Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy: An Evidence Update

Evidence Update for the Washington State Health Technology Assessment Program

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This health technology assessment 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 policy makers 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.

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Bottom Line

This evidence update includes studies published since the original evidence review 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 they would likely not change the conclusions of the 2012 evidence report.

The guidelines from the National Comprehensive Cancer Network (NCCN) include recommendations to consider the use of SRS and SBRT for the cancers covered in the HTCC 2013 decision: central nervous system (CNS) cancers and medically inoperable early-stage non-small cell lung cancer (NSCLC). The NCCN guidelines recommend consideration of treatment using SRS or SBRT for a number of additional indications, including cancers of the liver, pancreas, and prostate.

A review of coverage policies from a Medicare Local Coverage Determination (LCD) applying to Washington and three private payers (Aetna, Cigna, and Regence) found that all 4 of these payers provide coverage for the cancers covered in the HTCC 2013 decision. Each of these 4 payers provides coverage for additional indications, although there is little consistency among these 4 payers for which indications are covered.

Background

The Washington State HTCC commissioned an evidence review in 2012 on the effectiveness of SRS and SBRT for treating various cancers.[1] On March 22, 2013, using that evidence review to guide decision making, the committee adopted the following coverage determination:

- SRS for 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 NSCLC, stage 1; and
  - Evaluation includes multidisciplinary team analysis, including surgical input.[2]
- All other indications are non-covered

The Washington Health Technology Assessment program contracted with the Center for Evidence-based Policy (Center) in 2016 to conduct an updated evidence search on this topic and produce a brief on the included eligible studies to help determine whether the previous

coverage policy decision should be reviewed. The Center completed an evidence update in January 2017,[3] and the Washington State Health Care Authority did not find the evidence sufficient to commission an updated full review on the topic. This document is a second evidence update, commissioned in October 2018. This evidence update is based on a search for studies published since the 2017 evidence update report search and summarizes the findings of all relevant studies published since the 2012 full evidence review.

Methods

To identify studies published since the 2017 evidence update, Center researchers conducted Ovid searches of MEDLINE, the Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register database. The search strategies are in Appendix A. Studies were included if they met the criteria outlined in the PICO below. We also examined NCCN's recommended treatment algorithms for recommendations on the use of SRS, SBRT, or stereotactic ablative radiotherapy (SABR) for all cancers. We assessed coverage policies for Medicare and 3 private payers: Aetna, Cigna, and Regence. The U.S. National Library of Medicine's data on clinical studies (ClinicalTrials.gov) was searched for phase 3 and phase 4 trials that assess the effectiveness of SRS, SBRT, or SABR.

For each indication, we determined a bottom-line conclusion that was based on our assessment of the likelihood that studies published since 2012 would change the conclusion of the prior evidence review. For indications that are covered in the HTCC's current 2013 decision, we looked for evidence that the treatment is not as effective or safe as a comparator. For indications that are not covered in the HTCC's current decision, we looked for evidence of a significant benefit or harm favoring SRS or SBRT. If we found new evidence that might change the conclusion regarding any indication covered in the 2012 report, then we would recommend that the HTCC commission a full update of the report. If we found that the new evidence would likely not change the conclusion of the 2012 report for any indication, then we would recommend that the HTCC not commission a full update of the report at this time.

PICO

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 therapy (EBRT), surgery, no treatment

Outcomes

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

Key Questions

1) What is the evidence of efficacy and effectiveness for SRS and SBRT compared to conventional EBRT for the following patients:

a. Patients with CNS tumors
b. Patients with non-CNS cancers

2) What are the potential harms of SRS and SBRT compared to conventional EBRT? What is the incidence of these harms? This includes consideration of progression of treatment in unnecessary or inappropriate ways.

3) What is the evidence that SRS and SBRT have differential efficacy, effectiveness, or safety issues in subpopulations including differences by:

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

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

For Key Questions 1 to 3, the following inclusion criteria were applied to individual studies:

- Treatments delivered in 10 or fewer fractions
- Published, peer-reviewed, English-language articles
- Comparative study designs (prospective, retrospective, and randomized or controlled clinical trials)
- Other specific inclusion criteria for individual studies:
  - CNS cancers: eligible study design with a minimum sample size of 20 participants
  - Cancers of the breast, colon, head, neck, lung, prostate: eligible study design with a minimum sample size of 50 participants
  - Other non-CNS cancers: eligible study design with a minimum sample size of 20 participants

These exclusion criteria were applied to all studies:

- Does not include patient-important outcomes
- Does not meet sample size criteria
- Treatments delivered in 11 or more fractions

- Data for treatment planning (e.g., dosing) or treatment delivery (e.g., accuracy)
- Non-cancer indications (e.g., trigeminal neuralgia)
- Non-English publication
- Study conducted in a location that is not sufficiently representative of the U.S. (i.e., in a lower or middle income country)
- Study does not include human subjects

For Key Question 4, studies providing comparative cost data and relevant economic evaluations, cost-effectiveness analyses, and other economic simulation modeling studies were included. The exclusion criteria above apply to the economic studies considered for Key Question 4.

Findings

After deduplication, 2,331 documents were found in the searches. After title and abstract screening, 265 were identified for full-text review. After full-text review, 69 studies were eligible for this evidence update, as shown in Figure 1. Table 1 shows the number of included articles by cancer and study design. The list of studies excluded at the full-text level, with exclusion reasons, is in Appendix D.

