  - Brain metastasis
  - Base of skull
  - Recurring head and neck cancers (i.e. tonsil, larynx, tongue, sinus and mouth)

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Washington State Health Care Authority

SRS/SBRT

Agency Key Questions

Safety = Medium Concern

- Higher risk for toxicity because of higher dose per fraction
- Treatment of a new population of patients previously considered unresectable or medically inoperable
- What are the potential harms of SRS and SBRT compared to conventional external beam radiation therapy? What is the incidence of these harms? Include progression of treatment in unnecessary or inappropriate ways.

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Washington State Health Care Authority

SRS/SBRT

Agency Key Questions

Efficacy = High Concern

- Limited evidence to support therapeutic effectiveness of SRS/SBRT vs. EBRT
  - Less evidence to support therapeutic effectiveness of SRS/SBRT to surgical resection
- What is the evidence of effectiveness for SRS and SBRT compared to conventional external beam radiation therapy (EBRT) for patients with:
  - Central nervous system (CNS) tumors; and
  - Non-central nervous system cancers?

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Washington State Health Care Authority

SRS/SBRT

Agency Key Questions

Cost = High Concern

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

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Washington State Health Care Authority

SRS/SBRT

Agency Utilization

Agency	2008	2009	2010	2011	4-Year Total	% Change
PEB						
Agency Population	204,804	210,501	213,487	212,596		1.3%
Patients	49	55	60	70	205[1]	*11.3%
Amount Paid	$924,420	$1.5M	$1.8M	$1,1M	$5.3M	*12.7%
Average Paid/Patient	$18,866	$26,800	$29,535	$16,219	$25,882	2.4%
Treatment Courses (Courses/Patient)	55 (1.1)	62 (1.1)	74 (1.2)	81 (1.2)	264 (1.3)	*1.2%
Medicaid						
Agency Population	392,808	416,871	424,230	435,187		3.5%
Patients	61	75	97	115	294[1]	*19.5%
Amount Paid	$892,341	$1.2M	$1.2M	$1.3M	$4.7M	*15.0%
Average Paid/Patient	$14,629	$16,582	$12,640	$11,415	$15,901	-6.7%
Treatment Courses (Courses/ Patient)	80 (1.3)	102 (1.4)	128 (1.3)	147 (1.3)	424 (1.4)	*-0.8%

[1] Patients who were treated in multiple years are counted once in the 4-year total.
* Adjusted for population growth

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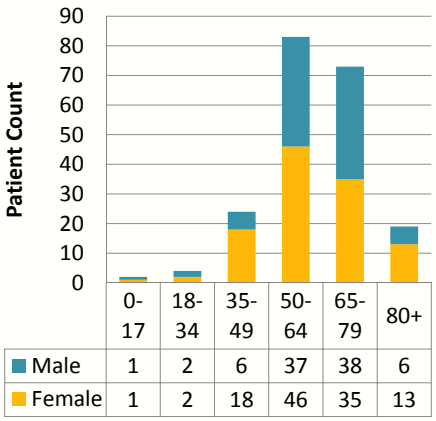
Washington State Health Care Authority

SRS/SBRT

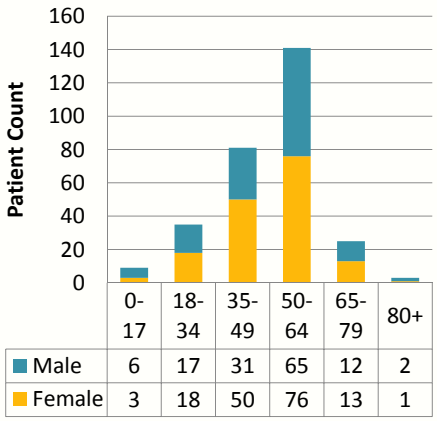
Agency Utilization

PEB SBRT Patients
By Age & Gender, 2008-2011



	0-17	18-34	35-49	50-64	65-79	80+
Male	1	2	6	37	38	6
Female	1	2	18	46	35	13

Medicaid SBRT Patients
By Age & Gender, 2008-2011



	0-17	18-34	35-49	50-64	65-79	80+
Male	6	17	31	65	12	2
Female	3	18	50	76	13	1

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SRS/SBRT

Agency Utilization

Allowed Charges, Per Patient Average

	PEB Primary (w/o Medicare)	PEB Medicare	Medicaid
Breakdown 1			
Professional Services	$4,857	$2,547	$2,850
Facility	$39,322	$58,084	$15,841
Breakdown 2			
Planning charges	$6,573	$11,332	$1,749
Navigation/Imaging	$1,934	$2,736	$1,240
Delivery	$21,747	$9,630	$12,836
Other	$13,925	$36,933	$2,865
Average allowed amount /Treatment course	**$44,179**	**$60,630**	**$18,690**

