

# Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy: An Evidence Update

---

## Evidence Update

*June 10, 2022*

**Health Technology Assessment Program (HTA)**

Washington State Health Care Authority

PO Box 42712

Olympia, WA 98504-2712

(360) 725-5126

[www.hca.wa.gov/hta](http://www.hca.wa.gov/hta)

[shtap@hca.wa.gov](mailto:shtap@hca.wa.gov)

# Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy: An Evidence Update

---

Evidence Update

June 10, 2022

Prepared by:

Center for Evidence-based Policy  
Oregon Health & Science University  
3030 S Moody, Suite 250  
Portland, OR 97201  
Phone: 503.494.2182  
Fax: 503.494.3807

<http://centerforevidencebasedpolicy.org/>



**Authors:**

Megan Rushkin, MPH, Beth Shaw, MSc, Shannon Robalino, MSc, Valerie King, MD, MPH

The authors would also like to acknowledge Nicole Thompson, Erica Shaw, and Amanda Delzer Hill from the Center for Evidence-based Policy for their contributions to this work.

This evidence update report is based on research conducted by the Center for Evidence-based Policy (Center) under contract to the Washington State Health Care Authority (HCA). This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the authors, who are responsible for the content. These findings and conclusions do not necessarily represent the views of the Washington HCA and thus, no statement in this report shall be construed as an official position or policy of the HCA.

The information in this assessment is intended to assist health care decision makers, clinicians, patients, and policymakers in making evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

#### About the Center for Evidence-based Policy

The 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.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

## Table of Contents

Bottom Line.....	1
Background.....	1
Common Outcome Measures Reported in the Included Studies .....	1
Methods.....	2
PICO .....	3
Key Questions .....	4
Findings.....	4
Brain Cancer .....	4
Spinal Cancer.....	6
Lung Cancer.....	8
Pancreatic Cancer.....	15
Prostate Cancer.....	17
Liver Cancer.....	19
Head and Neck Cancer.....	31
Adrenal Cancer.....	32
Renal Cancer .....	32
Bone Cancer .....	34
Multiple Cancer Sites .....	36
Other Cancers.....	43
Ongoing Studies.....	43
Summary.....	43
References.....	44
Appendix A. Search Strategies.....	70
Ovid MEDLINE All.....	70
CENTRAL.....	71
Appendix B. Detailed Inclusion and Exclusion Criteria .....	72
Appendix C. Excluded Studies With Reasons.....	74
Appendix D. Ongoing Randomized Controlled Trials.....	82
Appendix E. Studies Included in the CADTH Systematic Review.....	94

## Bottom Line

This evidence update includes studies published since the original evidence review<sup>1</sup> conducted in 2012 that informed the coverage policy for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT), as adopted by the Washington State Health Technology Clinical Committee (HTCC) in March 2013. After summarizing the eligible studies in this evidence update, we have determined that the new studies may change the conclusions of the 2012 evidence report.

## Background

In 2012 the Washington State HTCC commissioned an evidence review on the effectiveness of SRS and SBRT for treating various cancers.<sup>1</sup> On March 22, 2013, using that evidence review to guide decision making, the committee adopted the following coverage determination<sup>2</sup>:

- 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 (NSCLC), stage 1; *and*
  - Evaluation includes multidisciplinary team analysis, including surgical input.
- All other indications are noncovered.

The Washington (WA) Health Technology Assessment (HTA) program contracted with the Center for Evidence-based Policy (Center) in 2016 and 2018 to conduct updated evidence searches on this topic and produce briefs on the included eligible studies to help determine whether the previous coverage policy decision should be reviewed. The Center completed these evidence updates in January 2017<sup>3</sup> and January 2019.<sup>4</sup> Based on the evidence updates, Washington State Health Care Authority did not find sufficient evidence to commission an updated full review on the topic at either time point. This document is the third evidence update, commissioned in October 2021. This evidence update is based on a search for studies published since the 2019 evidence update report search, and summarizes the findings of all relevant studies published since the 2012 full evidence review.

## Common Outcome Measures Reported in the Included Studies

In 2018, the US Food and Drug Administration (FDA) issued guidance on clinical trial endpoints for the approval and cancer drugs and biologics.<sup>5</sup> As part of the guidance, the FDA outlined the advantages and disadvantages of the key cancer outcomes measures (Table 1). The advantages and disadvantages of each outcome measure should be considered when assessing the impact of new studies on the existing coverage decision.

Table 1. Advantages and Disadvantages of Key Cancer Outcome Measures<sup>5</sup>

Outcome Measure	Advantages	Disadvantages
Overall survival	<ul style="list-style-type: none"> <li>• Easily and precisely measured</li> <li>• Generally based on objective and quantitative assessment</li> </ul>	<ul style="list-style-type: none"> <li>• May be affected by switch-over of control to treatment or subsequent therapies</li> <li>• Needs longer follow-up</li> <li>• Includes noncancer deaths</li> </ul>
Disease-free survival, event-free survival	<ul style="list-style-type: none"> <li>• Generally assessed earlier and with smaller sample size compared with survival studies</li> <li>• Generally based on objective and quantitative assessment</li> </ul>	<ul style="list-style-type: none"> <li>• Potentially subject to assessment bias, particularly in open-label studies</li> <li>• Definitions vary among studies</li> <li>• Balanced timing of assessments among treatment arms is critical</li> <li>• Includes noncancer deaths</li> </ul>
Progression-free survival, time to progression	<ul style="list-style-type: none"> <li>• Generally assessed earlier and with smaller sample size compared with survival studies</li> <li>• Measurement of stable disease included</li> <li>• Generally based on objective and quantitative assessment</li> </ul>	<ul style="list-style-type: none"> <li>• Potentially subject to assessment bias, particularly in open-label studies</li> <li>• Definitions vary among studies</li> <li>• Frequent radiological or other assessments</li> <li>• Balanced timing of assessments among treatment arms is critical</li> <li>• May not always correlate with survival</li> </ul>
Objective response rate	<ul style="list-style-type: none"> <li>• Generally assessed earlier and with smaller sample size compared with survival studies</li> <li>• Effect on tumor attributable to drug(s) or other treatment, not natural history</li> <li>• Generally based on objective and quantitative assessment</li> </ul>	<ul style="list-style-type: none"> <li>• Definitions vary among studies</li> <li>• Frequent radiological or other assessments</li> <li>• May not always correlate with survival</li> </ul>
Complete response rate	<ul style="list-style-type: none"> <li>• Generally assessed earlier and with smaller sample size compared with survival studies</li> <li>• Effect on tumor attributable to drug(s) or other treatment, not natural history</li> <li>• Generally based on objective and quantitative assessment</li> </ul>	<ul style="list-style-type: none"> <li>• Definitions vary among studies</li> <li>• Frequent radiological or other assessments</li> <li>• May not always correlate with survival</li> </ul>

Source. Adapted from the US Food and Drug Administration guidance for industry on cancer approval endpoints.<sup>5</sup>

## Methods

To identify studies published since the 2019 evidence update, we conducted updated searches of Ovid MEDLINE All, Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register database (from September 2018 through December 2021). We updated the search strategies used in previous reports, to reflect newer searching methods and to improve the efficiency of the strategies (Appendix A). We also searched the ScanMedicine registry for upcoming and ongoing studies that would likely be included in an updated evidence review.

Our approach to screening and reviewing eligible studies was as follows:

- We screened the retrieved references and ongoing study records against the inclusion criteria (Appendix B)

- We assessed the likelihood, by indication, of recent evidence triggering an update to the 2012 coverage determination for SRS and SBRT
- If there was sufficient evidence to support updating the 2012 decision, we discontinued the review of the literature and reported our findings to the WA HTA team and the Agency Medical Directors

We summarized the findings of any eligible published systematic reviews and health technology assessments in the following manner. If there were 2 or more comparable reviews identified and 1 is more recent or more comprehensive, then the other review(s) was not summarized, and the rationale for selection was documented in the evidence update. We also summarized eligible randomized controlled trials (RCTs) when the results of the RCT differed from the conclusion of a systematic review. If there were fewer than 2 systematic reviews identified for an intervention, then all individual eligible primary studies, including comparative observational studies, were summarized.

We reported harms from eligible noncomparative observational studies, if they were not already included in a systematic review. We did not assess the risk of bias of the eligible reviews or primary studies.

We reported a narrative description of the search results along with key study characteristics of the included reviews and primary studies:

- The number of studies included (for systematic reviews) and number of participants (for all study designs)
- The intervention studied
- Comparators to the intervention
- Relevant outcomes reported in the publication

We also highlighted any discrepancies and differences across systematic reviews and individual primary studies.

For each indication, we provided an overall assessment of the evidence of effectiveness and harms and its potential impact on the 2012 coverage decision. No policy recommendations were made, but we noted policy considerations raised by the evidence. The summary assessment will provide the WA HTA team and the Agency Medical Directors with information about whether there is new evidence that may warrant a reconsideration of the existing coverage policy.

## PICO

Appendix B provides detailed inclusion and exclusion criteria used to guide the selection of eligible studies.

### Populations

- Adults and children with CNS and non-CNS malignancies where treatment by 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

- KQ1. What is the evidence of effectiveness for SRS and SBRT for the following patients:
- a. Patients with CNS tumors
  - b. Patients with non-CNS cancers?
- KQ2. What are the potential harms of SRS and SBRT? What is the incidence of these harms? This includes consideration of progression of treatment in unnecessary or inappropriate ways.
- KQ3. What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations, including differences by:
- a. Sex
  - b. Age
  - c. Site and type of cancer
  - d. Stage and grade of cancer
  - e. Setting, provider characteristics, equipment, quality assurance standards and procedures
- KQ4. What is the evidence of cost and cost-effectiveness of SRS and SBRT?

## Findings

We identified 1,869 unique publications in our updated searches, with 140 articles screened at the full-text stage. Of these, 57 studies reported in 59 publications were eligible for inclusion in this report.<sup>6-64</sup> The list of studies excluded at the full-text level, with exclusion reasons, is in Appendix C.

## Brain Cancer

### History

In 2013, the HTCC adopted the following coverage determination for brain cancers:

- SRS for CNS primary and metastatic tumors is a covered benefit for adults and children when the following criteria are met<sup>2</sup>:
  - 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.

In the 2017 evidence update, 7 systematic reviews,<sup>65-71</sup> 6 RCTs,<sup>72-77</sup> and 14 comparative nonrandomized studies<sup>78-91</sup> were identified. Three economic studies were also identified at that time.<sup>92-94</sup> The evidence update concluded that there was additional evidence to support the prior HTCC conclusion that SRS is an effective treatment for brain cancer.<sup>3</sup>

In the 2019 evidence update,<sup>4</sup> a further 27 primary studies and 2 systematic reviews were identified (2 systematic reviews,<sup>95,96</sup> 3 RCTs reported in 4 publications,<sup>97-100</sup> 23 comparative



observational studies,<sup>101-123</sup> and 1 review of economic studies<sup>124</sup>). The authors of the 2019 evidence update concluded that<sup>4</sup>:

- The identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review for brain cancer, because additional studies published since 2012 confirmed that survival rates for SRS were the same or improved compared to conventional radiotherapy without additional risk of harms.
- The identified new studies of economic outcomes were unlikely to change the conclusions of the 2012 evidence review for brain cancer because additional studies published since 2012 confirmed that SRS is cost-effective compared to conventional radiotherapy.

### Findings in This Evidence Update

Since the most recent evidence update report,<sup>4</sup> we identified 2 recently published RCTs on the effectiveness of SRS for cancers of the brain.<sup>14,15</sup>

- Bergman and colleagues<sup>15</sup> compared fractionated SRS in combination with bevacizumab-based chemotherapy with bevacizumab-based chemotherapy alone in 35 patients with high-grade glioma. The mean age of the patients was 51 years in the SRS and chemotherapy group and 59 in the chemotherapy-alone group.<sup>15</sup> The majority of participants were male: 82% in the SRS and chemotherapy group and 65% in the chemotherapy-alone group.<sup>15</sup> No race or ethnicity data were reported.<sup>15</sup> The RCT was conducted at a single institution in the US.<sup>15</sup>
- Kayama and colleagues<sup>14</sup> compared salvage SRS with whole-brain radiotherapy in 271 patients with brain metastases. The mean age of the patients was 63 years in the SRS group and 61 in the whole-brain radiotherapy group.<sup>14</sup> Both groups were well-balanced in terms of sex, with 49% of participants being male in the SRS group and 51% in the whole-brain radiotherapy group.<sup>14</sup> No race or ethnicity data were reported.<sup>14</sup> The RCT was conducted across 43 sites in Japan.<sup>14</sup>

We also identified 1 comparative observational study of SRS for people with brain cancer.<sup>16,125</sup>

- Alvarez-Pinzon and colleagues<sup>16</sup> evaluated the outcomes for 128 people with primary CNS lymphoma treated with SRS in combination with methotrexate or with methotrexate alone. The mean age of the participants was 57 years in the SRS group and 58 in the methotrexate group.<sup>16</sup> The proportion of male participants was 47% in each group.<sup>16</sup> No race or ethnicity data were reported.<sup>16</sup> The observational study analyzed data from patients enrolled in the Brain Tumor Registry study.<sup>16</sup>

We did not identify any economic studies of SBRT in brain cancer.

Table 2. Summary Characteristics of Included Studies of SRS for Brain Cancer

Study	Population	Description	Relevant Outcomes
Randomized controlled trials			
Bergman et al., 2020 <sup>15</sup>	Patients with bevacizumab-resistant recurrent malignant glioma	35 patients in total; 18 allocated to SRS in combination with chemotherapy and 35 to chemotherapy alone	• Safety
Kayama et al., 2018 <sup>14</sup>	Patients with brain metastases	271 patients in total; 134 allocated to SRS and 137 to whole-brain radiotherapy	• Safety

Study	Population	Description	Relevant Outcomes
Comparative observational studies			
Alvarez-Pinzon et al., 2021 <sup>16</sup>	Patients with primary central nervous system lymphoma	128 patients in total; 55 treated with SRS in combination with methotrexate and 73 with methotrexate alone	• Safety

Abbreviations. SRS: stereotactic radiosurgery.

### Effectiveness

Brain cancers are a covered indication, so we report only the harms from the 3 eligible studies.<sup>14-16</sup>

### Harms

Patients receiving treatment, including SRS, for brain cancer experienced toxicities; however, these were often mild. Across the 3 studies, 1 death was attributed to treatment (whole-brain radiotherapy).<sup>14-16</sup>

### Toxicity and Other Adverse Events

- Patients in the SRS in combination with chemotherapy and the chemotherapy alone group experienced toxicities attributable to treatment (6 grade 3 vs. 4 grade 3 toxicities).<sup>15</sup> No patient in either group experienced grade 4 or 5 toxicities.<sup>15</sup>
- Patients receiving SRS or whole-brain radiotherapy experienced few toxicities, with rates of grade 3 and hematologic toxicities of less than 5%.<sup>14</sup> Nonhematologic toxicity rates were 7.6% in the SRS group and 9.6% in the whole-brain radiotherapy group.<sup>14</sup> More people in the whole-brain radiotherapy group experienced grade 2 to grade 4 radiation dermatitis, loss of appetite, nausea, cognitive dysfunction, and memory disturbance.<sup>14</sup>
- No patients receiving SRS in combination with methotrexate experienced clinical or radiosurgical toxicity.<sup>16</sup> Side effects were mild, and no patients reported mental symptoms or cognitive deterioration.<sup>16</sup>

### Serious Adverse Events, Including Deaths

- In 1 RCT comparing SRS plus chemotherapy with chemotherapy alone, no patients in either group experienced radionecrosis.<sup>15</sup>
- In 1 RCT comparing SRS and whole-brain radiotherapy, 1 patient died of general prostration which was attributed to the comparator whole-brain radiotherapy treatment.<sup>14</sup>
- In 1 registry-based study, 7 people died in the initial therapy phase (1 in the SRS in combination with methotrexate group and 6 in the methotrexate alone group).<sup>16</sup>

### Bottom Line

Based on prior evidence updates and newly identified evidence, we conclude that at this time, the newly identified studies on harms are unlikely to change the conclusions of the 2012 evidence review. Brain cancers are a covered indication, and we did not identify any strong signals of harm for the use of SRS in this population.

## Spinal Cancer

### History

In 2013, the HTCC adopted the following coverage determination for spinal cancer<sup>2</sup>:

- SBRT is covered for adults and children for the following conditions when the following criteria are met:
  - For cancers of spine/paraspinal structures; *and*
  - Evaluation includes multidisciplinary team analysis, including surgical input.

In the 2017 evidence update,<sup>3</sup> 2 additional comparative observational studies were identified.<sup>126,127</sup> The 2017 update also identified 1 cost-effectiveness study.<sup>128</sup> The 3 studies included people with spinal metastases; no studies evaluated SBRT in people with primary cancers of the spine.<sup>126-128</sup> The 2017 evidence update concluded that there was insufficient evidence to indicate that SRS is an effective treatment for spinal cancers.<sup>3</sup>

In the 2019 evidence update,<sup>4</sup> a new RCT was identified (reported in 2 publications).<sup>129,130</sup> The update also identified 1 review of economic studies of SBRT, including in spinal cancers.<sup>124</sup> The authors of the evidence update report concluded that<sup>4</sup>:

- The identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review for spinal cancer because the additional 2 RCTs and 2 comparative observational studies confirm that the mean overall survival duration or overall survival rates for SRS were the same or better compared to conventional radiotherapy, without additional risk of harms.
- The identified new studies of economic outcomes were unlikely to change the conclusions of the 2012 evidence review.

### Findings in This Evidence Update

Since the most recent evidence update report,<sup>4</sup> we identified 2 recently published studies: 1 RCT<sup>13</sup> and 1 retrospective comparative study.<sup>12</sup>

- Sahgal and colleagues<sup>13</sup> randomized 229 patients with painful spinal metastasis to SBRT or conventional external beam radiotherapy. The median age of patients was 63 years in the SBRT group and 65 years in the conventional external beam radiotherapy group.<sup>13</sup> The proportion of men was 52% in the SBRT group and 53% in the conventional external beam radiotherapy group.<sup>13</sup> No race or ethnicity data were reported.<sup>13</sup> The RCT was conducted at 13 hospitals in Canada and 5 hospitals in Australia.<sup>13</sup>
- Vargas and colleagues<sup>12</sup> reviewed the medical records of 90 patients who received SBRT or conventionally fractionated EBRT for metastatic spinal tumors. The mean age of participants was 60 years in the SBRT group and 57 in the EBRT group.<sup>12</sup> The proportion of men was 53% in the SBRT group and 49% in the external beam radiotherapy group.<sup>12</sup> No race or ethnicity data were reported.<sup>12</sup> The propensity-matched study was conducted at a single site in the US.<sup>12</sup>

We did not identify any economic studies of SBRT in spinal cancer.

Table 3. Summary Characteristics of Included Studies of SBRT for Spinal Cancer

Study	Population	Description	Relevant Outcomes
Randomized controlled trials			
Sahgal et al., 2021 <sup>13</sup> NCT02512965	Patients with painful spinal metastasis	229 patients in total; 114 allocated to SBRT and 115 to conventional external beam radiotherapy	• Safety

Study	Population	Description	Relevant Outcomes
Comparative studies			
Vargas et al., 2020 <sup>12</sup>	Patients with metastatic spine tumors	90 patients in total; 45 treated with SBRT and 45 with conventional external beam radiotherapy	• Safety

Abbreviation. SBRT: stereotactic body radiotherapy.

### Effectiveness

Spinal cancers are a covered indication, so we report only the harms from the 2 eligible studies.<sup>12,13</sup>

### Harms

Based on evidence from 1 RCT and 1 retrospective study, patients with spinal metastases treated with SBRT or conventional external beam radiotherapy experienced few adverse effects.<sup>12,13</sup> However, significantly more patients treated with SBRT had vertebral body fractures than patients treated with conventional external beam radiotherapy.<sup>12</sup>

### Toxicity and Other Adverse Events

- No grade 5 events were observed in 1 RCT comparing SBRT and conventional external beam radiotherapy.<sup>13</sup> The most common grade 3 to grade 4 adverse events was grade 3 pain (5% vs. 4%; *P* value not reported).<sup>13</sup> Overall, the majority of vertebral compression fractures were grade 1 in severity (30 of 32); 1 patient in the SBRT group had a grade 3 vertebral compression fracture and 1 patient in the conventional external beam radiotherapy group had a grade 4 vertebral compression fracture.<sup>13</sup> In the conventional external beam radiotherapy group, progression to symptomatic spinal cord compression was observed in 2 patients.<sup>13</sup> No radiation myelopathy events and no premature discontinuations of assigned treatments due to treatment-related toxicity were observed.<sup>13</sup>
- In 1 retrospective study, more patients in the SBRT group had vertebral body fractures than patients in the conventional external beam radiotherapy group at 5 years (22% vs. 7%; *P* = .04).<sup>12</sup>

### Serious Adverse Events, Including Deaths

- At 6 months, 24% of patients randomized to SBRT or to conventional external beam radiotherapy had died.<sup>13</sup> All of these individuals died from the underlying cancer, other than 2 patients in the SBRT group who died from a *Legionella* infection.<sup>13</sup>

### Bottom Line

Based on prior evidence updates and newly identified evidence, we conclude that the newly identified studies on harms are unlikely to change the conclusions of the 2012 evidence review. Spinal cancer is a covered indication, and we did not identify any strong signals of harm for the use of SBRT in this population.

## Lung Cancer

### History

In 2013, the HTCC adopted the following coverage determination for lung cancer<sup>2</sup>:

- SBRT is covered for adults and children for the following conditions when the following criteria are met:
  - For inoperable NSCLC, stage 1; *and*
  - Evaluation includes multidisciplinary team analysis, including surgical input.

In the 2017 evidence update,<sup>3</sup> 30 additional studies were identified.<sup>131-160</sup> Of the 30 studies, 5 were systematic reviews,<sup>131,132,136,153,160</sup> 1 was an RCT (reported in 2 publications),<sup>150,159</sup> 21 were comparative studies,<sup>134,135,137-139,141-149,151,152,154-158</sup> and 1 was a cost-effectiveness modeling study.<sup>140</sup> The evidence update concluded there was additional evidence to support use of SBRT as an effective treatment for NSCLC.<sup>3</sup>

In the 2019 evidence update,<sup>4</sup> a further 18 primary and secondary studies were identified: 3 systematic reviews,<sup>161-163</sup> 13 comparative studies,<sup>133,164-175</sup> 1 RCT,<sup>176</sup> and 1 cost-effectiveness analysis.<sup>177</sup> The authors of the evidence update concluded that<sup>4</sup>:

- The identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review for inoperable early-stage NSCLC because additional studies were published since 2012 confirming that overall survival rates were the same or improved for SBRT compared to conventional radiotherapy without additional risk of harms.
- The identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review for operable early-stage NSCLC because studies published since 2012 showed mixed results.
- The identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review for patients with lung metastases because no RCTs had been published since 2012.
- The identified new studies of economic outcomes were unlikely to change the conclusions of the 2012 evidence review because studies published since 2012 showed mixed results.

### *Findings in This Evidence Update*

Since the most recent evidence update report,<sup>4</sup> we identified 2 recently published systematic reviews on the effectiveness of SBRT for operable early-stage NSCLC.<sup>58</sup>

- Cao and colleagues<sup>58</sup> assessed the clinical outcomes of SBRT compared with surgery for patients with early-stage NSCLC. The systematic review included 32 studies (1 pooled analysis of 2 RCTs, and 31 observational studies), with 23 studies included in a meta-analysis.<sup>58</sup>
- Ijsseldijk and colleagues<sup>53</sup> compared overall survival and oncologic outcomes of surgical resection and SBRT in people with stage 1 NSCLC. The systematic review included 100 observational studies, comprising 67,893 patients.<sup>53</sup>

We also identified 1 RCT,<sup>17</sup> 4 comparative studies,<sup>38-40,50</sup> and 3 noncomparative studies<sup>22,24,33</sup> published since the searches in the newly identified systematic reviews.

- Ball and colleagues<sup>17</sup> randomized 101 people with stage I NSCLC to SBRT or to standard radiotherapy. The mean age of the patients was 74 years in the SBRT group and 75 in the radiotherapy group.<sup>17</sup> The majority of patients were male, with 55% in the SBRT group and 57% in the radiotherapy group. No race or ethnicity data were reported.<sup>17</sup> The RCT was conducted in 11 hospitals in Australia and 3 hospitals in New Zealand.<sup>17</sup> Although the study

design was an RCT, as the majority of patients had medically inoperable cancer, we report only the harms in this evidence update.

- Lo and colleagues<sup>40</sup> compared outcomes for patients with early stage large cell neuroendocrine carcinoma (LCNEC) of the lung after SBRT and after surgery. The study used data from the US National Cancer Database, including 3,209 patients recorded as having lung cancer stage T1-2N0M0 treated with surgery (lobectomy or pneumonectomy) or SBRT.<sup>40</sup> Overall, 53% of patients were aged 68 and younger, and 52% were male.<sup>40</sup> The majority of participants identified as White (66%), with 9% identifying as African American and 3% as other.<sup>40</sup>
- Wegner and colleagues<sup>38</sup> analyzed data from the US National Cancer Database comparing outcomes for 754 people with LCNEC of the lung treated with SBRT or conventional radiotherapy. Overall, 53% of patients were aged 73 and younger, with 52% being male.<sup>38</sup> The majority of participants identified as White (88%), with 10% identifying as African American and 2% as other.<sup>38</sup>
- Kanzaki and colleagues<sup>50</sup> compared the outcomes of SBRT and surgery in 82 people with pulmonary metastasis from epithelial tumors. In the SBRT group, the mean age was 67 years and 67% of participants were male.<sup>50</sup> In the pulmonary metastasectomy group, the mean age was 61 years and 59% of participants were male.<sup>50</sup> No data on race or ethnicity were reported.<sup>50</sup> The retrospective study was conducted at a single institution in Japan.<sup>50</sup>
- Nelson and colleagues<sup>39</sup> compared the outcomes for 381 people with colorectal pulmonary metastases treated with SBRT, surgery (wedge resection), or both SBRT and surgery.<sup>39</sup> The mean age of the participants was 62 years in the SBRT group, 57 in the wedge resection group, and 55 in the SBRT with surgery group.<sup>39</sup> The proportion of male participants was 62% in the SBRT group, 57% in the wedge resection group, and 65% in the SBRT with surgery group.<sup>39</sup> No data on race or ethnicity were reported.<sup>39</sup> The retrospective study was conducted at a single institution in the US.<sup>39</sup>
- Chipko and colleagues<sup>33</sup> analyzed the safety outcomes of SBRT in 100 people treated for malignant lung tumors in a noncomparative study. The median age of the participants was 67 and the minority were male (41%).<sup>33</sup> No data on race or ethnicity were reported.<sup>33</sup> The study was a retrospective study of patients treated at a single center in the US.<sup>33</sup>
- Rodrigues and colleagues<sup>24</sup> analyzed data from 218 patients with early-stage primary lung tumors treated with SBRT. The median age was 73 years, and 79% of participants were male.<sup>24</sup> No data on race or ethnicity were reported.<sup>24</sup> The retrospective noncomparative study was conducted at a single institution in Portugal.<sup>24</sup>
- Sharma and colleagues<sup>22</sup> described the outcomes of SBRT for 206 people with inoperable pulmonary oligometastases in a noncomparative study. The median age of the participants was 68 years, and 59% were male.<sup>22</sup> No data on race or ethnicity were reported.<sup>22</sup> The retrospective study was conducted at a single institution in the Netherlands.<sup>22</sup>

We did not identify any economic studies of SBRT in lung cancer.

Table 4. Summary Characteristics of Included Studies of SBRT for Lung Cancer

Study	Population	Description	Relevant Outcomes
<b>Systematic reviews</b>			
Cao et al., 2019 <sup>58</sup>	Patients with early NSCLC	Included 32 studies; total number of patients not reported overall; search date through January 2018	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Cancer-specific survival</li> <li>• Disease-free survival</li> <li>• Recurrence-free survival</li> <li>• Periprocedural morbidity</li> <li>• Mortality</li> </ul>
Ijsseldijk et al., 2021 <sup>53</sup>	Patients with stage I NSCLC	Included 100 studies, comprising 67,893; search from January 2000 to March 2018	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-free survival</li> <li>• Mortality</li> </ul>
<b>Primary studies</b>			
<i>Randomized controlled trials</i>			
Ball et al., 2019 <sup>17</sup> ; NCT01014130	Patients with biopsy-confirmed stage I (T1–T2aN0M0) NSCLC	101 patients in total; 66 allocated to SBRT and 35 to standard radiotherapy	<ul style="list-style-type: none"> <li>• Safety</li> </ul>
<i>Comparative observational studies</i>			
Kanzaki et al., 2020 <sup>50</sup>	Patients with pulmonary metastasis from epithelial tumors	82 patients in total; 21 treated with SBRT, 59 with surgery, and 2 with both	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression-free survival</li> <li>• Local tumor control</li> <li>• Safety</li> </ul>
Lo et al., 2020 <sup>40</sup>	Patients with LCNEC of the lung	3,209 patients in total; 238 treated with SBRT and 2,971 with surgery	<ul style="list-style-type: none"> <li>• Overall survival</li> </ul>
Nelson et al., 2019 <sup>39</sup>	Patients with colorectal pulmonary metastases	381 patients in total; 37 treated with SBRT, 327 with wedge resection, and 17 with both	<ul style="list-style-type: none"> <li>• Local tumor control</li> </ul>
Wegner et al., 2020 <sup>38</sup>	Patients with LCNEC of the lung	754 patients in total; 238 treated with SBRT and 516 with conventional radiotherapy	<ul style="list-style-type: none"> <li>• Overall survival</li> </ul>
<i>Noncomparative studies (harms only)</i>			
Chipko et al., 2019 <sup>33</sup>	Patients with malignant lung tumors	100 patients treated with SBRT	<ul style="list-style-type: none"> <li>• Safety (chest wall pain and rib fractures)</li> </ul>
Rodrigues et al., 2020 <sup>24</sup>	Patients with early-stage primary lung tumors	218 patients treated with SBRT	<ul style="list-style-type: none"> <li>• Safety</li> </ul>
Sharma et al., 2019 <sup>22</sup>	Patients with inoperable pulmonary oligometastases	206 patients treated with SBRT	<ul style="list-style-type: none"> <li>• Safety</li> </ul>

Abbreviations. LCNEC: large cell neuroendocrine carcinoma; NSCLC: non-small cell lung cancer; SBRT: stereotactic body radiation therapy.

## Effectiveness

Inoperable stage 1 NSCLC is a covered indication, so we do not report any effectiveness data for this population.

Based on 2 systematic reviews of SBRT and surgery for people with operable NSCLC, surgery appears to be the more effective treatment, with improved survival and tumor control.<sup>53,58</sup> Based on 2 registry studies, SBRT may be an effective option for people with LCNEC of the lung when compared with conventional radiotherapy, but may not be as effective as surgery.<sup>38,40</sup> Based on 2 retrospective studies, SBRT may be an effective option for pulmonary metastases when compared with surgery, but the results are mixed.<sup>39,50</sup>

## Overall Survival

### Operable Non–Small Cell Lung Cancer

- In the systematic review by Cao and colleagues,<sup>58</sup> 16 studies reported on overall survival for 10,333 patients who received SBRT and 142,293 unmatched patients who received surgery for early NSCLC. A further 14 studies reported on 8,946 patients who received SBRT and 8,942 matched patients who received surgery.<sup>58</sup> Pooled data from the studies showed that surgery was associated with significantly greater overall survival in both the unmatched group (odds ratio [OR], 2.49; 95% confidence interval [CI], 2.10 to 2.94) and the matched group (OR, 1.71; 95% CI, 1.52 to 1.93).<sup>58</sup> When compared with SBRT, lobectomy was also associated with improved overall survival (OR, 2.68 unmatched; 95% CI, 2.04 to 3.5; OR, 1.61; 95% CI, 1.23 to 2.12).<sup>58</sup> Similarly, in unmatched patients, sublobar resection remained superior in terms of overall survival (OR, 1.54; 95% CI, 1.36 to 1.75); however, there were insufficient studies to pool data from the matched patients.<sup>58</sup> Patients with early NSCLC after surgery also had significantly better cancer-specific survival than patients who received SBRT.<sup>58</sup>
- A systematic review in patients with stage I NSCLC found that<sup>53</sup>:
  - Surgery was associated with significantly better overall survival rates than SBRT at 5 years in the propensity-matched cohorts (risk ratio [RR], 1.54; 95% CI, 1.28 to 1.83).
  - Lobar resection was associated with significantly better overall survival rates than SBRT at 5 years in the propensity-matched cohorts (RR, 1.71; 95% CI, 1.63 to 1.85).
  - Mixed resection was associated with significantly better overall survival rates than SBRT at 5 years in the propensity-matched cohorts (RR, 1.37; 95% CI, 1.01 to 1.85).
  - Sublobar resection was associated with similar overall survival rates to SBRT at 5 years in the propensity-matched cohorts (RR, 1.33; 95% CI, 0.92 to 1.93).
  - Comparative studies showed similar results, with surgery being associated with significantly better overall survival at 3 and 5 years, regardless of the type of surgery. However, there was no difference between groups for overall survival at 1 year.