Figure 1. PRISMA Study Flow Diagram

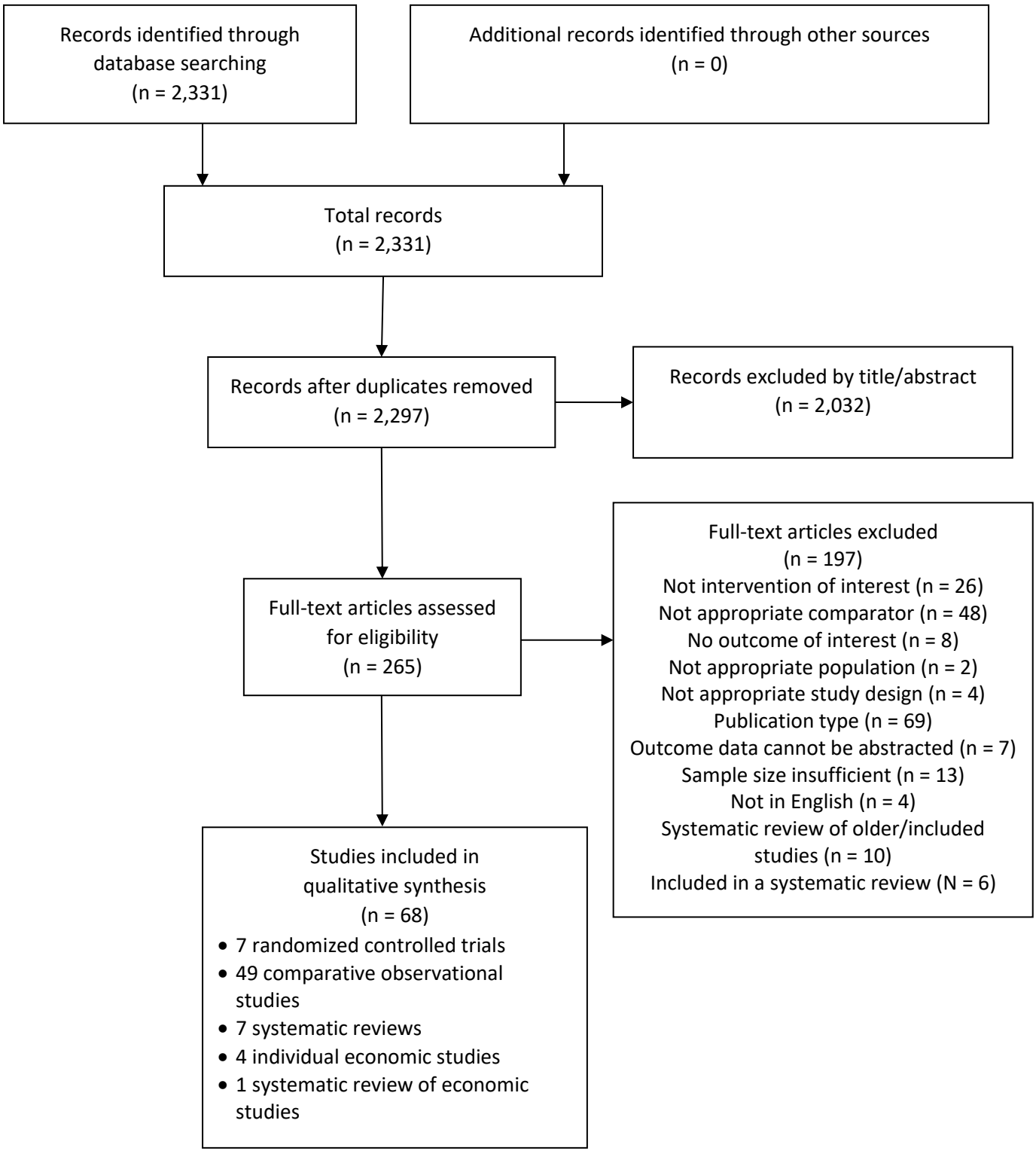

Table 1. Number of Included Studies by Study Type and Indication: 2018 Update

	Systematic Review	Randomized Controlled Trial	Comparative Observational	Economic
Brain cancer	2	4	22	0
Spinal cancer	0	2	0	0
Lung cancer	3	1	12	1
Pancreatic cancer	1	0	5	0
Prostate cancer	0	0	3	1
Liver cancer	0	0	2	2
Head and neck cancer	0	0	4	0
Bone metastases	1	0	0	0
Adrenal cancer	0	0	1	0
TOTAL	7	7	49	4 + 1 SR*

*Abbreviation. SR: systematic review. Note. *SR includes economic studies of brain, bone, liver, lung, pancreas, and prostate cancers.*

In the 2017 update, 1,968 records were identified after deduplication, and 66 of those publications were included in this update. Combining the search results from both updates yielded 135 studies published since the 2012 evidence review. Table 2 shows the number of studies by indication and study type across these 2 evidence updates. A summary of the findings of these studies is presented below for each indication.

Table 2. Number of Included Studies by Study Type and Indication: Update Since 2012

	Systematic Review	Randomized Controlled Trial	Comparative Observational	Economic
Brain cancer	10	6	37	2
Spinal cancer	0	2	2	0
Lung cancer	7	3	27	1
Pancreatic cancer	2	0	6	0
Prostate cancer	1	0	8	1
Liver cancer	0	0	5	2
Head and neck cancer	0	0	4	0
Bone metastases	1	0	0	0
Adrenal cancer	1	0	1	0
Meningioma/Schwannoma	0	0	2	0
TOTAL	22	11	92	6 + 1 SR*

*Abbreviation. SR: systematic review. Note. *SR includes economic studies of brain, bone, liver, lung, pancreas, and prostate cancers.*

Brain Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for brain cancer because additional studies have been published since 2012 confirming that survival rates for SRS were the same or improved compared to conventional radiotherapy without additional risk of harms.

The updated searches identified 10 systematic reviews[4-13] published since the 2012 update; 2 of these systematic reviews were published in 2017.[8,13]

- Khan et al.[8] published a 2017 systematic review comparing SRS alone to whole brain radiation therapy (WBRT) alone and SRS plus WBRT. The authors conducted a meta-analysis of 5 RCTs (N = 763).[8] WBRT had a decreased overall survival rate compared to SRS plus WBRT, although the difference was not statistically significant (hazard ratio [HR], 1.19; 95% CI, 0.96 to 1.43; *P* = .12).[8] Local control was statistically significantly worse in WBRT compared to SRS plus WBRT (HR, 2.05; 95% CI, 1.36 to 3.09, *P* < .001).[8] There were no statistically significant differences in adverse events when comparing the SRS plus WBRT group to the WBRT alone group (odds ratio [OR], 1.16; 95% CI, 0.77 to 1.76; *P* = .48).[8]
- Yuan et al.[13] published a network meta-analysis in 2017 generating an indirect comparison of SRS, SRS plus WBRT, and WBRT. In the indirect comparisons, SRS alone had a statistically significantly improved 1-year survival rate than WBRT alone (OR, 2.54; 95% CI, 1.56 to 4.58). Adding SRS to WBRT improved the 1-year survival rate compared to WBRT alone (OR WBRT alone vs. WBRT + SRS, 0.48; 95% CI, 0.27 to 0.81).[13]

Our search identified 6 additional RCTs showing mixed results.

- Patients aged 3 to 25 years with benign and low-grade brain tumors (N = 100) were randomly assigned to receive SRS or conventional radiotherapy.[14] Full-scale intelligence quotient scores during the 5-year follow-up period were significantly greater in the SRS group compared to the control group (mean difference, 1.48; *P* = .04).[14] Overall survival at 5 years was not statistically significantly different between groups (86% vs. 91%; *P* = .54).[14]
- SRS was compared to WBRT after total or subtotal resection in an RCT of patients with single brain metastasis (N = 59).[15] Overall survival at 2 years was significantly worse in the SRS group compared to the WBRT group (10% vs. 37%; *P* = .046).[15]
- Additional analyses of the 2016 RCT by Kepka et al.[15] were conducted on quality of life outcomes, and 37 of the 59 participants were eligible for analyses.[16] At 2 months, quality of life scores were statistically significantly better in the SRS groups compared to WBRT groups for drowsiness (19.9 vs. 36.2; *P* = .048) and for appetite loss (8.9 vs. 30.2; *P* = .03).[16]
- SRS was compared to observation of patients treated with chemotherapy for asymptomatic cerebral oligometastases from NSCLC in an RCT (N = 105).[17] The median overall survival times were not statistically significantly different between the SRS and observation groups (14.6 months; 95% CI, 9.2 to 20.0 vs. 15.3 months; 95% CI, 7.2 to 23.4; *P* = .42).[17]

- Patients with resected brain metastases (1 to 3 brain metastases) were randomly assigned to SRS or observation (N = 132).[18] Absence of local recurrence at 12 months was statistically significantly greater in the SRS group compared to the control group (72% vs. 43%; HR, 0.46; 95% CI, 0.24 to 0.88; *P* = .02).[18]
- SRS + WBRT was compared to WBRT alone in an RCT of participants with 1 to 3 brain metastases (N = 331).[19] Overall, there was no statistically significant difference in median overall survival time between the 2 groups, but among participants with graded prognostic assessment 3.5 to 4, median overall survival time was statistically significantly longer in the SRS plus WBRT group compared to the WBRT alone group (21.0 months vs. 10.3 months; *P* = .05).[19]

Our search identified 37 comparative observational studies.[20-56]

Economic Studies

The identified new studies of economic outcomes are unlikely to change the conclusions of the 2012 evidence review for brain cancer because additional studies have been published since 2012 confirming that SRS is cost-effective compared to conventional radiotherapy. The systematic review by Lester-Coll[57] included 5 economic studies of brain cancer that compared SRS to WBRT or surgery, and our search identified 2 additional economic studies comparing SRS to surgery.[58,59] All of these studies showed SRS to be cost-effective relative to the comparators.[57-59]

Spinal Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for spinal cancer because 2 RCTs and 2 comparative observational studies have been published since 2012 confirming that mean overall survival duration or overall survival rates for SRS were the same or better compared to conventional radiotherapy without additional risk of harms.[60-63]

