Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy: An Evidence Update

Evidence Update for the Washington State Health Technology Assessment Program

January 2017

Center for Evidence-based Policy
Oregon Health & Science University
3030 SW Moody, Suite 250
Portland, OR 97201
Phone: 503.494.2182
Fax: 503.494.3807
www.ohsu.edu/policycenter
# Table of Contents

- Bottom Line Conclusion .................................................................................................................. 1
- Background ...................................................................................................................................... 1
- Methods .......................................................................................................................................... 1
  - PICO ........................................................................................................................................... 2
  - Key Questions .......................................................................................................................... 2
- Findings ........................................................................................................................................... 3
  - Brain Cancer ............................................................................................................................... 4
  - Non-Small-Cell Lung Cancer (NSCLC) ...................................................................................... 5
  - Prostate Cancer .......................................................................................................................... 5
  - Pancreatic Cancer ....................................................................................................................... 7
  - Liver Cancer ............................................................................................................................... 7
  - Spinal Cancers ............................................................................................................................ 7
  - Adrenal Cancer ........................................................................................................................... 8
- References ....................................................................................................................................... 9
- Appendix A. Search Strategies .......................................................................................................... 20
  - EBM Reviews: Cochrane Central Register of Controlled Trials and EBM Reviews: Cochrane Database of Systematic Reviews .................................................................................. 20
  - Ovid MEDLINE® ....................................................................................................................... 20
- Appendix B. Excluded Studies .......................................................................................................... 22
**Bottom Line Conclusion**
A review of the studies published since the original evidence review conducted in March 2012 does not provide sufficient evidence to amend the current coverage policy for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT), as adopted by the Health Technology Clinical Committee in March 2013. The current review did not find sufficient evidence to indicate that SRS or SBRT is an effective treatment for any cancer that is not already included in the coverage policy. Likewise, there is not sufficient evidence to indicate that SRS or SBRT are ineffective for the cancers that are currently covered.

**Background**
The Washington State Health Technology Clinical Committee completed an evidence review in 2012 on the effectiveness of SRS and SBRT for treating various cancers. On March 22, 2013, the committee adopted the following coverage determination:

- SRS for central nervous system (CNS) primary and metastatic tumors is a covered benefit for adults and children when the following criteria are met:
  - Patient functional status score (i.e., Karnofsky score) is greater than or equal to 50; and
  - Evaluation includes multidisciplinary team analysis (e.g., tumor board), including surgical input.

- SBRT is covered for adults and children for the following conditions when the following criteria are met:
  - For cancers of spine/paraspinal structures: or
  - For inoperable non-small cell lung cancer, stage 1; and
  - Evaluation includes multidisciplinary team analysis (e.g., tumor board), including surgical input.

The Washington Health Technology Assessment program contracted with the Center for Evidence-based Policy (Center) to conduct an updated evidence search on this topic and produce a brief on the included eligible studies to help determine whether the previous coverage policy decision should be reviewed.

**Methods**
To identify studies published since the 2012 evidence review, Center researchers conducted a literature search using Ovid MEDLINE®, Cochrane Database of Systematic Reviews, and Cochrane Controlled Trials Register database. The search strategies for each database are in Appendix A.

Studies were included if they met the criteria outlined in the PICO below and the following inclusion criteria by location of tumor for individual studies:

- Treatments delivered in 10 or fewer fractions
• Published, peer-reviewed, English-language articles
• Systematic reviews, technology assessments, randomized controlled trials (RCTs), and non-randomized, comparative study designs (prospective, retrospective, and controlled clinical trials)

The following are additional inclusion criteria for individual studies specifically:
• Eligible study design with a minimum sample size of 20 participants for CNS cancers
• Eligible study design with a minimum sample size of 50 participants for cancers of the breast, colon, head and neck, lung, and prostate
• Eligible study design with a minimum sample size of 20 participants for other non-CNS cancers
• All relevant economic evaluations, cost-effectiveness analyses, and economic simulation models

For interpretation of findings from economic analyses, Center researchers used the generally accepted willingness to pay threshold of $100,000 per quality-adjusted life-year (QALY) (Neumann, Cohen, & Weinstein, 2014).