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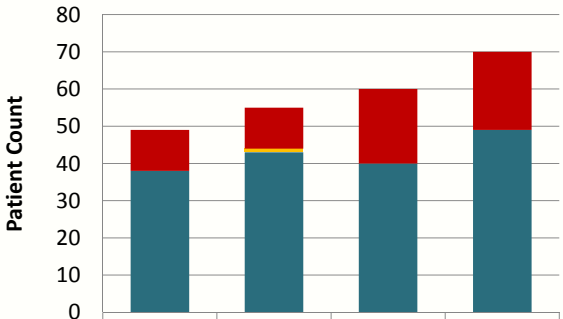
Washington State Health Care Authority

SRS/SBRT

Agency Utilization

PEB SBRT Patients
By Treatment Category, 2008-2011



	2008	2009	2010	2011
Other	11	11	20	21
Spinal	0	1	0	0
Cranial	38	43	40	49

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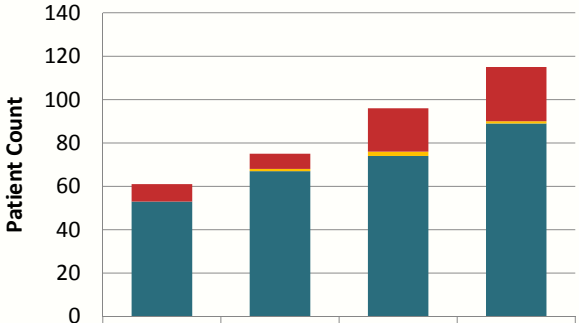
SRS/SBRT

Agency Utilization

Medicaid SBRT Patients
By Treatment Category, 2008-2011



	2008	2009	2010	2011
Other	8	7	20	25
Spinal	0	1	2	1
Cranial	53	67	74	89

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SRS/SBRT

Agency Considerations

- The evidence supporting SRS/SBRT vs. EBRT is generally of low quality
  - RCTs: brain metastases, glioblastoma multiforme
- Acute and late radiation morbidity reporting is mixed
- Cost analyses are difficult because of the myriad of treatment options
  - IMRT, EBRT, surgery, palliative care

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Washington State Health Care Authority

SRS/SBRT

AMD Recommendations

Cover with conditions:

- Medically inoperable or unresectable primary brain neoplasm or metastatic disease
  - For patients with a Karnofsky score $\geq$ 70
  - Life expectancy $\geq$ 6 months; or
  - Limited tumor volume on presentation
- Medically inoperable or unresectable early stage NSCLC
  - For patients with a Karnofsky score $\geq$ 70; or
  - Life expectancy $\geq$ 6 months
- Symptomatic primary or metastatic spinal or paraspinal tumor with
  - History of previous radiation treatment to area; or
  - Requirement of high dose radiotherapy
- All other diagnoses subject to agency discretion

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Washington State Health Care Authority

SRS/SBRT

Questions?

More Information:

http://hta.hca.wa.gov/stereotactic_radiation.html

Washington State Health Care Authority

SRS/SBRT

Code	SRS/SBRT Specific Codes	Cranial/ Other	Type
61795	Stereotactic computer assisted volumetric (navigational) procedure, intracranial, extracranial, or spinal	Both	Navi-gation
61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion	Cranial	Delivery
61797	Each additional cranial lesions, simple	Cranial	Delivery
61798	Complex cranal lesion	Cranial	Delivery
61799	Each additional cranial lesion, complex	Cranial	Delivery
61800	Application of stereotactic headframe for stereotactic radiosurgery	Cranial	Delivery
63620/1	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion (63621 each add'l)	Spinal	Delivery
77371	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesions(s) consisting of 1 session; multi-source Cobalt 60 based	Cranial	Delivery
77372	As 77371, but linear accelerator based	Cranial	Delivery

Washington State Health Care Authority

Code	SRS/SBRT Specific Codes	Cranial/ Other	Type
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions	Other	Delivery
77432	Stereotactic radiation treatment management of cranial lesions(s) (complete course of treatment -1 session)	Cranial	Planning
77435	Stereotactic body radiation therapy, tx management, per tx course, 1 or more lesions, w/ image guidance, max 5	Other	Planning
G0173	Linear accelerator based stereotactic radio-surgery, complete course of therapy in 1 session	Both	Delivery
G0251	Linear accelerator based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, maximum five sessions per course of tx.	Both	Delivery
G0339/40	Image-guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session or first session (5 fractions for G0340)	Both	Delivery