The 2 RCTs analyzed data from the same study, examining pain outcomes[60] and quality of life outcomes.[61]

- Pain response measured on the visual analog scale (VAS) was assessed in patients with spinal metastases (N = 55) randomly assigned to receive SBRT or 3-D conformal radiotherapy.[60] At 6 months, the SBRT group had significantly lower VAS scores (13.7 vs. 21.4; *P* = .002).[60]
- Quality of life outcomes were assessed at 3 and 6 months, comparing the SBRT group to the 3-D conformal radiotherapy group (N = 55).[61] At both time points, there were no significant differences between cohorts on functional impairment, psychosocial aspects, or fatigue (*P* > .05 for all).[61]

In the 2 comparative observational studies, the SBRT groups had statistically significantly improved survival rates compared to conventional radiotherapy groups.[62,63]

- SRS was compared to conventional radiotherapy in patients treated for spinal metastasis from hepatocellular carcinoma (N = 59).[63] Mean overall survival duration was statistically significantly greater in the SRS group compared to the conventional radiotherapy group (7 months vs. 3 months; *P* = .04).[63]
- In a retrospective cohort study, participants who received SRS were matched to those who received EBRT (N = 13 pairs). All participants were treated for spinal metastasis from renal cell carcinoma and followed for 6 months.[62] At 6 months, there was a statistically significantly improved progression-free survival rate for participants treated with SRS compared to those treated with EBRT (*P* = .01).[62]

Economic Studies

The identified new studies of economic outcomes are unlikely to change the conclusions of the 2012 evidence review. One economic study by Kim et al.[64] has been published since the 2012 evidence review, which was included in the systematic review by Lester-Coll et al.[57] This U.S. study compared SBRT to EBRT, using a willingness-to-pay threshold of $100,000 per QALY gained, and the study found SBRT to not be cost-effective relative to EBRT, with an incremental cost-effectiveness ratio (ICER) of $124,552 per QALY.[64]

Lung Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for inoperable early-stage NSCLC because additional studies have been published since 2012 confirming that overall survival rates were the same or improved for SBRT compared to conventional radiotherapy without additional risk of harms.

Three systematic reviews that summarized observational studies for inoperable, early stage NSCLC were published in 2017[65-67] and 1 systematic review was published in 2015.[68] All 4 of these systematic reviews concluded that SBRT was more effective than observation or other forms of radiotherapy.[65-67] Two comparative observational studies were identified that showed improved overall survival rates for SBRT compared to no treatment.[69,70] The one published RCT by Nyman et al.[71] in 2016 showed improved overall survival rates for SBRT versus conventional radiotherapy, although this difference was not statistically significant.

- In the RCT by Nyman et al.,[71] SBRT was compared to conventional 3-D radiotherapy among patients with inoperable stage I NSCLC (N = 102). The median follow-up period was 37 months, and there was no statistically significant difference in overall survival rates (HR, 0.75; 95% CI, 0.43 to 1.30).[71] There was no significant difference in pneumonitis (19% vs. 34%; *P* = .26), and statistically significantly less esophagitis in the SBRT group compared to the control group (8% vs. 30%; *P* = .006).[71]

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for operable early-stage NSCLC because studies published since 2012 showed mixed results. Two publications reported on RCTs among operable NSCLC patients.[72,73]

- Chang et al.[73] reported results combining data from 2 RCTs in 2015 among operable stage I NSCLC patients (N = 58), comparing SABR to lobectomy with mediastinal lymph node dissection or sampling. The SABR group had an improved overall survival rate compared to the lobectomy group (HR, 0.14; 95% CI, 0.02 to 1.19).[73] Whether this difference is statistically significant is uncertain. The authors reported inconsistent results with a *P* value of .037 (statistically significant) and a 95% CI with the null effect (HR = 1; not statistically significant).[73]
- Louie et al.[72] reported quality of life outcomes from the Dutch ROSEL trial (N = 22), which was 1 of the 2 RCTs in the study by Chang et al.[73] The SABR group scored better on 22 of the 25 quality of life measures, although global health status was the only measure that was statistically significantly better in the SABR group compared to surgery (HR, 0.19; 95% CI, 0.04 to 0.91; *P* = .04).[72]

We identified 5 systematic reviews that assessed survival rates for SBRT vs. surgery in operable early-stage NSCLC patients. The 2014 systematic review by Zhang et al.[74] showed that the SBRT group had statistically significantly decreased overall survival rate compared to the surgical group (HR, 1.82; 95% CI, 1.38 to 2.40; *P* < .001), and the other 4 systematic reviews concluded that there was no evidence that SBRT had improved survival outcomes compared to surgery.[65,66,75,76] Our search identified 22 additional comparative observational studies that compared SBRT to surgery.[77-98]

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for patients with lung metastases because no RCTs have been published since 2012. The update searches identified 3 comparative observations studies.[99-101]

- SBRT was compared to surgery among patients with lung oligometastases from colorectal cancer (N = 170). [99] In a multivariable analysis, there was no statistically significant difference in overall survival rates in the SBRT group compared to the surgery group (HR, 1.71; 95% CI, 0.82 to 3.54; *P* = .15).[99]
- SBRT was compared to conventional radiotherapy among patients with lung metastases from a variety of cancers (N = 182). [100] The local failure rates did not statistically significantly differ between the 2 groups (HR, 0.60; 95% CI, 0.25 to 1.41; *P* = .24).[100]
- SRS was compared to surgical resection in patients who developed pulmonary metastasis after diagnosis with nonmetastatic osteosarcoma of the extremity (N = 58).[101] Overall survival at 2 years did not significantly differ between the 2 groups (40.7% vs. 48.3%; *P* > .05).[101]

Economic Studies

The identified new studies of economic outcomes are unlikely to change the conclusions of the 2012 evidence review because studies published since 2012 showed mixed results. Five economic studies of lung cancer were included in the systematic review by Lester-Coll[57] and were

published since 2012.[57] These studies compared SBRT to conventional radiotherapy or surgery with mixed results.[57]

One additional cost-effectiveness analysis was published in 2018 that compared SBRT to surgery for operable early-stage NSCLC.[102] The analyses showed that the costs of SBRT were €1,492.84 (approximately $1,700) less than surgery, and patients treated with SBRT had 0.54 QALYs more than surgery patients, so SBRT was both more effective and less costly than surgery.[102]

Pancreatic Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for pancreatic cancer because no RCTs have been published since 2012. Two systematic reviews were published since the 2012 evidence review.[103,104] The American Society of Clinical Oncology conducted a systematic review to inform 2016 guidelines on locally advanced, unresectable pancreatic cancer.[103] This systematic review included only RCTs, and the 2 RCTs on SRS and SBRT were included in the 2012 evidence review. Buwenge et al.[104] published a systematic review of robotic SBRT in 2015 that included 5 single-arm studies of patients with unresectable or locally advanced adenocarcinoma (total N = 99).[104] The authors concluded that the outcomes of SBRT were similar to the outcomes in previous studies of chemo-radiation with conventional fractionation, and that gastrointestinal toxicity is a concern with robotic SBRT, especially at the duodenal level.[104]

Our searches identified 6 comparative observational studies published since the 2012 evidence review.[105-110] Three comparative observational studies compared SBRT to intensity-modulated radiation therapy (IMRT), and all found no statistically significant differences between the groups in terms of survival and other outcomes.[105,107,108]

- A 2017 study of patients with unresectable stage I to III pancreatic adenocarcinoma (N = 270) compared SBRT to IMRT and found no statistically significant differences between groups in overall survival rates, local or distant failure, or rates of subsequent resection.[108]
- SBRT was compared to IMRT for patients with borderline resectable and locally advanced pancreatic cancer (N = 91), and the study found no statistically significant differences between the groups on resection, perioperative outcomes, and survival outcomes.[105]
- A comparative study (N = 41) of SBRT and IMRT for patients with locally advanced unresectable pancreatic cancer found no significant difference in overall survival rates (P = .13), although SBRT showed a significantly improved local disease-free survival rate compared to IMRT (P = .004).[107]