PICO

Populations:
Adults and children with CNS and non-CNS malignancies for which treatment with radiation therapy is appropriate

Interventions:
SRS or SBRT with devices such as Gamma Knife®, CyberKnife®, TomoTherapy®

Comparators:
Conventional (conformal) external beam radiation therapy (EBRT), surgery, no treatment

Outcomes:
Survival rate, duration of symptom-free remission, quality of life, harms including radiation exposure and complications, cost, cost-effectiveness

Key Questions
1. What is the evidence of effectiveness for SRS and SBRT compared to conventional EBRT for the following patients:
   a. Patients with CNS tumors?
   b. Patients with non-CNS cancers?

2. What are the potential harms of SRS and SBRT compared to conventional EBRT? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.
3. What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations? Include consideration of the following characteristics:
   a. Gender
   b. Age
   c. Site and type of cancer
   d. Stage and grade of cancer
   e. Setting, provider characteristics, equipment, quality assurance standards and procedures

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

**Findings**

After de-duplication, 1,968 documents were found in the searches, including 1,808 from Ovid MEDLINE®, 139 from Cochrane Central Register of Controlled Trials, and 21 from Cochrane Database of Systematic Reviews. After title and abstract screening by CM and VK, out of the 1,968 documents, 154 were identified for full-text review. After full-text review, CM and VK determined that 83 studies were eligible for this evidence update (Figure 1). Table 1 shows the number of included articles by cancer and type of study.
Table 1: Number of Included Articles by Cancer and Type of Study

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Total</th>
<th>Systematic Reviews &amp; Meta-Analysis</th>
<th>Randomized Controlled Studies</th>
<th>Comparative and Other Studies</th>
<th>Cost-Effectiveness Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Cancer</td>
<td>31</td>
<td>8</td>
<td>6</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Non-Small-Cell Lung Cancer</td>
<td>29</td>
<td>5</td>
<td>2</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Liver Cancer</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Spinal Cancer</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Adrenal Cancer</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cancers with single comparative study</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>7*</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>83</td>
<td>16</td>
<td>8</td>
<td>53</td>
<td>6</td>
</tr>
</tbody>
</table>

*Single comparative studies were identified for each of these seven cancers: cervical (Gill et al., 2014), extracranial oligometastases (Kao, Timmins, Ozao-Choy, & Packer, 2016), juxtapapillary choroidal melanoma (Krema et al., 2013), oropharyngeal (Al-Mamgani et al., 2013), pulmonary metastases from osteosarcoma (W. Yu et al., 2014), recurrent atypical meningiomas (Talacchi et al., 2016), and malignancy anywhere in the body after SRS (Rahman et al., 2014).

**Brain Cancer**

There is some additional evidence to support the conclusion that SRS is an effective treatment for brain cancer. The most recent systematic review is an update to the Cochrane systematic review that examined SRS plus whole brain radiation therapy (WBRT) versus WBRT alone for the treatment of brain metastases (Patil et al., 2016). The authors conducted meta-analyses for overall survival, median survival, and local failure using two trials with a total of 358 participants. Patil et al. (2016) found a non-significant reduction in overall survival in the SRS+WBRT group compared to the WBRT group, although the difference between groups was close to statistical significance (hazard ratio [HR], 0.82, 95% confidence interval [CI], 0.65 to 1.02; p = .08). For patients with one brain metastasis, median survival was significantly longer in SRS+WBRT compared to WBRT alone (6.5 months vs. 4.9 months; p = .04) (Patil et al., 2016). Patients in the SRS+WBRT group had decreased local failure compared to patients who received WBRT alone (HR, 0.27; 95% CI, 0.14 to 0.52; p < .0001) (Patil et al., 2016).