### Large Cell Neuroendocrine Carcinoma

- In an propensity-matched analysis of the US National Cancer Database, people treated for LCNEC of the lung with SBRT had a significantly shorter median overall survival rate compared with surgery (34.6 months vs. 57.2 months;  $P < .001$ ), with a significantly lower 5-year overall survival rate (25% vs. 48%;  $P < .001$ ).<sup>40</sup> Similar results were seen with an unmatched analysis.<sup>40</sup> Multivariate analysis also showed that older age, higher comorbidity



score, male sex, higher T stage, and treatment with SBRT were significantly associated with decreased overall survival.<sup>40</sup>

- In a propensity-matched analysis of the US National Cancer Database, people treated with SBRT for LCNEC of the lung had a significantly longer median overall survival rate compared with conventional radiotherapy (34.7 months vs. 23.7 months;  $P = .02$ ).<sup>38</sup> The use of conventional radiotherapy was marginally associated with worse survival in a multivariate Cox regression model (hazard ratio [HR], 1.21; 95% CI, 1.00 to 1.46).<sup>38</sup>

#### Pulmonary Metastases

- In a retrospective analysis, people with pulmonary metastases treated with SBRT or surgery had similar overall survival rates (52% vs. 77% at 3 years;  $P = .10$ ).<sup>50</sup>

#### Progression-free Survival

##### Pulmonary Metastases

- In a retrospective analysis, people with pulmonary metastases treated with SBRT had significantly lower progression-free survival rates than patients treated with surgery (11% vs. 42% at 3 years;  $P = .01$ ).<sup>50</sup>

#### Disease-free Survival

##### Operable Non–Small Cell Lung Cancer

- In the systematic review by Cao and colleagues,<sup>58</sup> pooled data from 5 studies in unmatched patients and 7 studies in matched patients, patients who received surgery had significantly better disease-free survival than patients who received SBRT (OR, 2.13 unmatched; 95% CI, 1.65 to 2.75; OR, 1.83 matched; 95% CI, 1.06 to 3.16).<sup>58</sup>
- A systematic review in patients with stage I NSCLC found that<sup>53</sup>:
  - In the propensity-matched cohorts, surgery was associated with significantly better disease-free survival rates than SBRT at 3 years (RR, 1.78; 95% CI, 1.24 to 2.55) and at 5 years (RR, 1.50; 95% CI, 1.19 to 1.89).
  - Comparative studies showed similar results with surgery being associated with significantly greater disease-free survival at 1, 3, and 5 years.

#### Local Tumor Control

##### Operable Non–Small Cell Lung Cancer

- In the systematic review by Cao and colleagues<sup>58</sup> which pooled data from 6 studies in unmatched patients and 6 studies in matched patients, patients who received surgery had significantly lower locoregional recurrence rates than patients who received SBRT (OR for freedom from locoregional recurrence, 5.44 unmatched; 95% CI, 1.68 to 17.56; OR for freedom from locoregional recurrence, 2.91 matched; 95% CI, 1.49 to 5.71).<sup>58</sup> However, patients who received surgery had similar odds of distant recurrence to patients who received SBRT (OR, 1.50; 0.96 to 2.34).<sup>58</sup>

#### Pulmonary Metastases

- In a retrospective analysis, people with pulmonary metastases treated with SBRT or surgery had similar local control rates (92% vs. 88% at 3 years;  $P = .48$ ).<sup>50</sup>
- In a propensity-score matched analysis, people treated with SBRT and surgery had similar rates of local treatment failure at 2 years (SBRT: 29.4%; 95% CI, 13.8% to 45.0%; surgery:

14.1%; 95% CI, 9.8% to 18.5%) and at 5 years (SBRT: 37.3%; 95% CI, 21.1% to 53.6%; surgery: 18.4%; 95% CI, 12.1% to 24.7%).<sup>39</sup> However, in the unmatched analysis, SBRT was significantly associated with a higher risk of local recurrence when compared with surgery (HR, 3.28; 95% CI, 1.53 to 7.04).<sup>39</sup>

### Harms

Patients treated with SBRT, surgery, or radiotherapy all were at risk for some form of adverse event.

### Toxicity and Other Adverse Events

- In the systematic review by Cao and colleagues,<sup>58</sup> the most commonly reported adverse events after SBRT were fatigue, radiation pneumonitis, chest pain, and rib fractures. For surgery, the most commonly reported adverse events were prolonged air leak, pneumonia, pulmonary embolism, cardiac arrhythmia, and myocardial infarction.<sup>58</sup>
- In the RCT by Ball and colleagues<sup>17</sup> comparing SBRT and radiotherapy, 1 grade 4 event occurred after SBRT (1 patient developed dyspnea). In total, 9 grade 3 adverse events occurred (7 in the SBRT group and 2 in the radiotherapy group).<sup>17</sup> The cumulative time at risk was 153 years for patients in the SBRT group and 66 years for patients in the standard radiotherapy group.<sup>17</sup>
- Patients with metastatic lung cancer had similar rates of treatment-associated complications in the SBRT and the pulmonary metastasectomy group (24% vs. 20%;  $P = .76$ ).<sup>50</sup> The treatment-associated complications in the SBRT group were radiation-induced pneumonitis and pneumonia.<sup>50</sup>
- In a noncomparative, retrospective study of SBRT in 100 patients treated with SBRT for malignant lung tumors, the chest wall pain-free survival was 75% at 3 years and 67% at 5 years.<sup>33</sup> Chest wall pain was seen in 33 of 118 treatments (28%) and the mean time to development was 12.5 months (range, 0 to 50 months).<sup>33</sup> No clinical parameters or medication appeared to be associated with chest wall pain.<sup>33</sup> Rib fractures occurred in 118 treatments (29%) and the mean time to development was 22 months.<sup>33</sup> The fracture-free survival rate was 72% at 3 years and 65% at 5 years.<sup>33</sup> Rib fractures were significantly more common in women, patients with lower bone mass density, and people who identified as African American.<sup>33</sup>
- In a noncomparative retrospective study of SBRT in 218 patients with early-stage primary lung tumors treated with SBRT, no acute grade 3 or higher toxicities were observed and 1 patient experienced a grade 3 late toxicity of dyspnea.<sup>24</sup>
- In a noncomparative retrospective study of SBRT in 206 patients with inoperable pulmonary oligometastases, 5 grade 3 adverse events were reported (dyspnea, chest pain, and dyspnea with fatigue).<sup>22</sup>

### Serious Adverse Events, Including Deaths

- In the systematic review by Cao and colleagues,<sup>58</sup> periprocedural mortality (defined as death within the same admission or within 30 days of the procedure) was 0% for SBRT and 0% to 8% for surgery across the included studies in patients with early NSCLC.
- In the systematic review by Ijsseldijk and colleagues<sup>53</sup> comparing SBRT and resection in people with stage I NSCLC:

- In the propensity-matched cohorts, the 30-day mortality rate after SBRT was 0%, and after surgery, 3%. After 90 days, 2 patients had died after SBRT and 93 patients died after surgery.
- In the comparative studies, there was no deaths within 30 days of SBRT or surgery and there was no difference in mortality between the groups at 90 days.
- In the RCT by Ball and colleagues<sup>17</sup> comparing SBRT and radiotherapy, no treatment-related deaths were observed.
- No treatment-related deaths were observed in a retrospective analysis of 206 patients with inoperable pulmonary oligometastases treated with SBRT.<sup>22</sup>

### Bottom Line

Based on prior evidence updates and newly identified evidence, we conclude that at this time, the newly identified studies on effectiveness, harms, and cost-effectiveness are unlikely to change the conclusions of the 2012 evidence review, because of the lack of identified RCTs for lung cancer. Inoperable stage I NSCLC remains a covered indication, and we did not identify any strong signals of harm for the use of SBRT in this population.

## Pancreatic Cancer

### History

In the 2012 report presented to the HTCC,<sup>1</sup> the overall strength of evidence for pancreatic cancer was assessed as very low for effectiveness and harms, based on 1 systematic review and 4 case series.<sup>178-182</sup> The 2012 report<sup>1</sup> also concluded that the overall strength of evidence on cost-effectiveness for pancreatic cancer was very low, based on 1 economic modeling study.<sup>183</sup>

In the 2017 evidence update,<sup>3</sup> a further 2 studies were identified; 1 systematic review of case series<sup>184</sup> and 1 comparative observational study.<sup>185</sup> The evidence update concluded that there was insufficient evidence to indicate that SBRT was an effective treatment for pancreatic cancer.<sup>3</sup> In the 2019 evidence update,<sup>4</sup> 1 additional systematic review<sup>186</sup> and 5 comparative observational studies<sup>187-191</sup> were identified. A further 2 economic studies were also identified: 1 systematic review<sup>124</sup> and 1 cost-effectiveness study.<sup>192</sup> The authors of the 2019 update concluded that the identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review for pancreatic cancer because no RCTs had been published since 2012.<sup>3</sup> The newly identified economic evidence was also assessed as unlikely to change the conclusions of the 2012 review.

### Findings in This Evidence Update

Since the most recent evidence update report,<sup>4</sup> we identified 1 recently published retrospective study.

- Arcelli and colleagues<sup>60</sup> compared the outcomes of SBRT and conventionally fractionated chemoradiotherapy (CRT), with or without chemotherapy, in 80 patients with locally advanced pancreatic cancer. The median age of the participants was 67 years in both treatment groups.<sup>60</sup> The proportion of participants who were male was 67% in the SBRT group and 60% in the conventionally fractionated CRT group.<sup>60</sup> No race or ethnicity data were reported.<sup>60</sup> The study was conducted in 15 organizations in Italy.<sup>60</sup>

We did not identify any newly published economic studies of SBRT for pancreatic cancer.

Table 5. Summary Characteristics of Included Studies of SBRT for Pancreatic Cancer

Study	Population	Description	Relevant Outcomes
Comparative observational studies			
Arcelli et al., 2019 <sup>60</sup> PAULA-1	Patients with locally advanced pancreatic cancer	80 patients in total; 40 treated with SBRT and 40 with conventionally fractionated chemoradiation	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression-free survival</li> <li>• Distant metastases-free survival</li> <li>• Local tumor control</li> <li>• Safety</li> </ul>

Abbreviation. SBRT: stereotactic body radiotherapy.

### Effectiveness

Based on 1 retrospective study, SBRT was as effective as conventionally fractionated CRT for locally advanced pancreatic cancer, and may be associated with better local tumor control.<sup>60</sup>

#### Overall Survival

- Patients with locally advanced pancreatic cancer treated with SBRT had similar overall survival rates to patients treated with conventionally fractionated CRT (median, 16 months vs. 21 months; at 1 year, 79.8% vs. 73.8%; at 2 years, 14.7% vs. 40.1%;  $P = .47$ ).<sup>60</sup>

#### Progression-free Survival

- Patients with locally advanced pancreatic cancer treated with SBRT had similar progression-free survival rates to patients treated with conventionally fractionated CRT (median, 14 months vs. 12 months; at 1 year, 59.1% vs. 49.2%; at 2 years, 59.1% vs. 32.4%;  $P = .75$ ).<sup>60</sup>

#### Distant Metastases-free Survival

- Patients with locally advanced pancreatic cancer treated with SBRT had similar distant metastases-free survival rates to patients treated with conventionally fractionated CRT (median, 16 months vs. 12 months; at 1 year, 64.5% vs. 49.3%; at 2 years, 20.3% vs. 41.7%;  $P = .61$ ).<sup>60</sup>

#### Local Tumor Control

- Patients with locally advanced pancreatic cancer treated with SBRT had a significantly longer period of local tumor control to patients treated with conventionally fractionated CRT (median, 22 months vs. 16 months; at 1 year, 80.4% vs. 53.1%; at 2 years, 49.8% vs. 40.5%;  $P = .02$ ).<sup>60</sup>

### Harms

Patients treated with SBRT and conventionally fractionated CRT have similar rates of grade 1 and 2 gastrointestinal toxicities, based on 1 retrospective study.<sup>60</sup>

#### Toxicity and Other Adverse Events

- Patients with locally advanced pancreatic cancer treated with SBRT had similar rates of grade 1 and 2 acute and late gastrointestinal toxicities to patients treated with conventionally fractionated CRT.<sup>60</sup>

## Bottom Line

Based on prior evidence updates and newly identified evidence, we conclude that at this time, the newly identified studies on effectiveness and harms are unlikely to change the conclusions of the 2012 evidence review, because of the lack of RCTs for pancreatic cancer.

## Prostate Cancer

### History

In the 2012 report presented to the HTCC,<sup>1</sup> the overall strength of evidence was assessed as very low for harms, based on 4 case series.<sup>193-196</sup> No comparative studies on the effectiveness of SBRT in this population were identified.<sup>1</sup>

In the 2017 evidence update,<sup>3</sup> a further 7 studies were identified: 1 systematic review,<sup>197</sup> 5 comparative observational studies,<sup>198-202</sup> and 1 economic study.<sup>203</sup> The evidence update concluded that there was insufficient evidence to indicate SBRT was an effective treatment for prostate cancer.<sup>3</sup> In the 2019 evidence update,<sup>4</sup> 4 additional comparative observational studies were included,<sup>204-207</sup> and again, the authors of the update concluded that the identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review for prostate cancer because no RCTs had been published since 2012.<sup>3</sup>

The 2019 evidence update did identify 1 review of economic studies of SBRT<sup>124</sup> and 1 cost-utility study<sup>208</sup> and concluded that the identified new studies of economic outcomes were unlikely to result in a rating of either low-quality or stronger evidence of cost-effectiveness.<sup>4</sup>

### Findings in This Evidence Update

Since the most recent evidence update report,<sup>4</sup> we identified 2 recently published RCTs and 1 individual patient data analysis.<sup>9,46,59</sup>

- Brand and colleagues<sup>59</sup> randomized 874 men with low-risk to intermediate-risk localized prostate cancer to SBRT or conventionally fractionated or moderately hypofractionated radiotherapy. The mean age of participants was 70 years in both treatment groups.<sup>59</sup> In the SBRT group, 8% of participants identified as Black, 1% as East Asian, 5% as South Asian, 85% as White, fewer than 1% as mixed heritage, and 1% as other ethnicity.<sup>59</sup> In the conventionally fractionated or moderately hypofractionated radiotherapy group, 6% of participants identified as Black, 1% as East Asian, 2% as South Asian, 89% as White, fewer than 1% as of mixed heritage, and 2% as of other ethnicity.<sup>59</sup> The RCT was conducted at 37 centers in the UK, Ireland, and Canada.<sup>59</sup>
- Phillips and colleagues<sup>46</sup> randomized 54 men with recurrent hormone-sensitive prostate cancer and 1 to 3 metastases to SBRT or to observation only. The median age of participants in both treatment groups was 68 years.<sup>46</sup> No race or ethnicity data were reported.<sup>46</sup> The RCT was conducted in 3 sites in the US.<sup>46</sup>
- van Dams and colleagues<sup>9</sup> pooled data from 344 patients with high-risk prostate cancer who received SBRT, with or without androgen deprivation therapy. The median age of the participants was 72 years.<sup>9</sup> No race or ethnicity data were reported.<sup>9</sup> Patient-level data was obtained from 7 institutions with phase 2 studies and prospective databases.<sup>9</sup>

We did not identify any newly published economic studies of SBRT for prostate cancer.

Table 6. Summary Characteristics of Included Studies of SBRT for Prostate Cancer

Study	Population	Description	Relevant Outcomes
<b>Randomized controlled trials</b>			
Brand et al., 2019 <sup>59</sup> ; NCT01584258; PACE-B	Patients with low-risk to intermediate-risk localized prostate cancer	874 patients in total; 433 allocated to SBRT and 441 to conventionally fractionated or moderately hypofractionated radiotherapy	<ul style="list-style-type: none"> <li>• Quality of life</li> <li>• Safety</li> </ul>
Phillips et al., 2020 <sup>46</sup> ; NCT02680587; ORIOLE	Patients with recurrent hormone-sensitive prostate cancer and 1 to 3 metastases	54 patients in total; 36 allocated to SBRT and 18 to observation alone	<ul style="list-style-type: none"> <li>• Progression-free survival</li> <li>• Safety</li> </ul>
<b>Noncomparative studies (harms only)</b>			
van Dams et al., 2021 <sup>9</sup>	Patients with high-risk prostate cancer	344 patients treated with SBRT	<ul style="list-style-type: none"> <li>• Safety</li> </ul>

Abbreviation. SBRT: stereotactic body radiation therapy.

### Effectiveness

Based on 1 RCT, there is limited evidence that patients with prostate cancer treated with SBRT had better progression-free survival than people who underwent observation alone.<sup>46</sup>

#### Progression-free Survival

- In 1 RCT, patients treated with SBRT had significantly longer progression-free survival than people undergoing observation alone (HR, 0.30; 95% CI, 0.11 to 0.81).<sup>46</sup>

#### Quality of Life

- Patients in the SBRT and the conventionally fractionated or moderately hypofractionated radiotherapy groups had similar quality of life scores.<sup>59</sup> No other measures of effectiveness were reported.<sup>59</sup>

### Harms

Data from 2 RCTs and 1 observational study suggests that SBRT treatment does not appear to be associated with higher rates of adverse events than other active treatments, and is unlikely to be associated with increased mortality.<sup>9,46,59</sup>

#### Toxicity and Other Adverse Events

- In 1 RCT, patients in the SBRT and the conventionally fractionated or moderately hypofractionated radiotherapy groups experienced similar numbers of grade 2 or more severe gastrointestinal toxic events (10% vs. 12%; difference, -1.9 percentage points; 95% CI, -6.2 to 2.4) and grade 2 or worse genitourinary toxicity (23% vs. 27%; difference, -4.2 percentage points; 95% CI, -10.0 to 1.7).<sup>59</sup>
- In 1 RCT, no grade 3 or higher adverse events were observed in patients randomized to SBRT or to observation.<sup>46</sup>
- In an individual patient data analysis, 18% of patients who received SBRT for high-risk prostate cancer experienced grade 2 or high genitourinary toxicity and 5% experienced acute grade 2 or more gastrointestinal toxicity.<sup>9</sup> No acute grade 3 toxicities were seen.<sup>9</sup>

## Serious Adverse Events, Including Deaths

- No deaths occurred in an RCT comparing SBRT and conventionally fractionated or moderately hypofractionated radiotherapy for localized prostate cancer.<sup>59</sup>

### Bottom Line

We identified 1 RCT showing that SBRT was associated with longer progression-free survival than observation alone; however, overall survival was not reported in either of the eligible RCTs.<sup>46,59</sup>

Based on prior evidence updates and newly identified evidence, we conclude that at this time, the newly identified studies on effectiveness and harms are unlikely to change the conclusions of the 2012 evidence review, because of the lack of effectiveness data, specifically overall survival, from RCTs for prostate cancer.

## Liver Cancer

### History

In the 2012 report presented to the HTCC,<sup>1</sup> the evidence for effectiveness and harms of SBRT for hepatocellular carcinoma was assessed as being of very low certainty, with any conclusions about benefit and harms being uncertain. The report included 2 poor-methodological-quality systematic reviews of case series<sup>181,209</sup> and 7 case series for hepatocellular carcinoma.<sup>210-216</sup>

In the 2017 evidence update, a further 3 comparative observational studies were identified.<sup>217-219</sup> The evidence update concluded there was insufficient evidence to indicate SBRT is an effective treatment for hepatocellular carcinoma.<sup>3</sup> In the 2019 evidence update,<sup>4</sup> 3 additional comparative observational studies were included,<sup>220-222</sup> and again, the authors of the update concluded that the identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review for liver cancer because no RCTs had been published since 2012.<sup>3</sup>

The 2019 evidence update did identify 3 economic studies of SBRT for hepatocellular carcinoma<sup>223-225</sup> and concluded that the identified new studies of economic outcomes were unlikely to result in a rating of either low-quality or stronger evidence of cost-effectiveness.<sup>4</sup>

### Findings in This Evidence Update

Since the most recent evidence update report,<sup>4</sup> we identified 3 recently published systematic reviews on the effectiveness of SBRT compared with radio-frequency ablation (RFA) for liver cancer.<sup>49,54,55</sup>

- Eriguchi and colleagues<sup>55</sup> reviewed studies using propensity matching to compare the effectiveness of SBRT compared with RFA. The systematic review included 6 studies, comprising 2,107 patients with hepatocellular carcinoma.<sup>55</sup>
- Facciorusso and colleagues<sup>54</sup> reviewed 9 retrospective studies comparing SBRT with RFA in 6,545 patients with hepatocellular carcinoma.
- Lee and colleagues<sup>49</sup> reviewed studies comparing SBRT and RFA in people with early hepatocellular carcinoma and liver metastases. The review included 11 studies, comprising 2,238 patients.<sup>49</sup>

We also identified 3 recently published systematic reviews of noncomparative studies of SBRT for hepatocellular carcinoma,<sup>23,25,32</sup> published since the most recent evidence update report.<sup>4</sup> Although the reviews reported effectiveness outcomes (specifically local tumor control and overall survival), they did not compare effectiveness with a comparator of interest, and these outcomes are not reported further in this report.<sup>23,25,32</sup>

- Dobrzycka and colleagues<sup>32</sup> reviewed 16 noncomparative studies of SBRT in 973 patients with hepatocellular carcinoma.
- Rim and colleagues<sup>25</sup> reviewed 32 noncomparative studies of SBRT in 1,950 patients with hepatocellular carcinoma. Although the review reported effectiveness outcomes (specifically local tumor control and overall survival), they did not compare effectiveness with a comparator of interest, and these outcomes are not reported further in this report.<sup>25</sup>
- Shanker and colleagues<sup>23</sup> evaluated the use of SBRT in the management of primary hepatocellular carcinoma. The systematic review included 49 cohorts comprising 2,846 participants.<sup>23</sup> Although the review reported effectiveness outcomes (specifically local tumor control and overall survival), they did not compare effectiveness with a comparator of interest, and these outcomes are not reported further in this report.<sup>23</sup>

We have reported outcomes from each of the 6 identified reviews as the results from each review vary, although in many cases, the reviews include a similar set of included primary studies.

We did not identify any RCTs evaluating SBRT for hepatocellular carcinoma. We identified 8 comparative studies published since the search dates of the included systematic reviews.<sup>41-44,48,51,52,61</sup>

- Jeong and colleagues<sup>52</sup> compared the effectiveness of SBRT and RFA in 266 patients with a small hepatocellular carcinoma, defined as 3 cm or smaller. Most participants were male (76.7%), with a median age of 60 (age range, 40 to 90 years).<sup>52</sup> No race or ethnicity data were reported.<sup>52</sup> The study was conducted in a single center in South Korea.<sup>52</sup>
- Jun and colleagues<sup>51</sup> compared the effectiveness of SBRT plus transarterial chemoembolization (TACE) with TACE alone in 199 patients with hepatocellular carcinoma of 5 cm or smaller. Patients were propensity-score matched, the majority of the group was male (65% SBRT+TACE; 64% TACE).<sup>51</sup> and were aged around 60 years (mean, 62.6 SBRT+TACE; 62.8 TACE).<sup>51</sup> No race or ethnicity data were reported.<sup>51</sup> The study was conducted in 4 tertiary hospitals in South Korea.<sup>51</sup>
- Nabavizadeh and colleagues<sup>48</sup> compared the effectiveness of SBRT and thermal ablation, both after TACE, in 190 patients with a single inoperable hepatocellular carcinoma in a propensity-matched study. Most participants were male (74.7%), with a median age of 60 (range, 57 to 65).<sup>48</sup> No race or ethnicity data were reported.<sup>48</sup> The study was conducted in a university hospital in the US.<sup>48</sup>
- Sebastian and colleagues<sup>61</sup> used the US National Cancer Database to compare overall survival of patients with intrahepatic cholangiocarcinoma treated with CRT, SBRT, or transarterial radioembolization (TARE). The majority of patients were male in the CRT group (67%) but the minority were male in the SBRT (45%) and TARE (46%) groups.<sup>61</sup> Median age was 71 years (interquartile range [IQR], 61 to 80) in the CRT group, 65 (IQR, 57.5 to 74.5) in the SBRT group, and 67 (IQR, 61 to 74) in the TARE group.<sup>61</sup> Most participants were White (92.6% CRT; 85.0% SBRT; 85.2% TARE), with around 3 to 4% of participants categorized as



Black (3.7% CRT; 3.3% SBRT; 3.7% TARE) and 4% to 12% as other (3.7% CRT; 11.7% SBRT; 11.1% TARE).<sup>61</sup>

- Shen and colleagues<sup>44</sup> compared SBRT and TACE in 188 patients with a medium-sized (3 cm to 8 cm) hepatocellular carcinoma using propensity-score matching. Most participants were male (76.1% SBRT; 63.4% TACE) and had a median age of 64 in the SBRT group (range, 37 to 86) and 67 in the TACE group (range, 29 to 88).<sup>44</sup> No race or ethnicity data were reported.<sup>44</sup> The study analyzed data from a single hospital cancer registry in Taiwan.<sup>44</sup>
- Wang and colleagues<sup>43</sup> evaluated the safety and efficacy of SBRT following RFA and continued RFA in people with Barcelona Clinic Liver Cancer (BCLC) stages 0 to B1 hepatocellular carcinoma, using propensity-score matching. In the unmatched sample, most participants were male (87.6%) and had a mean age of 70.6 years.<sup>43</sup> No race or ethnicity data were reported.<sup>43</sup> The study was conducted in 2 hospitals in Japan.<sup>43</sup>
- Wong and colleagues (2019)<sup>42</sup> compared the effectiveness of SBRT after TACE with TACE alone in people with nonresectable hepatocellular carcinoma in a propensity score-matched study. In the unmatched group, the majority of the patients were male (85.7% SBRT+TACE; 79.2% TACE), with a median age of 61 in the SBRT after TACE group (range, 28 to 87) and 69 in the TACE alone group (range, 20 to 94).<sup>42</sup> No race or ethnicity data were reported.<sup>42</sup> The study was conducted in 2 hospitals in Hong Kong.<sup>42</sup>
- Wong and colleagues (2021)<sup>41</sup> compared the efficacy and safety of SBRT as a bridging treatment for liver transplantation for hepatocellular carcinoma. Patients were prospectively enrolled for SBRT treatment and outcomes were compared with a retrospective group of patients who had received treatment using TACE or high-intensity focused ultrasound (HIFU).<sup>41</sup> The majority of participants were male (65.0% SBRT; 84.7% TACE; 80.4% HIFU), and had a median age of 59.6 in the SBRT group (range, 36 to 69), 58.1 in the TACE group (range, 42 to 69), and 59.5 in the HIFU group (range, 38 to 68).<sup>41</sup> No race or ethnicity data were reported.<sup>41</sup> The study was conducted in a single hospital in Hong Kong.<sup>41</sup>

We also identified 5 noncomparative studies reporting on harms published since the search dates of the included systematic reviews.

- Kibe and colleagues<sup>29</sup> evaluated the feasibility of markerless SBRT for hepatocellular carcinoma. The study included 180 patients, with majority male participants (70%) and a median age of 74 (range, 46 to 93).<sup>29</sup> No race or ethnicity data were reported.<sup>29</sup> The study was conducted in a single hospital in Japan.<sup>29</sup>
- Loi and colleagues<sup>28</sup> reviewed the use of SBRT for advanced hepatocellular carcinoma in 128 patients. The median age of participants was 75 (range, 20 to 91). No data on sex, race or ethnicity were reported.<sup>28</sup> The study was conducted at a single site in Italy.<sup>28</sup>
- Mathew and colleagues<sup>27</sup> reviewed the long-term outcomes of SBRT in 297 people with localized hepatocellular carcinoma without vascular invasion, who were ineligible for other liver-directed therapies. The majority of participants were male (74%), with a median age of 69.3 (range, 22 to 94). The majority of participants were Caucasian (69%); 16% identified as Asian, 7% as African-American, and 8% as other.<sup>27</sup> The study was conducted in 1 site in Canada and 1 in the US.<sup>27</sup>
- Park and colleagues<sup>26</sup> reported on the use of SBRT in 290 patients with hepatocellular carcinoma. The majority of patients were male (79.3%), with a median age of 61 (36 to 90).<sup>26</sup>

No race or ethnicity data were reported.<sup>26</sup> The study was conducted in a single site in South Korea.<sup>26</sup>

- Voglhuber and colleagues<sup>19</sup> analyzed data from 115 patients treated with SBRT for liver metastases. The participants were mixed in terms of sex (51.3% male) and had a median age of 66.1 (range, 34.7 to 86.1).<sup>19</sup> No race or ethnicity data were reported.<sup>19</sup> The study was conducted at a single site in Germany.<sup>19</sup>

We also identified 1 study reporting on the costs and cost-effectiveness of SBRT.