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Washington State Health Care Authority

Code	SRS/SBRT Non-specific Associated Codes	Cranial/ Other	Type
77011	CT guidance for stereotactic localization	Both	Navigation
20665	Removal of fixation device	Cranial	Delivery
77014	CT guidance -placement of radiation therapy flds	Both	Navigation
77261/2/3	Radiation Therapy Planning: Simple, intermediate, complex	Both	Planning
77280/85 77290/5/9	Set radiation therapy field, simple, intermediate, complex (0) or 3 dimensional (5)	Both	Planning
77300	Radiation Therapy Dose Plan	Both	Planning
77321	Special Teletx Port Plan	Both	Planning
77332/3/4	Radiation tx aids (simple, intermediate, complex)	Both	Planning
77336	Continuing medical physics consultation	Both	Planning
77370	Special medical radiation physics consultation	Both	Planning
77470	Special Radiation Treatment management (extra planning for SRS)	Both	Planning
70551/2/3	MRI Brain	Cranial	Planning

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Washington State Health Care Authority

Stereotactic Radiosurgery (SRS) and Body Radiation Therapy (SBRT)

Presented by: Martha Gerrity MD, MPH, PhD
Date: November 16, 2012

Introduction

- Background
- PICO and Key Questions
- Methods
- Findings
- MAUDE Database, Guidelines and Policies
- Overall Summary
- Limitations of the Evidence

Background – Use of Radiation Therapy

- Half of cancer patients receive radiation, alone or in combination with surgery or chemotherapy
- Radiation therapy delivers high energy waves to tissues to destroy cancer cells
- Damage to normal tissues also causes adverse effects

Background – Modalities Used to Deliver RT

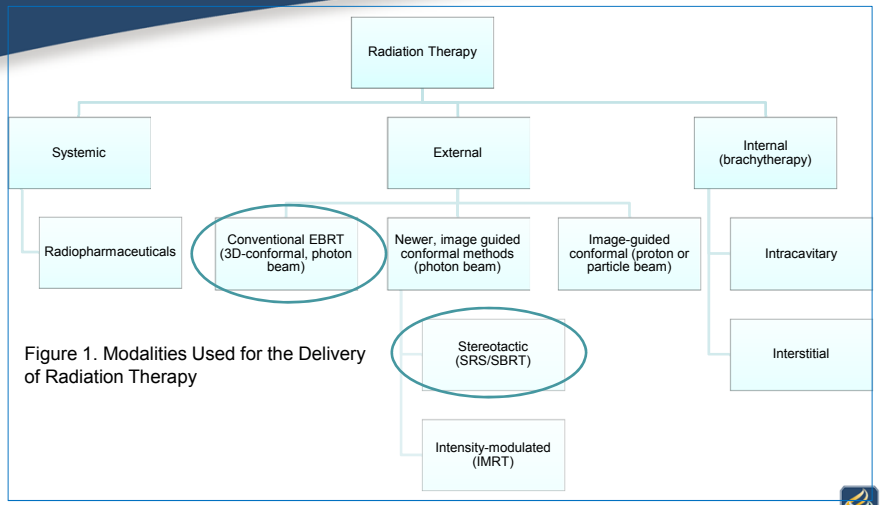

Figure 1. Modalities Used for the Delivery of Radiation Therapy

Background – *SRS/SRT and SBRT technology*

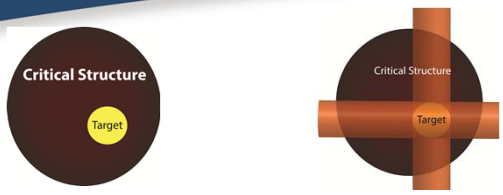

Figure 2. Conventional EBRT Radiation Field

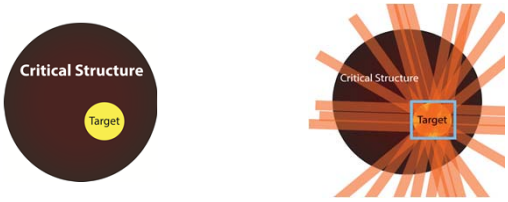

Figure 3. SRS Radiation Field

Background – Clinical Overview

Cancer Site	Incidence (per 100,000)* (2005 – 2009)	5-year Survival* (2002 - 2008)
Lung	62.6	15.9%
- Localized (Stage I)		52.2%
- Regional (Stage II/III)		25.1%
- Distant (Stage IV)		3.7%
Brain and spine	6.5	33.5%
Colorectal	46.3	63.4%
Liver/bile duct	7.5	15.2%
Eye/orbit	0.8	83.1%
Prostate	154.8	99.2%
Breast	124.3	89%