Center researchers identified 30 other studies on brain cancer that met inclusion criteria. Of the 30, seven were systematic reviews (Cage et al., 2013; Elaimy et al., 2013; Gans et al., 2013; Goyal et al., 2015; Patil et al., 2012; Y. Y. Soon, Tham, Lim, Koh, & Lu, 2014; Yang Yu Soon, Tham, Lim, Koh, & Lu, 2016); six were RCTs (Aoyama, Tago, & Shirato, 2015; El Gantery, Abd El Baky, El Hussieny, Mahmoud, & Youssef, 2014; El Gantery, El Baky, El Hussieny, Mahmoud, & Youssef,
Non-Small-Cell Lung Cancer (NSCLC)
There is some additional evidence to support the conclusion that SBRT is an effective treatment for NSCLC. The most recent systematic review concluded that use of SBRT has the possibility of improved local control and overall survival compared to historical controls (Jones et al., 2015).

Center researchers found insufficient evidence to conclude that SBRT is effective for treating operable NSCLC. A meta-analysis of six studies (n = 864 matched patients) found a superior three-year overall survival rate after surgery compared with SBRT (odds ratio [OR], 1.82; 95% CI, 1.38 to 2.40; p < .0001) (Zhang et al., 2014). There is one small RCT (n=22) of stereotactic ablative radiotherapy (SABR) compared to surgery in patients with operable stage I NSCLC. In this trial, six patients in the surgery group died compared to one patient in the SABR group. The estimated overall survival percentage at three years was 95% (95% CI, 85% to 100%) in the SABR group compared with 79% (95% CI, 64% to 97%) in the surgery group (HR, 0.14; 95% CI, 0.017 to 1.190; log-rank p = .04) (J. Y. Chang et al., 2015). Another article on the same RCT found that global health-related quality of life and indirect costs were significantly more favorable and less expensive with SABR compared to surgery (Louie et al., 2015).

Center researchers identified 30 other studies on brain cancer that met inclusion criteria. Of the 30, three were systematic reviews (Bilal, Mahmood, Rajashanker, & Shah, 2012; Solda et al., 2013; Zheng et al., 2014); 21 were comparative studies (Chiang et al., 2016; T. Crabtree et al., 2013; T. D. Crabtree et al., 2014; Ezer et al., 2015; Hamaji et al., 2015; Kastelijn et al., 2015; Koshy, Malik, Mahmood, Husain, & Sher, 2015; Lucas et al., 2014; Matsuo et al., 2014; Mokhles et al., 2015a; Mokhles et al., 2015b; Nakagawa, Negoro, Matsuoka, Okumura, & Dodo, 2014; Nanda et al., 2015; Parashar et al., 2015; Puri et al., 2015; Robinson et al., 2013; Shaverdian, Wang, Steinberg, & Lee, 2015; Shirvani et al., 2014; Shirvani et al., 2012; van den Berg, Klinkenberg, Groen, & Widder, 2015; Varlotto et al., 2013); one was a cost-effectiveness study (Shah et al., 2013); and there were no other RCTs.

Prostate Cancer
Center researchers found insufficient evidence to indicate that SBRT is an effective treatment for prostate cancer. One systematic review of case series looked at outcomes from SBRT and included 14 studies with a total of 1472 patients (Tan, Siva, Foroudi, & Gill, 2014).
Five comparative studies were identified: one study analyzed PSA slope (Anwar et al., 2014); one examined genitourinary toxicity (J. B. Yu et al., 2014); and the other three assessed patient quality of life outcomes (Evans et al., 2015; Helou et al., 2014; Katz, Ferrer, Suarez, & Multicentric Spanish Group of Clinically Localized Prostate Cancer, 2012).

- One study (n = 75) compared SBRT to conventionally fractionated EBRT for patients with low to low-intermediate risk prostate cancer. The PSA slope for SBRT was significantly greater than conventionally fractionated EBRT (p < .05) at two and three years after treatment, although the PSA slopes for the two groups were similar during the first year (Anwar et al., 2014).

- SBRT was compared to intensity-modulated radiation therapy (IMRT) among a national sample of Medicare beneficiaries with prostate cancer in one study (n = 4,005). Genitourinary toxicity was significantly higher in the SBRT group compared to IMRT group at six and 24 months after treatment (15.6% vs. 12.6%; OR, 1.29; 95% CI; 1.05 to 1.53; p = 0.009 and 43.9% vs. 36.3%; OR, 1.38; 95% CI, 1.12 to 1.63; p = .001, respectively) (J. B. Yu et al., 2014).