- Parikh and colleagues<sup>63</sup> conducted a secondary analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database comparing outcomes and costs for people with stage I or II hepatocellular carcinoma and treated with RFA or SBRT as the initial treatment within 6 months of diagnosis. The majority of participants were male (62.5% SBRT; 62.3% RFA), with a median age of 77 in the SBRT group and 73 in the RFA group.<sup>63</sup> Most participants were White (74% SBRT; 57.8% RFA), with 7.8% of participants in the RFA group categorized as Black and 34.4% as other.<sup>63</sup> Data for people who identified as Black and other participants were not available for people in the SBRT group because of small numbers (only 32 patients in total were included in the SBRT group).<sup>63</sup>

Table 7. Summary Characteristics of Included Studies of SBRT for Liver Cancer

Study	Population	Description	Relevant Outcomes
<b>Systematic reviews</b>			
Dobrzycka et al., 2019 <sup>32</sup>	Patients with hepatocellular carcinoma	Included 16 noncomparative studies, comprising 973 patients Search date through May 2019	<ul style="list-style-type: none"> <li>• Safety, including treatment-related mortality</li> </ul>
Eriguchi et al., 2021 <sup>55</sup>	Patients with hepatocellular carcinoma	Included 6 propensity score-matched studies, comprising 2,107 patients; search date through October 2020	<ul style="list-style-type: none"> <li>• Local tumor control</li> <li>• Overall survival</li> <li>• Safety, including treatment-related mortality</li> </ul>
Facciorusso et al., 2021 <sup>54</sup>	Patients with hepatocellular carcinoma	Included 9 retrospective studies, comprising 6,545 patients; search date through September 2020	<ul style="list-style-type: none"> <li>• Recurrence-free survival</li> <li>• Overall survival</li> <li>• Safety</li> </ul>
Lee et al., 2020 <sup>49</sup>	Patients with early hepatocellular carcinoma and liver metastases	Included 11 studies (8 in early hepatocellular carcinoma and 3 in liver metastases), comprising 2,238 patients; search date not reported	<ul style="list-style-type: none"> <li>• Local tumor control</li> <li>• Overall survival</li> <li>• Safety</li> </ul>
Rim et al., 2019 <sup>25</sup>	Patients with hepatocellular carcinoma	Included 32 noncomparative studies, comprising 1,950 patients;	<ul style="list-style-type: none"> <li>• Safety</li> </ul>

Study	Population	Description	Relevant Outcomes
		search date through April 2018	
Shanker et al., 2021 <sup>23</sup>	Patients with primary hepatocellular carcinoma	Included 49 noncomparative cohort studies, comprising 2,846 patients; search date from January 2005 to December 2019	<ul style="list-style-type: none"> <li>• Safety</li> </ul>
<b>Primary studies</b>			
<i>Comparative observational studies</i>			
Jeong et al., 2021 <sup>52</sup>	Patients with newly diagnosed or recurrent small hepatocellular carcinoma	266 patients in total; 87 treated with SBRT and 179 with RFA	<ul style="list-style-type: none"> <li>• Local tumor control</li> <li>• Recurrence-free survival</li> <li>• Overall survival</li> <li>• Safety</li> </ul>
Jun et al., 2018 <sup>51</sup>	Patients with hepatocellular carcinoma	199 patients in total; 85 treated with SBRT+TACE and 114 with TACE alone	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression-free survival</li> <li>• Local tumor control</li> <li>• Safety</li> </ul>
Nabavizadeh et al., 2021 <sup>48</sup>	Patients with inoperable hepatocellular carcinoma	190 patients in total; 90 treated with TACE then SBRT and 100 with TACE then TA	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression-free survival</li> <li>• Safety</li> </ul>
Sebastian et al., 2019 <sup>61</sup>	Patients with unresected intrahepatic cholangiocarcinoma	170 patients in total; 61 treated with CRT, 37 with SBRT, and 72 with TARE	<ul style="list-style-type: none"> <li>• Overall survival</li> </ul>
Shen et al., 2019 <sup>44</sup>	Patients with medium-sized (3 to 8 cm) hepatocellular carcinoma	188 patients in total; 46 treated with SBRT and 142 with TACE	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Infield control</li> <li>• Safety</li> </ul>
Wang et al., 2021 <sup>43</sup>	Patients with BCLC stages 0 to B1 hepatocellular carcinoma	98 patients in total; 26 treated with RFA then SBRT and 72 with continued RFA	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression-free survival</li> <li>• Safety</li> </ul>
Wong et al., 2019 <sup>42</sup>	Patients with nonresectable hepatocellular carcinoma	251 patients in total; 49 treated with TACE then SBRT and 202 with TACE alone	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression-free survival</li> <li>• Safety</li> </ul>
Wong et al., 2021 <sup>41</sup> , NCT03950102	Patients with hepatocellular carcinoma accepted on a transplant waiting list	150 patients in total; 40 treated with SBRT, 59 with TACE, and 51 with HIFU	<ul style="list-style-type: none"> <li>• Local tumor control</li> <li>• Safety</li> <li>• Survival post-transplant</li> </ul>
<i>Noncomparative studies (harms only)</i>			
Kibe et al., 2021 <sup>29</sup>	Patients with hepatocellular carcinoma	180 patients who received marker-less SBRT	<ul style="list-style-type: none"> <li>• Safety</li> </ul>

Study	Population	Description	Relevant Outcomes
Loi et al., 2021 <sup>28</sup>	Patients with advanced hepatocellular carcinoma	128 patients who received SBRT	• Safety
Mathew et al., 2020 <sup>27</sup>	Patients with localized hepatocellular carcinoma without vascular invasion, who were ineligible for other liver-directed therapies	297 patients received SBRT	• Safety
Park et al., 2020 <sup>26</sup>	Patients with hepatocellular carcinoma	290 patients who received SBRT	• Safety
Voglhuber et al., 2021 <sup>19</sup>	Patients with liver metastases	115 patients who received SBRT	• Safety
<b>Economic studies</b>			
Parikh et al., 2018 <sup>63</sup>	Patients with stage I or II hepatocellular carcinoma and treated with RFA or SBRT as the initial treatment within 6 months of diagnosis	440 patients in total; 32 treated with SBRT and 408 with RFA	• Costs

Abbreviations. BCLC: Barcelona Clinical Liver Cancer; CRT: chemoradiotherapy; HIFU: high-intensity focused ultrasound; RFA: radiofrequency ablation; SBRT: stereotactic body radiation therapy; TA: thermal ablation; TACE: transarterial chemoembolization; TARE; transarterial radioembolization.

## Effectiveness

### Overall Survival

#### SBRT vs. RFA

Systematic reviews of observational studies, and observational studies comparing SBRT and RFA, showed mixed results for overall survival.

- Based on a meta-analysis of 6 nonrandomized studies, patients who received SBRT had similar overall survival rates to patients who received RFA (HR, 1.17; 95% CI, 0.92 to 1.48).<sup>55</sup> However, when the 3 propensity-matched studies that did not use the BCLC staging score were pooled, patients who received RFA had better overall survival rates than patients who received SBRT (HR, 1.41; 95% CI, 1.21 to 1.65).<sup>55</sup>
- Based on a meta-analysis of 5 nonrandomized studies, patients who received SBRT had similar overall survival rates to patients who received RFA (HR, 1.03; 95% CI, 0.72 to 1.47).<sup>54</sup>
- Based on a meta-analysis of 7 nonrandomized studies, patients who received RFA had higher overall survival rates than patients who received SBRT (OR, 1.43; 95% CI, 1.05 to 1.95).<sup>49</sup>
- In 1 retrospective study in 266 patients, people with a small hepatocellular carcinoma who were treated with SBRT had significantly lower overall survival rates than patients treated with RFA (univariate analysis HR, 1.81; 95% CI, 1.14 to 2.89).<sup>52</sup> However, in multivariate analyses and when adjusted for baseline differences between groups, there was no difference in overall survival between SBRT and RFA for small hepatocellular carcinoma.<sup>52</sup>
- In 1 retrospective study in 98 patients with BCLC stages 0 to B1 hepatocellular carcinoma, patients treated with RFA then SBRT had similar rates of overall survival to patients treated with continued RFA (at year 1, 95.2% vs. 90.5%; at year 3, 87.3% vs. 73.3%; at year 5, 74.8% vs. 43.6%;  $P = .09$ ).<sup>43</sup>

## SBRT vs. TACE

Observational studies comparing SBRT and TACE showed mixed results for overall survival.

- In 1 retrospective study in 199 patients, people with hepatocellular carcinoma who were treated with SBRT in combination with TACE had similar overall survival rates to people treated with TACE alone (at year 1, 98.8% vs. 99.7%; at year 3, 89.1% vs. 83.3%; at year 5, 80.7% vs. 71.0%;  $P = .21$ ).<sup>51</sup> No difference was also found between treatment groups for overall survival in a univariate analysis (HR, 0.72; 95% CI, 0.38 to 1.38).<sup>51</sup>
- In 1 retrospective study in 190 patients, people with inoperable hepatocellular carcinoma who were treated with SBRT after TACE had significantly worse overall survival rates than people treated with TA after TACE (univariate subdistribution hazard ratio [sHR], 2.55; 95% CI, 1.80 to 3.61; multivariate sHR, 2.70; 95% CI, 1.83 to 3.97).<sup>48</sup> For the subset of patients with BCLC stage A hepatocellular carcinoma and Child-Pugh stage A cirrhosis, there was no difference in overall survival between the treatment groups ( $P = .11$ ).<sup>48</sup>
- In 1 retrospective study in 188 patients with medium-sized hepatocellular carcinoma, patients treated with SBRT had better overall survival rates compared with patients treated with TACE (univariate HR, 0.62; 95% CI, 0.40 to 0.95; multivariate HR, 0.37; 95% CI, 0.21 to 0.64).<sup>44</sup> For patients with newly diagnosed hepatocellular carcinoma, there was no difference between SBRT and TACE for overall survival (reported graphically;  $P = .83$ ).<sup>44</sup> For patients with recurrent disease, SBRT was associated with significantly better overall survival (reported graphically;  $P < .001$ ).<sup>44</sup>
- In 1 retrospective study in 251 patients with nonresectable hepatocellular carcinoma, patients who received SBRT after TACE had significantly better overall survival than patients who received TACE alone (at year 1, 67.2% vs. 43.9%; at year 2, 47.1% vs. 24.2%; at year 3, 36.5% vs. 13.3%;  $P = .003$ ; univariate HR, 0.55; 95% CI, 0.37 to 0.82; multivariate HR, 0.37; 95% CI, 0.24 to 0.56).<sup>42</sup>

## SBRT vs. TACE or HIFU

Based on 1 observational study with SBRT as bridging therapy, TACE and HIFU were associated with similar overall survival rates in patients with hepatocellular carcinoma and who were on the waiting list for transplantation.

- In 1 study where participants were prospectively enrolled for SBRT, patients treated with SBRT as bridging therapy had similar rates of overall survival to patients treated with TACE or HIFU (reported graphically;  $P = .29$ ).<sup>41</sup>

## SBRT vs. CRT or TARE

Based on 1 observational study, SBRT was associated with significantly better overall survival than CRT or TARE.

- In an analysis of the US National Cancer Database, patients with unresected intrahepatic cholangiocarcinoma treated with SBRT had significantly better overall survival rates compared with CRT (HR, 0.37; 95% CI, 0.20 to 0.68) and compared with TARE (HR, 0.40; 95% CI, 0.22 to 0.74).<sup>61</sup> These differences were also statistically significant using multivariate analysis and inverse probability of treatment weighting analysis, used to account for confounding.<sup>61</sup>

## Recurrence-free Survival

### SBRT vs. RFA

Based on a meta-analysis, SBRT is associated with better recurrence-free survival than RFA.

- Based on a meta-analysis of 6 nonrandomized studies, patients who received SBRT had significantly better recurrence-free survival rates than patients who received RFA (HR, 0.50; 95% CI, 0.33 to 0.76).<sup>54</sup>
- In 1 retrospective study in 266 patients, people with small hepatocellular carcinoma who were treated with SBRT had similar intrahepatic recurrence-free survival rates to patients treated with RFA (univariate analysis HR, 1.29; 95% CI, 0.94 to 1.77).<sup>52</sup> Similar results were also seen in multivariate analyses and when adjusted for baseline differences between groups.<sup>52</sup>

## Progression-free Survival

### SBRT vs. RFA

Based on 1 observational study, SBRT and RFA had similar rates of progression-free survival.

- In 1 retrospective study in 98 patients with BCLC stages 0 to B1 hepatocellular carcinoma, patients treated with RFA then SBRT had similar rates of progression-free survival to patients treated with continued RFA (at year 1, 66.7% vs. 52.4%; at year 2, 31.4% vs. 28.6%;  $P = .31$ ).<sup>43</sup>

### SBRT vs. TACE

Results from 3 observational studies show mixed results for SBRT on progression-free survival.

- In 1 retrospective study in 199 patients, people with hepatocellular carcinoma who were treated with SBRT in combination with TACE had significantly better progression-free survival than people treated with TACE alone (at year 1, 56.5% vs. 32.3%; at year 3, 42.2% vs. 21.6%;  $P = .02$ ).<sup>51</sup> In a univariate analysis, SBRT in combination with TACE was associated with better progression-free survival (HR, 0.67; 95% CI, 0.48 to 0.99); however, in the multivariate analysis, there was no difference between groups (HR, 0.69; 95% CI, 0.48 to 1.00).<sup>51</sup> However, in people with 1 to 2 nodules, SBRT in combination with TACE was associated with better progression-free survival than TACE alone in both univariate and multivariate analyses.<sup>51</sup>
- In 1 retrospective study in 190 patients, people with inoperable hepatocellular carcinoma who were treated with SBRT after TACE had worse progression-free survival rates than people treated with TA after TACE (univariate sHR, 1.85; 95% CI, 1.25 to 2.76; multivariate sHR, 1.71; 95% CI, 1.10 to 2.65).<sup>48</sup> For the subset of patients with BCLC stage A hepatocellular carcinoma and Child-Pugh stage A cirrhosis, there was no difference in overall survival between the treatment groups ( $P = .19$ ).<sup>48</sup>
- In 1 retrospective study in 251 patients with nonresectable hepatocellular carcinoma, patients who received SBRT after TACE had significantly better progression-free survival than patients who received TACE alone (at year 1, 32.5% vs. 21.4%; at year 2, 20.1% vs. 12.1%; at year 3, 15.1% vs. 5.1%;  $P = .01$ ; univariate HR, 0.62; 95% CI, 0.42 to 0.90; multivariate HR, 0.47; 95% CI, 0.32 to 0.70).<sup>42</sup>

## Local Tumor Control

### SBRT vs. RFA

Systematic reviews and observational studies show that SBRT has similar or better tumor control than RFA.

- Based on a meta-analysis of 6 nonrandomized studies, patients who received SBRT had significantly better local tumor control than patients who received RFA (HR, 0.39; 95% CI, 0.30 to 0.50).<sup>55</sup>
- Based on a meta-analysis of 3 nonrandomized studies, patients who received SBRT had similar local tumor control (defined as complete response) to patients who received RFA (OR, 1.30; 95% CI, 0.17 to 9.95).<sup>54</sup>
- Based on a meta-analysis of 7 nonrandomized studies, patients who received SBRT had better local tumor control than patients who received RFA (83.7% vs. 71.8%;  $P = .02$ ).<sup>49</sup> When analyzed by cancer stage, there was no difference in local tumor control for people with early hepatocellular carcinomas (84.5% vs. 79.5%;  $P = .43$ ) but people with liver metastases who received SBRT had better local tumor control than people who received RFA (83.6% vs. 60.0%;  $P < .001$ ).<sup>49</sup>
- In 1 retrospective study in 266 patients, people with small hepatocellular carcinoma who were treated with SBRT had similar local tumor control rates to patients treated with RFA (univariate analysis HR, 1.29; 95% CI, 0.94 to 1.77).<sup>52</sup> Similar results were also seen in multivariate analyses and when adjusted for baseline differences between groups.<sup>52</sup>

### SBRT vs. TACE

Observational studies show that SBRT has similar or better local tumor control than TACE.

- In 1 retrospective study in 199 patients, people with hepatocellular carcinoma who were treated with SBRT in combination with TACE had significantly better local tumor control than people treated with TACE alone (at year 1, 91.9% vs. 69.9%; at year 3, 89.9% vs. 44.8%; at year 5, 89.9% vs. 44.8%;  $P < .001$ ).<sup>51</sup>
- In 1 retrospective study in 190 patients, people with inoperable hepatocellular carcinoma who were treated with SBRT after TACE had similar levels of local tumor control to people treated with TA after TACE (reported graphically;  $P = .28$ ).<sup>48</sup>
- In 1 retrospective study in 188 patients with medium-sized hepatocellular carcinoma, patients treated with SBRT had similar infield control rates to with patients treated with TACE (univariate HR, 0.49; 95% CI, 0.22 to 1.10), but when adjusted for prognostic factors, SBRT was associated with better infield control (multivariate HR, 0.33; 95% CI, 0.14 to 0.78).<sup>44</sup> For patients with newly diagnosed hepatocellular carcinoma, there was no difference between SBRT and TACE for infield control (reported graphically;  $P = .59$ ).<sup>44</sup> For patients with recurrent disease, SBRT was associated with significantly better overall survival (reported graphically;  $P = .02$ ).<sup>44</sup>
- In 1 retrospective study in 251 patients with nonresectable hepatocellular carcinoma, patients who received SBRT after TACE had significantly better disease control than patients who received TACE alone (98.0% vs. 56.7%; results also reported graphically;  $P < .001$ ).<sup>42</sup>

### SBRT vs. TACE or HIFU

Based on 1 observational study, SBRT is associated with better tumor control than TACE or HIFU.

- In 1 study where participants were prospectively enrolled for SBRT, patients treated with SBRT as bridging therapy were significantly more likely to have better tumor control than patients treated with TACE or HIFU (92.3% vs. 43.5% vs. 33.3%;  $P = .02$ ).<sup>41</sup> Pathological complete response was also significantly more frequent after SBRT as bridging therapy compared with TACE and HIFU (48.1% vs. 25.0% vs. 17.9%;  $P = .037$ ).<sup>41</sup>

### Harms

Patients treated with SBRT, RFA, TACE, or HIFU all were at risk of experiencing an adverse event, and these were often mild in nature. Based on 2 systematic reviews, people receiving SBRT or RFA appeared to have similar rates of adverse events.

### Toxicity and Other Adverse Events

#### SBRT vs. RFA

- In the review by Eriguchi and colleagues,<sup>55</sup> 4 studies reported on toxicity. Overall, rates of grade 3 or higher toxicities ranged from 0% to 11%, and were not significantly different between SBRT and RFA.<sup>55</sup> The rates of liver failure-related mortality was similar for SBRT and RFA at 3 years ( $P = .52$ ).<sup>55</sup>
- In the review by Lee and colleagues,<sup>49</sup> grade 3 or higher toxicity rates ranged from 0 to 12% for SBRT and RFA across 9 studies.
- Patients receiving SBRT were significantly more likely to experience complications than patients who received RFA (23.2% vs. 17.0%; OR, 1.63; 95% CI, 1.01 to 2.64).<sup>54</sup>
- In 1 retrospective study in 266 patients, no grade 3 or higher elevation in the levels of transaminases or bilirubin was observed in the SBRT or RFA groups.<sup>52</sup> In the SBRT group, 1 patient died due to hepatic failure of unknown cause 4 months after treatment.<sup>52</sup> Overall, 1 grade 3 or higher adverse event was seen in each of the SBRT and the RFA treatment groups (1.1% vs. 0.6%;  $P$  value not reported).<sup>52</sup>
- In 1 retrospective study in 98 patients with BCLC stages 0 to B1 hepatocellular carcinoma, the cumulative rates of a Child–Pugh score deterioration of 2 or more in the RFA followed by SBRT group was 23.8% and 33.3% in the continued RFA group ( $P > .05$ ).<sup>43</sup> No grade 3 or more adverse events in both groups (SBRT after RFA or continued RFA) were observed.<sup>43</sup>

#### SBRT vs. TACE

- In 1 retrospective study in 199 patients, people with hepatocellular carcinoma treated with SBRT in combination with TACE had similar rates of worsening Child-Pugh scores within 3 months of treatment (9.4% vs. 5.5%;  $P = .12$ ) and elevated liver transaminases (9.4% vs. 4.8%;  $P = .24$ ) compared with people treated with TACE alone.<sup>51</sup>
- In 1 retrospective study in 190 patients, a total of 24 patients (from 138 patients with sufficient follow-up data) experienced treatment-related hepatotoxicity, with higher rates of toxicity in the SBRT group compared with the TACE group (27% vs. 9%;  $P = .01$ ).<sup>51</sup>
- In 1 retrospective study in 188 patients with medium-sized hepatocellular carcinoma, patients in both the SBRT and TACE groups experienced liver toxicities.<sup>44</sup> In the SBRT group, 9 patients had radiation-induced liver disease (RILD) and 7 had worsening Child-Turcotte-Pugh scores.<sup>44</sup> No patients died of hepatic failure in the SBRT group.<sup>44</sup> In the TACE group, 26 patients had hepatic failure, with 2 patients dying of TACE-related hepatic failure within 1 month of treatment.<sup>44</sup>



- In 1 retrospective study in 251 patients with nonresectable hepatocellular carcinoma, patients who received SBRT after TACE experienced significantly more grade 3 and greater toxicities than patients who received TACE alone, including elevated bilirubin and aspartate aminotransferase levels; however, severe toxicity was relatively rare overall.<sup>42</sup>

#### SBRT vs. TACE or HIFU

- In 1 study where participants were prospectively enrolled for SBRT, patients treated with SBRT as bridging therapy had similar rates of toxicity compared to patients treated with TACE or HIFU.<sup>41</sup>

#### SBRT

- Overall, 53 (5.4%) patients experienced grade 3 or higher toxicity complications.<sup>32</sup> Hepatic toxicity grade 3 or higher occurred in around 5.0 to 6.5% of patients.<sup>32</sup> There were no treatment-related deaths reported.<sup>32</sup>
- Based on data from 23 noncomparative cohort studies of SBRT, the most commonly reported complications of grade 3 or higher were gastrointestinal or hepatic toxicities, with a pooled rate of 3.9% (95% CI, 2.6 to 5.6) for gastrointestinal toxicities and 4.7% (95% CI, 3.4 to 6.5) for hepatic toxicities.<sup>25</sup> Rates did not differ significantly by tumor size or by radiation dose (dichotomized to a median equivalent dose in 2 Gy per fractions of less than 80 and 80 or more).<sup>25</sup>
- When studies were pooled in the review by Shanker and colleagues,<sup>23</sup> the population-weighted median grade 3 liver or gastrointestinal toxicity rates were 6.5% (IQR, 3.2 to 16; based on 2,853 lesions) and mean grades 4 to 5 rates were 1.4% for SBRT (IQR, 0 to 2.1; based on 1,784 lesions).<sup>23</sup> Larger lesions and higher doses of radiation were significantly associated with greater toxicity in the unadjusted analysis; but when adjusted for lesion size, higher doses of radiation were no longer associated with increases in grades 4 to 5 toxicity.<sup>23</sup>
- In 1 retrospective study evaluating markerless SBRT in 180 patients with hepatocellular carcinoma, grade 3 hypoalbuminemia and thrombocytopenia were observed in 1 of 173 (0.6%) and 5 of 173 (2.9%) patients as acute hematologic toxicities and in 0 and 3 (1.7%) patients at baseline, respectively.<sup>29</sup> No grade 3 or higher nonhematological hepatic or gastrointestinal acute toxicities were observed.<sup>29</sup> Nonclassic RILD occurred in 4 patients (2.0%), all of which were caused by the worsening of the Child-Pugh score by 2 points or more from baseline.<sup>29</sup>
- In 1 retrospective study of SBRT for advanced hepatocellular carcinoma, acute and late toxicity occurred in 26% and 8% of SBRT courses.<sup>28</sup> In a multivariate analysis, BCLC stage B to C was significantly associated with increased toxicity (HR, 2.9; 95% CI, 1.10 to 7.65).<sup>28</sup>
- In 1 retrospective study of SBRT for localized hepatocellular carcinoma, low rates of clinical toxicity were observed.<sup>27</sup> Overall, 15.9% of patients experienced a worsening Child-Pugh score and 21.2% had a worsening in albumin-bilirubin score grade, 3 months after SBRT.<sup>27</sup> No patients developed classic RILD or grade 4 liver enzyme toxicity.<sup>27</sup> In 3 patients, biliary toxicity developed at 1 month, 1.5 months, and 30 months after SBRT.<sup>27</sup> After 10 months posttreatment, 1 patient died, which was considered to be related to possible late toxicity from a duodenal ulcer and an upper gastrointestinal bleed.<sup>27</sup>
- In 1 retrospective study of SBRT for hepatocellular carcinoma, 2.8% of patients experienced grade 3 or higher hepatic toxicities and 5.5% had elevated Child-Pugh scores.<sup>26</sup> At 2 months after the completion of SBRT, 1 patient who experienced grade 4 hyperbilirubinemia died

due to hepatic failure.<sup>26</sup> Overall, toxicities were mild and no patients had to discontinue treatment because of adverse events.

- In 1 retrospective study of SBRT for liver metastases, 8.7% of patients experienced grade 3 adverse events, with 70.4% of patients experience acute toxicities of any grade.<sup>19</sup>

### Serious Adverse Events, Including Deaths

#### SBRT vs. RFA

- Patients receiving SBRT and RFA had similar rates of serious adverse events (7.8% vs. 6.9%; OR, 1.38; 95% CI, 0.28 to 6.71).<sup>54</sup>
- In the review by Lee and colleagues,<sup>49</sup> around 5% of people experienced serious complications with SBRT and RFA.

#### SBRT vs. TACE

- In 1 retrospective study in 251 patients with nonresectable hepatocellular carcinoma, 32 (100%) patients who received SBRT after TACE and 78 (85.7%) patients who received TACE alone died of cancer-related reasons.<sup>42</sup>

#### SBRT

- In 1 retrospective study of SBRT for advanced hepatocellular carcinoma, a grade 3 adverse event (acute liver failure and ascites requiring paracentesis) was reported in 1 patient.<sup>28</sup>
- Treatment-related death from SBRT was not observed in a retrospective study of SBRT in 180 patients with hepatocellular carcinoma.<sup>29</sup>

### Economic Studies

#### SBRT vs. RFA

Based on 1 economic analysis, SBRT does not appear to be cost-effective when compared with RFA.

- In 1 retrospective study using data from the SEER database, patients treated with SBRT had significantly lower overall costs than patients treated with RFA (median, \$51,746 vs. \$85,016;  $P = .002$ ).<sup>63</sup> Patients treated with SBRT also had significantly lower inpatient costs (\$23,360 vs. \$54,053;  $P = .002$ ) but significantly higher 90-day outpatient costs (\$15,478 vs. \$5,760;  $P < .001$ ).<sup>63</sup> SBRT appeared to be cost-effective when compared with RFA (incremental cost-effectiveness ratio [ICER] of \$56,301 per life-year gained in the overall group and \$1,412 in the propensity score-matched group) in the base case analysis.<sup>63</sup> Bootstrap estimates for the median ICER also showed that SBRT was cost-effective for the overall group (median ICER, \$61,164; 95% CI, -\$420,299 to \$367,960) and for the propensity score-matched group (median ICER, \$12,592; 95% CI, -251,874 to \$390,198); however, the upper 95% CI for both estimates showed that SBRT may not be cost-effective.<sup>63</sup> Overall, 85% of the overall population median ICER estimates and 92% of the propensity score-matched group median ICER estimates were below \$100,000 (the assumed threshold).<sup>63</sup>

### Bottom Line

Based on prior evidence updates and newly identified evidence, we conclude that at this time, the newly identified studies on effectiveness and harms, and cost-effectiveness modeling based

on registry and claims data are unlikely to change the conclusions of the 2012 evidence review, because of the lack of identified RCTs for liver cancer.

## Head and Neck Cancer

### History

In the 2012 report presented to the HTCC,<sup>1</sup> the overall strength of evidence was assessed as very low for harms for head and neck cancers (specifically, ocular and glomus jugulare), based on 1 systematic review and 7 case series.<sup>226-233</sup> No comparative effectiveness or economic studies were identified.<sup>1</sup>

In the 2017 evidence update,<sup>3</sup> no additional studies were identified. In the 2019 evidence update,<sup>4</sup> 4 comparative observational studies were identified.<sup>234-237</sup> The authors of the 2019 update concluded that the identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review for head and neck cancer because no RCTs had been published since 2012.<sup>3</sup>

### Findings in This Evidence Update

Since the most recent evidence update report,<sup>4</sup> we identified 1 recently published retrospective noncomparative study.

- Baker and colleagues<sup>36</sup> evaluated outcomes for 195 people with oropharyngeal squamous cell carcinoma treated with SBRT. The median age of the participants was 61 years, and 63% were male.<sup>36</sup> No data on race or ethnicity were reported.<sup>36</sup> The study was conducted in a single center in the Netherlands.<sup>36</sup>

We did not identify any newly published economic studies of SBRT for head and neck cancer.

Table 8. Summary Characteristics of Included Studies of SBRT for Head and Neck Cancer

Study	Population	Description	Relevant Outcomes
Noncomparative studies (harms only)			
Baker et al., 2019 <sup>36</sup>	Patients with oropharyngeal squamous cell carcinoma	195 patients treated with SBRT	• Safety

Abbreviation. SBRT: stereotactic body radiotherapy.

### Effectiveness

We did not identify any new eligible studies reporting on the effectiveness of SBRT for people with head and neck cancers.

### Harms

Based on 1 retrospective analysis, people who receive SBRT may experience grade 3 or higher adverse events.

### Toxicity and Other Adverse Events

- In 1 retrospective study, patients with oropharyngeal squamous cell carcinoma treated with SBRT had a cumulative incidence of grade 3 or higher toxicities of 28% at 5 years.<sup>36</sup> People who smoked or who had a Charlson Comorbidity Index of 2 or more were significantly more

likely to experience grade 3 or higher toxicities.<sup>36</sup> The cumulative incidence of grade 3 or higher mucosal ulcers or soft tissue necrosis at 5 years was 18%.<sup>36</sup> People who smoked or in whom the tonsil was the subsite were significantly more likely to grade 3 or higher mucosal ulcers or soft tissue necrosis.<sup>36</sup> The 5-year cumulative incidence of grade 3 or higher osteoradionecrosis was 9%.<sup>36</sup> Tooth extraction prior to treatment was significantly associated with an increased risk of grade 3 or higher osteoradionecrosis.<sup>36</sup> The 5-year cumulative incidence of grade 3 or higher difficulty swallowing or weight loss was 12%.<sup>36</sup> People who smoked or who had a Charlson Comorbidity Index of 2 or more were significantly more likely to experience grade 3 or higher difficulty swallowing or weight loss.<sup>36</sup>

### **Bottom Line**

Based on prior evidence updates and newly identified evidence, we conclude that at this time, the newly identified studies on effectiveness and harms are unlikely to change the conclusions of the 2012 evidence review, because of the lack of RCTs for head and neck cancers.

## **Adrenal Cancer**

### **History**

In the 2012 report presented to the HTCC,<sup>1</sup> the overall strength of evidence was assessed as very low for effectiveness and harms for adrenal metastases, based on 2 case series.<sup>238,239</sup> No economic studies were identified.<sup>1</sup>

In the 2017 evidence update,<sup>3</sup> 1 additional systematic review was identified.<sup>240</sup> In the 2019 evidence update,<sup>4</sup> 1 new comparative observational study was identified.<sup>241</sup> The authors of the 2019 update concluded that the identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review for adrenal cancer because no RCTs had been published since 2012.<sup>3</sup>

### **Findings in This Evidence Update**

We did not identify any new eligible studies of SBRT in this population.

### **Bottom Line**

Based on prior evidence updates and identified evidence, we conclude that at this time, the newly identified studies on effectiveness and harms are unlikely to change the conclusions of the 2012 evidence review, because of the lack of RCTs for adrenal cancer.

## **Renal Cancer**

### **History**

In the 2012 report presented to the HTCC,<sup>1</sup> no primary studies reported on the effectiveness of SBRT for renal cancer alone. In the 2017 and 2019 evidence updates,<sup>3,4</sup> no new studies were identified. No recommendation to update the original review was made in 2017 or 2019.<sup>3,4</sup>

### **Findings in This Evidence Update**

Since the most recent evidence update report,<sup>4</sup> we identified 1 recently published systematic review and 1 comparative study on the effectiveness of SBRT for renal cell carcinoma.<sup>37,64</sup>

- Correa and colleagues<sup>64</sup> reviewed 26 studies of SBRT for primary renal cell carcinoma, representing 372 patients with 383 tumors. Although the review reported on local tumor

control,<sup>64</sup> the meta-analysis was noncomparative, so we report only harms in this evidence update.

- Uhlig and colleagues<sup>37</sup> compared the outcomes for renal cell carcinoma treated with SBRT, partial nephrectomy, cryoablation, or radiofrequency or microwave ablation.<sup>37</sup> Overall, 91,965 patients with stage I renal cell carcinoma were identified from the US National Cancer Database.<sup>37</sup> The median age of participants was 71 years in the propensity-match group, with 63% being male.<sup>37</sup> The majority of participants identified as White (88%), with 9% identifying as African American and 2% identifying as of another race or ethnicity.<sup>37</sup>

We did not identify any newly published economic studies of SBRT for renal cancer.