*National Cancer Institute (2011) from the SEER database

Background – FDA Approval and Use of SRS and SBRT

- SRS/SBRT devices are approved for sale through the FDA 510(k) approval process
  - No requirement for comparative studies on efficacy or safety
  - This report provides a broader analysis of the evidence than required by the FDA
- SRS/SBRT use is growing in the US
  - Radiation oncologists reported use of SBRT was 65% in 2010, up from 30% in 2007 (Pan 2011)

PICO and Key Questions (KQ)

Population: Adults and children with malignancies where treatment by radiation therapy is appropriate

Intervention: SRS/SRT (brain) or SBRT (body)

Comparator: Conventional external beam radiation therapy (EBRT), *although surgery and/or chemotherapy may be used for specific cancers*

Outcomes:
KQ1: Survival & tumor control rates, quality of life
KQ2: Harms including radiation complications
KQ3: Subpopulations, pediatric (0 – 18 years)
KQ4: Cost, cost-effectiveness

Methods – Evidence

- 'Best evidence' systematic review (SR) methods
- Search strategy
  - Recent, good quality SRs & technology assessments
    - MEDLINE and Cochrane search for subsequently published individual studies
  - MEDLINE search for studies if no SR/TA
    - 2002 through April 2012
  - 124 references from AHRQ TA of SBRT reviewed
- References from public review of KQs and Draft Report

Methods – Additional Inclusion Criteria*

- KQ 1 & 3
  - Central nervous system (CNS)
    - n ≥ 20; comparative studies
  - Non-CNS (Breast, Colon, H&N, Lung, Prostate)
    - n ≥ 50; comparative studies
  - Non-CNS (other cancers)
    - n ≥ 20; comparative and non-comparative studies
- KQ 2
  - n ≥ 50; comparative and non-comparative studies
  - n ≥ 20 for pediatric populations and serious harms
- KQ 4 – Comparative and non-comparative studies

*excluded dose & dosimetry studies

Methods – GRADE Ratings of Overall Strength of Evidence (SOE)

Dual ratings of study quality (risk of bias) - *Good, fair, poor*

1. Establish initial SOE		2. Consider lowering or raising SOE		3. Final SOE
Study design	Initial confidence in estimate of effect	↓ Lower if	↑ Higher if	
Randomized trials	High confidence	High Risk of Bias Inconsistency Indirectness Imprecision Publication Bias	Large Effect Dose response All plausible confounding and bias would reduce a demonstrated effect	High ⊕⊕⊕⊕ Moderate ⊕⊕⊕◯ Low ⊕⊕◯◯ Very Low ⊕◯◯◯
Observational studies	Low confidence			

Adapted from Guyatt, G., & Oxmann, A. (2012). GRADE Guidelines – an introduction to the 10th-13th articles in the series. *Journal of Clinical Epidemiology*, [epub ahead of print].

Methods – Guidelines and Policy

- Guidelines from national and key specialty organizations published after 2006
  - Dual rating of methodologic quality (Appraisal of Guidelines Research and Evaluation [AGREE])
    - *Good, fair, poor*
- Select payer policies
  - Medicare National and Local Coverage Determinations (NCD/LCD), Aetna, Blue Cross Blue Shield, and GroupHealth

Results

- 3,034 citations were reviewed for inclusion
  - 959 submitted during public comment for KQs, 48 for draft report
- 253 studies met inclusion criteria (Appendix F)
  - 12 SRs and TAs
  - 241 individual studies (only 7 RCTs)
  - 2 case series (CS) of pediatric patients, 51 CS included pediatric patients but did not stratify results based on age
- Subsequent Medline and Cochrane searches for RCTs after public review
  - April 2012 – October 10, 2012
  - No studies identified

Findings - Overview

- Findings are grouped by cancer and strength of evidence, starting with comparative studies
  - *Brain metastases* (*including subgroups*)
  - Primary brain tumors (*glioblastoma*, glioma, pituitary)
  - Head and neck (H&N)
- Non comparative studies
  - Lung cancer (inoperable Stage 1 non-small cell)
  - Spine
  - All other cancers
- Only two case series focused on children
  - Ependymomas (Kano 2010); gliomas (Marcus 2005)