- One study (n = 803) included a multi-institutional pooled cohort analysis of patient-reported quality of life before and after IMRT, brachytherapy, or SBRT for localized prostate cancer. In a multivariate analysis, quality of life outcomes were not significantly different between the SBRT and IMRT groups in the urinary irritation or obstruction (p = .55), urinary incontinence (p = .74), and sexual domains (p = .57), but SBRT was associated with a better bowel score (+6.7 points; p < .0002) (Evans et al., 2015).

- SABR was compared to high-dose rate brachytherapy plus hypofractionated EBRT in a study (n = 207) that investigated quality of life in patients treated for localized prostate cancer. For the percentage of patients with a minimally clinical important change, SABR had significantly better quality of life outcomes in urinary function and bother (p < .0001), bowel function (p = .02), and sexual function (p = .04) and bother (p = .03) (Helou et al., 2014).

- Another study (n=339) assessed quality of life in patients treated for clinically localized prostate cancer with SBRT or radical prostatectomy. The largest differences in quality of life occurred in the first six months after treatment. There were larger declines in the surgery group compared to SBRT in urinary and sexual quality of life, and a larger decline in SBRT compared to surgery for bowel quality of life (Katz et al., 2012).

A cost-effectiveness study analyzed SBRT compared to IMRT for low-risk prostate cancer. The incremental cost-effectiveness ratios for IMRT over robotic SBRT and non-robotic BRT were $285,000 and $591,100 per QALY gained, respectively, making both significantly above the generally accepted willingness to pay threshold (Sher, Parikh, Mays-Jackson, & Punglia, 2014).
**Pancreatic Cancer**

Center researchers found insufficient evidence to indicate that SBRT is an effective treatment for pancreatic cancer. In one systematic review of case series of pancreatic cancer treated with robotic radiosurgery, the authors concluded that the outcomes of SBRT were similar to the outcomes in previous studies of chemo-radiation with conventional fractionation. (Buwenge et al., 2015). A comparative study (n = 41) of SBRT and IMRT for patients with locally advanced unresectable pancreatic cancer found no significant difference in overall survival between the two therapies, although SBRT showed significantly better local disease-free survival than IMRT (p = .004) (J. C. Lin, Jen, Li, Chao, & Tsai, 2015).

**Liver Cancer**

Center researchers found insufficient evidence to indicate that SBRT is an effective treatment for liver cancer. Three comparative studies were found:

- One study (n = 224) compared SBRT to radiofrequency ablation for inoperable, nonmetastatic hepatocellular carcinoma. Overall survival rates for SBRT compared to radiofrequency ablation were not significantly different at one year (74% vs. 70%) or two years (46% vs. 53%) (Wahl et al., 2016).
- SBRT was compared to selective internal radiotherapy in one study (n = 189) of hepatocellular carcinoma. After adjusting for confounding factors, there was no significant difference in overall survival (HR, 0.72; 95% CI, 0.49 to 1.07; p = .11) for selective internal radiotherapy compared to SBRT (Oladeru et al., 2016).
- One study (n = 365) compared SBRT combined with transcatheter arterial chemoembolization (TACE) to TACE alone for small, solitary, hypervascular hepatocellular carcinoma. Disease-free survival time of the 12 patients without previous treatments in the SBRT group was significantly higher than that of the TACE-alone group (15.7 months vs. 4.2 months; p = .03) (Honda et al., 2013).

**Spinal Cancers**

Center researchers found insufficient evidence to indicate that SRS is an effective treatment for spinal cancers. No studies were identified related to primary cancers of the spine. Center researchers found three studies (two comparative, one cost-effectiveness) related to spinal metastases. The two comparative studies showed a benefit of SRS for spinal metastases:

- Among patients treated for spinal metastasis from hepatocellular carcinoma, overall survival was significantly greater in those treated (n = 27) with SRS compared to those treated with conventional radiation therapy (n = 32) (7 months vs. 3 months; p = .035) (U. K. Chang, Kim, Han, & Lee, 2014).
- In a matched-pair comparative study (n = 13 pairs) of patients treated for spinal metastasis from renal cell carcinoma, patients were followed for six months, and there was significantly greater progression-free survival for those treated with SRS compared to those treated with external radiation therapy (p = .01) (Sohn et al., 2014).
The cost-effectiveness study of palliation of vertebral bone metastases showed that the incremental cost-effectiveness ratio for SBRT was $124,552 per QALY gained, which is greater than the willingness to pay threshold (H. Kim, Rajagopalan, Beriwal, Huq, & Smith, 2015).