**Table 9. Summary Characteristics of Included Studies of SBRT for Renal Cancer**

Study	Population	Description	Relevant Outcomes
<b>Systematic reviews</b>			
Correa et al., 2019 <sup>64</sup>	Patients with primary renal cell carcinoma	Included 26 studies (11 prospective and 15 retrospective), comprising 372 patients; search date through February 2019	• Safety
<b>Primary studies</b>			
<i>Comparative observational studies</i>			
Uhlig et al., 2020 <sup>37</sup>	Patients with stage I renal cell carcinoma	91,965 patients in total; 174 treated with SBRT, 82,913 with partial nephrectomy, 5,446 with cryoablation, and 3,432 with radiofrequency or microwave ablation; 636 patients included in the propensity-matched analysis	• Overall survival

*Abbreviation. SBRT: stereotactic body radiotherapy.*

### Effectiveness

SBRT did not appear to be an effective treatment for renal cell carcinoma, based on 1 propensity-matched analysis.<sup>37</sup>

### Overall Survival

- In a propensity-matched analysis from the US National Cancer Database, patients who received a partial nephrectomy had significantly higher overall survival rates than people who received SBRT (88% vs. 76% at 3 years; 84% vs. 58% at 5 years; HR, 0.29; 95% CI, 0.19 to 0.46).<sup>37</sup> Similarly, patients who received cryoablation had significantly higher overall survival rates than people who received SBRT (84% vs. 76% at 3 years; 77% vs. 58% at 5 years; HR, 0.40; 95% CI, 0.26 to 0.60) as did patients who received radiofrequency or microwave ablation (87% vs. 76% at 3 years; 76% vs. 58% at 5 years; HR, 0.46; 95% CI, 0.31 to 0.67).<sup>37</sup>

### Harms

SBRT was not associated with significant harms, based on 1 systematic review of noncomparative studies.<sup>64</sup>

## Toxicity and Other Adverse Events

- Based on a pooled analysis of 23 noncomparative studies, the rate of grade 3 to 4 toxicities was 1.5% (95% CI, 0% to 4.3%; range, 0% to 25.0%).<sup>64</sup> The majority of toxicity was mild, with nausea, fatigue, or dermatitis observed in 37.5% (grade 1) and 8.8% (grade 2) of patients.<sup>64</sup>

## Serious Adverse Events, Including Deaths

- In a systematic review of 26 studies, none reported any treatment-related deaths.<sup>64</sup>

## Bottom Line

Based on prior evidence updates and newly identified evidence, we conclude that at this time, the newly identified studies on effectiveness and harms are unlikely to change the conclusions of the 2012 evidence review, because of the lack of effectiveness data from RCTs for renal cancer.

## Bone Cancer

### History

In the 2012 report presented to the HTCC,<sup>1</sup> no primary studies reported on the effectiveness of SBRT for bone metastases.

In the 2017 evidence update,<sup>3</sup> no new studies were identified. In the 2019 evidence update,<sup>4</sup> 4 additional comparative observational studies were included,<sup>204-207</sup> and again, the authors of the update concluded that the identified new studies of effectiveness and safety were unlikely to change the conclusions of the 2012 evidence review because no RCTs had been published since 2012.<sup>3</sup>

The 2019 evidence update<sup>4</sup> did identify 1 systematic review of noncomparative studies.<sup>242</sup> No recommendation to update the original review was made.<sup>4</sup>

### Findings in This Evidence Update

Since the most recent evidence update report,<sup>4</sup> we identified 2 recently published RCTs on the effectiveness of SBRT for bone metastases.

- Nguyen and colleagues<sup>47</sup> randomized 160 people with painful bone metastases to high-dose single-fraction SBRT or standard multifraction radiotherapy. The mean age of participants was 62 years in the high-dose single-fraction SBRT group and 63 years in the standard multifraction radiotherapy group.<sup>47</sup> The majority of participants were male (60% overall; 61% in the SBRT group and 60% in the standard radiotherapy group).<sup>47</sup> In the high-dose single-fraction SBRT group, 84% of participants identified as Caucasian, 2% as African American, 9% as Hispanic, 4% as Asian, and 1% as of other race or ethnicity.<sup>47</sup> In the standard multifraction radiotherapy group, 75% of participants identified as Caucasian, 10% as African American, 5% as Hispanic, 2% as Asian, and 8% as of other race or ethnicity.<sup>47</sup> The RCT was conducted at a single tertiary cancer care center in the US.<sup>47</sup>
- Pielkenrood and colleagues<sup>45</sup> randomized 110 patients with bone metastases to SBRT or to conventional EBRT. The median age of participants was 65 years in the SBRT group and 63 in the conventional EBRT group.<sup>45</sup> The proportion of participants was 53% in the SBRT group and 70% in the conventional EBRT group.<sup>45</sup> No race or ethnicity data were reported.<sup>45</sup> The RCT was conducted at a single tertiary medical center in the Netherlands.<sup>45</sup>

Table 10. Summary Characteristics of Included Studies of SBRT for Bone Cancer

Study	Population	Description	Relevant Outcomes
Randomized controlled trials			
Nguyen et al., 2019 <sup>47</sup> ; NCT02163226	Patients with radiologically confirmed painful bone metastases	160 patients in total; 81 allocated to SBRT and 79 to standard multifraction radiotherapy	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression</li> <li>• Local failure</li> <li>• Safety</li> </ul>
Pielkenrood et al., 2021 <sup>45</sup> ; NCT02364115; VERTICAL	Patients with painful bone metastases	178 patients in total; 55 allocated to SBRT and 55 to conventional external beam radiation therapy	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Safety</li> </ul>

Abbreviation. SBRT: stereotactic body radiotherapy.

### Effectiveness

Based on 2 RCTs, SBRT and conventional radiotherapy appear to be associated with similar overall survival rates.<sup>45,47</sup>

#### Overall Survival

- In 1 noninferiority trial, patients in the high-dose single-fraction SBRT and standard multifraction radiotherapy groups had similar overall survival rates (median, 6.7 months; 95% CI, 4.6 to 10.9 months;  $P = .37$  between groups).<sup>47</sup> However, the quality-adjusted overall survival time was significantly higher in the SBRT group when compared with the standard multifraction radiotherapy group.<sup>47</sup>
- In 1 RCT, patients in the SBRT and conventional EBRT had similar survival rates at 90 days (84% vs. 84%;  $P \geq .05$ ).<sup>45</sup>

#### Local Tumor Control

- In 1 noninferiority trial, patients in the high-dose single fraction SBRT and standard multifraction radiotherapy groups had similar rates of local failure (HR, 0.18; 95% CI, 0.02 to 1.47).<sup>47</sup> Among the 81 patients in the intent-to-treat group given SBRT, none had local failures, leading to a cumulative incidence of local failure of 0% at 6 months and up to 24 months.<sup>47</sup> Among the 79 patients in the intent-to-treat group given multifraction radiotherapy, 6 experienced local failure, giving a 4.2% cumulative incidence of local failure at 6 months, 5.9% at 12 months, and 9.7% at 24 months ( $P = .02$ ).<sup>47</sup>

#### Quality of Life

- In 1 noninferiority trial, patients in the high-dose single fraction SBRT and standard multifraction radiotherapy groups both experienced improved quality of life scores 12 months after treatment, but there were no statistically significant differences between the groups.<sup>47</sup>

### Harms

Based on 2 RCTs, SBRT and conventional radiotherapy appear to be associated with similarly low levels of adverse events.<sup>45,47</sup>

## Toxicity and Other Adverse Events

- Patients in the high-dose single-fraction SBRT and standard multifraction radiotherapy groups experienced similar rates of adverse events (grade 3 nausea, 1.2% vs. 5.0%; grade 3 vomiting, 0% vs. 2.5%; grade 3 fatigue, 9.9% vs. 5.1%; all  $P > .05$ ), radiation dermatitis (1.2% vs. 2.5%;  $P = .62$ ), and fracture (1.2% vs. 0%;  $P = .99$ ).<sup>47</sup>
- In 1 RCT, no grade 3 or 4 toxicities related to treatment were observed.<sup>45</sup>

## Bottom Line

We identified 2 RCTs showing that SBRT may be associated with similar outcomes to standard multifraction radiotherapy, with no additional harms.<sup>45,47</sup>

Based on prior evidence updates and newly identified evidence, we conclude that at this time, the newly identified RCTs on effectiveness and harms of SBRT in people with bone metastases are unlikely to change the conclusions of the 2012 evidence review, as no outcomes are shown to be improved with SBRT when compared to conventional radiotherapy.

## Multiple Cancer Sites

### History

In the 2012 report presented to the HTCC,<sup>1</sup> no comparative studies were identified on multiple cancer sites. The report included 5 case series of SBRT for multiple tumor sites.<sup>243-247</sup> The report concluded that the overall strength of evidence was very low for effectiveness and harms.<sup>1</sup>

No new studies were identified in either the 2017 or 2019 evidence updates.<sup>3,4</sup>

### Findings in This Evidence Update

Since the most recent evidence update report,<sup>4</sup> we identified 2 recently published systematic reviews on the effectiveness of SBRT for metastatic cancers.<sup>10,11</sup>

- Yegya-Ramen and colleagues<sup>11</sup> assessed the efficacy and safety of SBRT for oligometastatic gynecologic malignancies. The systematic review included 16 studies (3 prospective and 13 retrospective), comprising 667 patients with oligometastatic gynecologic cancer.<sup>11</sup>
- Zaorsky and colleagues<sup>10</sup> assessed the efficacy and safety of SBRT for metastatic renal cell carcinoma.<sup>10</sup> The systematic review included 28 studies (1 prospective and 27 retrospective), comprising 1,602 patients with metastatic renal cell carcinoma.<sup>10</sup>

Although both of the systematic reviews reported on effectiveness outcomes, such as overall survival and local tumor control, there was no comparison of SBRT versus other treatment options.<sup>10,11</sup> We therefore only report on the harms outcomes from the systematic reviews.<sup>10,11</sup>

We identified 2 RCTs; 1 evaluating SBRT in combination with drug therapy<sup>57</sup> and 1 evaluating SBRT in combination with palliative standard of care.<sup>6</sup>

- Curti and colleagues<sup>57</sup> compared the use of SBRT after high-dose interleukin-2 with interleukin-2 alone for metastatic melanoma in 44 patients. The mean age of the participants was 53 in the SBRT group and 57.5 in the interleukin-2 alone group ( $P$  value, not significant).<sup>57</sup> There were 6 female participants (of 24; 25.0%) in the SBRT group and 4 (of 20; 20.0%) in the interleukin-2 alone group ( $P$  value, not significant).<sup>57</sup> No data on race or ethnicity were reported.<sup>57</sup> The study was conducted at a single clinic in the US.<sup>57</sup>



- Palma and colleagues<sup>6,7</sup> compared SBRT plus palliative standard of care with palliative standard of care alone in 99 patients with a controlled primary malignancy and 1 to 5 metastatic lesions. The median age of the participants was 67 (IQR, 59 to 74) in the SBRT group and 69 (IQR, 64 to 75) in the standard care group.<sup>6,7</sup> There were 26 female participants in the SBRT group and 14 in the standard care group (26 of 66 vs. 14 of 33; 39.4% vs. 24.4%; *P* value not reported).<sup>6,7</sup> No data on race or ethnicity were reported.<sup>6,7</sup> The study was conducted at 10 hospitals in Canada, the Netherlands, Scotland, and Australia.<sup>6,7</sup>

We also identified 1 comparative<sup>56</sup> and 7 noncomparative observational studies<sup>18,20,21,30,31,34,35</sup> published since the 2019 evidence update.

- De Bleser and colleagues<sup>56</sup> compared outcomes and toxicity between SBRT and elective nodal radiotherapy (ENRT) in 506 patients with oligorecurrent prostate cancer. The median age at diagnosis of prostate cancer was 63 (IQR, 58 to 68) in the SBRT group and 63 (IQR, 59 to 68) in the ENRT group.<sup>56</sup> No data on race or ethnicity were reported.<sup>56</sup> The study was conducted in 15 treatment centers across Europe and Australia.<sup>56</sup>
- Berkovic and colleagues<sup>35</sup> reported on the treatment efficacy and toxicity of patients treated by robotic SBRT in 104 patients with oligorecurrent lung metastases. The median age was 66.3 (range, 28.2 to 87.6) and 49 patients were female (47.1%).<sup>35</sup> No data on race or ethnicity were reported.<sup>35</sup> The study was conducted in a single center in Belgium.<sup>35</sup>
- Chalkidou and colleagues<sup>34</sup> conducted a prospective registry-based study of SBRT in 1,422 patients with solid cancer and extracranial oligometastases. The median age was 69 (IQR, 62 to 76) and 475 participants were female (33.4%).<sup>34</sup> No data on race or ethnicity were reported.<sup>34</sup> The study was conducted in 17 hospitals in England.<sup>34</sup>
- Franzese and colleagues<sup>31</sup> reported outcomes for 207 patients who received SBRT for oligometastatic renal cancer. The median age was 66.6 (range, 29.8 to 86.4) and 48 participants were female (76.8%).<sup>31</sup> No data on race or ethnicity were reported.<sup>31</sup> The study was conducted in a number of institutions across Italy.<sup>31</sup> A cohort of 58 patients from 1 center was also included in the systematic review by Zaorsky and colleagues.<sup>10</sup>
- Grozman and colleagues<sup>30</sup> reported on their experience of SBRT in 164 patients with large tumors (gross tumor volume of 70 cc or greater). The median age was 70 (range, 24 to 92) and 81 participants (49%) were female.<sup>30</sup> No data on race or ethnicity were reported.<sup>30</sup> The study was conducted in a single center in Sweden.<sup>30</sup>
- Sogono and colleagues<sup>21</sup> reported outcomes for 371 patients with oligometastatic disease who received single-fraction SBRT. The median age was 67 (range, 23 to 95) and 126 participants were female (34%).<sup>21</sup> No data on race or ethnicity were reported.<sup>21</sup> The study was conducted at a single center in Australia.<sup>21</sup>
- Sutura and colleagues<sup>20</sup> reported on outcomes, including quality of life, in 147 patients with oligometastatic disease. The median age was 62.5 (IQR, 54.7 to 70.1) and 75 participants (51.0%) were female.<sup>20</sup> The majority of participants were Caucasian (66.9%), with 2.7% identified as African American, 0.7% as Asian, and 29.2% as unknown.<sup>20</sup> The study was a multisite study, but study locations were not specified.<sup>20</sup>
- Yamamoto and colleagues<sup>18</sup> investigated factors affecting the local control of pulmonary oligometastases treated by SBRT and its association with survival. The study included 1,378 patients, of whom 553 (35.7%) were female, with a median age of 72 (IQR, 63 to 78)

overall.<sup>18</sup> No data on race or ethnicity were reported.<sup>18</sup> The study was conducted in 78 sites in Japan.<sup>18</sup>

Although some of the noncomparative studies reported on effectiveness outcomes, as outlined in the inclusion and exclusion criteria (Appendix B), we only report the harms for this evidence update.

We also identified 1 cost-effectiveness analysis, by Mehrens and colleagues,<sup>62</sup> based on the SABR-COMET trial.<sup>7</sup>

Table 11. Summary Characteristics of Included Studies of SRS or SBRT for Multiple Cancer Sites

Study	Population	Description	Relevant Outcomes
<b>Systematic reviews</b>			
Yegya-Raman et al., 2020 <sup>11</sup>	Patients with oligometastatic gynecologic cancer	Included 16 studies, comprising 667 patients; search date through May 2020	• Safety
Zaorsky et al., 2019 <sup>10</sup>	Patients with metastatic renal cell carcinoma	Included 28 studies, comprising 1,602 patients; search date 1970 through 2019	• Safety
<b>Primary studies</b>			
<i>Randomized controlled trials</i>			
Curti et al., 2020 <sup>57</sup> ; NCT01416831	Patients with metastatic melanoma	44 patients randomized; 24 allocated to SBRT after high-dose interleukin-2 and 20 to interleukin-2 alone	• Tumor response • Progression-free survival • Overall survival • Safety
Palma et al., 2019 <sup>6-8</sup> ; NCT01446744; SABR-COMET	Patients with a controlled primary malignancy and 1 to 5 metastatic lesions	99 patients randomized; 66 allocated to SBRT in combination with palliative standard of care and 33 to palliative standard of care alone	• Overall survival • Quality of life • Toxicity • Progression-free survival • Local tumor control
<i>Comparative observational studies</i>			
De Bleser et al., 2019 <sup>56</sup>	Patients with oligorecurrent prostate cancer	506 patients in total; 309 treated with SBRT and 197 with ENRT	• Metastasis-free survival • Castration-resistant prostate cancer-free survival • Toxicity-free survival • Safety
<i>Noncomparative studies (harms only)</i>			
Berkovic et al., 2020 <sup>35</sup>	Patients with oligorecurrent lung metastases	104 patients treated with SBRT	• Safety
Chalkidou et al., 2021 <sup>34</sup>	Patients with solid cancer and extracranial oligometastases	1,422 patients treated with SBRT	• Safety

Study	Population	Description	Relevant Outcomes
Franzese et al., 2021 <sup>31</sup>	Patients with oligometastatic renal cancer	207 patients treated with SBRT	• Safety
Grozman et al., 2021 <sup>30</sup>	Patients with large tumors	164 patients treated with SBRT	• Safety
Sogono et al., 2021 <sup>21</sup>	Patients with oligometastatic disease	371 patients treated with SBRT	• Safety
Sutera et al., 2019 <sup>20</sup> ; NCT01345552	Patients with oligometastatic disease	147 patients treated with SBRT	• Safety
Yamamoto et al., 2020 <sup>18</sup>	Patients with pulmonary oligometastatic disease	1,378 patients treated with SBRT	• Safety
<b>Economic studies</b>			
Mehrens et al., 2021 <sup>62</sup> NCT01446744 SABR-COMET	Patients with a controlled primary malignancy and 1 to 5 metastatic lesions	Cost-effectiveness analysis, from a health care perspective in the US	• Incremental cost-effectiveness ratio

Abbreviations. ENRT: elective nodal radiotherapy; SBRT: stereotactic body radiation therapy.

## Effectiveness

### Overall Survival

Based on 2 RCTs, SBRT may be associated with better outcomes than palliative standard of care, but not other active treatments (specifically, interleukin-2).

- In 1 RCT, patients with advanced melanoma who were treated with SBRT after interleukin-2 therapy had similar overall survival rates to people treated with interleukin-2 therapy alone (median overall survival, 1.80 years vs. 1.76 years;  $P > .05$ ).<sup>57</sup>
- In 1 RCT, patients with a controlled primary malignancy and 1 to 5 metastatic lesions treated with SBRT had similar overall survival rates to patients in the palliative standard of care group (median overall survival, 41 months vs. 28 months; HR, 0.57; 95% CI, 0.30 to 1.10).<sup>7</sup> However, in the longer-term, patients treated with SBRT lived significantly longer than patients in the palliative standard of care group (median overall survival, 50 months vs. 28 months; HR, 0.47; 95% CI, 0.27 to 0.81).<sup>6</sup>

### Metastasis-free Survival

SBRT may be less effective than ENRT for oligorecurrent prostate cancer, but data are limited to a single retrospective observational study.

- In 1 retrospective observational study, patients with hormone-sensitive nodal oligorecurrent prostate cancer treated with SBRT were significantly less likely to live without metastasis than people treated with ENRT ( $P = .03$ ).<sup>56</sup> For patients presenting with only 1 node at recurrence, ENRT resulted in longer metastasis-free survival than SBRT (adjusted hazard ratio [aHR], 0.50; 95% CI, 0.30 to 0.85); however there was no difference between groups with more than 1 lymph node involved (aHR, 0.92; 95% CI, 0.54 to 1.59).<sup>56</sup> The rates of castration-resistant prostate cancer-free survival were similar between groups (88% vs. 87%;  $P = .05$ ).<sup>56</sup>

### Progression-free Survival

Based on 2 RCTs, SBRT may be associated with better outcomes than palliative standard of care, but not other active treatments (specifically, interleukin-2).

- In 1 RCT, patients with advanced melanoma treated with SBRT after interleukin-2 therapy had similar progression-free survival rates to people treated with interleukin-2 therapy alone (median progression-free survival, 0.45 years vs. 0.29 years;  $P > .05$ ).<sup>57</sup>
- In 1 RCT, patients with a controlled primary malignancy and 1 to 5 metastatic lesions treated with SBRT were significantly more likely to live longer without progression than patients in the palliative standard of care group (median progression-free survival, 12 months vs. 6 months; HR, 0.47; 95% CI, 0.30 to 0.76), with similar results seen in the longer term.<sup>6,7</sup>

### Local Tumor Control

Studies, including 2 RCTs and 1 retrospective observational study, show mixed results for the effectiveness of SBRT for local tumor control.

- In 1 RCT, patients with advanced melanoma treated with SBRT after interleukin-2 therapy had an overall response rate of 54% (21% complete response; 33% partial response; 21% stable disease; 25% progressive disease).<sup>57</sup> In patients treated with interleukin-2 therapy alone the overall response rate was 35% (15% complete response; 20% partial response; 25% stable disease; 40% progressive disease;  $P$  value not reported).<sup>57</sup> The disease control rate was significantly higher in the SBRT after interleukin-2 group (75% vs. 60%;  $P = .34$ ).<sup>57</sup>
- In 1 RCT, patients with a controlled primary malignancy and 1 to 5 metastatic lesions treated with SBRT were significantly more likely to achieve lesional control than patients in the palliative standard of care group (75% vs. 49% of lesions, an increase of 26%; 95% CI, 10 to 41).<sup>7</sup> Similar results were seen at the longer-term follow-up.<sup>6</sup>
- In 1 retrospective observational study, patients with hormone-sensitive nodal oligorecurrent prostate cancer treated with SBRT were significantly less likely to live without progression than people treated with ENRT ( $P < .001$ ).<sup>56</sup>

### Quality of Life

SBRT does not appear to be associated with improved quality of life, based on 1 RCT.

- In 1 RCT, patients with a controlled primary malignancy and 1 to 5 metastatic lesions had a similar quality of life overall, and on the subscales of physical, social, emotional, and functional wellbeing, to that of patients in the palliative standard of care group at either time point (reported graphically; all  $P > .40$ ).<sup>6-8</sup>

### Harms

Patients receiving SBRT for a range of advanced and metastatic cancers experienced a range of adverse events. Treatment-related deaths were rare.

### Toxicity and Other Adverse Events

- In a systematic review of SBRT in people with oligometastatic gynecologic (primarily ovarian) cancer, no grade 3 or higher toxicities were observed in the majority of included studies (9 of 16; 56%).<sup>11</sup> In 6 studies with grade 3 or higher toxicity events, rates ranged from 2.6% to 10%.<sup>11</sup> A further phase I study in 12 patients reported much higher rates, with 2 grade 4 toxicities occurring in 1 patient, and at least 10 grade 3 toxicities occurring in an unspecified number of participants.<sup>11</sup>

- In a meta-analysis of 13 studies in people with metastatic renal cell carcinoma, the incidence of grade 3 to 4 toxicity was 0.7% (95% CI, 0.0 to 2.1; range, 0% to 4.0%) for extracranial disease and 1.1% (95% CI, 0.0 to 7.4; range, 0% to 6.0%) for intracranial disease.<sup>10</sup> Across the 28 included studies, 2 treatment-related deaths were reported, with 1 patient dying from a fatal gastric hemorrhage and 1 due to bleeding from the tumor.<sup>10</sup>
- In 1 RCT, toxicities associated with interleukin-2 were observed in patients receiving treatment for advanced melanoma.<sup>57</sup> The majority of toxicities were transient and resolved with treatment or stopping interleukin-2 treatment.<sup>57</sup>
- In 1 RCT, patients with a controlled primary malignancy and 1 to 5 metastatic lesions were significantly more likely to experience grade 2 or higher adverse events than patients in the palliative standard of care group (29% vs. 9%;  $P = .03$ ).<sup>7</sup>
- In 1 retrospective observational study, patients with hormone-sensitive nodal oligorecurrent treated with SBRT were significantly less likely to experience grade 3 or higher toxicities compared with people treated using ENRT ( $P = .009$ ).<sup>56</sup>
- In 1 retrospective study of 104 patients with oligorecurrent lung metastases, most patients developed no toxicity or grade 1 acute and late toxicity.<sup>35</sup> Acute and late grade 3 radiation pneumonitis was observed in 1 and 2 patients respectively.<sup>35</sup>
- In a large prospective registry-based study, 2,410 adverse events were reported in 959 patients with oligometastatic cancer who received SBRT.<sup>34</sup> The most common grade 3 or worse adverse event was fatigue.<sup>34</sup> The most common grade 4 adverse event was increased liver enzymes.<sup>34</sup>
- In a retrospective study of 207 patients with oligometastatic kidney cancer treated with SBRT, no patients experienced grade 3 or higher toxicities.<sup>31</sup>
- In a retrospective study of 164 patients with large tumors (gross tumor volume of 70 cc or greater), 24 patients experienced grade 3 toxicity, with a further 4 patients experiencing grade 4 toxicity.<sup>30</sup> There were 10 cases of possible grade 5 toxicities.<sup>30</sup>
- In a retrospective study of 371 patients with extracranial oligometastases, 12 patients experienced grade 3 or 4 toxicity.<sup>21</sup>
- In a prospective study of 147 patients with oligometastatic cancer, 2.0% of patients experienced acute grade 3 or higher toxicity and 1.4% of patients experienced late grade 3 or higher toxicity.<sup>20</sup>
- In a retrospective study of 1,378 patients with pulmonary oligometastases, 26 of 1,040 patients experienced grade 3 or higher adverse events.<sup>18</sup> There were 10 cases of grade 5 adverse events, including hemoptysis and radiation pneumonitis.<sup>18</sup>

#### Serious Adverse Events, Including Deaths

- In a systematic review of SBRT for metastatic renal cell carcinoma, 2 treatment-related deaths were reported across 28 studies (1 patient died of a fatal gastric hemorrhage and 1 due to bleeding from the tumor).<sup>10</sup>
- In 1 RCT of SBRT for advanced melanoma, 1 patients developed respiratory failure after SBRT and interleukin-2 treatment and subsequently died.<sup>57</sup>
- In 1 RCT, 3 patients with a controlled primary malignancy and 1 to 5 metastatic lesions died after treatment with SBRT, and their death was attributed as being possibly, probably, or definitely related to treatment.<sup>6</sup>

- In 1 retrospective study of 104 patients with oligorecurrent lung metastases treated with SBRT, 1 patient died due to a possible radiation therapy-induced pulmonary hemorrhage.<sup>35</sup>
- In a large prospective registry-based study, patients with oligometastatic cancer who received SBRT died because of adverse events.<sup>34</sup>
- No patients died of treatment-related complications in a retrospective study of 371 patients with extracranial oligometastases.<sup>21</sup>

### **Economic Outcomes**

Based on the increased overall and progression-free survival shown with SBRT when compared with palliative standard of care, patients in the SBRT group showed 0.78 incremental quality-adjusted life-years (QALYs) over the trial duration (6 years) and 1.34 incremental QALYs over the long-term analysis (16 years).<sup>62</sup> Treatment with SBRT was associated with a marginal increase in costs compared to standard care alone (\$304,656 vs. \$303,523 for 6 years; \$402,888 vs. \$350,708 for 16 years).<sup>62</sup> At 6 years, the incremental cost-effectiveness ratio was \$1,446 per QALY, and at 16 years, \$38,874 per QALY.<sup>62</sup> Overall, therapy with SBRT remained cost-effective until treatment costs of \$88,969 over the trial duration of 6 years, which is 7.6 times the average cost).<sup>62</sup> However, the model was sensitive to the ongoing annual costs of oligo- and poly-metastatic disease states.<sup>62</sup>

### **Bottom Line**

We identified 2 new RCTs in this evidence update. In the RCT by Curti and colleagues,<sup>57</sup> 44 patients with metastatic melanoma were randomized to SBRT followed by high-dose interleukin-2 or interleukin-2 alone. Patients who received SBRT had significantly better disease control than patients who did not receive SBRT.<sup>57</sup> However, there was no significant difference between groups for overall survival or progression-free survival. In the RCT by Palma and colleagues (SABR-COMET),<sup>6,7</sup> 99 patients with a controlled primary malignancy and 1 to 5 metastatic lesions were randomized to SBRT in combination with palliative care or palliative care alone. Patients in the SBRT group had significantly better overall survival and progression-free survival than patients who received palliative standard of care.<sup>6</sup> SBRT did not appear to have any negative effects on quality of life.<sup>6</sup> A cost-effectiveness analysis also showed that SBRT is cost-effective when compared with palliative standard of care for up to 16 years.<sup>62</sup>

Based on prior evidence updates and newly identified evidence, we conclude that at this time, the newly identified RCTs on effectiveness and harms of SBRT in people with a controlled primary malignancy and 1 to 5 metastatic lesions and in people with metastatic melanoma are unlikely to change the conclusions of the 2012 evidence review because the lack of evidence of effectiveness from more than 1 RCT in these diverse populations.

Of further note: In 2022, the Canadian Agency for Drugs and Technologies in Health published the latest version of a living systematic review evaluating stereotactic ablative radiotherapy for the treatment of oligometastatic cancer.<sup>248</sup> Based on 3 RCTs and 10 nonrandomized studies (see Appendix E), the authors of the living systematic review concluded that there may be overall survival and progression-free benefits associated with SBRT in combination with standard of care, when compared with standard of care alone.<sup>248</sup> However, the authors also called for more high-quality RCTs with sufficient sample sizes and longer-term data to address uncertainties in the evidence.<sup>248</sup>

## Other Cancers

### History

In the 2012 report presented to the HTCC,<sup>1</sup> studies on the use of SBRT for colorectal cancer was reviewed. Based on 2 case series,<sup>249,250</sup> the evidence on harms was assessed as being of very low quality. No new studies were identified in the 2017 or 2019 evidence updates.<sup>3,4</sup>

### Findings in This Evidence Update

We did not identify any new eligible studies of SBRT for colorectal cancer.

### Bottom Line

Based on prior evidence updates and newly identified evidence, we conclude that at this time, the newly identified studies on effectiveness and harms are unlikely to change the conclusions of the 2012 evidence review, because of the lack of RCTs for colorectal cancer.

### Ongoing Studies

We identified 60 ongoing phase 3 or 4 ongoing RCTs (Appendix D). Of these eligible RCTs, there were:

- 10 RCTs in brain cancer
- 1 RCT in spinal cancer
- 7 RCTs in lung cancer
- 4 RCTs in pancreatic cancer
- 16 RCTs in prostate cancer
- 10 RCTs in liver cancer
- 1 RCT in head and neck cancer
- No RCTs in adrenal cancer
- 3 RCTs in bone cancer
- 6 RCTs in multiple cancer sites
- 1 RCT in breast cancer

Estimated completion dates range from February 2020 to December 2030. We have been inclusive when selecting the ongoing studies, and some of these may not meet our strict inclusion criteria once published. However, we have included these for information to show how newer SBRT-related and SRS-related studies are being conducted and what these studies are evaluating and comparing.

### Summary

In this evidence review, we identified studies on the use of SBRT for 12 cancer sites or cancer types overall (renal and bone cancers are new sections added to this update because of new eligible studies). After summarizing the effectiveness, harms, and economic outcomes from eligible studies in this evidence update, we have determined that these outcomes may change the conclusions of the 2012 evidence report.