Three other studies analyzed data from the National Cancer Database (NCDB). Two of these NCDB studies found that the SBRT groups had significantly decreased overall survival rates compared to groups treated with conventionally fractionated radiation therapy.[109,110] The other study found significantly longer median survival time among the SBRT group compared to the

EBRT group, but no statistically significant difference between SBRT and IMRT in overall survival rates.[106]

- A 2018 study using the NCDB assessed overall survival among patients with inoperable pancreatic cancer who were treated with chemotherapy, with or without definitive radiation therapy (N = 13,004).[110] Compared to the chemotherapy alone group, patients receiving SBRT had a decreased overall survival rate (HR, 0.71; 95% CI, 0.64 to 0.80) than those receiving conventional radiation (HR, 0.80; 95% CI, 0.77 to 0.84).[110]
- SBRT was compared to conventionally fractionated radiation therapy in a study among patients with cT2-4/N0-1/M0 adenocarcinoma of the pancreas (N = 8,450).[109] The SBRT group had an improved overall survival rate compared to the conventional radiation group in a multivariable analysis (HR, 0.84; 95% CI, 0.75 to 0.93; *P* < .001).[109]
- A 2017 study using the NCDB compared SBRT, EBRT, and IMRT among patients with unresected pancreatic cancer who also received chemotherapy (N = 14,331).[106] The unadjusted median survival time for SBRT, EBRT, and IMRT was 13.9 months, 10.9 months, and 12.0 months.[106] In a matched analyses, SBRT remained superior to EBRT (log-rank *P* = .02), but was not statistically significantly different compared to IMRT (log-rank *P* = .049).[106]

Economic Studies

The identified new studies of economic outcomes are unlikely to change the conclusions of the 2012 evidence review. Our search and a review of studies in the systematic review by Lester-Coll et al.[57] identified 1 economic study of SBRT for pancreatic cancer published since 2012.[111] This Taiwanese study by Leung et al.[111] compared treatment using gemcitabine to gemcitabine plus SBRT and gemcitabine plus IMRT.[111] The gemcitabine plus SBRT group had a lower ICER than gemcitabine plus IMRT, but neither of these groups had an ICER below the World Health Organization standard for being cost-effective (3 times the per-capita gross domestic product).[111]

Prostate Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for prostate cancer because no RCTs have been published since 2012. The 1 identified systematic review included only data from uncontrolled studies (n = 14 studies) with a total of 1,472 participants.[112] We identified 9 comparative observational studies.[113-121] Most of these studies generally found better outcomes in the SBRT groups than comparator groups (EBRT, IMRT, brachytherapy, prostatectomy).

Among the 8 comparative observational studies, 7 included participants with localized or low-risk prostate cancer.[113,115-121] Two of these studies assessed gastrointestinal or genitourinary toxicity.[120,121]

- The Surveillance, Epidemiology, and End Results Program (SEER)-Medicare linked data were used to identify men with localized prostate cancer who were treated with SBRT, IMRT, or brachytherapy (N = 33,597).[121] SBRT had equivalent gastrointestinal toxicity compared to

brachytherapy and IMRT, and SBRT had a statistically significantly higher rate of erectile dysfunction than brachytherapy and IMRT at 2-year follow-up ($P < .001$).[121] The SBRT group had a higher rate of urinary incontinence than IMRT ($P < .001$) and a lower rate of urinary incontinence compared with brachytherapy ($P < .001$).[121]

- SBRT was compared to IMRT among a national sample of Medicare beneficiaries with prostate cancer in 1 study (N = 4,005).[120] Genitourinary toxicity was significantly higher in the SBRT group compared to the IMRT group at 6 months (15.6% vs. 12.6%; OR, 1.29; 95% CI, 1.05 to 1.53; $P = .009$) and 24 months after treatment (43.9% vs. 36.3%; OR, 1.38; 95% CI, 1.12 to 1.63; $P = .001$.[120]

Another study assessed prostate-specific antigen (PSA) slope, which is a chemical marker and thus an indirect outcome.[113]

- One study (N = 75) compared SBRT to conventionally fractionated EBRT for patients with low- to low-intermediate-risk prostate cancer.[113] The rate of decline in PSA was statistically significantly greater in the SBRT group compared to the conventionally fractionated EBRT group ($P < .05$) at 2 and 3 years after treatment, although the PSA slopes for the 2 groups were not significantly different during the first year ($P > .05$).[113]

Four additional studies assessed quality of life outcomes among participants with localized prostate cancer.[115-118]

- One study (N = 803) included a multi-institutional pooled cohort analysis of patient-reported quality of life before and after SBRT, IMRT, or brachytherapy for localized prostate cancer.[115] In a multivariable analysis, quality of life outcomes were not significantly different between the SBRT and IMRT groups in urinary irritation or obstruction ($P = .55$), urinary incontinence ($P = .74$), and sexual function ($P = .57$), but SBRT was associated with a better bowel score than IMRT (+6.7 points; 95% CI, 3.2 to 10; $P < .001$).[115]
- SABR was compared to high-dose rate brachytherapy plus hypofractionated EBRT in a study that investigated quality of life in patients (N = 207) treated for localized prostate cancer.[116] For the percentage of patients with a minimally clinical important change, SABR had significantly better quality of life, showing better outcomes in urinary function (20% vs. 54%; $P < .001$), bowel function (31% vs. 37%; $P = .02$), and sexual function (34% vs. 53%; $P = .03$).[116]
- Another study (N = 339) assessed quality of life in patients treated for clinically localized prostate cancer with SBRT or radical prostatectomy.[118] The largest differences in quality of life occurred in the first 6 months after treatment.[118] There were larger declines in the surgery group compared to the SBRT group in urinary and sexual quality of life measures, and a larger decline in the SBRT group compared to the surgery group for bowel-related quality of life (*P* values not reported).[118]
- Quality of life was assessed among patients (N = 912) with clinically localized prostate cancer treated with SBRT or moderate hypofractionation radiotherapy.[117] The SBRT group

was significantly less likely to experience worsening in bowel symptoms at 2 years (25.3% vs. 37.4%; P = .002) and urinary symptoms (14.0% vs. 32.8%; P < .001).[117] No significant differences were found in sexual symptom scores between the 2 groups.[117]

We identified 1 study of participants with advanced prostate cancer.[114]

- Among patients (N = 63) with oligometastatic recurrence of hormone-sensitive prostate cancer, treatment with SBRT was compared to treatment not including SBRT.[114] The time from first diagnosis of metastasis to the start of androgen deprivation therapy was significantly longer in the SBRT group compared to the control group (17.3 months; 95% CI, 13.7 to 20.9 vs. 4.19 months; 95% CI, 0.0 to 9.0; P < .001.[114] The mean time between diagnosis of metastasis to disease progression during androgen deprivation therapy was significantly longer for the SBRT group compared to the control group (66.6 months; 95% CI, 53.5 to 79.8 vs. 36.41 months; 95% CI, 26.0 to 46.8; P = .02).[114]

Economic Studies

The identified new studies of economic outcomes are unlikely to result in a rating of either low-quality or stronger evidence of cost-effectiveness. The systematic review by Lester-Coll et al.[57] included 5 economic studies for prostate cancer published from 2012 to 2106, and our search identified 1 additional economic study published in 2017.[122] All identified studies in the review by Lester-Coll et al. compared SBRT to IMRT, finding that SBRT was dominant over IMRT in ICER analyses, or that SBRT was cost saving compared to IMRT.[57] The additional study from 2017 was a cost-utility analysis of SBRT versus low-dose rate brachytherapy for localized prostate cancer and found SBRT to be dominant over brachytherapy with a reduction in cost of $2,615.[122]