Table of Symbols and Abbreviations

Abbreviations	Symbols (SRS/SBRT Compared to EBRT)
OS = overall survival	↔ = no significant difference
LC = local control	↕ = inconsistent evidence
QoL = quality of life	↑ = increased
RPA = recursive partitioning analysis	↓ = decreased
EBRT = external beam radiation treatment	
WBRT = whole brain radiation treatment	

Brain Metastases – Background

- Brain metastases are common
  - 40% of cancer patients
    - ~30% have a single metastasis
  - Lung, breast, melanoma, colon, renal
- Steroids and WBRT have been the mainstays of treatment
- Surgery has been considered for some patients with single metastasis, good performance status (PS), and stable systemic disease

Brain Metastases – Findings

- 3 comparisons for SRS and WBRT
  - SRS+WBRT vs WBRT alone
  - SRS+WBRT vs SRS alone (*see report*)
  - SRS alone vs WBRT alone
  - SRS for recurrent or progressive brain metastases (case series only)
- Overall evidence base
  - 7 SRs (6 RCTs), 12 cohort studies, and 25 case series

Brain Metastases – SRS+WBRT vs WBRT

Overall evidence base

- 3 good quality SRs (Linskey 2010; Patil 2010; Tsao 2012)
  - 3 RCTs (only 2 published)
    - Andrews (2004), fair quality
      - 333 adults, 1 – 3 metastases, good PS
    - Kondziolka (1999), poor quality
      - 27 adults, 2 – 4 metastases, good PS
  - No cohort studies

Brain Metastases – SRS+WBRT vs WBRT

Strength of Evidence	Findings
KQ1: Moderate	↔ Overall survival (HR 0.82, 95% CI 0.65 to 1.01) ↑ Local tumor control (HR 0.27, 95% CI 0.14 to 0.52)
KQ2: Moderate	↔ Acute and late toxicities
KQ3: Low	Single brain metastasis and RPA Class 1 ↑ Median survival (single brain mets, 6.5 vs 4.9 months; RPA Class 1, 11.6 vs 9.6 months) ↑ Local tumor control ↓ Worsened PS at 6 months

Brain Metastases – SRS vs WBRT

Overall evidence base

- 1 good quality SR (Linskey 2010)
  - No RCTs
  - 6 cohort studies
    - 1 fair quality prospective cohort (Li 2000)
    - 3 retrospective cohort with concurrent controls (Rades 2007 – fair quality; Wang 2002 – fair quality; Lee 2008 – poor quality)
    - 2 poor quality retrospective cohort with historical controls (Kocher 2004; Datta 2004)

Brain Metastases – SRS vs WBRT

Strength of Evidence	Findings
KQ1: Low	↑ Overall survival (narrative summary of 4 cohort studies)
KQ2: Low	↔ Acute and late toxicities
KQ3: None	No studies

Brain Metastases – SRS for Recurrent or Progressive Metastases

Overall evidence base

- 1 good quality SR (Ammirati 2009)
  - No RCTs
  - No comparative studies
  - 12 small case series (n = 12 to 54)
- Harms were inconsistent

Brain Metastases – KQ 4 Economic Studies

- 1 fair quality SR (Chang 2011b) identified
  - 2 poor quality economic studies addressed the various comparisons of SRS and WBRT
  - All studies took the perspective of the healthcare system
  - There was great uncertainty in any estimates of cost-effectiveness for SRS due to assumptions in the models

Brain Metastases – KQ 4 Economic Studies

Strength of Evidence	Findings
KQ4: Very low	**SRS alone is more cost-effective than WBRT alone or in combination with SRS**
SRS+WBRT vs. WBRT	ICER: $12,289 Incremental QALY: $10,753
SRS vs. WBRT	$17,622/QALY (SRS) vs $10,381/QALY (WBRT)

Glioblastoma (Multiforme)

Overall evidence base

- 1 RCT, 2 cohorts, 3 case series
  - Souhami (2004), fair quality RCT
    - 203 adults, newly diagnosed tumors ≤ 4 cm, good PS (KPS ≥ 60)
    - SRS followed by EBRT+carmustine versus EBRT+carmustine
  - Cohort studies
    - Nwokedi (2002), poor quality , n=64 newly diagnosed
    - Kong (2008), poor quality, n=114 with recurrent disease