## References

1. Gerrity M, Thielke A, Leof A, et al. *Stereotactic radiosurgery and stereotactic body radiation therapy: October 2012 updated evidence report* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2012.
2. Health Technology Clinical Committee. Stereotactic radiation surgery and stereotactic body radiation therapy. 2013; [https://www.hca.wa.gov/assets/program/sbrt\\_final\\_findings\\_decision\\_041713\[1\].pdf](https://www.hca.wa.gov/assets/program/sbrt_final_findings_decision_041713[1].pdf). Accessed April 13, 2022.
3. Mosbaek C, King V, Harrod C. *Stereotactic radiosurgery and stereotactic body radiation therapy: an evidence update* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2017.
4. Mosbaek C, King V, Harrod C. *Stereotactic radiosurgery and stereotactic body radiation therapy: an evidence update*. Portland, OR: Oregon Health and Science University; 2019.
5. US Food and Drug Administration. Clinical trial endpoints for the approval of cancer drugs and biologics. Guidance for industry. 2018; <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics>. Accessed May 5, 2022.
6. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol*. 2020;38(25):2830-2838. doi: 10.1200/JCO.20.00818 Accessed 20200602//.
7. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*. 2019;393(10185):2051-2058. doi: 10.1016/S0140-6736(18)32487-5.
8. Olson R, Senan S, Harrow S, et al. Quality of life outcomes after stereotactic ablative radiation therapy (SABR) versus standard of care treatments in the oligometastatic setting: a secondary analysis of the SABR-COMET randomized trial. *Int J Radiat Oncol Biol Phys*. 2019;105(5):943-947. doi: 10.1016/j.ijrobp.2019.08.041 Accessed 20190827//.
9. van Dams R, Jiang NY, Fuller DB, et al. Stereotactic body radiotherapy for high-risk localized carcinoma of the prostate (SHARP) consortium: analysis of 344 prospectively treated patients. *Int J Radiat Oncol Biol Phys*. 2021;110(3):731-737. doi: 10.1016/j.ijrobp.2021.01.016 Accessed 20210123//.
10. Zaorsky NG, Lehrer EJ, Kothari G, Louie AV, Siva S. Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28



- studies. *Eur Urol Oncol*. 2019;2(5):515-523. doi: 10.1016/j.euo.2019.05.007 Accessed 20190711//.
11. Yegya-Raman N, Cao CD, Hathout L, et al. Stereotactic body radiation therapy for oligometastatic gynecologic malignancies: a systematic review. *Gynecol Oncol*. 2020;159(2):573-580. doi: 10.1016/j.ygyno.2020.08.010 Accessed 20200909//.
  12. Vargas E, Susko MS, Mummaneni PV, Braunstein SE, Chou D. Vertebral body fracture rates after stereotactic body radiation therapy compared with external-beam radiation therapy for metastatic spine tumors. *J Neurosurg Spine*. 2020:1-7. doi: 10.3171/2020.5.SPINE191383 Accessed 20200814//.
  13. Sahgal A, Myrehaug SD, Siva S, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. *Lancet Oncol*. 2021;22(7):1023-1033. doi: 10.1016/S1470-2045(21)00196-0.
  14. Kayama T, Sato S, Sakurada K, et al. Effects of surgery with salvage stereotactic radiosurgery versus surgery with whole-brain radiation therapy in patients with one to four brain metastases (JCOG): a phase III, noninferiority, randomized controlled trial. *J Clin Oncol*. 2018;36(33):JCO2018786186. doi: 10.1200/JCO.2018.78.6186.
  15. Bergman D, Modh A, Schultz L, et al. Randomized prospective trial of fractionated stereotactic radiosurgery with chemotherapy versus chemotherapy alone for bevacizumab-resistant high-grade glioma. *J Neurooncol*. 2020;148(2):353-361. doi: 10.1007/s11060-020-03526-4 Accessed 20200522//.
  16. Alvarez-Pinzon AM, Wolf A, Valerio JE, Borro M, Herrera D, Alonso JR. Gamma knife stereotactic radiosurgery as an effective tool in primary CNS lymphoma: evaluation of stereotactic radiosurgery and methotrexate treatment in a prospective and observational clinical research study. *Clin Neurol Neurosurg*. 2021;201. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02231509/full>.
  17. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *Lancet Oncol*. 2019;20(4):494-503. doi: 10.1016/S1470-2045(18)30896-9.
  18. Yamamoto T, Niibe Y, Aoki M, et al. Analyses of the local control of pulmonary oligometastases after stereotactic body radiotherapy and the impact of local control on survival. *BMC Cancer*. 2020;20(1):997. doi: 10.1186/s12885-020-07514-9 Accessed 20201014//.
  19. Voglhuber T, Eitz KA, Oechsner M, Vogel MME, Combs SE. Analysis of using high-precision radiotherapy in the treatment of liver metastases regarding toxicity and

- survival. *BMC cancer*. 2021;21(1):780.  
<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med1&NEWS=N&AN=34229642> Accessed 20210706//.
20. Sutera P, Clump DA, Kalash R, et al. Initial results of a multicenter phase 2 trial of stereotactic ablative radiation therapy for oligometastatic cancer. *Int J Radiat Oncol Biol Phys*. 2019;103(1):116-122. doi: 10.1016/j.ijrobp.2018.08.027 Accessed 20180825//.
  21. Sogono P, Bressel M, David S, et al. Safety, efficacy, and patterns of failure after single-fraction stereotactic body radiation therapy (SBRT) for oligometastases. *Int J Radiat Oncol Biol Phys*. 2021;109(3):756-763. doi: 10.1016/j.ijrobp.2020.10.011 Accessed 20201015//.
  22. Sharma A, Duijm M, Oomen-de Hoop E, et al. Survival and prognostic factors of pulmonary oligometastases treated with stereotactic body radiotherapy. *Acta oncologica (Stockholm, Sweden)*. 2019;58(1):74-80.  
<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med16&NEWS=N&AN=30280633> Accessed 20181003//.
  23. Shanker MD, Moodaley P, Soon W, Liu HY, Lee YY, Pryor DI. Stereotactic ablative radiotherapy for hepatocellular carcinoma: a systematic review and meta-analysis of local control, survival and toxicity outcomes. *J Med Imaging Radiat Oncol*. 2021;65(7):956-968. doi: 10.1111/1754-9485.13309 Accessed 20210815//.
  24. Rodrigues I, Figueiredo T, Gagean J, et al. Prognostic factors and clinical outcomes after stereotactic radiotherapy for primary lung tumors. *Rep Pract Oncol Radiother*. 2020;25(6):943-950. doi: 10.1016/j.rpor.2020.09.015 Accessed 20201003//.
  25. Rim CH, Kim HJ, Seong J. Clinical feasibility and efficacy of stereotactic body radiotherapy for hepatocellular carcinoma: a systematic review and meta-analysis of observational studies. *Radiother Oncol*. 2019;131:135-144. doi: 10.1016/j.radonc.2018.12.005 Accessed 20181231//.
  26. Park S, Jung J, Cho B, et al. Clinical outcomes of stereotactic body radiation therapy for small hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2020;35(11):1953-1959. doi: 10.1111/jgh.15011 Accessed 20200220//.
  27. Mathew AS, Atenafu EG, Owen D, et al. Long term outcomes of stereotactic body radiation therapy for hepatocellular carcinoma without macrovascular invasion. *Eur J Cancer*. 2020;134:41-51.  
<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med17&NEWS=N&AN=32460180> Accessed 20200524//.

28. Loi M, Comito T, Franzese C, et al. Stereotactic body radiotherapy in hepatocellular carcinoma: patient selection and predictors of outcome and toxicity. *J Cancer Res Clin Oncol*. 2021;147(3):927-936. doi: 10.1007/s00432-020-03389-2 Accessed 20200918//.
29. Kibe Y, Takeda A, Tsurugai Y, et al. Feasibility of marker-less stereotactic body radiotherapy for hepatocellular carcinoma. *Acta Oncol*. 2022;61(1):104-110. doi: 10.1080/0284186X.2021.2001566 Accessed 20211117//.
30. Grozman V, Onjukka E, Wersall P, et al. Extending hypofractionated stereotactic body radiotherapy to tumours larger than 70cc - effects and side effects. *Acta oncologica (Stockholm, Sweden)*. 2021;60(3):305-311. <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=33448899> Accessed 20210115//.
31. Franzese C, Marvaso G, Francolini G, et al. The role of stereotactic body radiation therapy and its integration with systemic therapies in metastatic kidney cancer: a multicenter study on behalf of the AIRO (Italian Association of Radiotherapy and Clinical Oncology) genitourinary study group. *Clin Exp Metastasis*. 2021;38(6):527-537. doi: 10.1007/s10585-021-10131-w Accessed 20211108//.
32. Dobrzycka M, Spychalski P, Rostkowska O, et al. Stereotactic body radiation therapy for early-stage hepatocellular carcinoma - a systematic review on outcome. *Acta Oncol*. 2019;58(12):1706-1713. doi: 10.1080/0284186X.2019.1657942 Accessed 20190829//.
33. Chipko C, Ojwang J, Gharai LR, Deng X, Mukhopadhyay N, Weiss E. Characterization of chest wall toxicity during long-term follow up after thoracic stereotactic body radiation therapy. *Pract Radiat Oncol*. 2019;9(3):e338-e346. doi: 10.1016/j.prro.2019.01.012 Accessed 20190204//.
34. Chalkidou A, Macmillan T, Grzeda MT, et al. Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study. *Lancet Oncol*. 2021;22(1):98-106. doi: 10.1016/S1470-2045(20)30537-4.
35. Berkovic P, Gulyban A, Defraene G, et al. Stereotactic robotic body radiotherapy for patients with oligorecurrent pulmonary metastases. *BMC Cancer*. 2020;20(1):402. doi: 10.1186/s12885-020-06906-1 Accessed 20200508//.
36. Baker S, Verduijn GM, Petit S, et al. Long-term outcomes following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma. *Acta Oncol*. 2019;58(6):926-933. doi: 10.1080/0284186X.2019.1581375 Accessed 20190227//.
37. Uhlig A, Uhlig J, Trojan L, Kim HS. Stereotactic body radiotherapy for stage I renal cell carcinoma: national treatment trends and outcomes compared to partial nephrectomy

- and thermal ablation. *J Vasc Interv Radiol*. 2020;31(4):564-571. doi: 10.1016/j.jvir.2019.11.009 Accessed 20200229//.
38. Wegner RE, Abel S, Colonias A. Stereotactic ablative body radiotherapy versus conventionally fractionated radiotherapy for early stage large cell neuroendocrine carcinoma of the lung. *Lung Cancer Manag*. 2020;9(3):LMT32. doi: 10.2217/Imt-2020-0004 Accessed 20200421//.
  39. Nelson DB, Tayob N, Nguyen QN, et al. Local failure after stereotactic body radiation therapy or wedge resection for colorectal pulmonary metastases. *J Thorac Cardiovasc Surg*. 2019;158(4):1234-1241 e1216. doi: 10.1016/j.jtcvs.2019.02.133 Accessed 20190511//.
  40. Lo H, Abel S, Finley G, Weksler B, Colonias A, Wegner RE. Surgical resection versus stereotactic body radiation therapy in early stage bronchopulmonary large cell neuroendocrine carcinoma. *Thorac Cancer*. 2020;11(2):305-310. doi: 10.1111/1759-7714.13260 Accessed 20191220//.
  41. Wong TC, Lee VH, Law AL, et al. Prospective study of stereotactic body radiation therapy for hepatocellular carcinoma on waitlist for liver transplant. *Hepatology*. 2021;74(5):2580-2594. doi: 10.1002/hep.31992 Accessed 20210930//.
  42. Wong TC, Chiang CL, Lee AS, et al. Better survival after stereotactic body radiation therapy following transarterial chemoembolization in nonresectable hepatocellular carcinoma: a propensity score matched analysis. *Surg Oncol*. 2019;28:228-235. doi: 10.1016/j.suronc.2019.01.006 Accessed 20190129//.
  43. Wang F, Numata K, Takeda A, et al. Safety and efficacy study: short-term application of radiofrequency ablation and stereotactic body radiotherapy for Barcelona Clinical Liver Cancer stage 0-B1 hepatocellular carcinoma. *PLoS One*. 2021;16(1):e0245076. doi: 10.1371/journal.pone.0245076 Accessed 20210105//.
  44. Shen PC, Chang WC, Lo CH, et al. Comparison of stereotactic body radiation therapy and transarterial chemoembolization for unresectable medium-sized hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2019;105(2):307-318. doi: 10.1016/j.ijrobp.2019.05.066 Accessed 20190605//.
  45. Pielkenrood BJ, van der Velden JM, van der Linden YM, et al. Pain response after stereotactic body radiation therapy versus conventional radiation therapy in patients with bone metastases-a phase 2 randomized controlled trial within a prospective cohort. *Int J Radiat Oncol Biol Phys*. 2021;110(2):358-367.  
<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02247481/full>.

46. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol.* 2020;6(5):650-659. doi: 10.1001/jamaoncol.2020.0147.
47. Nguyen QN, Chun SG, Chow E, et al. Single-fraction stereotactic vs conventional multifraction radiotherapy for pain relief in patients with predominantly nonspine bone metastases: a randomized phase 2 trial. *JAMA Oncol.* 2019;5(6):872-878. doi: 10.1001/jamaoncol.2019.0192.
48. Nabavizadeh N, Jahangiri Y, Rahmani R, et al. Thermal ablation versus stereotactic body radiotherapy after transarterial chemoembolization for inoperable hepatocellular carcinoma: a propensity score-weighted analysis. *AJR Am J Roentgenol.* 2021;217(3):691-698. doi: 10.2214/AJR.20.24117 Accessed 20200930//.
49. Lee J, Shin I-S, Yoon WS, Koom WS, Rim CH. Comparisons between radiofrequency ablation and stereotactic body radiotherapy for liver malignancies: meta-analyses and a systematic review. *Radiother Oncol.* 2020;145:63-70.  
<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med18&NEWS=N&AN=31923711> Accessed 20200107//.
50. Kanzaki R, Suzuki O, Kanou T, et al. The short-term outcomes of pulmonary metastasectomy or stereotactic body radiation therapy for pulmonary metastasis from epithelial tumors. *J Cardiothorac Surg.* 2020;15(1):43. doi: 10.1186/s13019-020-1079-4 Accessed 20200227//.
51. Jun BG, Kim SG, Kim YD, et al. Combined therapy of transarterial chemoembolization and stereotactic body radiation therapy versus transarterial chemoembolization for  $\leq 5$ cm hepatocellular carcinoma: propensity score matching analysis. *PLoS One.* 2018;13(10):e0206381. doi: 10.1371/journal.pone.0206381 Accessed 20181031//.
52. Jeong Y, Lee KJ, Lee SJ, et al. Radiofrequency ablation versus stereotactic body radiation therapy for small ( $\leq 3$  cm) hepatocellular carcinoma: A retrospective comparison analysis. *J Gastroenterol Hepatol.* 2021;36(7):1962-1970. doi: 10.1111/jgh.15442 Accessed 20210305//.
53. Ijsseldijk MA, Shoni M, Siegert C, et al. Oncologic outcomes of surgery versus SBRT for non-small-cell lung carcinoma: a systematic review and meta-analysis. *Clin Lung Cancer.* 2021;22(3):e235-e292. doi: 10.1016/j.clcc.2020.04.017 Accessed 20200507//.
54. Facciorusso A, Chierici A, Cincione I, et al. Stereotactic body radiotherapy vs radiofrequency ablation for the treatment of hepatocellular carcinoma: a meta-analysis. *Expert Rev Anticancer Ther.* 2021;21(6):681-688. doi: 10.1080/14737140.2021.1891887 Accessed 20210223//.

55. Eriguchi T, Takeda A, Tateishi Y, et al. Comparison of stereotactic body radiotherapy and radiofrequency ablation for hepatocellular carcinoma: systematic review and meta-analysis of propensity score studies. *Hepatol Res.* 2021;51(7):813-822. doi: 10.1111/hepr.13647 Accessed 20210505//.
56. De Bleser E, Jereczek-Fossa BA, Pasquier D, et al. Metastasis-directed therapy in treating nodal oligorecurrent prostate cancer: a multi-institutional analysis comparing the outcome and toxicity of stereotactic body radiotherapy and elective nodal radiotherapy. *Eur Urol.* 2019. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01964903/full>.
57. Curti B, Crittenden M, Seung SK, et al. Randomized phase II study of stereotactic body radiotherapy and interleukin-2 versus interleukin-2 in patients with metastatic melanoma. *J Immunother Cancer.* 2020;8(1). doi: 10.1136/jitc-2020-000773.
58. Cao C, Wang D, Chung C, et al. A systematic review and meta-analysis of stereotactic body radiation therapy versus surgery for patients with non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2019;157(1):362-373 e368. doi: 10.1016/j.jtcvs.2018.08.075 Accessed 20180915//.
59. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol.* 2019;20(11):1531-1543. doi: 10.1016/S1470-2045(19)30569-8.
60. Arcelli A, Buwenge M, Macchia G, et al. Stereotactic body radiotherapy vs conventionally fractionated chemoradiation in locally advanced pancreatic cancer: a multicenter case-control study (PAULA-1). *Cancer Med.* 2020;9(21):7879-7887. doi: 10.1002/cam4.3330.
61. Sebastian NT, Tan Y, Miller ED, Williams TM, Alexandra Diaz D. Stereotactic body radiation therapy is associated with improved overall survival compared to chemoradiation or radioembolization in the treatment of unresectable intrahepatic cholangiocarcinoma. *Clin Transl Radiat Oncol.* 2019;19:66-71. <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=pnm4&NEWS=N&AN=31517072> Accessed 20190726//.
62. Mehrens D, Unterrainer M, Corradini S, et al. Cost-effectiveness analysis of local treatment in oligometastatic disease. *Front Oncol.* 2021;11:667993. doi: 10.3389/fonc.2021.667993 Accessed 20210615//.
63. Parikh ND, Marshall VD, Green M, et al. Effectiveness and cost of radiofrequency ablation and stereotactic body radiotherapy for treatment of early-stage hepatocellular carcinoma: an analysis of SEER-medicare. *J Med Imaging Radiat Oncol.* 2018;62(5):673-681. doi: 10.1111/1754-9485.12754.

64. Correa RJM, Louie AV, Zaorsky NG, et al. The emerging role of stereotactic ablative radiotherapy for primary renal cell carcinoma: a systematic review and meta-analysis. *Eur Urol Focus*. 2019;5(6):958-969. [https://www.eurofocus.europeanurology.com/article/S2405-4569\(19\)30157-9/fulltext](https://www.eurofocus.europeanurology.com/article/S2405-4569(19)30157-9/fulltext) Accessed 20190624//.
65. Cage TA, Clark AJ, Aranda D, et al. A systematic review of treatment outcomes in pediatric patients with intracranial ependymomas. *J Neurosurg Pediatr*. 2013;11(6):673-681. doi: 10.3171/2013.2.PEDS12345.
66. Elaimy AL, Mackay AR, Lamoreaux WT, et al. Clinical outcomes of Gamma knife radiosurgery in the salvage treatment of patients with recurrent high-grade glioma. *World Neurosurg*. 2013;80(6):872-878. doi: 10.1016/j.wneu.2013.02.030.
67. Gans JH, Raper DM, Shah AH, et al. The role of radiosurgery to the tumor bed after resection of brain metastases. *Neurosurgery*. 2013;72(3):317-325; discussion 325-316. doi: 10.1227/NEU.0b013e31827fcd60.
68. Goyal S, Silk AW, Tian S, et al. Clinical management of multiple melanoma brain metastases: a systematic review. *JAMA Oncol*. 2015;1(5):668-676. doi: 10.1001/jamaoncol.2015.1206.
69. Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. *Cochrane Database Syst Rev*. 2012;9(9):CD006121. doi: 10.1002/14651858.CD006121.pub3.
70. Soon YY, Tham IW, Lim KH, Koh WY, Lu JJ. Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. *Cochrane Database Syst Rev*. 2014;3(3):CD009454. doi: 10.1002/14651858.CD009454.pub2.
71. Soon YY, Tham WI, Lim KH, Koh YW, Lu JJ. Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. *Cochrane Database Syst Rev*. 2016;9.
72. Aoyama H, Tago M, Shirato H. Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases: secondary analysis of the JROSG 99-1 randomized clinical trial. *JAMA Oncology*. 2015;1(4):457-464.
73. El Gantery MM, Abd El Baky HM, El Hossieny HA, Mahmoud M, Youssef O. Management of brain metastases with stereotactic radiosurgery alone versus whole brain irradiation alone versus both. *Radiat Oncol*. 2014;9:116. doi: 10.1186/1748-717X-9-116.

74. El Gantery MM, El Baky HMA, El Hossieny HA, Mahmoud M, Youssef O. Management of brain metastases with stereotactic radiosurgery alone versus whole brain irradiation alone versus both. *Radiation Oncology*. 2014;9(1).
75. Lim SH, Lee JY, Lee MY, et al. Randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2014;32(15 SUPPL. 1).
76. Lim SH, Lee JY, Lee MY, et al. A randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small-cell lung cancer. *Ann Oncol*. 2015;26(4):762-768. doi: 10.1093/annonc/mdu584.
77. Sperduto PW, Shanley R, Luo X, et al. Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation therapy versus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the graded prognostic assessment (GPA). *Int J Radiat Oncol Biol Phys*. 2014;90(3):526-531. doi: 10.1016/j.ijrobp.2014.07.002.
78. Adas YG, Yazici O, Kekilli E, et al. Whole brain radiotherapy combined with stereotactic radiosurgery versus stereotactic radiosurgery alone for brain metastases. *Asian Pac J Cancer Prev*. 2015;16(17):7595-7597. doi: 10.7314/apjcp.2015.16.17.7595.
79. Baykara M, Kurt G, Buyukberber S, et al. Management of brain metastases from non-small cell lung cancer. *J Cancer Res Ther*. 2014;10(4):915-921. doi: 10.4103/0973-1482.137939.
80. Bougie E, Masson-Cote L, Mathieu D. Comparison between surgical resection and stereotactic radiosurgery in patients with a single brain metastasis from non-small cell lung cancer. *World Neurosurg*. 2015;83(6):900-906. doi: 10.1016/j.wneu.2015.01.029.
81. Fauchon F, Hasselblatt M, Jouvet A, et al. Role of surgery, radiotherapy and chemotherapy in papillary tumors of the pineal region: a multicenter study. *J Neurooncol*. 2013;112(2):223-231. doi: 10.1007/s11060-013-1050-5.
82. Gerber NK, Yamada Y, Rimner A, et al. Erlotinib versus radiation therapy for brain metastases in patients with EGFR-mutant lung adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2014;89(2):322-329. doi: 10.1016/j.ijrobp.2014.02.022.
83. Hsieh J, Elson P, Otvos B, et al. Tumor progression in patients receiving adjuvant whole-brain radiotherapy vs localized radiotherapy after surgical resection of brain metastases. *Neurosurgery*. 2015;76(4):411-420. doi: 10.1227/NEU.0000000000000626.



84. Kim HJ, Huh JW, Jung TY, et al. Clinical outcome with Gamma-knife surgery or surgery for brain metastases from colorectal cancer. *J Clin Neurosci*. 2013;20(10):1417-1421. doi: 10.1016/j.jocn.2012.12.020.
85. Lin CH, Hsu KH, Chang SN, et al. Increased survival with the combination of stereotactic radiosurgery and gefitinib for non-small cell lung cancer brain metastasis patients: a nationwide study in Taiwan. *Radiat Oncol*. 2015;10:127. doi: 10.1186/s13014-015-0431-7.
86. Lin L, Zhao CH, Ge FJ, et al. Patients with brain metastases derived from gastrointestinal cancer: clinical characteristics and prognostic factors. *Clin Transl Oncol*. 2016;18(1):93-98. doi: 10.1007/s12094-015-1341-8.
87. Patel KR, Prabhu RS, Kandula S, et al. Intracranial control and radiographic changes with adjuvant radiation therapy for resected brain metastases: whole brain radiotherapy versus stereotactic radiosurgery alone. *J Neurooncol*. 2014;120(3):657-663. doi: 10.1007/s11060-014-1601-4.
88. Rades D, Kueter JD, Meyners T, et al. Single brain metastasis: resection followed by whole-brain irradiation and a boost to the metastatic site compared to whole-brain irradiation plus radiosurgery. *Clin Neurol Neurosurg*. 2012;114(4):326-330. doi: 10.1016/j.clineuro.2011.10.042.
89. Rades D, Veninga T, Hornung D, Wittkugel O, Schild SE, Gliemroth J. Single brain metastasis: whole-brain irradiation plus either radiosurgery or neurosurgical resection. *Cancer*. 2012;118(4):1138-1144. doi: 10.1002/cncr.26379.
90. Skeie BS, Enger PO, Brogger J, et al. Gamma knife surgery versus reoperation for recurrent glioblastoma multiforme. *World Neurosurg*. 2012;78(6):658-669. doi: 10.1016/j.wneu.2012.03.024.
91. Tian LJ, Zhuang HQ, Yuan ZY. A comparison between cyberknife and neurosurgery in solitary brain metastases from non-small cell lung cancer. *Clin Neurol Neurosurg*. 2013;115(10):2009-2014. doi: 10.1016/j.clineuro.2013.06.006.
92. Kimmell KT, LaSota E, Weil RJ, Marko NF. Comparative effectiveness analysis of treatment options for single brain metastasis. *World Neurosurg*. 2015;84(5):1316-1332. doi: 10.1016/j.wneu.2015.06.021.
93. Vuong DA, Rades D, Le AN, Busse R. The cost-effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of brain metastasis in Vietnam from the perspective of patients and families. *World Neurosurg*. 2012;77(2):321-328. doi: 10.1016/j.wneu.2011.05.050.

94. Vuong DA, Rades D, van Eck AT, Horstmann GA, Busse R. Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: stereotactic radiosurgery versus surgical resection. *Clin Neurol Neurosurg*. 2013;115(3):276-284. doi: 10.1016/j.clineuro.2012.05.005.
95. Khan M, Lin J, Liao G, et al. Comparison of WBRT alone, SRS alone, and their combination in the treatment of one or more brain metastases: review and meta-analysis. *Tumour Biol*. 2017;39(7):1010428317702903. doi: 10.1177/1010428317702903.
96. Yuan X, Liu WJ, Li B, Shen ZT, Shen JS, Zhu XX. A Bayesian network meta-analysis of whole brain radiotherapy and stereotactic radiotherapy for brain metastasis. *Medicine (Baltimore)*. 2017;96(34):e7698. doi: 10.1097/MD.00000000000007698.
97. Jalali R, Gupta T, Goda JS, et al. Efficacy of stereotactic conformal radiotherapy vs conventional radiotherapy on benign and low-grade brain tumors: a randomized clinical trial. *JAMA Oncol*. 2017;3(10):1368-1376.  
[https://jamanetwork.com/journals/jamaoncology/articlepdf/2629956/jamaoncology\\_Jalali\\_2017\\_oi\\_170022.pdf](https://jamanetwork.com/journals/jamaoncology/articlepdf/2629956/jamaoncology_Jalali_2017_oi_170022.pdf).
98. Kepka L, Tyc-Szczepaniak D, Bujko K, et al. Stereotactic radiotherapy of the tumor bed compared to whole brain radiotherapy after surgery of single brain metastasis: results from a randomized trial. *Radiother Oncol*. 2016;121(2):217-224. doi: 10.1016/j.radonc.2016.10.005.
99. Kepka L, Tyc-Szczepaniak D, Osowiecka K, Sprawka A, Trabska-Kluch B, Czeremczynska B. Quality of life after whole brain radiotherapy compared with radiosurgery of the tumor bed: results from a randomized trial. *Clin Transl Oncol*. 2018;20(2):150-159. doi: 10.1007/s12094-017-1703-5.
100. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1040-1048. doi: 10.1016/S1470-2045(17)30414-X.
101. Bates JE, Youn P, Peterson CR, 3rd, et al. Radiotherapy for brain metastases from renal cell carcinoma in the targeted therapy era: the University of Rochester experience. *Am J Clin Oncol*. 2017;40(5):439-443. doi: 10.1097/COC.0000000000000186.
102. Bir SC, Patra DP, Maiti TK, Bollam P, Minagar A, Nanda A. Direct comparison of Gamma knife radiosurgery and microsurgery for small size meningiomas. *World Neurosurg*. 2017;101:170-179. doi: 10.1016/j.wneu.2017.01.105.
103. Chen L, Shen C, Redmond KJ, et al. Use of stereotactic radiosurgery in elderly and very elderly patients with brain metastases to limit toxicity associated with whole brain

- radiation therapy. *Int J Radiat Oncol Biol Phys.* 2017;98(4):939-947. doi: 10.1016/j.ijrobp.2017.02.031.
104. Doherty MK, Korpany GJ, Tomasini P, et al. Treatment options for patients with brain metastases from EGFR/ALK-driven lung cancer. *Radiother Oncol.* 2017;123(2):195-202. doi: 10.1016/j.radonc.2017.03.007.
  105. Golfinos JG, Hill TC, Rokosh R, et al. A matched cohort comparison of clinical outcomes following microsurgical resection or stereotactic radiosurgery for patients with small- and medium-sized vestibular schwannomas. *J Neurosurg.* 2016;125(6):1472-1482. doi: 10.3171/2015.12.JNS151857.
  106. Halasz LM, Uno H, Hughes M, et al. Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. *Cancer.* 2016;122(13):2091-2100. doi: 10.1002/cncr.30009.
  107. Kann BH, Park HS, Johnson SB, Chiang VL, Yu JB. Radiosurgery for brain metastases: changing practice patterns and disparities in the United States. *J Natl Compr Canc Netw.* 2017;15(12):1494-1502. doi: 10.6004/jnccn.2017.7003.
  108. Klingenstein A, Furweger C, Muhlhofer AK, et al. Quality of life in the follow-up of uveal melanoma patients after enucleation in comparison to CyberKnife treatment. *Graefes Arch Clin Exp Ophthalmol.* 2016;254(5):1005-1012. doi: 10.1007/s00417-015-3216-7.
  109. Li B, Dai ZX, Chen YD, et al. Systemic therapy after radiotherapy significantly reduces the risk of mortality of patients with 1-3 brain metastases: a retrospective study of 250 patients. *Chin Med J (Engl).* 2017;130(24):2916-2921. doi: 10.4103/0366-6999.220296.
  110. Li D, Weng JC, Zhang GJ, et al. Proposed treatment paradigm for intracranial chondrosarcomas based on multidisciplinary coordination. *World Neurosurg.* 2018;109:e517-e530. doi: 10.1016/j.wneu.2017.10.013.
  111. Liu X, Shan B, Wang M, Xu J. World Health Organization grade II meningiomas: the role of adjuvant/salvage Gamma knife surgery after initial surgery and prognostic factor assessment. *World Neurosurg.* 2018;109:e352-e362. doi: 10.1016/j.wneu.2017.09.178.
  112. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol.* 2017;35(10):1070-1077. doi: 10.1200/JCO.2016.69.7144.
  113. Mix M, Elmarzouky R, O'Connor T, Plunkett R, Prasad D. Clinical outcomes in patients with brain metastases from breast cancer treated with single-session radiosurgery or

- whole brain radiotherapy. *J Neurosurg.* 2016;125(Suppl 1):26-30. doi: 10.3171/2016.7.GKS161541.
114. Nanda A, Thakur JD, Sonig A, Missios S. Microsurgical resectability, outcomes, and tumor control in meningiomas occupying the cavernous sinus. *J Neurosurg.* 2016;125(2):378-392. doi: 10.3171/2015.3.JNS142494.
  115. Patel KR, Burri SH, Boselli D, et al. Comparing pre-operative stereotactic radiosurgery (SRS) to post-operative whole brain radiation therapy (WBRT) for resectable brain metastases: a multi-institutional analysis. *J Neurooncol.* 2017;131(3):611-618. doi: 10.1007/s11060-016-2334-3.
  116. Pintea B, Baumert B, Kinfe TM, Gousias K, Parpaley Y, Bostrom JP. Early motor function after local treatment of brain metastases in the motor cortex region with stereotactic radiotherapy/radiosurgery or microsurgical resection: a retrospective study of two consecutive cohorts. *Radiat Oncol.* 2017;12(1):177. doi: 10.1186/s13014-017-0917-6.
  117. Rachinger W, Oehlschlaegel F, Kunz M, et al. Cystic craniopharyngiomas: microsurgical or stereotactic treatment? *Neurosurgery.* 2017;80(5):733-743. doi: 10.1227/NEU.0000000000001408.
  118. Rades D, Janssen S, Bajrovic A, Khoa MT, Veninga T, Schild SE. A matched-pair analysis comparing whole-brain radiotherapy with and without a stereotactic boost for intracerebral control and overall survival in patients with one to three cerebral metastases. *Radiat Oncol.* 2017;12(1):69. doi: 10.1186/s13014-017-0804-1.
  119. Rades D, Janssen S, Dziggel L, et al. A matched-pair study comparing whole-brain irradiation alone to radiosurgery or fractionated stereotactic radiotherapy alone in patients irradiated for up to three brain metastases. *BMC Cancer.* 2017;17(1):30. doi: 10.1186/s12885-016-2989-3.
  120. Sanghvi SM, Lischalk JW, Cai L, et al. Clinical outcomes of gastrointestinal brain metastases treated with radiotherapy. *Radiat Oncol.* 2017;12(1):43. doi: 10.1186/s13014-017-0774-3.
  121. Troude L, Boucekine M, Montava M, Lavieille JP, Regis JM, Roche PH. Adjunctive Gamma knife surgery or wait and scan policy after optimal resection of large vestibular schwannomas: clinical and radiologic outcomes. *World Neurosurg.* 2018;118:e895-e905. doi: 10.1016/j.wneu.2018.07.093.
  122. Talacchi A, Muggioli F, De Carlo A, Nicolato A, Locatelli F, Meglio M. Recurrent atypical meningiomas: combining surgery and radiosurgery in one effective multimodal treatment. *World Neurosurg.* 2016;87:565-572. doi: 10.1016/j.wneu.2015.10.013.