Liver Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for liver cancer because no RCTs have been published since 2012. No systematic reviews were identified, and 5 comparative observational studies were identified.[123-127] All 5 comparative observational studies were among patients with hepatocellular carcinoma.[123-127] Two of these studies compared SBRT to radiotherapy or resection, and none of these studies found any statistically significant differences in overall survival rates.[126,127]

- SBRT was compared to selective internal radiotherapy in a study (N = 189) of hepatocellular carcinoma.[126] After adjusting for confounding factors, there was no significant difference between groups in overall survival rates (HR, 0.72; 95% CI, 0.49 to 1.07; P = .11).[126]
- SABR was compared to liver resection for patients with small hepatocellular carcinoma with 1 or 2 nodules (N = 117).[127] After propensity score matching, there were no statistically significant differences between the SABR and resection groups in overall survival at 1 year (100% vs. 96.7%), 3 years (91.8% vs. 89.3%), or 5 years (74.3% vs. 69.2%) (log-rank test P = .41).[127]

Two comparative observational studies compared SBRT plus transarterial chemoembolization (TACE) to TACE alone,[123,124] and another compared SBRT to palliative care.[125] These 3 studies all found that adding SBRT improved survival outcomes.[123-125]

- SBRT combined with TACE was compared to TACE alone for small, solitary, hypervascular hepatocellular carcinoma (N = 365).[124] Mean disease-free survival time for patients without previous treatments in the SBRT plus TACE group was significantly higher than that of the TACE-alone group (15.7 months vs. 4.2 months; *P* = .03)[124]
- SBRT alone, SBRT plus TACE, and TACE alone were compared among patients with primary hepatocellular carcinoma (N = 121).[123] Median survival time was 3 months for the SBRT group, 7 months for the TACE group, and 20 months for the SBRT plus TACE group (*P* < .001).[123]
- Short-term survival after SBRT or palliative care was compared among patients with hepatocellular carcinoma with portal vein tumor thrombosis (N = 138).[125] The median overall survival time was longer in the SBRT group compared to the palliative care group (6.1 months; 95% CI, 4.71 to 7.49 vs. 3.0 months; 95% CI, 2.72 to 3.28; *P* = .003).[125]

Economic Studies

The identified new studies of economic outcomes are unlikely to result in a rating of either low-quality or stronger evidence of cost-effectiveness. One economic study of liver cancer[128] was included in the systematic review by Lester-Coll et al.,[57] and 2 other economic studies were identified on our search.[129,130]

- The cost-effectiveness of SBRT was compared to sorafenib for patients with advanced hepatocellular carcinoma in a Taiwanese study.[128] Using a willingness-to-pay threshold according to World Health Organization guidelines (3 times the per-capita gross domestic product), the probability of cost-effectiveness was 100% for SBRT and 0% for sorafenib.[128]
- In a U.S. study, cost-effectiveness was assessed for SBRT and radiofrequency ablation (RFA) among patients with hepatocellular carcinoma.[130] Four treatment strategies were simulated: SBRT followed by SBRT for local progression, RFA followed by RFA, RFA followed by SBRT, and SBRT followed by RFA.[130] Using a willingness-to-pay threshold of $100,000 per QALY, among the 4 treatments, RFA followed by SBRT was preferred in 65.8% of simulations.[130]
- SBRT was compared to RFA in a cost-effectiveness analysis of treating unresectable liver metastases in colorectal cancer patients, using a willingness-to-pay threshold of $100,000 per QALY gained.[129] SBRT was not cost-effective relative to RFA, with an ICER of $164,660 per QALY gained.[129]

Head and Neck Cancers

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for head or neck cancer because no new RCTs have been published. The updated searches identified 4 comparative observational studies with mixed results.

- Patients with recurrent head and neck cancers (N = 176) were treated with SBRT, IMRT, or charged particle radiotherapy.[131] One-year overall survival rates were not statistically significantly different for the SBRT group compared to the charged particle radiotherapy group (55% vs. 68%; *P* value not reported).[131]
- Patients with T1-2N0-3 oropharyngeal carcinoma (N = 250) were treated with IMRT followed by a boost with SBRT or brachytherapy.[132] After 3 years, there were no significant differences between the SBRT and brachytherapy groups in local control (97% vs. 94%; *P* = .33), disease-free survival (92% vs. 86%; *P* = .15), or overall survival (81% vs. 83%; *P* = .83).[132]
- Treatment of nasopharyngeal carcinoma patients (N = 329) was compared for chemotherapy and chemotherapy plus SRS.[133] The 2-year overall survival rate was significantly higher in the chemotherapy plus SRS group compared to the chemotherapy alone group (91.51% vs. 76.32%; *P* = .003).[133]
- SBRT was compared to charged particle radiotherapy among patients undergoing reirradiation for head and neck cancers (N = 50).[134] The 1-year overall survival rates were significantly lower for the SBRT group compared to the charged particle radiotherapy group (36.3% vs. 67.1%; *P* < .001).[134]

Economic Studies

No economic studies were identified since the 2012 report.

Adrenal Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for adrenal cancer because no new RCTs have been published. The update searches identified 1 systematic review[135] of non-comparative studies, 1 comparative observational study,[136] and no RCTs.

- The systematic review of non-comparative studies for the treatment of adrenal metastases included 9 studies of SBRT with a total of 178 patients, and no statistical analyses were performed.[135] The authors concluded that if therapy is in the patient's interest, then surgery appears to be the best option and SABR is a reasonable alternative in inoperable patients.[135]
- In the 2017 study by Yuan et al.,[136] patients with adrenal gland metastases from hepatocellular carcinoma (N = 144) were treated with helical tomotherapy or conventional radiotherapy (2-D or 3-D conformal radiotherapy). Cumulative survival probability was significantly higher in the helical tomotherapy group compared to the conventional radiotherapy group (*P* = .47), although this difference was not statistically significant in a multivariable analysis (*P* value not reported).[136]

Economic Studies

No economic studies were identified since the 2012 report.

Other Cancers

For bone metastases, a single systematic review was identified, conducted to inform a 2017 American Society for Radiation Oncology guideline on palliative radiation therapy for bone metastases.[137] The included studies of SBRT were all non-comparative, and no statistical analyses were conducted.[137]

A single comparative observational study was identified for recurrent atypical meningiomas.[138] In this study, patients with recurrent atypical meningiomas (N = 46) were followed for 20 years after treatment using SRS or surgery.[138] The disease-free intervals were not statistically significantly different between the 2 groups (*P* value not reported).[138]

There was 1 study on the risk of malignancy anywhere in the body after SRS or non-SRS treatments for meningioma or schwannoma.[139] Patients treated with SRS were identified from a University of Florida database for patients treated for meningiomas (N = 640) or intracranial schwannomas (N = 705).[139] The cancer rates for these SRS-treated patients were compared with cancer rates in non-SRS-treated patients identified from the SEER database.[139] The cancer rate in meningioma patients treated with SRS was 3.96% (binomial 95% CI, 1.85 to 7.94) compared to the expected rate of 10%, and the cancer rate in schwannoma patients treated with SRS was 4.93% (binomial 95% CI, 2.61 to 8.89) compared to the expected rate of 12.5%.[139]

Guidelines

Each guideline from NCCN was reviewed for discussion of various terms used to refer to stereotactic radiosurgery: usually SRS, SBRT, or SABR. Recommendations in NCCN guidelines are categorized based on levels of evidence (determined by number of trials, trial design, and consistency of data) and consensus:

- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
- Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate[140]

A summary of each of the NCCN guidelines that discuss stereotactic radiosurgery is presented below (with the specific term for stereotactic radiosurgery used from the guideline), followed by a list of the NCCN guidelines that did not discuss these procedures. The NCCN guidelines recommend consideration of SRS and SBRT for the indications covered in the 2013 HTCC decision. The NCCN guidelines recommend consideration of SRS and SBRT for a number of other indications that are not covered in the 2013 HTCC decision, including cancers of the liver, pancreas, and prostate.