Glioblastoma (Multiforme)

Strength of Evidence	Findings
KQ1: Low	↔ Overall survival ↔ QoL
KQ2: Low	↑ Symptomatic radionecrosis (3% - 5%), sometimes leading to surgery
KQ3: None	No studies
KQ4: None	No studies

Glioma

- Background
  - Most common primary tumor of the brain
  - Classified by histology (e.g. astrocytes) and pathologic grade (low vs. high)
- *Overall evidence base*
  - 1 cohort, poor quality
    - 114 patients with recurrent malignant glioma treated with salvage SRS, 360 historical controls
  - 8 case series (1 fair, 7 poor quality)
    - Marcus (2005), prospective CS, n=50 pediatric patients, progressive low grade glioma

Glioma

Strength of Evidence	Findings
KQ1: Very low	↕ Median survival
KQ2: Very low	Symptomatic radionecrosis, occasionally leading to surgery for mass effect
KQ3: Very low (*Peds only*, Marcus 2005)	OS 98% at 5 years and 82% at 8 years 4% progressed to anaplastic astrocytoma, 8% developed Moya Moya syndrome (CVA & seizures)
KQ4: None	No studies

Pituitary Adenoma

Overall evidence base

- 2 cohort, 13 case series
  - Cohort studies
    - Kong (2007), fair quality
      - 125 patients with primary pituitary adenoma
    - Puataweepong (2009), poor quality
      - 72 patients primary & recurrent pituitary adenomas
  - Case series (4 fair and 9 poor quality)

Pituitary Adenoma

Strength of Evidence	Findings
KQ1: Low	↔ Overall survival ↔ Local tumor control
KQ2: Very low	↓ New hypopituitarism (61% vs 72%, p=NR) Headache, nausea, fatigue, edema visual deficits, cranial nerve palsies
KQ3: None	No studies
KQ4: None	No studies

Head and Neck

Overall evidence base

- 1 cohort, poor quality (Ozygit 2011)
  - 51 patients with primary or recurrent nasopharyngeal carcinoma
- 6 case series, poor quality
  - 3 CS – patients with primary & recurrent nasopharyngeal carcinoma
  - 2 CS – patients with squamous cell carcinoma of the H&N
  - 1 CS – patients with various cancers

Head and Neck

Strength of Evidence	Findings*
KQ1: Very low	↔ Overall survival ↔ Local tumor control
KQ2: Very low	↓ Serious (≥ Grade 3) late complications (20% vs. 48%, p = 0.04) including death, cranial neuropathy, carotid blow out, radionecrosis, trismus, xerostomia
KQ3: None	No studies
KQ4: None	No studies

*primarily nasopharyngeal carcinoma

Lung Cancer – NSCLC

- Background
  - 3- to 5-year survival with surgical resection estimated up to 60% to 80% depending on tumor size
  - 5-year survival with EBRT estimated 15% to 30%
- *Overall evidence base*
  - 1 poor quality SR (Chi 2010) included 35 CS of pts with inoperable Stage I NSCLC
  - 33 additional CS
- Majority of studies focused on patients with inoperable Stage 1 NSCLC

Lung Cancer – Inoperable Stage 1 NSCLC

Strength of Evidence	Findings
KQ1: Very low	3-year overall survival (38% to 59%) 5-year overall survival (45%)* OS, Stage 1A (tumor ≤ 3 cm) better than Stage 1B
KQ2: Very low	Serious acute toxicities (range, 2% to 5%) Late toxicities (fatigue, pneumonitis, esophagitis, dermatitis, and chest wall pain) (2% to 10%)
KQ3: None	No studies
KQ4: Very low	↕ Cost and cost-effectiveness

* 5-yr survival with EBRT for inoperable Stage I NSCLC estimated 15% to 30%

Spine Cancer

Overall evidence base

- 1 fair quality SR (29 case series), 13 CS, 1 poor quality economic study

Strength of Evidence	Findings
KQ1: Very low	Local tumor control, pain control, QoL
KQ2: Very low	Esophagitis, nausea, spinal fractures, neurologic complications
KQ3: None	No studies
KQ4: Very low	SBRT costs > EBRT costs

Abdominal, Primary Brain, H&N (Glomus Jugulare, Ocular), Prostate

- All studies identified for these cancers and tumors are case series
  - Case series were predominately poor and fair quality
- Only one fair quality CS focused on children (Kano 2010)
  - 21 children (mean age, 7 years) who had resection and SRS for ependymomas
  - Median survival after SRS was 27.6 months (95% CI, 12 to 36 months)
  - 1-year OS was 85%, 2-year OS was 53%, and 3-year was 23%