123. Rahman M, Neal D, Baruch W, Bova FJ, Frentzen BH, Friedman WA. The risk of malignancy anywhere in the body after linear accelerator (LINAC) stereotactic radiosurgery. *Stereotact Funct Neurosurg.* 2014;92(5):323-333. doi: 10.1159/000365225.
124. Lester-Coll NH, Sher DJ. Cost-effectiveness of stereotactic radiosurgery and stereotactic body radiation therapy: a critical review. *Curr Oncol Rep.* 2017;19(6):41. doi: 10.1007/s11912-017-0599-0.
125. Nasioudis D, Persaud A, Taunk NK, Latif NA. Brain metastases from gynecologic malignancies: prevalence and management. *Am J Clin Oncol.* 2020;43(6):418-421. doi: 10.1097/COC.0000000000000689.
126. Sohn S, Chung CK, Sohn MJ, et al. Stereotactic radiosurgery compared with external radiation therapy as a primary treatment in spine metastasis from renal cell carcinoma: a multicenter, matched-pair study. *J Neurooncol.* 2014;119(1):121-128. doi: 10.1007/s11060-014-1455-9.
127. Chang UK, Kim MS, Han CJ, Lee DH. Clinical result of stereotactic radiosurgery for spinal metastasis from hepatocellular carcinoma: comparison with conventional radiation therapy. *J Neurooncol.* 2014;119(1):141-148. doi: 10.1007/s11060-014-1463-9.
128. Kim H, Rajagopalan MS, Beriwal S, Huq MS, Smith KJ. Cost-effectiveness analysis of single fraction of stereotactic body radiation therapy compared with single fraction of external beam radiation therapy for palliation of vertebral bone metastases. *Int J Radiat Oncol Biol Phys.* 2015;91(3):556-563. doi: 10.1016/j.ijrobp.2014.10.055.
129. Sprave T, Verma V, Forster R, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. *Radiother Oncol.* 2018;128(2):274-282. doi: 10.1016/j.radonc.2018.04.030.
130. Sprave T, Verma V, Forster R, et al. Quality of life following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy for vertebral metastases: secondary analysis of an exploratory phase II randomized trial. *Anticancer Res.* 2018;38(8):4961-4968. doi: 10.21873/anticancer.12814.
131. Zheng X, Schipper M, Kidwell K, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. *Int J Radiat Oncol Biol Phys.* 2014;90(3):603-611. doi: 10.1016/j.ijrobp.2014.05.055.
132. Zhang B, Zhu F, Ma X, et al. Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: a systematic review and meta-analysis. *Radiother Oncol.* 2014;112(2):250-255. doi: 10.1016/j.radonc.2014.08.031.

133. Yu W, Tang L, Lin F, et al. Stereotactic radiosurgery, a potential alternative treatment for pulmonary metastases from osteosarcoma. *Int J Oncol.* 2014;44(4):1091-1098. doi: 10.3892/ijo.2014.2295.
134. Varlotto J, Fakiris A, Flickinger J, et al. Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non-small cell lung cancer treated with resection or stereotactic radiosurgery. *Cancer.* 2013;119(15):2683-2691. doi: 10.1002/cncr.28100.
135. van den Berg LL, Klinkenberg TJ, Groen HJM, Widder J. Patterns of recurrence and survival after surgery or stereotactic radiotherapy for early stage NSCLC. *J Thorac Oncol.* 2015;10(5):826-831. doi: 10.1097/JTO.0000000000000483.
136. Solda F, Lodge M, Ashley S, Whittington A, Goldstraw P, Brada M. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. *Radiother Oncol.* 2013;109(1):1-7. doi: 10.1016/j.radonc.2013.09.006.
137. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys.* 2012;84(5):1060-1070. doi: 10.1016/j.ijrobp.2012.07.2354.
138. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. *JAMA Surg.* 2014;149(12):1244-1253. doi: 10.1001/jamasurg.2014.556.
139. Shaverdian N, Wang PC, Steinberg M, Lee P. The patient's perspective on stereotactic body radiation therapy (SBRT) vs. surgery for treatment of early stage non-small cell lung cancer (NSCLC). *Lung Cancer.* 2015;90(2):230-233. doi: 10.1016/j.lungcan.2015.07.009.
140. Shah A, Hahn SM, Stetson RL, Friedberg JS, Pechet TT, Sher DJ. Cost-effectiveness of stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. *Cancer.* 2013;119(17):3123-3132. doi: 10.1002/cncr.28131.
141. Robinson CG, DeWees TA, El Naqa IM, et al. Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer. *J Thorac Oncol.* 2013;8(2):192-201. doi: 10.1097/JTO.0b013e31827ce361.
142. Puri V, Crabtree TD, Bell JM, et al. Treatment outcomes in stage I lung cancer: a comparison of surgery and stereotactic body radiation therapy. *J Thorac Oncol.* 2015;10(12):1776-1784. doi: 10.1097/JTO.0000000000000680.
143. Parashar B, Port J, Arora S, et al. Analysis of stereotactic radiation vs. wedge resection vs. wedge resection plus cesium-131 brachytherapy in early stage lung cancer. *Brachytherapy.* 2015;14(5):648-654. doi: 10.1016/j.brachy.2015.04.001.

144. Nanda RH, Liu Y, Gillespie TW, et al. Stereotactic body radiation therapy versus no treatment for early stage non-small cell lung cancer in medically inoperable elderly patients: a National Cancer Data Base analysis. *Cancer*. 2015;121(23):4222-4230. doi: 10.1002/cncr.29640.
145. Nakagawa T, Negoro Y, Matsuoka T, Okumura N, Dodo Y. Comparison of the outcomes of stereotactic body radiotherapy and surgery in elderly patients with cT1-2N0M0 non-small cell lung cancer. *Respir Investig*. 2014;52(4):221-226. doi: 10.1016/j.resinv.2014.01.002.
146. Mokhles S, Verstegen N, Maat AP, et al. Comparison of clinical outcome of stage I non-small cell lung cancer treated surgically or with stereotactic radiotherapy: results from propensity score analysis. *Lung Cancer*. 2015;87(3):283-289. doi: 10.1016/j.lungcan.2015.01.005.
147. Mokhles S, Nuyttens JJ, Maat AP, et al. Survival and treatment of non-small cell lung cancer stage I-II treated surgically or with stereotactic body radiotherapy: patient and tumor-specific factors affect the prognosis. *Ann Surg Oncol*. 2015;22(1):316-323. doi: 10.1245/s10434-014-3860-x.
148. Matsuo Y, Chen F, Hamaji M, et al. Comparison of long-term survival outcomes between stereotactic body radiotherapy and sublobar resection for stage I non-small-cell lung cancer in patients at high risk for lobectomy: a propensity score matching analysis. *Eur J Cancer*. 2014;50(17):2932-2938. doi: 10.1016/j.ejca.2014.09.006.
149. Lucas JT, Jr., Kuremsky JG, Soike M, et al. Comparison of accelerated hypofractionation and stereotactic body radiotherapy for stage 1 and node negative stage 2 non-small cell lung cancer (NSCLC). *Lung Cancer*. 2014;85(1):59-65. doi: 10.1016/j.lungcan.2014.04.003.
150. Louie AV, van Werkhoven E, Chen H, et al. Patient reported outcomes following stereotactic ablative radiotherapy or surgery for stage IA non-small-cell lung cancer: results from the ROSEL multicenter randomized trial. *Radiother Oncol*. 2015;117(1):44-48. doi: 10.1016/j.radonc.2015.08.011.
151. Koshy M, Malik R, Mahmood U, Husain Z, Sher DJ. Stereotactic body radiotherapy and treatment at a high volume facility is associated with improved survival in patients with inoperable stage I non-small cell lung cancer. *Radiother Oncol*. 2015;114(2):148-154. doi: 10.1016/j.radonc.2014.12.004.
152. Kastelijjn EA, El Sharouni SY, Hofman FN, et al. Clinical outcomes in early-stage NSCLC treated with stereotactic body radiotherapy versus surgical resection. *Anticancer Res*. 2015;35(10):5607-5614. <https://www.ncbi.nlm.nih.gov/pubmed/26408733>.

153. Jones GC, Kehrer JD, Kahn J, et al. Primary treatment options for high-risk/medically inoperable early stage NSCLC patients. *Clin Lung Cancer*. 2015;16(6):413-430. doi: 10.1016/j.clcc.2015.04.001.
154. Hamaji M, Chen F, Matsuo Y, et al. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. *Ann Thorac Surg*. 2015;99(4):1122-1129. doi: 10.1016/j.athoracsur.2014.11.009.
155. Ezer N, Veluswamy RR, Mhango G, Rosenzweig KE, Powell CA, Wisnivesky JP. Outcomes after stereotactic body radiotherapy versus limited resection in older patients with early-stage lung cancer. *J Thorac Oncol*. 2015;10(8):1201-1206. doi: 10.1097/JTO.0000000000000600.
156. Crabtree TD, Puri V, Robinson C, et al. Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or stereotactic radiation therapy. *J Thorac Cardiovasc Surg*. 2014;147(4):1183-1191; discussion 1191-1182. doi: 10.1016/j.jtcvs.2013.11.057.
157. Crabtree T, Puri V, Timmerman R, et al. Treatment of stage I lung cancer in high-risk and inoperable patients: comparison of prospective clinical trials using stereotactic body radiotherapy (RTOG 0236), sublobar resection (ACOSOG Z4032), and radiofrequency ablation (ACOSOG Z4033). *J Thorac Cardiovasc Surg*. 2013;145(3):692-699. doi: 10.1016/j.jtcvs.2012.10.038.
158. Chiang A, Thibault I, Warner A, et al. A comparison between accelerated hypofractionation and stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer (NSCLC): results of a propensity score-matched analysis. *Radiother Oncol*. 2016;118(3):478-484. doi: 10.1016/j.radonc.2015.12.026.
159. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol*. 2015;16(6):630-637. doi: 10.1016/S1470-2045(15)70168-3.
160. Bilal H, Mahmood S, Rajashanker B, Shah R. Is radiofrequency ablation more effective than stereotactic ablative radiotherapy in patients with early stage medically inoperable non-small cell lung cancer? *Interact Cardiovasc Thorac Surg*. 2012;15(2):258-265. doi: 10.1093/icvts/ivs179.
161. Falkson CB, Vella ET, Yu E, et al. Radiotherapy with curative intent in patients with early-stage, medically inoperable, non-small-cell lung cancer: a systematic review. *Clin Lung Cancer*. 2017;18(2):105-121 e105. doi: 10.1016/j.clcc.2016.10.008.
162. Murray P, Franks K, Hanna GG. A systematic review of outcomes following stereotactic ablative radiotherapy in the treatment of early-stage primary lung cancer. *Br J Radiol*. 2017;90(1071):20160732. doi: 10.1259/bjr.20160732.



163. Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: executive summary of an ASTRO evidence-based guideline. *Pract Radiat Oncol*. 2017;7(5):295-301. doi: 10.1016/j.prro.2017.04.014.
164. Jeppesen SS, Hansen NCG, Schytte T, Hansen O. Survival of localized NSCLC patients without active treatment or treated with SBRT. *Acta Oncol*. 2018;57(2):219-225. doi: 10.1080/0284186X.2017.1374558.
165. Bibault JE, Dussart S, Pommier P, et al. Clinical outcomes of several IMRT techniques for patients with head and neck cancer: a propensity score-weighted analysis. *Int J Radiat Oncol Biol Phys*. 2017;99(4):929-937. doi: 10.1016/j.ijrobp.2017.06.2456.
166. Cornwell LD, Echeverria AE, Samuelian J, et al. Video-assisted thoracoscopic lobectomy is associated with greater recurrence-free survival than stereotactic body radiotherapy for clinical stage I lung cancer. *J Thorac Cardiovasc Surg*. 2018;155(1):395-402. doi: 10.1016/j.jtcvs.2017.07.065.
167. Eba J, Nakamura K, Mizusawa J, et al. Stereotactic body radiotherapy versus lobectomy for operable clinical stage IA lung adenocarcinoma: comparison of survival outcomes in two clinical trials with propensity score analysis (JCOG1313-A). *Jpn J Clin Oncol*. 2016;46(8):748-753. doi: 10.1093/jjco/hyw058.
168. Koyi H, Hillerdal G, Kolbeck KG, Brodin D, Liv P, Branden E. Non-small cell lung cancer (NSCLC) in octogenarians in clinical practice. *Anticancer Res*. 2016;36(10):5397-5402. doi: 10.21873/anticancer.11115.
169. Miyazaki T, Yamazaki T, Nakamura D, et al. Surgery or stereotactic body radiotherapy for elderly stage I lung cancer? A propensity score matching analysis. *Surg Today*. 2017;47(12):1476-1483. doi: 10.1007/s00595-017-1536-4.
170. Paul S, Lee PC, Mao J, Isaacs AJ, Sedrakyan A. Long term survival with stereotactic ablative radiotherapy (SABR) versus thoracoscopic sublobar lung resection in elderly people: national population based study with propensity matched comparative analysis. *BMJ*. 2016;354:i3570. doi: 10.1136/bmj.i3570.
171. Presley CJ, Soulos PR, Tinetti M, Montori VM, Yu JB, Gross CP. Treatment burden of Medicare beneficiaries with stage I non-small-cell lung cancer. *J Oncol Pract*. 2017;13(2):e98-e107. doi: 10.1200/JOP.2016.014100.
172. Rosen JE, Salazar MC, Wang Z, et al. Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer. *J Thorac Cardiovasc Surg*. 2016;152(1):44-54 e49. doi: 10.1016/j.jtcvs.2016.03.060.

173. Wang P, Zhang D, Guo XG, et al. A propensity-matched analysis of surgery and stereotactic body radiotherapy for early stage non-small cell lung cancer in the elderly. *Medicine (Baltimore)*. 2016;95(52):e5723. doi: 10.1097/MD.0000000000005723.
174. Filippi AR, Guerrera F, Badellino S, et al. Exploratory analysis on overall survival after either surgery or stereotactic radiotherapy for lung oligometastases from colorectal cancer. *Clin Oncol (R Coll Radiol)*. 2016;28(8):505-512. doi: 10.1016/j.clon.2016.02.001.
175. Fleming C, Rimner A, Foster A, Woo KM, Zhang Z, Wu AJ. Palliative efficacy and local control of conventional radiotherapy for lung metastases. *Ann Palliat Med*. 2017;6(Suppl 1):S21-S27. doi: 10.21037/apm.2017.03.08.
176. Nyman J, Hallqvist A, Lund JA, et al. SPACE - a randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol*. 2016;121(1):1-8. doi: 10.1016/j.radonc.2016.08.015.
177. Paix A, Noel G, Falcoz PE, Levy P. Cost-effectiveness analysis of stereotactic body radiotherapy and surgery for medically operable early stage non small cell lung cancer. *Radiother Oncol*. 2018;128(3):534-540. doi: 10.1016/j.radonc.2018.04.013.
178. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer*. 2009;115(3):665-672. doi: 10.1002/cncr.24059.
179. Didolkar MS, Coleman CW, Brenner MJ, et al. Image-guided stereotactic radiosurgery for locally advanced pancreatic adenocarcinoma results of first 85 patients. *J Gastrointest Surg*. 2010;14(10):1547-1559. doi: 10.1007/s11605-010-1323-7.
180. Seo Y, Kim MS, Yoo S, et al. Stereotactic body radiation therapy boost in locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2009;75(5):1456-1461. doi: 10.1016/j.ijrobp.2009.01.042.
181. Zamboglou C, Messmer MB, Becker G, Momm F. Stereotactic radiotherapy in the liver hilum. Basis for future studies. *Strahlenther Onkol*. 2012;188(1):35-41. doi: 10.1007/s00066-011-0002-2.
182. Rwigema JC, Parikh SD, Heron DE, et al. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas. *Am J Clin Oncol*. 2011;34(1):63-69. doi: 10.1097/COC.0b013e3181d270b4.
183. Murphy JD, Chang DT, Abelson J, et al. Cost-effectiveness of modern radiotherapy techniques in locally advanced pancreatic cancer. *Cancer*. 2012;118(4):1119-1129. doi: 10.1002/cncr.26365.

184. Buwenge M, Cellini F, Silvestris N, et al. Robotic radiosurgery in pancreatic cancer: a systematic review. *World J Gastroenterol*. 2015;21(31):9420-9429. doi: 10.3748/wjg.v21.i31.9420.
185. Lin JC, Jen YM, Li MH, Chao HL, Tsai JT. Comparing outcomes of stereotactic body radiotherapy with intensity-modulated radiotherapy for patients with locally advanced unresectable pancreatic cancer. *Eur J Gastroenterol Hepatol*. 2015;27(3):259-264. doi: 10.1097/MEG.0000000000000283.
186. Balaban EP, Mangu PB, Khorana AA, et al. Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2016;34(22):2654-2668. doi: 10.1200/JCO.2016.67.5561.
187. Chapman BC, Gleisner A, Rigg D, et al. Perioperative outcomes and survival following neoadjuvant stereotactic body radiation therapy (SBRT) versus intensity-modulated radiation therapy (IMRT) in pancreatic adenocarcinoma. *J Surg Oncol*. 2018;117(5):1073-1083. doi: 10.1002/jso.25004.
188. de Geus SWL, Eskander MF, Kasumova GG, et al. Stereotactic body radiotherapy for unresected pancreatic cancer: a nationwide review. *Cancer*. 2017;123(21):4158-4167. doi: 10.1002/cncr.30856.
189. Park JJ, Hajj C, Reingold M, et al. Stereotactic body radiation vs. intensity-modulated radiation for unresectable pancreatic cancer. *Acta Oncol*. 2017;56(12):1746-1753. doi: 10.1080/0284186X.2017.1342863.
190. Zhong J, Patel K, Switchenko J, et al. Outcomes for patients with locally advanced pancreatic adenocarcinoma treated with stereotactic body radiation therapy versus conventionally fractionated radiation. *Cancer*. 2017;123(18):3486-3493. doi: 10.1002/cncr.30706.
191. Zhong J, Switchenko J, Behera M, et al. Chemotherapy with or without definitive radiation therapy in inoperable pancreatic cancer. *Ann Surg Oncol*. 2018;25(4):1026-1033. <https://link.springer.com/content/pdf/10.1245%2Fs10434-017-6322-4.pdf>.
192. Leung HW, Chan AL, Muo CH. Cost-effectiveness of gemcitabine plus modern radiotherapy in locally advanced pancreatic cancer. *Clin Ther*. 2016;38(5):1174-1183. doi: 10.1016/j.clinthera.2016.03.005.
193. Friedland JL, Freeman DE, Masterson-McGary ME, Spellberg DM. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. *Technol Cancer Res Treat*. 2009;8(5):387-392. doi: 10.1177/153303460900800509.

194. Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M. Stereotactic body radiotherapy as boost for organ-confined prostate cancer. *Technol Cancer Res Treat*. 2010;9(6):575-582. doi: 10.1177/153303461000900605.
195. King CR, Brooks JD, Gill H, Presti JC, Jr. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012;82(2):877-882. doi: 10.1016/j.ijrobp.2010.11.054.
196. Townsend NC, Huth BJ, Ding W, et al. Acute toxicity after cyberknife-delivered hypofractionated radiotherapy for treatment of prostate cancer. *Am J Clin Oncol*. 2011;34(1):6-10. doi: 10.1097/COC.0b013e3181c4c7c4.
197. Tan TJ, Siva S, Foroudi F, Gill S. Stereotactic body radiotherapy for primary prostate cancer: a systematic review. *J Med Imaging Radiat Oncol*. 2014;58(5):601-611. doi: 10.1111/1754-9485.12213.
198. Anwar M, Weinberg V, Chang AJ, Hsu IC, Roach M, 3rd, Gottschalk A. Hypofractionated SBRT versus conventionally fractionated EBRT for prostate cancer: comparison of PSA slope and nadir. *Radiat Oncol*. 2014;9:42. doi: 10.1186/1748-717X-9-42.
199. Evans JR, Zhao S, Daignault S, et al. Patient-reported quality of life after stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), and brachytherapy. *Radiother Oncol*. 2015;116(2):179-184. doi: 10.1016/j.radonc.2015.07.016.
200. Helou J, Morton G, Zhang L, et al. A comparative study of quality of life in patients with localized prostate cancer treated at a single institution: stereotactic ablative radiotherapy or external beam+high dose rate brachytherapy boost. *Radiother Oncol*. 2014;113(3):404-409. doi: 10.1016/j.radonc.2014.10.013.
201. Katz A, Ferrer M, Suarez JF, Multicentric Spanish Group of Clinically Localized Prostate C. Comparison of quality of life after stereotactic body radiotherapy and surgery for early-stage prostate cancer. *Radiat Oncol*. 2012;7:194. doi: 10.1186/1748-717X-7-194.
202. Yu JB, Cramer LD, Herrin J, Soulos PR, Potosky AL, Gross CP. Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. *J Clin Oncol*. 2014;32(12):1195-1201. doi: 10.1200/JCO.2013.53.8652.
203. Sher DJ, Parikh RB, Mays-Jackson S, Punglia RS. Cost-effectiveness analysis of SBRT versus IMRT for low-risk prostate cancer. *Am J Clin Oncol*. 2014;37(3):215-221. doi: 10.1097/COC.0b013e31827a7d2a.
204. Bouman-Wammes EW, van Dodewaard-De Jong JM, Dahele M, et al. Benefits of using stereotactic body radiotherapy in patients with metachronous oligometastases of hormone-sensitive prostate cancer detected by [18F]fluoromethylcholine PET/CT. *Clin Genitourin Cancer*. 2017;15(5):e773-e782. doi: 10.1016/j.clgc.2017.03.009.

205. Halpern JA, Sedrakyan A, Hsu WC, et al. Use, complications, and costs of stereotactic body radiotherapy for localized prostate cancer. *Cancer*. 2016;122(16):2496-2504. doi: 10.1002/cncr.30101.
206. Johnson SB, Soulos PR, Shafman TD, et al. Patient-reported quality of life after stereotactic body radiation therapy versus moderate hypofractionation for clinically localized prostate cancer. *Radiother Oncol*. 2016;121(2):294-298. doi: 10.1016/j.radonc.2016.10.013.
207. Shaverdian N, Verruttipong D, Wang PC, et al. Exploring value from the patient's perspective between modern radiation therapy modalities for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2017;97(3):516-525. doi: 10.1016/j.ijrobp.2016.11.007.
208. Helou J, Torres S, Musunuru HB, et al. Stereotactic body radiotherapy versus low dose rate brachytherapy for localised prostate cancer: a cost-utility analysis. *Clin Oncol (R Coll Radiol)*. 2017;29(11):718-731. doi: 10.1016/j.clon.2017.08.002.
209. Tao C, Yang LX. Improved radiotherapy for primary and secondary liver cancer: stereotactic body radiation therapy. *Anticancer Res*. 2012;32(2):649-655. <https://www.ncbi.nlm.nih.gov/pubmed/22287758>.
210. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2011;81(4):e447-453. doi: 10.1016/j.ijrobp.2011.04.011.
211. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. *Cancer*. 2011;117(17):4060-4069. doi: 10.1002/cncr.25997.
212. Katz AW, Carey-Sampson M, Muhs AG, Milano MT, Schell MC, Okunieff P. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. *Int J Radiat Oncol Biol Phys*. 2007;67(3):793-798. doi: 10.1016/j.ijrobp.2006.10.025.
213. Lee WY, Cho DY, Lee HC, et al. Outcomes and cost-effectiveness of Gamma knife radiosurgery and whole brain radiotherapy for multiple metastatic brain tumors. *J Clin Neurosci*. 2009;16(5):630-634. doi: 10.1016/j.jocn.2008.06.021.
214. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol*. 2009;27(10):1572-1578. doi: 10.1200/JCO.2008.19.6329.
215. Shun SC, Chiou JF, Lai YH, et al. Changes in quality of life and its related factors in liver cancer patients receiving stereotactic radiation therapy. *Support Care Cancer*. 2008;16(9):1059-1065. doi: 10.1007/s00520-007-0384-y.

216. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol*. 2008;26(4):657-664. doi: 10.1200/JCO.2007.14.3529.
217. Honda Y, Kimura T, Aikata H, et al. Stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2013;28(3):530-536. doi: 10.1111/jgh.12087.
218. Oladeru OT, Miccio JA, Yang J, Xue Y, Ryu S, Stessin AM. Conformal external beam radiation or selective internal radiation therapy-a comparison of treatment outcomes for hepatocellular carcinoma. *J Gastrointest Oncol*. 2016;7(3):433-440. doi: 10.21037/jgo.2015.10.04.
219. Wahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol*. 2016;34(5):452-459. doi: 10.1200/JCO.2015.61.4925.
220. Cai Y, Chang Q, Xiao E, Shang QL, Chen Z. Transcatheter arterial chemoembolization (TACE) combined with gamma-knife compared to TACE or Gamma-knife alone for hepatocellular carcinoma. *Medicine (Baltimore)*. 2018;97(22):e10890. doi: 10.1097/MD.00000000000010890.
221. Lu XJ, Dong J, Ji LJ, Xiao LX, Ling CQ, Zhou J. Tolerability and efficacy of Gamma knife radiosurgery on hepatocellular carcinoma with portal vein tumor thrombosis. *Oncotarget*. 2016;7(3):3614-3622. doi: 10.18632/oncotarget.6118.
222. Su TS, Liang P, Liang J, et al. Long-term survival analysis of stereotactic ablative radiotherapy versus liver resection for small hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2017;98(3):639-646. doi: 10.1016/j.ijrobp.2017.02.095.
223. Kim H, Gill B, Beriwal S, Huq MS, Roberts MS, Smith KJ. Cost-effectiveness analysis of stereotactic body radiation therapy compared with radiofrequency ablation for inoperable colorectal liver metastases. *Int J Radiat Oncol Biol Phys*. 2016;95(4):1175-1183. doi: 10.1016/j.ijrobp.2016.02.045.
224. Leung HW, Liu CF, Chan AL. Cost-effectiveness of sorafenib versus SBRT for unresectable advanced hepatocellular carcinoma. *Radiat Oncol*. 2016;11:69. doi: 10.1186/s13014-016-0644-4.
225. Pollom EL, Lee K, Durkee BY, et al. Cost-effectiveness of stereotactic body radiation therapy versus radiofrequency ablation for hepatocellular carcinoma: a Markov modeling study. *Radiology*. 2017;283(2):460-468. doi: 10.1148/radiol.2016161509.

226. Al-Wassia R, Dal Pra A, Shun K, et al. Stereotactic fractionated radiotherapy in the treatment of juxtapapillary choroidal melanoma: the McGill University experience. *Int J Radiat Oncol Biol Phys.* 2011;81(4):e455-462. doi: 10.1016/j.ijrobp.2011.05.012.
227. Dieckmann K, Georg D, Zehetmayer M, Rottenfusser A, Potter R. Stereotactic photon beam irradiation of uveal melanoma: indications and experience at the University of Vienna since 1997. *Strahlenther Onkol.* 2007;183 Spec No 2:11-13. doi: 10.1007/s00066-007-2005-6.
228. Emara K, Weisbrod DJ, Sahgal A, et al. Stereotactic radiotherapy in the treatment of juxtapapillary choroidal melanoma: preliminary results. *Int J Radiat Oncol Biol Phys.* 2004;59(1):94-100. doi: 10.1016/j.ijrobp.2003.10.007.
229. Guss ZD, Batra S, Limb CJ, et al. Radiosurgery of glomus jugulare tumors: a meta-analysis. *Int J Radiat Oncol Biol Phys.* 2011;81(4):e497-502. doi: 10.1016/j.ijrobp.2011.05.006.
230. Krema H, Somani S, Sahgal A, et al. Stereotactic radiotherapy for treatment of juxtapapillary choroidal melanoma: 3-year follow-up. *Br J Ophthalmol.* 2009;93(9):1172-1176. doi: 10.1136/bjo.2008.153429.
231. Modorati G, Miserocchi E, Galli L, Picozzi P, Rama P. Gamma knife radiosurgery for uveal melanoma: 12 years of experience. *Br J Ophthalmol.* 2009;93(1):40-44. doi: 10.1136/bjo.2008.142208.
232. Muller K, Nowak PJ, Naus N, et al. Lacrimal gland radiosensitivity in uveal melanoma patients. *Int J Radiat Oncol Biol Phys.* 2009;74(2):497-502. doi: 10.1016/j.ijrobp.2008.08.010.
233. Somani S, Sahgal A, Krema H, et al. Stereotactic radiotherapy in the treatment of juxtapapillary choroidal melanoma: 2-year follow-up. *Can J Ophthalmol.* 2009;44(1):61-65. doi: 10.3129/i08-177.
234. Shan GP, Wang BB, Zheng P, Du FL, Yang YW. Efficacy and safety of chemotherapy combined with stereotactic radiotherapy in the treatment of nasopharyngeal carcinoma. *Med Sci Monit.* 2017;23:5630-5636. doi: 10.12659/msm.903903.
235. Yamazaki H, Demizu Y, Okimoto T, et al. Comparison of re-irradiation outcomes for charged particle radiotherapy and robotic stereotactic radiotherapy using Cyberknife for recurrent head and neck cancers: a multi-institutional matched-cohort analysis. *Anticancer Res.* 2016;36(10):5507-5514. doi: 10.21873/anticancer.11132.
236. Yamazaki H, Demizu Y, Okimoto T, et al. Reirradiation for recurrent head and neck cancers using charged particle or photon radiotherapy. *Strahlenther Onkol.* 2017;193(7):525-533. doi: 10.1007/s00066-017-1129-6.

237. Al-Mamgani A, Van Rooij P, Sewnaik A, et al. Brachytherapy or stereotactic body radiotherapy boost for early-stage oropharyngeal cancer: comparable outcomes of two different approaches. *Oral Oncol.* 2013;49(10):1018-1024. doi: 10.1016/j.oraloncology.2013.07.007.
238. Casamassima F, Livi L, Masciullo S, et al. Stereotactic radiotherapy for adrenal gland metastases: university of Florence experience. *Int J Radiat Oncol Biol Phys.* 2012;82(2):919-923. doi: 10.1016/j.ijrobp.2010.11.060.
239. Chawla S, Chen Y, Katz AW, et al. Stereotactic body radiotherapy for treatment of adrenal metastases. *Int J Radiat Oncol Biol Phys.* 2009;75(1):71-75. doi: 10.1016/j.ijrobp.2008.10.079.
240. Gunjur A, Duong C, Ball D, Siva S. Surgical and ablative therapies for the management of adrenal 'oligometastases' - a systematic review. *Cancer Treat Rev.* 2014;40(7):838-846. doi: 10.1016/j.ctrv.2014.04.001.
241. Yuan BY, Hu Y, Zhang L, Chen YH, Dong YY, Zeng ZC. Radiotherapy for adrenal gland metastases from hepatocellular carcinoma. *Clin Transl Oncol.* 2017;19(9):1154-1160. doi: 10.1007/s12094-017-1654-x.
242. Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: update of an ASTRO evidence-based guideline. *Pract Radiat Oncol.* 2017;7(1):4-12. doi: 10.1016/j.prr.2016.08.001.
243. Levine AM, Coleman C, Horasek S. Stereotactic radiosurgery for the treatment of primary sarcomas and sarcoma metastases of the spine. *Neurosurgery.* 2009;64(2 Suppl):A54-59. doi: 10.1227/01.NEU.0000339131.28485.4A.
244. McCammon R, Schefter TE, Gaspar LE, Zaemisch R, Gravidahl D, Kavanagh B. Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys.* 2009;73(1):112-118. doi: 10.1016/j.ijrobp.2008.03.062.
245. Milano MT, Katz AW, Muhs AG, et al. A prospective pilot study of curative-intent stereotactic body radiation therapy in patients with 5 or fewer oligometastatic lesions. *Cancer.* 2008;112(3):650-658. doi: 10.1002/cncr.23209.
246. Milano MT, Katz AW, Okunieff P. Patterns of recurrence after curative-intent radiation for oligometastases confined to one organ. *Am J Clin Oncol.* 2010;33(2):157-163. doi: 10.1097/COC.0b013e3181979238.
247. Scorsetti M, Bignardi M, Alongi F, et al. Stereotactic body radiation therapy for abdominal targets using volumetric intensity modulated arc therapy with RapidArc: feasibility and



- clinical preliminary results. *Acta Oncol.* 2011;50(4):528-538. doi: 10.3109/0284186X.2011.558522.
248. Canadian Agency for Drugs and Technologies in Health. Stereotactic ablative radiotherapy for the treatment of oligometastatic cancer: a clinical review as part of a health technology assessment v2.0. 2022; <https://cadth.ca/stereotactic-ablative-radiotherapy-treatment-oligometastatic-cancer>. Accessed March 24, 2022.
249. Hoyer M, Roed H, Traberg Hansen A, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. *Acta Oncol.* 2006;45(7):823-830. doi: 10.1080/02841860600904854.
250. Kang JK, Kim MS, Kim JH, et al. Oligometastases confined one organ from colorectal cancer treated by SBRT. *Clin Exp Metastasis.* 2010;27(4):273-278. doi: 10.1007/s10585-010-9325-0.