Bone Cancer

- SRS, IMRT, or particle beam therapy (proton, carbon ion, or other heavy ions) should be considered to allow high-dose therapy while maximizing the sparing of normal tissues. (category 2A)[141]

Central Nervous System Cancers

- SRS is preferred when safe, to both the resection cavity and any non-resected brain metastases, especially for low tumor volumes. (category 2A)[142]
- For surgical candidates, SRS plus WBRT is recommended if only 1 brain lesion is involved. (category 1)[142]
- In limited brain metastases, SRS may be equally effective as WBRT, while providing significant cognitive protection.[142] The definition of limited brain metastases is evolving and depends on the specific clinical situation. (category 2A)[142]
- With extensive brain metastases, SRS can be considered. (category 2A)[142]
- SRS and SBRT are appropriate for recurrence of metastatic spine cancer after previous radiation, and may be preferred for patients with oligometastatic disease with the goal of tumor ablation, and in tumors considered radioresistant. (category 2A)[142]
- SRS can be considered for recurrence of spine or brain cancers. (category 2A)[142]
- SRS is a treatment option for meningioma. (category 2A)[142]
    - SRS is recommended for World Health Organization grade I meningioma when using tight margins or close to critical structures. (category 2A)[142]
- It has not been established that SRS has a role in management of low-grade gliomas. (category 2A)[142]
    - Stereotactic radiotherapy may be a palliative option with anaplastic gliomas and glioblastomas for select patients with good performance status and small recurrent tumors. (category 2A)[142]

Cervical Cancer

- SBRT is not an appropriate, routine alternative to brachytherapy. (category 2A)[143]
- SBRT may be applied to isolated metastatic sites and can be considered for reirradiation of limited disease. (category 2A)[143]

Anal Carcinoma, Colon Cancer, Rectal Cancer

- With anal carcinoma, SBRT can be considered for treatment of primary and nodal recurrence in low volume metastatic disease.[144] With low volume liver oligometastasis, SBRT may be appropriate, depending upon response to systemic therapy. (category 2A)[144]
- In colon cancer patients, for resectable synchronous or metachronous liver of lung metastases, resection is preferred over SBRT or image-guided ablation. (category 2A)[145]

- For patients with a limited number of liver or lung metastases, SBRT, IMRT, or 3-D conformal radiotherapy can be considered in highly selected cases. (category 2A)[145]

- For rectal cancer, resection is preferred over SBRT or image-guided ablation. (category 2A)[146]
  - SBRT is an option when resection is not feasible. (category 2A)[146]
  - SBRT can be considered for liver or lung oligometastases. (category 2A)[146]

Gestational Trophoblastic Neoplasia

- Stereotactic brain radiotherapy can be considered for patients with high-risk gestational trophoblastic neoplasia, FIGO stages II-III, and prognostic score ≥ 7 or stage IV. (category 2A)[147]

Head and Neck Cancers

- There is insufficient evidence to recommend SBRT for head and neck cancers. (category 2A)[148]
  - However, palliative radiation with SBRT, IMRT, or 3D conformation radiotherapy should be considered for advanced cancers when curative intent is not appropriate. (category 2A)[148]
  - Reirradiation with SBRT is advised only for patients who do not have circumferential carotid involvement. (category 2A)[148]

Hepatobiliary Cancers

- All tumors may be amenable to radiotherapy (SBRT, IMRT, or 3D conformation radiotherapy). (category 2A)[149]
- SBRT can be considered when ablation/embolization techniques have failed or are contraindicated. (category 2A)[149]

Kidney Cancer

- SBRT can be considered for relapse or Stage IV kidney cancer. (category 2A)[150]

Lung Cancer

- Early Stage, medically inoperable NSCLC patients may be candidates for SABR. (category 2A)[151,152]
- Selected patients with small cell lung cancer stage I-IIa (T1-2, N0, M0) who are medically inoperable may be candidates for SABR. (category 2A)[151]
- NCCN found insufficient data to make a recommendation on the use of SBRT in select patients with limited-stage small cell lung cancer.[151]

Occult Primary

- SBRT is an option for localized adenocarcinoma or carcinoma not otherwise specified with lung nodules. (category 2A)[153]

- SABR can be considered for localized disease with 1 to 3 metastases and pulmonary metastases. (category 2A)[153]

Pancreatic Adenocarcinoma

- SBRT is an option for first-line or second-line therapy for pancreatic adenocarcinoma with good performance status. (category 2A)[154]
- After resection, SBRT is an option when there is local recurrence in the pancreatic operative bed, respecting normal organ tolerances. (category 2A)[154]
- SBRT should be delivered at a high-volume center or as part of a clinical trial. (category 2A)[154]
- SBRT should be avoided if CT, MRI, or endoscopy shows direct invasion of the bowel or stomach. (category 2A)[154]

Prostate Cancer

- With prophylactic nodal radiation in intermediate- to high-risk patients, SBRT combined with androgen deprivation therapy can be considered when longer courses of EBRT would cause medical or social hardship. (category 2A)[155]
- SBRT can be considered for oligometastatic and palliative radiotherapy. (category 2A)[155]
- Definitive SBRT is acceptable when there is appropriate technology, physics, and clinical expertise. (category 2A)[155]

Skin Cancers

- With cutaneous melanoma, SBRT may offer more durable local control with ablative treatment for intact extracranial metastases. (category 2A)[156]
- With uveal melanoma, SRS is the non-preferred form of radiotherapy for primary or recurrent intraocular tumors. (category 2A)[157]
    - SRS is an option for uveal melanoma with largest diameter > 18mm, thickness > 10 mm, or thickness > 8 mm with optic nerve involvement. (category 2A)[157]
    - For distant metastatic disease, SRS can be considered for limited or symptomatic disease. (category 2A)[157]
- In squamous cell skin cancer, SBRT may be appropriate in palliative therapy for symptomatic sites in select patients. (category 2A)[158]

Soft Tissue Sarcoma

- SBRT is an option in head or neck, extremity or superficial trunk stage IV cancers involving a single organ and limited tumor bulk that are amenable to local therapy, and for isolated regional disease or nodes. (category 2A)[159]
- SBRT is a palliative option when there are disseminated metastases. (category 2A)[159]

Thymomas and Thymic Carcinomas

- For limited focal metastases, SBRT may be appropriate. (category 2A)[160]

Thyroid Carcinoma

- For CNS metastases, either resection or SRS is preferred for CNS lesions. (category 2A)[161]
- SBRT, EBRT, or surgical excision can be considered for symptomatic isolated skeletal metastases or asymptomatic metastases in weight-bearing sites. (category 2A)[161]

Uterine

- SBRT may be appropriate for patients with isolated metastases. (category 2A)[162]

The NCCN guidelines[163] for these cancers do not include discussion of SRS, SBRT, or SABR:

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- AIDS-related Kaposi sarcoma
- Bladder cancer
- Breast cancer
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Chronic myeloid leukemia
- Esophageal and esophagogastric junction cancers
- Gastric cancer
- Hairy cell leukemia
- Hodgkin lymphoma
- Malignant pleural mesothelioma
- Multiple myeloma or other plasma cell neoplasms
- Myelodysplastic syndromes
- Myeloproliferative neoplasms
- Neuroendocrine and adrenal tumors
- Non-Hodgkin's lymphomas
- Ovarian cancer
- Penile cancer
- Systemic mastocytosis
- Testicular cancer
- Vulvar cancer

Policies

No Medicare National Coverage Determinations were found pertaining to SRS or SBRT. One LCD was found applying to the state of Washington. We searched for private payer policies from Aetna, Cigna, and Regence. The coverage polices for the Medicare LCD,[164] Aetna,[165] Cigna,[166]

Regence,[167] and the 2013 HTCC decision are summarized in Table 3. The full coverage policies are in Appendix B.