MAUDE Database

- Manufacturers and Users Device Experience at FDA (MAUDE Database)
- Three reports of serious adverse events
  - Two patient deaths, one from metastatic lung and one from metastatic stomach cancer
  - One patient had a portal vein thrombosis and hepatic artery occlusion

Guidelines

- 16 guidelines were identified related to SRS or SBRT
  - 1 *good quality* – ACN (2008) [primary melanoma]
  - 2 *fair quality* – Scott [ACCP] (2007) [stage I/II NCSLC]; Tsao [ASTRO] (2012) [brain metastases]
  - 13 *poor quality*
    - IRSA (2008) [brain metastases]
    - All NCCN guidelines - Several attempts via phone and email to identify methods
- 11 ACR Appropriateness Criteria® were identified
  - *All Appropriateness Criteria® rated as fair quality*
- Recommendations varied by malignancy

Guidelines

Usually Not Appropriate / Not Recommended	May be Appropriate	Usually Appropriate/Recommended
Bone Metastases (ACR)	Brain Metastases (ACR, Ammirati, ASTRO)	Brain Metastases (IRSA, NCCN)
Brain Metastases (ACR)	Brain Metastases from Thyroid Cancer (American Thyroid Association)	Brain Metastases from Thyroid Cancer (NCCN)
Colon Cancer (NCCN)	Hepatocellular Carcinoma (NCCN)	
Low Grade Glioma (NCCN)	Melanoma (ACN)	
Non-spinal Bone Metastases (ACR)	Meningioma (NCCN)	
Pancreatic Adenocarcinoma (NCCN)	Metastatic Spinal Cancer (NCCN)	
Prostate Cancer (ACR)	Recurrent Head and Neck Cancer (ACR)	
Rectal Cancer (NCCN)	Soft Tissue Sarcoma (NCCN)	
Recurrent Rectal Cancer (ACR)	Stage I NSCLC (ACR) Stage I/II NSCLC (ACCP) Stage I Lung Cancer (NCCN)	
Stage I NSCLC (ACR)		

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Policies

- No NCDs
- Two regional LCDs are pertinent to Washington
  - L30318 (2011); L28366 (2011)
- L30318 (2011) covers SRS/SRT for intracranial tumors
  - Tumor has image-distinct margin
  - Hard to reach, unusual shape, near vital structure
  - Five or fewer metastases
  - Patient has a good PS (KPS > 50% or ECOG PS $\leq$ 2)
  - As boost treatment for larger lesions treated with WBRT or surgery, acoustic neuromas, pituitary adenomas, craniopharyngiomas, and glomus jugulare tumors

Policies

- L28366 (2011) covers SBRT for tumors of the lung, liver, kidney, pancreas and low/intermediate risk prostate cancer
  - aggressive treatment is justified
  - other forms of radiotherapy or focal therapy cannot be as safely or effectively utilized
  - the tumor can be targeted with acceptable risk to surrounding critical structures
  - the patient had previous radiotherapy to the same or adjacent sites
  - for germ cell and lymphoma, effective chemotherapy regimens have been exhausted or not feasible

Policies

- L28366 (2011) explicitly *does not cover* SBRT under the following conditions
  - treatment is unlikely to result in clinical cancer control and/or functional improvement
  - when there is wide-spread cerebral or extra-cranial metastases
  - the patient has a poor PS
  - Lesions of other sites (bone, breast, uterus, ovary, and other internal organs) are generally not covered, but may be in cases of recurrence after conventional EBRT

Overall Summary

Brain Metastases	Moderate SOE	Low SOE
SRS+WBRT vs WBRT	↔ Overall survival ↑ Local tumor control ↔ Acute and late toxicities (WBRT dose adjusted with SRS)	*For single metastasis and RPA Class 1*: ↑ Median survival ↑ Local tumor control ↓ Worsened PS at 6 months
SRS vs WBRT		↑ Overall survival ↔ Acute and late toxicities (harms)

Overall Summary

- **Glioblastoma** (SRS vs WBRT)
  - *Low* SOE
    ↔ Overall survival
    Symptomatic radionecrosis (3% to 5%), occasionally leading to surgery
- **Glioma** (SRS vs WBRT)
  - *Very low* SOE for all outcomes
- **Pituitary adenoma**
  - *Low* SOE
    ↔ Overall survival
    ↔ Local tumor control