## Appendix A. Search Strategies

### Ovid MEDLINE All

- 1 Radiosurgery/
- 2 (Radiosurg\* or SBRT).ti,ab,kf.
- 3 ((Stereotactic\* or robot\*) adj2 (Radiation\* or radio\* or irradiat\*)).ti,ab,kf.
- 4 ((LINAC\* or linear accelerat\*) adj3 radio\*).ti,ab,kf.
- 5 (Gamma Knife or GammaKnife or Cyber Knife or cyberknif\* or tomotherap\*).ti,ab,kf.
- 6 or/1-5
- 7 (animals/ not (animals/ and humans/)) or (bovine\$1 or canine\$1 or cat\$1 or chimpanzee\$1 or dog\$1 or feline\$1 or hen\$1 or mice or monkey\$1 or mouse or pig\$1 or porcine or rabbit\$1 or rat or rats or rattus or rhesus or rodent\$1 or zebrafish).ti.
- 8 6 not 7
- 9 limit 8 to english language
- 10 limit 9 to yr="2019 -Current"
- 11 (201809\* or 20181\*).dp,dt,ep,ez.
- 12 9 and (10 or 11)
- 13 (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Armenia or Azerbaijan or Bangladesh or Belize or Benin or Bhutan or Bolivia or Bosnia or Herzegovina or Botswana or Brazil or Burkina Faso or Burundi or Cabo Verde or Cambodia or Cameroon or Central African Republic or Chad or China or Colombia or Comoros or Congo or Congo or Cote d'Ivoire or Cuba or Djibouti or Dominica or Dominican Republic or Ecuador or Egypt or El Salvador or Equatorial Guinea or Eritrea).ti.
- 14 (Eswatini or Ethiopia or Fiji or Gabon or Gambia or Ghana or Grenada or Guatemala or Guinea or Guinea-Bissau or Guyana or Haiti or Honduras or India or Indonesia or Iran or Iraq or Jamaica or Jordan or Kenya or Kiribati or Kyrgyzstan or Laos or Lebanon or Lesotho or Liberia or Libya or Madagascar or Malawi or Maldives or Mali or Marshall Islands or Mauritania or Mexico or Micronesia or Moldova or Mongolia or Morocco or Mozambique or Myanmar or Namibia or Nepal).ti.
- 15 (Nicaragua or Niger or Nigeria or North Macedonia or Pakistan or Palestine or Papua New Guinea or Paraguay or Peru or Philippines or Rwanda or Saint Kitts or Nevis or Saint Lucia or Saint Vincent or the Grenadines or Samoa or Sao Tome or Principe or Senegal or Seychelles or Sierra Leone or Solomon Islands or South Africa or South Sudan or Sri Lanka or Sudan or Suriname or Syria or Tajikistan or Tanzania or Thailand or Timor-Leste or Togo or Tonga or Trinidad or Tobago or Tunisia or Turkmenistan or Uganda or Ukraine or Uzbekistan or Vanuatu or Venezuela or VietNam or Yemen or Zambia or Zimbabwe).ti.

16 africa/ or africa, northern/ or algeria/ or egypt/ or libya/ or morocco/ or tunisia/ or "africa south of the sahara"/ or africa, central/ or cameroon/ or central african republic/ or chad/ or congo/ or "democratic republic of the congo"/ or equatorial guinea/ or gabon/ or "sao tome and principe"/ or africa, eastern/ or burundi/ or djibouti/ or eritrea/ or ethiopia/ or kenya/ or rwanda/ or somalia/ or south sudan/ or sudan/ or tanzania/ or uganda/ or africa, southern/ or angola/ or botswana/ or eswatini/ or lesotho/ or malawi/ or mozambique/ or namibia/ or south africa/ or zambia/ or zimbabwe/ or africa, western/ or benin/ or burkina faso/ or cabo verde/ or cote d'ivoire/ or gambia/ or ghana/ or guinea/ or guinea-bissau/ or liberia/ or mali/ or mauritania/ or niger/ or nigeria/ or senegal/ or sierra leone/ or togo/

17 belize/ or el salvador/ or guatemala/ or honduras/ or nicaragua/ or bolivia/ or brazil/ or colombia/ or ecuador/ or guyana/ or paraguay/ or peru/ or suriname/ or venezuela/

18 "antigua and barbuda"/ or cuba/ or dominica/ or dominican republic/ or grenada/ or haiti/ or jamaica/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "trinidad and tobago"/

19 asia, central/ or kazakhstan/ or kyrgyzstan/ or tajikistan/ or turkmenistan/ or uzbekistan/ or cambodia/ or laos/ or myanmar/ or philippines/ or thailand/ or timor-leste/ or vietnam/ or bangladesh/ or bhutan/ or india/ or sikkim/ or afghanistan/ or iran/ or iraq/ or jordan/ or lebanon/ or syria/ or yemen/ or nepal/ or pakistan/ or sri lanka/ or china/ or beijing/ or macau/ or tibet/ or "democratic people's republic of korea"/ or mongolia/

20 albania/ or "bosnia and herzegovina"/ or moldova/ or ukraine/ or armenia/ or azerbaijan/

21 or/13-20

22 12 not 13

23 (malignan\* or epithelioma\* or carcinoma\*).ti,ab,kf.

24 22 and 23

## CENTRAL

1 [mh ^"Radiosurgery"] OR radiosurgery\*:ti,ab

2 (Radiosurg\* OR SBRT):ti,ab,kw

3 ((Stereotactic\* or robot\*) NEXT (Radiation\* or radio\* or irradiat\*)):ti,ab,kw

4 ((LINAC\* or linear accelerat\*) NEXT radio\*):ti,ab,kw

5 (Gamma Knife or GammaKnife or Cyber Knife or cyberknif\* or tomotherap\*):ti,ab,kw

6 #1 OR #2 OR #3 OR #4 OR #5 with Cochrane Library publication date Between Sep 2018 and Dec 2021

## Appendix B. Detailed Inclusion and Exclusion Criteria

Table B1. Detailed Inclusion and Exclusion Criteria for This Evidence Review

Study Component	Inclusion	Exclusion
Populations	<ul style="list-style-type: none"> <li>Adults and children with CNS and non-CNS malignancies where treatment by radiation therapy is appropriate</li> </ul>	<ul style="list-style-type: none"> <li>Studies in people with noncancer conditions (e.g., trigeminal neuralgia)</li> </ul>
Interventions	<ul style="list-style-type: none"> <li>SRS or SBRT with devices such as Gamma Knife, CyberKnife, TomoTherapy</li> </ul>	<ul style="list-style-type: none"> <li>Treatments delivered in 11 or more fractions</li> </ul>
Comparators	<ul style="list-style-type: none"> <li>Conventional (conformal) external beam radiation therapy (EBRT)</li> <li>Surgery</li> <li>No treatment</li> </ul>	<ul style="list-style-type: none"> <li>Comparators other than those stated</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>Effectiveness (for non-CNS and non-NSCLC cancers)               <ul style="list-style-type: none"> <li>Survival rate</li> <li>Duration of symptom-free remission</li> <li>Quality of life</li> </ul> </li> <li>Harms including radiation exposure and complications</li> <li>Cost</li> <li>Cost-effectiveness</li> </ul>	<ul style="list-style-type: none"> <li>Studies that do not report outcomes of interest</li> <li>Data for treatment planning (e.g., dosing) or treatment delivery (e.g., accuracy)</li> <li>Economic outcomes from studies performed in non-US countries</li> <li>Economic outcomes from studies performed in the US that were published more than 5 years ago</li> </ul>
Timing	<ul style="list-style-type: none"> <li>Any point in the care pathway</li> </ul>	<ul style="list-style-type: none"> <li>None stated</li> </ul>
Setting	<ul style="list-style-type: none"> <li>Any outpatient or inpatient clinical setting in countries categorized as very high on the UN Human Development Index</li> </ul>	<ul style="list-style-type: none"> <li>Emergency settings</li> <li>Nonclinical settings (e.g., studies in healthy volunteers, animal models of disease)</li> <li>Countries categorized other than very high on the UN Human Development Index</li> </ul>
Study Design	<ul style="list-style-type: none"> <li>For KQ1, KQ2, and KQ3               <ul style="list-style-type: none"> <li>Comparative study designs (prospective, retrospective, and randomized or controlled clinical trials)</li> </ul> </li> <li>For KQ2               <ul style="list-style-type: none"> <li>Comparative study designs</li> <li>Noncomparative study designs (<math>\geq 100</math> participants; for non-CNS and non-NSCLC cancers)</li> </ul> </li> <li>For KQ4               <ul style="list-style-type: none"> <li>Comparative cost data and relevant economic evaluations</li> <li>Cost-effectiveness analyses</li> <li>Economic simulation modeling studies</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Abstracts, conference proceedings, posters, editorials, letters</li> <li>Studies without a comparator</li> <li>Proof-of-principle studies (e.g., technology development or technique modification)</li> </ul>

Study Component	Inclusion	Exclusion
Sample Size	<ul style="list-style-type: none"> <li>• CNS cancers               <ul style="list-style-type: none"> <li>◦ Minimum sample size of 20 participants</li> </ul> </li> <li>• Cancers of the breast, colon, head, neck, lung, prostate               <ul style="list-style-type: none"> <li>◦ Minimum sample size of 50 participants</li> </ul> </li> <li>• Other non-CNS cancers               <ul style="list-style-type: none"> <li>◦ Minimum sample size of 20 participants</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Studies that do not meet the minimum sample size</li> </ul>
Publication	<ul style="list-style-type: none"> <li>• Published, peer-reviewed, English-language articles</li> </ul>	<ul style="list-style-type: none"> <li>• Studies with abstracts that do not allow study characteristics to be determined</li> <li>• Studies that cannot be located</li> <li>• Duplicate publications of the same study that do not report different outcomes or follow-up times, or single site reports from published multicenter studies</li> <li>• Studies published in languages other than English</li> </ul>

*Abbreviations. CNS: central nervous system; KQ: key question; NSCLC: non-small cell lung cancer; SBRT: stereotactic body radiation therapy; SRS: stereotactic radiation surgery; UN: United Nations.*

## Appendix C. Excluded Studies With Reasons

Reference	Exclusion Criteria
<b>Phase II Trial of Ipilimumab with Stereotactic Radiation Therapy for Metastatic Disease: outcomes, Toxicities, and Low-Dose Radiation-Related Abscopal Responses.</b> <i>Cancer immunology research</i> . 2019. 7:1903-1909	Intervention
Abel, Stephen, Hasan, Shaakir, White, Richard, Schumacher, Lana, Finley, Gene, Colonias, Athanasios, Wegner, Rodney E.. <b>Stereotactic ablative radiotherapy (SABR) in early stage non-small cell lung cancer: Comparing survival outcomes in adenocarcinoma and squamous cell carcinoma.</b> <i>Lung cancer (Amsterdam, Netherlands)</i> . 2019. 128:127-133	Comparator
Ager, Bryan J., Wells, Stacey M., Gruhl, Joshua D., Stoddard, Gregory J., Tao, Randa, Kokeny, Kristine E., Hitchcock, Ying J.. <b>Stereotactic body radiotherapy versus percutaneous local tumor ablation for early-stage non-small cell lung cancer.</b> <i>Lung cancer (Amsterdam, Netherlands)</i> . 2019. 138:6-12	Comparator
Alattar, Ali A., Bartek, Jiri, Jr., Chiang, Veronica L., Mohammadi, Alireza M., Barnett, Gene H., Sloan, Andrew, Chen, Clark C.. <b>Stereotactic Laser Ablation as Treatment of Brain Metastases Recurring after Stereotactic Radiosurgery: A Systematic Literature Review.</b> <i>World neurosurgery</i> . 2019. 128:134-142	Aim
Bagley, Alexander F., Garden, Adam S., Reddy, Jay P., Moreno, Amy C., Frank, Steven J., Rosenthal, David I., Morrison, William H., Gunn, Gary Brandon, Fuller, Clifton D., Shah, Shalin J., Ferrarotto, Renata, Sturgis, Erich M., Gross, Neil D., Phan, Jack. <b>Highly conformal reirradiation in patients with prior oropharyngeal radiation: Clinical efficacy and toxicity outcomes.</b> <i>Head &amp; neck</i> . 2020. 42:3326-3335	Aim
Bettinger D, Pinato DJ, Schultheiss M, et al. <b>Stereotactic body radiation therapy as an alternative treatment for patients with hepatocellular carcinoma compared to sorafenib: a propensity score analysis.</b> <i>Liver cancer</i> . 2019;8(4):281-294.	Comparator
Borius, Pierre-Yves, Regis, Jean, Carpentier, Alexandre, Kalamarides, Michel, Valery, Charles Ambroise, Latorzeff, Igor. <b>Safety of radiosurgery concurrent with systemic therapy (chemotherapy, targeted therapy, and/or immunotherapy) in brain metastases: a systematic review.</b> <i>Cancer metastasis reviews</i> . 2021. 40:341-354	Comparator
Chen, Yi-Xing, Zhuang, Yuan, Yang, Ping, Fan, Jia, Zhou, Jian, Hu, Yong, Zhu, Wen-Chao, Sun, Jing, Zeng, Zhao-Chong. <b>Helical IMRT-Based Stereotactic Body Radiation Therapy Using an Abdominal Compression Technique and Modified Fractionation Regimen for Small Hepatocellular Carcinoma.</b> <i>Technology in cancer research &amp; treatment</i> . 2020. 19:1533033820937002	Setting
Choi, Hoon Sik, Kang, Ki Mun, Jeong, Bae Kwon, Jeong, Hojin, Lee, Yun Hee, Ha, In Bong, Song, Jin Ho. <b>Effectiveness of stereotactic body radiotherapy for portal vein tumor thrombosis in patients with hepatocellular carcinoma and underlying chronic liver disease.</b> <i>Asia-Pacific journal of clinical oncology</i> . 2021. 17:209-215	Comparator
Churilla Thomas, M., Chowdhury Imran, H., Handorf, Elizabeth, Collette, Laurence, Collette, Sandra, Dong, Yanqun, Alexander Brian, M., Kocher, Martin, Soffiatti, Riccardo, Claus Elizabeth, B., et al.,. <b>Comparison of Local Control of Brain Metastases With Stereotactic Radiosurgery vs Surgical Resection: a Secondary Analysis of a Randomized Clinical Trial.</b> <i>JAMA oncology</i> . 2019. 5:243-247	Outcomes
de Almeida Bastos, D. C., Everson, R. G., de Oliveira Santos, B. F., Habib, A., Vega, R. A., Oro, M., Rao, G., Li, J., Ghia, A. J., Bi shop, A. J., et al.,. <b>A comparison of spinal laser interstitial thermotherapy with open surgery for metastatic thoracic epidural spinal cord compression.</b> <i>Journal of neurosurgery. Spine</i> . 2020. #volume#:1-9	Intervention

Reference	Exclusion Criteria
De Maria, Lucio, Terzi di Bergamo, Lodovico, Conti, Alfredo, Hayashi, Kazuhiko, Pinzi, Valentina, Murai, Taro, Lanciano, Rachele, Burneikiene, Sigita, Buglione di Monale, Michela, Magrini, Stefano Maria, Fontanella, Marco Maria. <b>CyberKnife for Recurrent Malignant Gliomas: A Systematic Review and Meta-Analysis.</b> <i>Frontiers in oncology</i> . 2021. 11:652646	Comparator
Dee, Edward Christopher, Muralidhar, Vinayak, King, Martin T., Martin, Neil E., D'Amico, Anthony V., Mouw, Kent W., Orio, Peter F., Nguyen, Paul L., Leeman, Jonathan E.. <b>Second malignancy probabilities in prostate cancer patients treated with SBRT and other contemporary radiation techniques.</b> <i>Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology</i> . 2021. 161:241-250	Outcomes
El-Modir, A., Anwar, M. S., Fernando, I. N., Doyle, Y.. <b>Palliative external-beam and stereotactic radiotherapy (SABR) for recurrent and oligometastatic ovarian cancer.</b> <i>International journal of gynecological cancer</i> . 2018. 28:670-	Publication Type
English, Keara, Brodin, N. Patrik, Shankar, Viswanathan, Zhu, Shaoyu, Ohri, Nitin, Golowa, Yosef S., Cynamon, Jacob, Bellemare, Sarah, Kaubisch, Andreas, Kinkhabwala, Milan, Kalnicki, Shalom, Garg, Madhur K., Guha, Chandan, Kabarriti, Rafi. <b>Association of Addition of Ablative Therapy Following Transarterial Chemoembolization With Survival Rates in Patients With Hepatocellular Carcinoma.</b> <i>JAMA network open</i> . 2020. 3:e2023942	Comparator
Ernani, Vinicius, Appiah, Adams Kusi, Baine, Michael J., Smith, Lynette M., Ganti, Apar Kishor. <b>The impact of histology in the outcomes of patients with early-stage non-small cell lung cancer (NSCLC) treated with stereotactic body radiation therapy (SBRT) and adjuvant chemotherapy.</b> <i>Cancer treatment and research communications</i> . 2020. 24:100197	Comparator
Faruqi, Salman, Chen, Hanbo, Fariselli, Laura, Levivier, Marc, Ma, Lijun, Paddick, Ian, Pollock, Bruce E., Regis, Jean, Sheehan, Jason, Suh, John, Yomo, Shoji, Sahgal, Arjun. <b>Stereotactic Radiosurgery for Postoperative Spine Malignancy: A Systematic Review and International Stereotactic Radiosurgery Society Practice Guidelines.</b> <i>Practical radiation oncology</i> . 2021. #/volume#: #pages#	Comparator
Franzese, Ciro, D'Agostino, Giuseppe, Di Brina, Lucia, Navarria, Pierina, De Rose, Fiorenza, Comito, Tiziana, Franceschini, Davide, Mancosu, Pietro, Tomatis, Stefano, Scorsetti, Marta. <b>Linac-based stereotactic body radiation therapy vs moderate hypofractionated radiotherapy in prostate cancer: propensity-score based comparison of outcome and toxicity.</b> <i>The British journal of radiology</i> . 2019. 92:20190021	Comparator
Furdova, A., Babal, P., Kobzova, D., Zahorjanova, P., Kapitanova, K., Sramka, M., Kralik, G., Furda, R., Krasnik, V.. <b>Uveal melanoma survival rates after single dose stereotactic radiosurgery.</b> <i>Neoplasma</i> . 2018. 65:965-971	Outcomes
Hara K, Takeda A, Tsurugai Y, et al. <b>Radiotherapy for Hepatocellular Carcinoma Results in Comparable Survival to Radiofrequency Ablation: A Propensity Score Analysis.</b> <i>Hepatology</i> . 2019;69(6):2533-2545. doi: 10.1002/hep.30591 Accessed 20190502//	Included in an included systematic reivew
Hardy-Abeloos, Camille, Lazarev, Stanislav, Ru, Meng, Kim, Edward, Fischman, Aaron, Moshier, Erin, Rosenzweig, Kenneth, Buckstein, Michael. <b>Safety and Efficacy of Liver Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma After Segmental Transarterial Radioembolization.</b> <i>International journal of radiation oncology, biology, physics</i> . 2019. 105:968-976	Intervention

Reference	Exclusion Criteria
Hasan, Shaakir, Abel, Stephen, Verma, Vivek, Webster, Patrick, Arscott, W. Tristram, Wegner, Rodney E., Kirichenko, Alexander, Simone, Charles B., 2nd. <u>Proton beam therapy versus stereotactic body radiotherapy for hepatocellular carcinoma: practice patterns, outcomes, and the effect of biologically effective dose escalation.</u> <i>Journal of gastrointestinal oncology</i> . 2019. 10:999-1009	Comparator
Hechtner, M., Krause, M., König, J., Appold, S., Hornemann, B., Singer, S., Baumann, M.. <u>Long-term quality of life in inoperable non-small cell lung cancer patients treated with conventionally fractionated compared to hyperfractionated accelerated radiotherapy - Results of the randomized CHARTWEL trial.</u> <i>Radiotherapy and oncology</i> . 2018. 126:283-290	Intervention
Hilal, Lara, Reyngold, Marsha, Wu, Abraham J., Araji, Abdallah, Abou-Alfa, Ghassan K., Jarnagin, William, Harding, James J., Gambarin, Maya, El Dika, Imane, Brady, Paul, Navilio, John, Berry, Sean L., Flynn, Jessica, Zhang, Zhigang, Tuli, Richard, Zinovoy, Melissa, Romesser, Paul B., Cuaron, John J., Crane, Christopher H., Hajj, Carla. <u>Ablative radiation therapy for hepatocellular carcinoma is associated with reduced treatment- and tumor-related liver failure and improved survival.</u> <i>Journal of gastrointestinal oncology</i> . 2021. 12:1743-1752	Comparator
Hong, Jiawei, Cao, Linping, Xie, Haiyang, Liu, Yuanxing, Yu, Jun, Zheng, Shusen. <u>Stereotactic body radiation therapy versus radiofrequency ablation in patients with small hepatocellular carcinoma: a systematic review and meta-analysis.</u> <i>Hepatobiliary surgery and nutrition</i> . 2021. 10:623-630	Setting
Huang, W. Y., Shen, P. C., Dai, Y. H., Yang, J. F., Lo, C. H.. <u>Stereotactic body radiotherapy versus transarterial chemoembolization for medium-sized hepatocellular carcinoma: a propensity score matching analysis.</u> <i>Liver cancer</i> . 2018. 7:214-	Publication Type
Isfahanian, N., Lukka, H., Dayes, I., Quan, K., Schnarr, K. L., Douvi, G., Goldberg, M., Wright, J., Swaminath, A., Chow, T., et al.,. <u>A Randomized Phase II Trial of Prostate Boost Irradiation With Stereotactic Body Radiotherapy (SBRT) or Conventional Fractionation (CF) External Beam Radiotherapy (EBRT) in Locally Advanced Prostate Cancer: the PBS Trial (NCT03380806).</u> <i>Clinical genitourinary cancer</i> . 2020. 18:e410-e415	Publication Type
Juloori, Aditya, Miller, Jacob A., Parsai, Shireen, Kotecha, Rupesh, Ahluwalia, Manmeet S., Mohammadi, Alireza M., Murphy, Erin S., Suh, John H., Barnett, Gene H., Yu, Jennifer S., Vogelbaum, Michael A., Rini, Brian, Garcia, Jorge, Stevens, Glen H., Angelov, Lilyana, Chao, Samuel T.. <u>Overall survival and response to radiation and targeted therapies among patients with renal cell carcinoma brain metastases.</u> <i>Journal of neurosurgery</i> . 2019. #volume#:1-9	Comparator
Kann, Benjamin H., Verma, Vivek, Stahl, John M., Ross, Rudi, Dosoretz, Arie P., Shafman, Timothy D., Gross, Cary P., Park, Henry S., Yu, James B., Decker, Roy H.. <u>Multi-institutional analysis of stereotactic body radiation therapy for operable early-stage non-small cell lung carcinoma.</u> <i>Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology</i> . 2019. 134:44-49	Comparator
Khan, Muhammad, Zhao, Zhihong, Arooj, Sumbal, Liao, Guixiang. <u>Impact of Tyrosine Kinase Inhibitors (TKIs) Combined With Radiation Therapy for the Management of Brain Metastases From Renal Cell Carcinoma.</u> <i>Frontiers in oncology</i> . 2020. 10:1246	Setting
Kim N, Cheng J, Jung I, et al. <u>Stereotactic body radiation therapy vs. radiofrequency ablation in Asian patients with hepatocellular carcinoma.</u> <i>Journal of hepatology</i> . 2020;73(1):121-129.	Included in an included systematic review



Reference	Exclusion Criteria
Kim N, Kim HJ, Won JY, et al. <u>Retrospective analysis of stereotactic body radiation therapy efficacy over radiofrequency ablation for hepatocellular carcinoma.</u> <i>Radiother Oncol.</i> 2019;131:81-87. doi: 10.1016/j.radonc.2018.12.013	Included in an included systematic review
Kim, B. S.,Yeon, J. Y.,Kim, J. S.,Hong, S. C.,Shin, H. J.,Lee, J. I.. <u>Gamma Knife Radiosurgery for ARUBA-Eligible Patients with Unruptured Brain Arteriovenous Malformations.</u> <i>Journal of Korean medical science.</i> 2019. 34:e232-	Population
Kong, F. Ms,He, C.,Zang, Y.,Althouse, S. K.,Tim, L.,Kesler, K.. <u>Long-term survival comparison of stereotactic radiotherapy versus surgery for elderly patients with clinical stage T1-T2 nonsmall cell lung cancer.</u> <i>Journal of clinical oncology.</i> 2018. 36:#pages#	Publication Type
Lee, Min Ho,Cho, Kyung-Rae,Choi, Jung Won,Kong, Doo-Sik,Seol, Ho Jun,Nam, Do-Hyun,Jung, Hyun Ae,Sun, Jong-Mu,Lee, Se-Hoon,Ahn, Jin Seok,Ahn, Myung-Ju,Park, Keunchil, Lee, Jung-Il. <u>Immune Checkpoint Inhibitors for Non-Small-Cell Lung Cancer with Brain Metastasis : The Role of Gamma Knife Radiosurgery.</u> <i>Journal of Korean Neurosurgical Society.</i> 2021. 64:271-281	Aim
Leung, Henry Wc,Lang, Hui-Chu,Wang, Shyh-Yau,Leung, John Hang,Chan, Agnes Lf. <u>Cost-utility analysis of stereotactic body radiotherapy plus cetuximab in previously irradiated recurrent squamous cell carcinoma of the head and neck.</u> <i>Expert review of pharmacoeconomics &amp; outcomes research.</i> 2021. 21:489-495	Setting
Li, J.,Dai, J.,Xian, P.,Xiong, L.,Song, Y.,Tang, X.,Li, Y.,Wu, Y.,Zhou, H.,Liu, N.. <u>Efficacy and safety of Prostate stereotactic body radiotherapy for metastatic castration-resistant prostate cancer: a prospective cohort study.</u> <i>Cancer treatment and research communications.</i> 2021. 27:#pages#	Setting
Liu, Howard Yu-Hao, Lee, Yoo-Young Dominique, Sridharan, Swetha, Choong, Ee Siang, Le, Hien, Wang, Wei, Khor, Richard, Chu, Julie, Oar, Andrew, Mott, Rebekah, Smart, Joanne, Jenkins, Trish, Anderson, Nigel, Cross, Shamira, Loo, Kee Fong, Wigg, Alan, Stuart, Katherine, Pryor, David. <u>Stereotactic body radiotherapy in the management of hepatocellular carcinoma: An Australian multi-institutional patterns of practice review.</u> <i>Journal of medical imaging and radiation oncology.</i> 2021. 65:365-373	Aim
Liu, Yang, Zhang, Zhiling, Han, Hui, Guo, Shengjie, Liu, Zhuowei, Liu, Mengzhong, Zhou, Fangjian, Dong, Pei, He, Liru. <u>Survival After Combining Stereotactic Body Radiation Therapy and Tyrosine Kinase Inhibitors in Patients With Metastatic Renal Cell Carcinoma.</u> <i>Frontiers in oncology.</i> 2021. 11:607595	Setting
Liu, Zhen, He, Shuting, Li, Liang. <u>Comparison of Surgical Resection and Stereotactic Radiosurgery in the Initial Treatment of Brain Metastasis.</u> <i>Stereotactic and functional neurosurgery.</i> 2020. 98:404-415	Setting
Long, Yanyan, Liang, Yan, Li, Shujie, Guo, Jing, Wang, Ying, Luo, Yan, Wu, Yongzhong. <u>Therapeutic outcome and related predictors of stereotactic body radiotherapy for small liver-confined HCC: a systematic review and meta-analysis of observational studies.</u> <i>Radiation oncology (London, England).</i> 2021. 16:68	Setting
Mallick, S., Kunhiparambath, H., Gupta, S., Benson, R., Sharma, S., Laviraj, M. A., Upadhyay, A. D., Julka, P. K., Sharma, D., Rath, G. K.. <u>Hypofractionated accelerated radiotherapy (HART) with concurrent and adjuvant temozolomide in newly diagnosed glioblastoma: a phase II randomized trial (HART-GBM trial).</u> <i>Journal of neuro-oncology.</i> 2018. 140:75-82	Setting

Reference	Exclusion Criteria
Mendiratta-Lala, Mishal, Masch, William, Shankar, Prasad R., Hartman, Holly E., Davenport, Matthew S., Schipper, Matthew J., Maurino, Chris, Cuneo, Kyle C., Lawrence, Theodore S., Owen, Dawn. <b>Magnetic Resonance Imaging Evaluation of Hepatocellular Carcinoma Treated With Stereotactic Body Radiation Therapy: Long Term Imaging Follow-Up.</b> <i>International journal of radiation oncology, biology, physics.</i> 2019. 103:169-179	Outcomes
Merola JP, Ocen J, Kumar S, Powell J, Hayhurst C. <b>Survival in melanoma brain metastases in the era of novel systemic therapies.</b> <i>Neurooncol Adv.</i> 2020;2(1):vdaa144. doi: 10.1093/nojnl/vdaa144	Outcomes
Modh, A., Bergman, D., Schultz, L., Snyder, J., Mikkelsen, T., Ryu, S., Siddiqui, M. S., Walbert, T.. <b>Randomized prospective trial of stereotactic radiosurgery versus chemotherapy for recurrent malignant glioma after second-line chemotherapy.</b> <i>Neuro-oncology.</i> 2018. 20:vi226-	Publication Type
Montorsi, Francesco, Larcher, Alessandro, Capitanio, Umberto. <b>Re: Rohann J.M. Correa, Alexander V. Louie, Nicholas G. Zaorsky, et al. The Emerging Role of Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma: A Systematic Review and Meta-Analysis.</b> <i>Eur Urol Focus.</i> In press. <a href="https://doi.org/10.1016/j.euf.2019.06.002">https://doi.org/10.1016/j.euf.2019.06.002</a> . <i>European urology focus.</i> 2021. 7:406	Publication Type
Munoz-Schuffenegger, Pablo, Barry, Aisling, Atenafu, Eshetu G., Kim, John, Brierley, James, Ringash, Jolie, Brade, Anthony, Dinniwel, Robert, Wong, Rebecca K. S., Cho, Charles, Kim, Tae Kyoung, Sapisochin, Gonzalo, Dawson, Laura A.. <b>Stereotactic body radiation therapy for hepatocellular carcinoma with Macrovascular invasion.</b> <i>Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology.</i> 2021. 156:120-126	Outcomes
Nasioudis D, Persaud A, Taunk NK, Latif NA. <b>Brain metastases from gynecologic malignancies: prevalence and management.</b> <i>Am J Clin Oncol.</i> 2020;43(6):418-421. doi: 10.1097/COC.0000000000000689.	Outcomes
Nichol, A., Raman, S., Mou, B., Hsu, F., Valev, B., Cheung, A., Vallieres, I., Beaton, L., Rackley, T., Gondara, L.. <b>Whole brain radiotherapy versus stereotactic radiosurgery in poor-prognosis patients with 1-10 brain metastases: a randomized feasibility study.</b> <i>Neuro-oncology.</i> 2019. 21:vi58-	Publication Type
Pan, Yang-Xun, Fu, Yi-Zhen, Hu, Dan-Dan, Long, Qian, Wang, Jun-Cheng, Xi, Mian, Liu, Shi-Liang, Xu, Li, Liu, Meng-Zhong, Chen, Min-Shan, Zhang, Yao-Jun. <b>Stereotactic Body Radiotherapy vs. Radiofrequency Ablation in the Treatment of Hepatocellular Carcinoma: A Meta-Analysis.</b> <i>Frontiers in oncology.</i> 2020. 10:1639	Setting
Parker, Sean M., Siochi, R. Alfredo, Wen, Sijin, Mattes, Malcolm D.. <b>Impact of Tumor Size on Local Control and Pneumonitis After Stereotactic Body Radiation Therapy for Lung Tumors.</b> <i>Practical radiation oncology.</i> 2019. 9:e90-e97	Aim
Parker, Tariq, Rigney, Grant, Kallos, Justiss, Stefko, S. Tonya, Kano, Hideyuki, Niranjan, Ajay, Green, Alexander L., Aziz, Tipu, Rath, Pamela, Lunsford, L. Dade. <b>Gamma knife radiosurgery for uveal melanomas and metastases: a systematic review and meta-analysis.</b> <i>The Lancet. Oncology.</i> 2020. 21:1526-1536	Study Design
Patel, Mayank, Colvin, Tyler, Kirkland, Robert Spencer, Marcrom, Samuel, Dobelbower, Michael, Spencer, Sharon A., Boggs, Drexell H., Popple, Richard, Shen, Sui, Wei, Benjamin, McDonald, Andrew. <b>Reduced Margin Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancers.</b> <i>Cureus.</i> 2020. 12:e8618	Comparator