All 4 of these payers cover SRS and SBRT for CNS cancers, NSCLC, and a variety of benign cranial tumors (e.g., vestibular schwannomas and meningiomas). There is not consistency among the payers for the other cancer indications. Some of the policies cover a particular cancer only if it is metastatic or recurrent.

Table 3. Coverage of SRS and SBRT by Indication

Indication	Medicare LCD***	Aetna	Cigna	Regence	WA HTCC Decision
CNS cancers (brain, spinal)	Yes	Yes	Yes	Yes	Yes
Lung, NSCLC, inoperable	Yes	Yes	Yes	Yes	Yes
Lung, NSCLC, operable	Yes	No	Yes	No	No
Lung, other cancer types	Yes	Yes*	No	Yes*	No
Adrenal gland cancer	Yes	No	No	No	No
Bone cancer	No	No	Yes*	No	No
Breast cancer	No	No	Yes*	No	No
Cervical cancer	No	No	Yes**	No	No
Colorectal cancer	No	No	Yes*	No	No
Head and neck cancer	Yes**	Yes**	Yes**	No	No
Hepatocellular carcinoma	No	Yes	No	Yes	No
Hepatobiliary Cancer	No	No	Yes	No	No
Kidney cancer	Yes	No	No	No	No
Liver cancer	Yes	Yes*	No	Yes	No
Melanoma	No	No	Yes*	No	No
Ocular/uveal melanomas	No	Yes	No	Yes	No
Osteosarcoma	No	No	No	Yes*	No
Pelvic cancer	Yes*	No	No	No	No
Sarcoma	No	No	Yes*	No	No
Pancreatic cancer	Yes	No	Yes	No	No
Prostate cancer	In clinical trials only	Yes	Yes	Yes	No
Renal cancer	No	No	Yes*	No	No
Acoustic neuromas/vestibular schwannomas	Yes	Yes	Yes	Yes	No
Meningiomas	Yes	Yes	Yes	Yes	No
Pituitary adenomas	Yes	No	Yes	Yes	No
Pineocytomas	Yes	No	Yes		No
Craniopharyngiomas	Yes	Yes	Yes	Yes	No
Glomus tumors	Yes	No	Yes	Yes	No
Hemangioblastomas	Yes	Yes	Yes	Yes	No
Chordomas	No	No	No	Yes	No

*Note. *Metastatic only; **Recurrent only; ***The Medicare LCD covers SBRT for tumors of any type arising in or near previously irradiated regions when a high level of precision and accuracy is needed to minimize injury to surrounding normal tissues, or where a high dose per fraction treatment is indicated.*

Studies Registered at ClincalTrials.gov

We searched the ClinicalTrials.gov database for phase 3 and phase 4 trials related to the effectiveness of SRS, SBRT, or SABR on tumors and identified 67 registered trials. A list of these trials is in Appendix C. Of these trials, 14 are reported as active and have completion dates within the next 2 years (by the end of 2020). Among these 14 studies, there are 2 RCTs for pancreatic cancer and 1 RCT and 1 nonrandomized study for prostate cancer. The other studies are RCTs for indications currently covered in the 2013 HTCC decision: brain cancer (4 RCTs), spinal cancer (2 RCTs), and NSCLC (3 RCTs).

There are 27 studies with completion dates prior to 2018, 8 of which are marked as completed:

- One study is included in this evidence update.[17]
- One study was included in the 2012 evidence review.
- Two of the studies were published before the search dates of the 2012 evidence review.
- Four studies have no relevant associated publications that we could identify.

The unpublished studies may contribute to a possible publication bias for this topic. Of the remaining 19 studies, 9 have been terminated, 2 were withdrawn, and 8 have unknown status with no publications listed.

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Appendix A. Search Strategies

Databases:

- Ovid MEDLINE(R) <1946 to October Week 3 2018>
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 23, 2018>

Search Strategy:

1 exp Radiosurgery/

2 (Radiosurg* or (Stereotactic* adj3 (Radiation* or radiother* or irradiat*)) or Gamma Knife or cyberknif* or tomotherapy* or SBRT or SRS or (robot* adj2 (irradiat* or radiat*) adj2 surg*) or (LINAC adj3 surg*)).mp.

3 1 or 2

4 limit 3 to (controlled clinical trial or meta analysis or practice guideline or randomized controlled trial)

5 exp Cohort Studies/

6 exp case-control studies/

7 3 and 5

8 limit 7 to yr="2002 -Current"

9 3 and 6

10 limit 9 to yr="2002 -Current"

11 limit 3 to systematic reviews

12 4 or 11

13 exp economics/ or ec.fs. or exp socioeconomic factors/ or ((cost* or econom* or financ*) adj3 (effectiv* or benefi*)).mp.

14 3 and 13

15 8 or 10 or 12 or 14

16 limit 15 to yr="2002 -Current"

17 limit 16 to english language

18 Comparative Study/

19 3 and 18

20 limit 19 to (english language and humans and yr="2002 -Current")

21 20 not 17

22 (201612* or 2017* or 2018*).ed.

23 17 and 22

24 19 and 22

25 limit 24 to english language

26 23 or 25

27 animals/

28 humans/

29 27 not (27 and 28)

30 26 not 29

31 remove duplicates from 30

Databases:

- EBM Reviews - Cochrane Central Register of Controlled Trials <September 2018>,
- EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 24, 2018>

Search Strategy:

1 radiosurg$.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]

2 (gamma knif$ or cyberknife* or tomotherapy* or SBRT or SRS).mp.

3 (stereotac$ adj3 (radiation or irradiat* or radiother$)).mp.

4 sbrt.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]

5 1 or 2 or 3 or 4

6 (2017* or 2018*).up.

7 5 and 6

8 limit 7 to yr="2016 -Current"

9 remove duplicates from 8

Appendix B. Coverage Policies

Medicare LCD

The following text is directly excerpted from the Medicare LCD.[164]

Cranial Lesions

Indications for SRS and SBRT:

- Primary central nervous system malignancies, generally used as a boost or salvage therapy for lesions < 5 cm
- Primary and secondary tumors involving the brain or spine parenchyma, meninges/dura, or immediately adjacent bony structures
- Benign brain tumors and spinal tumors such as meningiomas, acoustic neuromas, other schwannomas, pituitary adenomas, pineocytomas, craniopharyngiomas, glomus tumors, hemangioblastomas
- Cranial arteriovenous malformations, cavernous malformations, and hemangiomas
- Other cranial non-neoplastic conditions such as trigeminal neuralgia and select cases of medically refractory epilepsy. As a boost treatment for larger cranial or spinal lesions that have been treated initially with external beam radiation therapy or surgery (e.g., sarcomas, chondrosarcomas, chordomas, and nasopharyngeal or paranasal sinus malignancies)
- Metastatic brain or spine lesions, with stable systemic disease, Karnofsky Performance Status 40 or greater (or expected to return to 70 or greater with treatment), and otherwise reasonable survival expectations, OR an Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or less (or expected to return to 2 or less with treatment)
- Relapse in a previously irradiated cranial or spinal field where the additional stereotactic precision is required to avoid unacceptable vital tissue radiation

SRS is not considered medically necessary (for cranial lesions only) under the following circumstances:

- Treatment for anything other than a severe symptom or serious threat to life or critical functions
- Treatment unlikely to result in functional improvement or clinically meaningful disease stabilization, not otherwise achievable
- Patients with wide-spread cerebral or extra-cranial metastases with limited life expectancy unlikely to gain clinical benefit within their remaining life
- Patients with poor performance status (Karnofsky Performance Status < 40 or an ECOG Performance > 3)
- Cobalt-60 pallidotomy is non-covered
- Basic dosimetry calculations are limited to 1 unit for each arc in a linear accelerator system and 1 unit for each shot in Cobalt-60 system with a maximum of 10 units

- Treatment devices, complex is limited to one unit for each collimator in a linear accelerator system or one for each helmet in a cobalt-60 system. If the total number of units exceeds 6 or the number of isocenters plus 3 when multiple isocenters are necessary, a detailed explanation of medical necessity must be documented in the medical record.