Overall Summary

- **Head and Neck** (nasopharyngeal carcinoma)
  - *Very low* SOE for all outcomes
- **Inoperable Stage 1 NSCLC** (SBRT)
  - *Very low* SOE (no comparative studies)
    3-year overall survival (38% to 59%)
    5-year overall survival (45%)
    OS, Stage 1A (tumor ≤ 3 cm) better than Stage 1B
    Serious acute toxicities (2% to 5%), late toxicities (2% to 10%)
- **Spine** (SRS)
  - *Very low* SOE for all outcomes

Overall Summary

- All studies for the following tumors are case series yielding *very low SOE*
  - Abdominal (adrenal, colorectal, liver, pancreatic)
  - Primary brain tumors (astrocytomas, ependymomas, menningiomas, neurocytomas, schwannomas, multiple CNS tumors)
  - Glomus jugulare
  - Ocular
  - Prostate

Limitations of the Evidence

- Limited number of comparative studies (RCT and cohort)
- Many studies did not adjust for confounding variables
  - Other treatments (surgery, chemotherapy)
  - patient age
  - tumor stage
  - change in standards of care over time
  - radiation dose
- Vast majority of studies were case series with small sample sizes

Questions and comments?

OREGON HEALTH & SCIENCE UNIVERSITY

Stereotactic Radiosurgery (SRS) and Body Radiation Therapy (SBRT) – Additional Slides

Presented by: Martha Gerrity MD, MPH, PhD
Date: November 16, 2012

Background – SRS/SRT and SBRT

- Stereotactic radiosurgery (*SRS*) developed in the 1950s to treat inoperable brain tumors
  - Goal: deliver a *single, highly focused, high dose* of radiation while sparing the normal surrounding tissue
  - Photon beam radiation is used, but at much higher doses (e.g., 14 – 24 Gy) than conventional EBRT (e.g., 1.8 - 2.0 Gy per fraction/dose)
- Stereotactic radiotherapy (*SRT*) is 2 – 5 fractions
- In the 1990s, researchers began using SRT for cancers outside the CNS (*SBRT*)

Forrest Plot from Patil 2009: Overall Survival

Analysis 1.1. Comparison 1 WBRT plus Radiosurgery versus WBRT, Outcome 1 Overall Survival.

Review: Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases

Comparison: 1 WBRT plus Radiosurgery versus WBRT

Outcome: 1 Overall Survival

Study or subgroup	WBRT + SRS N	WBRT N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Andrews 2004	164	167	-0.18 (0.12)		92.8 %	0.84 [0.66, 1.06]
Kondziolka 1999	13	14	-0.52 (0.43)		7.2 %	0.59 [0.26, 1.38]
Total (95% CI)					**100.0 %**	**0.82 [0.65, 1.02]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0.0\%$

Test for overall effect: Z = 1.77 (P = 0.077)

0.2 0.5 1 2 5

Favours WBRT+SRS Favours WBRT

Absolute reduction 70 per 1000 (155 to -7)

Brain Metastases – SRS+WBRT vs SRS

Overall evidence base

- 2 good quality SRs identified 3 RCTs
  - RCTs
    - Aoyama (2006), good quality
      - 132 adults, 1 – 4 metastases, good PS
    - Chang (2009b), fair quality
      - 58 adults, 1 – 3 metastases, good PS
    - Kocher (2010), fair quality
      - 359 adults, 1 – 3 metastases, good PS

Brain Metastases – SRS+WBRT vs SRS

Strength of Evidence	Findings
KQ1: Moderate	↔ OS (HR 0.98, 95% CI 0.71 to 1.35) ↑ Local tumor control (HR 2.61, 95% CI 1.68 to 4.06) ↑ Distant tumor control (HR 2.15, 95% CI 1.55 to 2.99)
KQ1: Low	↔ QoL ↔ Functional independence ↔ Time to worsened performance status
KQ2: Low	↔ Acute and late toxicities
KQ3: None	No studies

Brain Metastases – KQ 4 Economic Studies

Strength of Evidence	Findings
KQ4: Very low	**SRS alone is more cost-effective than WBRT alone or in combination with SRS**
SRS+WBRT vs. WBRT	ICER: $12,289 Incremental QALY: $10,753
SRS vs. SRS+WBRT	ICER: $44,231 Incremental QALY: $41,783
SRS vs. WBRT	$17,622/QALY (SRS) vs $10,381/QALY (WBRT)