Reference	Exclusion Criteria
Quigg, M.,Barbaro, N. M.,Ward, M. M.,Chang, E. F.,Broshek, D. K.,Langfitt, J. T.,Yan, G.,Laxer, K. D.,Cole, A. J.,Sneed, P. K.,et al.,. <b>Visual field defects after radiosurgery versus temporal lobectomy for mesial temporal lobe epilepsy: findings of the ROSE trial.</b> <i>Seizure</i> . 2018. 63:62-67	Population
Raman, S.,Mou, B.,Hsu, F.,Valev, B.,Cheung, A.,Vallières, I.,Ma, R.,McKenzie, M.,Beaton, L.,Rackley, T.,et al.,. <b>Whole Brain Radiotherapy Versus Stereotactic Radiosurgery in Poor-Prognosis Patients with One to 10 Brain Metastases: a Randomised Feasibility Study.</b> <i>Clinical oncology (Royal College of Radiologists (Great Britain))</i> . 2020. 32:442-451	Intervention
Roman, J.,Vavra, P.,Ekrtova, T.,Skacelikova, E.,Ihnat, P.,Papalova, M.,Rehorkova, S.,Cvek, J.,. <b>Comparison of surgical intervention to Cyberknife R radiotherapy in the treatment of liver malignancies.</b> <i>Srovnani efektivity chirurgicke intervence s terapii Cyberknife R v lecbe jaternich malignit..</i> 2019. 98:408-413	Non-English
Schullian, P.,Putzer, D.,Laimer, G.,Levy, E.,Bale, R.,. <b>Feasibility, safety, and long-term efficacy of stereotactic radiofrequency ablation for tumors adjacent to the diaphragm in the hepatic dome: a case-control study.</b> <i>European radiology</i> . 2019. #volume#:#pages#	Comparator
Sebastian, N.,Merritt, R. E.,Abdel-Rasoul, M.,Wu, T.,Bazan, J. G.,Xu-Welliver, M.,Haglund, K.,D'Souza, D.,Kneuert, P. J.,Williams, T. M.,. <b>Recurrence after Stereotactic Body Radiation Therapy versus Lobectomy for Non-Small Cell Lung Cancer.</b> <i>Annals of thoracic surgery</i> . 2020. #volume#:#pages#	Outcomes
Sheth, Niki,Osborn, Virginia, Lee, Anna,Schreiber, David. <b>Stereotactic Ablative Radiotherapy Fractionation for Hepatocellular Carcinoma in the United States.</b> <i>Cureus</i> . 2020. 12:e8675	Outcomes
Shui, Yongjie,Yu, Wei,Ren, Xiaoqiu,Guo, Yinglu,Xu, Jing, Ma, Tao,Zhang, Bicheng,Wu, Jianjun,Li, Qinghai,Hu, Qiongge,Shen, Li,Bai, Xueli,Liang, Tingbo,Wei, Qichun. <b>Stereotactic body radiotherapy based treatment for hepatocellular carcinoma with extensive portal vein tumor thrombosis.</b> <i>Radiation oncology (London, England)</i> . 2018. 13:188	Setting
Sprave T, Verma V, Forster R, et al. <b>Local response and pathologic fractures following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy for spinal metastases - a randomized controlled trial.</b> <i>BMC Cancer</i> . 2018;18(1):859. doi: 10.1186/s12885-018-4777-8.	Outcomes
Sprave, T.,Forster, R.,Schlampp, I.,Hees, K.,Bruckner, T.,Bostel, T.,Welte, S.,Tonndorf -Martini, E.,Nicolay, N.,Debus, J.,et al.,. <b>Pain response after high dose single-fraction IMRT for patients with spinal bone metastases-a randomized controlled trial.</b> <i>Strahlentherapie und onkologie</i> . 2018. 194:66-	Publication Type
Sun, Jing,Wang, Quan,Hong, Zhi-Xian,Li, Wen-Gang,He, Wei-Ping,Zhang, Tao,Zhang, Ai-Min,Fan, Yu-Ze,Sun, Ying-Zhe,Zheng, Li,Duan, Xue-Zhang. <b>Stereotactic body radiotherapy versus hepatic resection for hepatocellular carcinoma (&lt;= 5 cm): a propensity score analysis.</b> <i>Hepatology international</i> . 2020. 14:788-797	Setting
Tjong, Michael C.,Malik, Nauman H.,Chen, Hanbo,Boldt, R. Gabriel,Li, George,Cheung, Patrick,Poon, Ian,Ung, Yee C.,Tsao, May,Louie, Alexander V.,. <b>Stereotactic ablative radiotherapy for malignant mediastinal and hilar lymphadenopathy: a systematic review.</b> <i>Journal of thoracic disease</i> . 2020. 12:2280-2287	Comparator
Tran, A. D.,Fogarty, G.,Nowak, A. K.,Diaby, V.,Hong, A.,Watts, C.,Morton, R. L.,. <b>Cost-Effectiveness of Subsequent Whole-Brain Radiotherapy or Hippocampal-Avoidant Whole-Brain Radiotherapy Versus Stereotactic Radiosurgery or Surgery Alone for Treatment of Melanoma Brain Metastases.</b> <i>Applied health economics and health policy</i> . 2020. 18:679-687	Setting

Reference	Exclusion Criteria
Trapani, Salvatore, Manicone, Moana, Sikokis, Angelica, D'Abbiere, Nunziata, Salaroli, Francesco, Ceccon, Giovanni, Buti, Sebastiano. <b>Effectiveness and safety of "real" concurrent stereotactic radiotherapy and immunotherapy in metastatic solid tumors: a systematic review.</b> <i>Critical reviews in oncology/hematology</i> . 2019. 142:9-15	Intervention
Trifiletti, D. M., Ballman, K. V., Brown, P. D., Anderson, S. K., Carrero, X. W., Cerhan, J. H., Whitton, A. C., Greenspoon, J., Parney, I. F., Laack, N. N., et al.,. <b>Optimizing Whole Brain Radiation Therapy Dose and Fractionation: results From a Prospective Phase 3 Trial (NCCTGN107C [Alliance]/CEC.3).</b> <i>International journal of radiation oncology, biology, physics</i> . 2020. 106:255-260	Intervention
Tsao, May N., Ven, Lieke In 't, Cheung, Patrick, Poon, Ian, Ung, Yee, Louie, Alexander V.,. <b>Stereotactic Body Radiation Therapy for Extracranial Oligometastatic Non-small-cell Lung Cancer: A Systematic Review.</b> <i>Clinical lung cancer</i> . 2020. 21:95-105.e1	Study Design
Ueno M, Takabatake H, Itasaka S, et al. <b>Stereotactic body radiation therapy versus radiofrequency ablation for single small hepatocellular carcinoma: a propensity-score matching analysis of their impact on liver function and clinical outcomes.</b> <i>Journal of gastrointestinal oncology</i> . 2021;12(5):2334-2344.	Included in an included systematic reivew
Uhlig, Johannes, Mehta, Sumarth, Case, Meaghan Dendy, Dhanasopon, Andrew, Blasberg, Justin, Homer, Robert J., Solomon, Stephen B., Kim, Hyun S.,. <b>Effectiveness of Thermal Ablation and Stereotactic Radiotherapy Based on Stage I Lung Cancer Histology.</b> <i>Journal of vascular and interventional radiology: JVIR</i> . 2021. 32:1022-1028.e4	Outcomes
Videtic, G. M., Reddy, C. A., Woody, N. M., Stephans, K. L.,. <b>Ten-Year Experience in Implementing Single-Fraction Lung SBRT for Medically Inoperable Early Stage Lung Cancer.</b> <i>International journal of radiation oncology biology physics</i> . 2020. 108:e86-	Comparator
Wang, Haiyin, Jin, Chunlin, Fang, Liang, Sun, Hui, Cheng, Wendi, Hu, Shanlian. <b>Health economic evaluation of stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma: a systematic review.</b> <i>Cost effectiveness and resource allocation : C/E</i> . 2020. 18:1	Setting
Wegner RE, Hasan S, Williamson RW, et al. <b>Management of brain metastases from large cell neuroendocrine carcinoma of the lung: improved outcomes with radiosurgery.</b> <i>Acta Oncol</i> . 2019;58(4):499-504. doi: 10.1080/0284186X.2018.1564841	Outcomes
Weiss, S., Churilla, T., Chowdhury, I., Handorf, E., Collette, L., Collette, S., Alexander, B., Kocher, M., Soffetti, R., Claus, E.,. <b>Comparison of local control of brain metastases with stereotactic radiosurgery versus surgical resection: a secondary analysis of EORTC 22952-26001.</b> <i>Neuro-oncology</i> . 2018. 20:iii324-	Publication Type
Welsh, J., Menon, H., Chen, D., Verma, V., Tang, C., Altan, M., Hess, K., de Groot, P., Nguyen, Q. N., Varghese, R., et al.,. <b>Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial.</b> <i>Journal for immunotherapy of cancer</i> . 2020. 8:#pages#	Comparator
Wu, J., Bai, H. X., Chan, L., Su, C., Zhang, P. J., Yang, L., Zhang, Z.,. <b>Sublobar resection compared with stereotactic body radiation therapy and ablation for early stage non-€"small cell lung cancer: a National Cancer Database study.</b> <i>Journal of thoracic and cardiovascular surgery</i> . 2020. #volume#: #pages#	Outcomes
Yang JF, Lo CH, Lee MS, et al. <b>Stereotactic ablative radiotherapy versus conventionally fractionated radiotherapy in the treatment of hepatocellular carcinoma with portal vein invasion: a retrospective analysis.</b> <i>Radiat Oncol</i> . 2019;14(1):180. doi: 10.1186/s13014-019-1382-1	Included in an included systematic reivew

Reference	Exclusion Criteria
Yu, Tosol,Shin, In-Soo,Yoon, Won Sup,Rim, Chai Hong. <u>Stereotactic Body Radiotherapy for Centrally Located Primary Non-Small-Cell Lung Cancer: A Meta-Analysis</u> . <i>Clinical lung cancer</i> . 2019. 20:e452-e462	Study Design

## Appendix D. Ongoing Randomized Controlled Trials

Table D1. Summary Study Characteristics of Eligible Ongoing Randomized Controlled Trials of SBRT for Cancer Treatment

Trial Number Location	Title	Comparison	Status	Completion Date
Brain cancer				
NCT01592968 US	<a href="#">Stereotactic radiosurgery or whole brain radiation therapy in treating patients with newly diagnosed nonmelanoma brain metastases</a>	SRS vs. WBRT	Active, not recruiting	September 2022
NCT03550391 US and Canada	<a href="#">Stereotactic radiosurgery compared with hippocampal-avoidant whole brain radiotherapy (HA-WBRT) plus memantine for 5 or more brain metastases</a>	SRS vs. WBRT in combination with memantine	Recruiting	December 2022
NCT03775330 Canada	<a href="#">Radiosurgery with or without whole brain radiation for multiple metastases</a>	SBRT with WBRT vs. SBRT alone	Recruiting	December 2022
NCT02953717 Netherlands	<a href="#">Cognitive outcome after SRS or WBRT in patients with multiple brain metastases (CAR-Study B)</a>	SRS vs. WBRT	Recruiting	January 2023
NCT04277403 Austria	<a href="#">HA-WBRT vs SRS in patients with multiple brain metastases (HipSter)</a>	SRS vs. WBRT	Recruiting	February 2023

Trial Number Location	Title	Comparison	Status	Completion Date
NCT03075072 US	<a href="#"><u>Hippocampal sparing whole brain radiation versus stereotactic radiation in patients with 5-20 brain metastases: a phase III, randomized trial</u></a>	SRS vs. WBRT	Recruiting	July 2023
NCT03297788 Germany	<a href="#"><u>Whole brain radiation therapy alone vs. radiosurgery for SCLC patients with 1-10 brain metastases (ENCEPHALON)</u></a>	SBRT vs. WBRT	Recruiting	October 2023
NCT05033691 Israel	<a href="#"><u>A study to evaluate the efficacy of osimertinib with early intervention SRS treatment compared to the continuation of osimertinib alone, in patients with EGFR Mutated NSCLC and asymptomatic brain metastases</u></a>	SRS with drug therapy vs. drug therapy alone	Recruiting	December 2024

Trial Number Location	Title	Comparison	Status	Completion Date
NCT04588246 US	<a href="#">Testing the addition of whole brain radiotherapy using a technique that avoids the hippocampus to stereotactic radiosurgery in people with cancer that has spread to the brain and come back in other areas of the brain after earlier stereotactic radiosurgery</a>	SBRT with WBRT and memantine vs. SBRT alone	Recruiting	January 2025
NCT04891471 Italy	<a href="#">WHOLE Brain Irradiation or STEReotactic Radiosurgery for five or more brain metastases (WHOBI-STER)</a>	SBRT vs. WBRT	Recruiting	September 2025
<b>Spinal cancer</b>				
NCT05317026 Canada	<a href="#">Increased early pain relief by adding vertebroplasty to SBRT</a>	SBRT in combination with vertebroplasty vs. SBRT	Not yet recruiting	August 2023
<b>Lung cancer</b>				
NCT01968941 Canada	<a href="#">Stereotactic body radiotherapy versus conventional radiotherapy in medically-inoperable non-small lung cancer patients (LUSTRE)</a>	SBRT vs. conventional radiotherapy	Active, not recruiting	April 2022



Trial Number Location	Title	Comparison	Status	Completion Date
NCT02417662 UK	<a href="#">Stereotactic ablative radiotherapy for oligometastatic non-small cell lung cancer (SARON)</a>	SBRT in combination with radiotherapy vs. standard care	Recruiting	August 2022
NCT02468024 US, Australia, Canada, and the UK	<a href="#">JoLT-Ca sublobar resection (SR) versus stereotactic ablative radiotherapy (SAbr) for Lung Cancer (STABLE-MATES)</a>	SBRT vs. surgery	Recruiting	December 2022
NCT03924869 US, Argentina, Australia, Austria, Brazil, Canada, France, Germany, Hungary, Italy, Japan, New Zealand, Norway, Poland, Russia, South Korea, Spain, Switzerland, Turkey, Ukraine, and the UK	<a href="#">Efficacy and safety study of stereotactic body radiotherapy (SBRT) with or without pembrolizumab (MK-3475) in adults with unresected stage I or II non-small cell lung cancer (NSCLC) (MK-3475-867/KEYNOTE-867)</a>	SBRT in combination with drug therapy vs. drug therapy alone	Recruiting	April 2025
NCT02984761 US	<a href="#">Veterans Affairs lung cancer surgery or stereotactic radiotherapy (VALOR)</a>	SBRT vs. surgery	Recruiting	September 2026
NCT03867175 US	<a href="#">Immunotherapy with or without SBRT in patients with stage IV non-small cell lung cancer</a>	SBRT in combination with drug therapy vs. drug therapy alone	Recruiting	July 2027

Trial Number Location	Title	Comparison	Status	Completion Date
NCT04929041 US	<a href="#">Testing the addition of radiation therapy to the usual treatment (immunotherapy with or without chemotherapy) for stage IV non-small cell lung cancer patients who are PD-L1 negative</a>	SBRT with immunotherapy/ chemotherapy vs. immunotherapy/ chemotherapy	Recruiting	December 2027
<b>Pancreatic cancer</b>				
NCT01926197 US and Canada	<a href="#">Phase III FOLFIRINOX (mFFX) +/- SBRT in locally advanced pancreatic cancer</a>	SBRT in combination with mFOLFIRINOX vs, mFOLFIRINOX alone	Active, not recruiting	September 2021
NCT05265663 Netherlands	<a href="#">Stereotactic radiotherapy vs best supportive care in unfit pancreatic cancer patients (PANCOSAR)</a>	SBRT vs. standard care	Recruiting	March 2024
NCT04998552 US	<a href="#">Safety of CyberKnife in patients with borderline resectable or locally advanced pancreatic adenocarcinoma</a>	SBRT vs. IMRT	Recruiting	June 2027

Trial Number Location	Title	Comparison	Status	Completion Date
NCT03704662 US	<a href="#">Preoperative fractionated radiation therapy versus stereotactic body radiation therapy for resectable or borderline resectable, or locally advanced type A pancreatic adenocarcinoma</a>	SBRT vs. conventional radiotherapy and chemotherapy	Recruiting	December 2030
<b>Prostate cancer</b>				
CTRI/2020/04/024465 Canada, India, Ireland, and the US	<a href="#">GRT and SBRT vs IGRT and hypofractionated IMRT for localized intermediate risk prostate cancer</a>	SBRT vs. IMRT	Recruiting	April 2021
NCT02339701 Hong Kong	<a href="#">Stereotactic body radiotherapy vs intensity-modulated radiotherapy in prostate cancer</a>	SBRT vs. conventional intensity-modulated radiotherapy	Recruiting	December 2021
NCT03449719 Italy	<a href="#">Phase II randomized trial of radiation therapy in oligometastatic mCRPC prostate cancer (ARTO)</a>	SBRT in combination with drug therapy vs. drug therapy alone	Not yet recruiting	September 2022
NCT04861415 Canada	<a href="#">SBRT vs. conventional fractionation with HDR boost for prostate cancer (SHARP)</a>	SBRT vs. conventionally fractionated radiation	Recruiting	December 2022

Trial Number Location	Title	Comparison	Status	Completion Date
NCT04115007 France	<a href="#">Prostate-cancer treatment using stereotactic radiotherapy for oligometastases ablation in hormone-sensitive patients (PRESTO)</a>	SBRT vs. standard care	Recruiting	January 2023
NCT04610372 Canada	<a href="#">5500/20 vs. SABR or Brachytherapy for Primary OligoMetastatic Prostate cancer Treatment (PROMPT)</a>	SBRT vs. conventional radiotherapy, high dose rate brachytherapy, or permanent seed implant brachytherapy	Recruiting	January 2023
NCT04870567 Russia	<a href="#">HDR brachytherapy vs SABR in early-intermediate prostate cancer</a>	SBRT vs. high dose rate brachytherapy	Recruiting	April 2023
NCT05067660 Finland	<a href="#">Targeted radiotherapy for recurrent prostate cancer (TASTEPRO)</a>	SBRT vs. standard salvage therapy	Not yet recruiting	December 2023
NCT03056638 US	<a href="#">Trial of ADT and SBRT versus SBRT for intermediate prostate cancer</a>	SBRT in combination with drug therapy vs. drug therapy alone	Active, not recruiting	February 2024
NCT05019846 Italy	<a href="#">SRT versus SRT+ADT in prostate cancer (SPA)</a>	SBRT with androgen deprivation therapy vs. SBRT	Recruiting	December 2024
NCT05209243 Spain	<a href="#">START-MET HS Prostate Cancer. : SbrT &amp; Androgen Receptor Therapy METastatic HSPC (START-MET)</a>	SBRT vs. standard care	Not yet recruiting	March 2025

Trial Number Location	Title	Comparison	Status	Completion Date
NCT02685397 Canada	<a href="#">Management of castration-resistant prostate cancer with oligometastases (PCS IX)</a>	SBRT in combination with drug therapy vs. drug therapy alone	Recruiting	April 2025
NCT03784755 Canada	<a href="#">Local ablative therapy for hormone sensitive oligometastatic prostate cancer (PLATON)</a>	SBRT vs. standard care	Recruiting	July 2025
NCT03367702 US, Canada, Hong Kong, India, Ireland, and Switzerland	<a href="#">Stereotactic body radiation therapy or intensity-modulated radiation therapy in treating patients with stage IIA-B prostate cancer</a>	SBRT vs. IMRT	Recruiting	December 2025
NCT03386045 Australia	<a href="#">Optimal prostate study</a>	SBRT vs. moderate hypofractionation or standard radiotherapy with SBRT booster	Recruiting	March 2026
ACTRN12618001806257 Australia	<a href="#">The NINJA Clinical Trial: Novel Integration of New prostate radiation schedules with adJuvant Androgen deprivation</a>	SBRT vs. high dose rate brachytherapy	Recruiting	December 2026
<b>Liver cancer</b>				
NCT03326375 South Korea	<a href="#">Comparison of SBRT and repeat TACE for HCC (STH)</a>	SBRT vs. repeat TACE	Unknown	March 2020

Trial Number Location	Title	Comparison	Status	Completion Date
NCT02820194 Italy	<a href="#">A trial on SBRT versus MWA for inoperable colorectal liver metastases (CLM)</a>	SBRT vs. microwave ablation	Recruiting	February 2022
NCT02921139 Taiwan	<a href="#">Comparing re-TACE versus SABR for post-prior-TACE incompletely regressed HCC: a randomized controlled trial (TASABR)</a>	SBRT vs. repeat TACE	Recruiting	November 2022
NCT02762266 US and Japan	<a href="#">Transarterial chemoembolization compared with stereotactic body radiation therapy or stereotactic ablative radiation therapy in treating patients with residual or recurrent liver cancer undergone initial transarterial chemoembolization</a>	SBRT vs. TACE	Active, not recruiting	December 2022
NCT03960008 US and Canada	<a href="#">Stereotactic body radiation therapy (SBRT) vs trans-arterial chemoembolization (TACE) as bridge to transplant (SBRT vs TACE)</a>	SBRT vs. TACE	Recruiting	December 2022
NCT04235660 US	<a href="#">Y90 radiation segmentectomy vs SBRT for HCC (SBRT vs Y90)</a>	SBRT vs. radiation segmentectomy	Recruiting	May 2024

Trial Number Location	Title	Comparison	Status	Completion Date
NCT01730937 US, Australia, Canada, Hong Kong, South Korea	<a href="#">Sorafenib tosylate with or without stereotactic body radiation therapy in treating patients with liver cancer</a>	SBRT followed by sorafenib vs. sorafenib alone	Active, not recruiting	June 2024
NCT04081168 Netherlands	<a href="#">COLLISION XL: unresectable colorectal liver metastases (3-5 cm): stereotactic body radiotherapy vs. microwave ablation (COLLISION-XL)</a>	SBRT vs. microwave ablation	Not yet recruiting	September 2024
NCT01918683 US	<a href="#">TACE with or without SBRT as bridging therapy for pre-transplant HCC patients</a>	SBRT in combination with TACE vs. TACE alone	Active, not recruiting	December 2026
NCT03895359 Canada	<a href="#">Transarterial chemoembolization (TACE) versus TACE plus stereotactic body radiation therapy (SBRT) in liver carcinoma (TACE)</a>	SBRT vs. TACE	Recruiting	June 2027
Head and neck cancer				
NCT04883671 US	<a href="#">Stereotactic body radiotherapy (SBRT) for early treatment of oligometastatic adenoid cystic carcinoma: The SOLAR Trial</a>	SBRT vs. standard care	Recruiting	June 2028
Adrenal cancer				
None identified				

Trial Number Location	Title	Comparison	Status	Completion Date
<b>Renal cancer</b>				
NCT03811665 Canada	<a href="#">Stereotactic body radiation therapy versus radiofrequency ablation for small renal masses (SBRT vs RFA)</a>	SBRT vs. radiofrequency ablation	Active, not recruiting	June 2022
<b>Bone cancer</b>				
NCT03597984 Italy	<a href="#">Reduction of pain symptoms with stereotactic radiotherapy on bone metastases (PREST)</a>	SBRT vs. conventional radiotherapy	Unknown	July 2019
NCT04693377 US	<a href="#">Cryoablation combined with stereotactic body radiation therapy for the treatment of painful bone metastases, the CROME Trial</a>	SBRT in combination with cryoablation vs. SBRT	Recruiting	April 2023
NCT03143322 France	<a href="#">Standard treatment +/- SBRT in solid tumors patients with between 1 and 3 bone-only metastases (STEREO-OS)</a>	SBRT vs. standard care	Recruiting	January 2026
<b>Multiple cancer sites</b>				
NCT03256981 UK	<a href="#">Stereotactic body radiotherapy for the treatment of OPD (HALT)</a>	SBRT in combination with drug therapy vs. drug therapy alone	Unknown	November 2021
NCT02756793 Canada	<a href="#">Stereotactic radiotherapy for oligo-progressive metastatic cancer (The STOP Trial)</a>	SBRT vs. standard care	Active, not recruiting	June 2022



Trial Number Location	Title	Comparison	Status	Completion Date
NCT02759783 Australia and the UK	<a href="#">Conventional care versus radioablation (stereotactic body radiotherapy) for extracranial oligometastases (CORE)</a>	SBRT vs. standard care	Active, not recruiting	October 2024
NCT03862911 Australia, Canada, Ireland, and the UK	<a href="#">Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic (1-3 metastases) cancer (SABR-COMET-3)</a>	SBRT vs. palliative radiotherapy	Recruiting	November 2028
NCT04498767 Belgium, France, and Switzerland	<a href="#">Stereotactic body radiotherapy in patients with rare oligometastatic cancers (OligoRARE)</a>	SBRT vs. palliative radiotherapy	Recruiting	August 2028
NCT03721341 Australia, Canada, Switzerland, and the UK	<a href="#">Stereotactic ablative radiotherapy for comprehensive treatment of 4-10 oligometastatic tumors (SABR-COMET 10)</a>	SBRT vs. standard care	Recruiting	January 2029
<b>Other cancer sites</b>				
NCT02089100 France	<a href="#">Trial of superiority of stereotactic body radiation therapy in patients with breast cancer (STEREO-SEIN)</a>	SBRT vs. standard care	Recruiting	February 2020

Abbreviations. IMRT: intensity-modulated radiation therapy; SBRT: stereotactic body radiation therapy; SRS: stereotactic radiation surgery; TACE: transarterial chemoembolization; UK: United Kingdom; WBRT: whole brain radiation therapy.

## Appendix E. Studies Included in the CADTH Systematic Review

Below are the studies included in the 2022 updated systematic review, “Stereotactic ablative radiotherapy for the treatment of oligometastatic cancer: a clinical review as part of a health technology assessment v2.0” published by the Canadian Agency for Drugs and Technologies in Health.<sup>248</sup>

Table E1. Studies Included in the CADTH Systematic Review<sup>248</sup>

Study Citation	Study Design	Status in Our Evidence Update
Buergy D, Wurschmidt F, Gkika E, et al. Stereotactic or conformal radiotherapy for adrenal metastases: patient characteristics and outcomes in a multicenter analysis. <i>Int J Cancer</i> . 2021;149(2):358-370. doi: 10.1002/ijc.33546	Retrospective comparative study	Not identified in our searches
De Bleser E, Jereczek-Fossa BA, Pasquier D, et al. Metastasis-directed therapy in treating nodal oligorecurrent prostate cancer: a multi-institutional analysis comparing the outcome and toxicity of stereotactic body radiotherapy and elective nodal radiotherapy. <i>Eur Urol</i> . 2019; 76(6):732-739. doi: 10.1016/j.eururo.2019.07.009	Retrospective comparative study	Included in this evidence update
Filippi AR, Guerrera F, Badellino S, et al. exploratory analysis on overall survival after either surgery or stereotactic radiotherapy for lung oligometastases from colorectal cancer. <i>Clin Oncol(R Coll Radiol)</i> . 2016;28(8):505-512. doi: 10.1016/j.clon.2016.02.001	Retrospective comparative study	Included in the 2019 evidence update
He Z, Chen G, Ouyang B, et al. Conformal radiation therapy or stereotactic body radiation therapy: institutional experience in the management of colorectal liver metastases by radiation therapy. <i>Technol Cancer Res Treat</i> . 2018;17:1533033818816080. doi: 10.1177/1533033818816080	Retrospective comparative study	Not an eligible study: study based in China
Hurmuz P, Onal C, Ozyigit G, et al. Treatment outcomes of metastasis-directed treatment using 68Ga-PSMA-PET/CT for oligometastatic or oligorecurrent prostate cancer: Turkish Society for Radiation Oncology group study (TROD 09-002). <i>Strahlenther Onkol</i> . 2020;196(11):1034-1043. doi: 10.1007/s00066-020-01660-6	Retrospective comparative study	Not identified in our searches
Iyengar P, Wardak Z, Gerber DE, et al. consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. <i>JAMA Oncol</i> . 2018;4(1):e173501. doi: 10.1001/jamaoncol.2017.3501	RCT	Excluded from the 2019 evidence update: insufficient sample size
Ji X, Zhao Y, He C, et al. Clinical effects of stereotactic body radiation therapy targeting the primary tumor of liver-only oligometastatic pancreatic cancer. <i>Front Oncol</i> . 2021;11:659987. doi: 10.3389/fonc.2021.659987	Retrospective comparative study	Not an eligible study: study based in China
Liu Y, Zhang Z, Han H, et al. Survival after combining stereotactic body radiation therapy and tyrosine kinase inhibitors in patients with metastatic renal cell carcinoma. <i>Front Oncol</i> . 2021;11:607595. doi: 10.3389/fonc.2021.607595	Retrospective comparative study	Not an eligible study: study based in China
Lodeweges JE, Klinkenberg TJ, Ubbels JF, Groen HJM, Langendijk JA, Widder J. Long-term outcome of surgery or stereotactic radiotherapy	See Widder et al., 2013	Not identified in prior

Study Citation	Study Design	Status in Our Evidence Update
for lung oligometastases. <i>J Thorac Oncol</i> . 2017;12(9):1442-1445. doi: 10.1016/j.jtho.2017.05.015		evidence updates
Olson R, Senan S, Harrow S, et al. Quality of life outcomes after stereotactic ablative radiation therapy (sabr) versus standard of care treatments in the oligometastatic setting: a secondary analysis of the SABR-COMET randomized trial. <i>Int J Radiat Oncol Biol Phys</i> . 2019;105(5):943-947. doi: 10.1016/j.ijrobp.2019.08.041	Ancillary publication – see Palma et al., 2019	Included in this evidence update
Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. <i>Lancet</i> . 2019;393(10185):2051-2058. doi: 10.1016/S0140-6736(18)32487-5	RCT	Included in this evidence update
Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. <i>J Clin Oncol</i> . 2020;38(25):2830-2838. doi: 10.1200/JCO.20.00818	Ancillary publication – see Palma et al., 2019	Included in this evidence update
Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. <i>JAMA Oncol</i> . 2020;6(5):650-659. doi: 10.1001/jamaoncol.2020.0147	RCT	Included in this evidence update
van de Ven S, van den Bongard D, Pielkenrood B, et al. Patient-reported outcomes of oligometastatic patients after conventional or stereotactic radiation therapy to bone metastases: an analysis of the PRESENT cohort. <i>Int J Radiat Oncol Biol Phys</i> . 2020;107(1):39-47. doi: 10.1016/j.ijrobp.2019.12.041	Secondary analysis of a prospective comparative study	Primary study not identified in prior evidence updates
Widder J, Klinkenberg TJ, Ubbels JF, Wiegman EM, Groen HJ, Langendijk JA. Pulmonary oligometastases: metastasectomy or stereotactic ablative radiotherapy? <i>Radiother Oncol</i> . 2013;107(3):409-413. doi: 10.1016/j.radonc.2013.05.024	Retrospective comparative study	Not identified in prior evidence updates

Abbreviation. CADTH: Canadian Agency for Drugs and Technologies in Health; RCT: randomized controlled trial.