**Adrenal Cancer**
Center researchers found insufficient evidence to indicate that SABR is an effective treatment for adrenal cancer. One study on adrenal cancer was included: a systematic review of non-comparative studies of SABR for the treatment of adrenal metastases with a total of 1,047 patients. No statistical analyses were performed. The authors concluded that if therapy is in the patient’s interest, then surgery appears to be the best option and SABR is a reasonable alternative in inoperable patients (Gunjur, Duong, Ball, & Siva, 2014).
References


ependymomas. *Journal of Neurosurgery Pediatrics.*, 11(6), 673-681. DOI: [http://dx.doi.org/10.3171/2013.2.PEDS12345](http://dx.doi.org/10.3171/2013.2.PEDS12345)


Lin, J. C., Jen, Y. M., Li, M. H., Chao, H. L., & Tsai, J. T. (2015). Comparing outcomes of stereotactic body radiotherapy with intensity-modulated radiotherapy for patients with locally...


Soon, Y. Y., Tham, I. W., Lim, K. H., Koh, W. Y., & Lu, J. J. (2014). Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. *Cochrane Database of Systematic Reviews, 3*, CD009454. DOI: [http://dx.doi.org/10.1002/14651858.CD009454.pub2](http://dx.doi.org/10.1002/14651858.CD009454.pub2)


non-small cell lung cancer: A systematic review and meta-analysis. *Radiotherapy & Oncology, 112*(2), 250-255. DOI: [http://dx.doi.org/10.1016/j.radonc.2014.08.031](http://dx.doi.org/10.1016/j.radonc.2014.08.031)

Appendix A. Search Strategies

EBM Reviews: Cochrane Central Register of Controlled Trials and EBM Reviews: Cochrane Database of Systematic Reviews
2005 to December 07, 2016

Search Strategy:

1. radiosurg$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2. gamma knif$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3. (stereotac$ adj3 radiother$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4. 1 or 2 or 3
5. limit 4 to yr="2012 -Current"

Ovid MEDLINE®
1946 to November Week 5 2016

Search Strategy:

1. exp Radiosurgery/
2. limit 1 to (controlled clinical trial or meta analysis or practice guideline or randomized controlled trial)
3. exp Cohort Studies/
4. exp case-control studies/
5. 1 and 3
6. limit 5 to yr="2002 -Current"
7. 1 and 4
8. limit 7 to yr="2002 -Current"
9. limit 1 to systematic reviews
10. 2 or 9
11. 6 or 8 or 10
12. limit 11 to yr="2002 -Current"
limit 12 to english language

Comparative Study/

1 and 14

limit 15 to (english language and humans and yr="2002 -Current")

16 not 13

(2016$ or 2015$ or 2014$ or 2013$ or (2012$ not (201201$ or 201202$ or 201203$))).ed.

19 13 and 18

20 15 and 18

limit 20 to english language

22 19 or 21

animals/

humans/

25 23 not (23 and 24)

22 not 25
Appendix B. Excluded Studies
See attachment
About the Center for Evidence-based Policy and the Washington Health Technology Assessment program

The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring that diverse and relevant perspectives are considered and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

The primary purpose of the Washington State Health Technology Assessment program is to ensure medical treatments and services paid for with state health care dollars are safe and proven to work. The primary goals are to make:

- Health care safer by relying on scientific evidence and a committee of practicing clinicians;
- Coverage decisions of state agencies more consistent;
- State-purchased health care more cost-effective by paying for medical tools and procedures that are proven to work; and
- Coverage decision processes that are more open and inclusive by sharing information, holding public meetings, and publishing decision criteria and outcomes.