Other Indications for SBRT

SBRT is indicated for primary tumors of and tumors metastatic to the lung, liver, kidney, adrenal gland, or pancreas as well as for pelvic and head and neck tumors that have recurred after primary irradiation when and only when each of the following criteria are met, and each specifically documented in the medical record:

- The patient's general medical condition (notably, the performance status) justifies aggressive treatment to a primary cancer or, for the case of metastatic disease, justifies aggressive local therapy to one or more discrete deposits of cancer within the context of efforts to achieve total clearance or clinically beneficial reduction in the patient's overall burden of systemic disease
- Other forms of radiotherapy, including but not limited to external beam and IMRT, cannot be safely or effectively utilized
- The tumor burden can be completely targeted with acceptable risk to critical normal structures
- If the tumor histology is germ cell or lymphoma, effective chemotherapy regimens have been exhausted and external beam radiation is ineffective or inappropriate for the patient as fully explained in the medical record

For patients with tumors of any type arising in or near previously irradiated regions, SBRT may be appropriate when a high level of precision and accuracy is needed to minimize the risk of injury to surrounding normal tissues. Also, in other cases where a high dose per fraction treatment is indicated SBRT may be appropriate. The necessity should be documented in the medical record.

Coverage may be considered at the Redetermination (Appeal) level on an individual basis for lesions when documentation clearly supports the necessity for high radiation dose per fraction and the necessity to avoid surrounding tissue exposure.

Low or intermediate risk prostate cancer may be covered when the patient is enrolled in an IRB-approved clinical trial and which clinical trial meets the "standards of scientific integrity and relevance to the Medicare population" described in IOM 100-03, National Coverage Determinations Manual, Chap 1, Part 1, section 20.32, B3a-k (with l-m desirable). Similarly, enrollment in a clinical registry compliant with the principles established in AHRQ's "Registries for Evaluating Patient Outcomes: A User's Guide," such as the Registry for Prostate Cancer Radiosurgery, may qualify the treatment for coverage.

Primary treatment of lesions of bone, breast, uterus, ovary, and other internal organs not listed earlier in this LCD as covered is non-covered. The literature does not support an outcome advantage over other conventional radiation modalities. However, SBRT treatment in the setting of recurrence after conventional radiation modalities have been utilized may be covered.

SBRT is not considered medically necessary under the following circumstances for any condition:

- Treatment unlikely to result in clinical cancer control or functional improvement
- The tumor burden cannot be completely
- Patients with poor performance status (Karnofsky Performance Status < 40 or ECOG status of 3 or worse)

Aetna

The following text is directly excerpted from the Aetna policy on stereotactic readiosurgery.[165]

Cranial SRS with a CyberKnife, Gamma Knife, or linear accelerator is considered medically necessary when used for any of the following indications:

- For treatment of members with symptomatic, small (< 3 cm) arteriovenous malformations, aneurysms, and benign tumors (acoustic neuromas (vestibular schwannomas), craniopharyngiomas, hemangiomas, meningiomas, pituitary adenomas, and neoplasms of the pineal gland) if the lesion is unresectable due to its deep intracranial location or if the member is unable to tolerate conventional operative intervention
- For treatment of brain malignancies (primary tumors or metastatic lesions)

SBRT with a CyberKnife, Gamma Knife, or linear accelerator is considered medically necessary for localized malignant conditions within the body where highly precise application of high-dose radiotherapy is required and clinically appropriate.

SRS for treatment of brain malignancies (primary tumors or metastatic lesions) is considered medically necessary in members with a good performance status (a score between 80 and 100 on the Karnofsky Performance Scale [i.e., at a minimum, able to perform normal activity with effort]), controlled systemic disease (defined as extracranial disease that is stable or in remission), and no more than 4 metastatic lesions. For treatment to additional lesions, further clinical justification may be needed.

SRS is considered medically necessary for ocular melanomas that are not amenable to surgical excision or other conventional forms of treatment.

SBRT is considered medically necessary for localized malignant conditions within the body where highly precise application of high-dose radiotherapy is required and clinically appropriate, including:

- Hepatocellular carcinoma in individuals with unresectable disease that is considered to be extensive and not suitable for liver transplantation or for individuals with local disease only

with a good performance status (a score between 80 and 100 on the Karnofsky Performance Scale) but who are not amenable to surgery due to comorbidities

- Prostate cancer in individuals with organ-confined prostate cancer with Gleason score ≤ 8 and PSA < 20
- NSCLC for inoperable stage I or II tumors
- Inoperable primary spinal tumors with compression or intractable pain
- Recurrent metastatic disease in a previously irradiated area
- Recurrent localized head and neck cancer
- Metastatic lesions to the liver when they are the sole site of disease and cannot be surgically resected or undergo accepted ablation techniques
- Metastatic disease to the lung when clinically appropriate and on a case-by-case basis

All other clinical sites or indications are considered experimental and investigational but will be considered on a case-by-case basis.

Cigna

The following text is directly excerpted from the Cigna policy on radiation therapy.[166]

Brain Metastases

SRS is considered medically necessary for an individual when ALL of the following criteria are met:

- Karnofsky Performance Status ≥ 70
- Systemic disease is under control or good options for systemic treatment are available
- Absence of leptomeningeal disease
- Primary histology is not germ cell, small cell, or lymphoma

Initial treatment with SRS for brain metastases is considered medically necessary when both of the following conditions are met:

- No lesion > 5 cm and all lesions can be treated in a single treatment plan in a single fraction (for SRS) or up to 5 fractions (for fractionated SRS)
- All lesions present on imaging must be targeted as a single episode of care. If this cannot be accomplished in a maximum of 5 fractions, each fraction must be billed as 3D conformal or IMRT, depending on the planning, as the definition of SRS is not met

In an individual who has received prior SRS, retreatment with SRS is considered medically necessary when ALL of the following conditions are met:

- No lesion > 5 cm and all lesions can be treated in a single treatment plan in a single fraction (for SRS) or up to 5 fractions (for fractionated SRS)
- The individual has not been treated with more than two episode of SRS in the past 9 months

- All lesions present on imaging must be targeted as a single episode of care.
- If this cannot be accomplished in a maximum of 5 fractions, each fraction must be billed as 3D conformal or IMRT, depending on the planning, as the definition of SRS is not met
- Life expectancy > 6 months
- Submission of recent consultation note and recent restaging studies

In an individual who has received prior WBRT, SRS is considered medically necessary if the life expectancy is greater than 3 months.

Post-operative SRS is considered medically necessary for the treatment of a combination of up to 4 resected and unresected lesions that are each < 4 cm in size.

Spinal

SRS is considered medically necessary for the treatment of an inoperable primary spinal tumor with compression or intractable pain.

Bone metastases

SBRT will be considered in cases that require treatment to a portion of the spine that has been previously irradiated. SBRT will also be considered for treatment of sarcoma, melanoma, and renal cell carcinoma that have metastasized to the spine.

Cervical cancer

With locoregional recurrence, SBRT may be considered based on a history of previous radiation to the same or abutting region and inability to deliver therapeutic doses of radiation with other techniques.

Head and neck cancer

With re-treatment for salvage after prior radiation, SBRT may be medically necessary in an individual who has no evidence of metastatic disease

Hepatobiliary Cancer

In primary liver cancer, SBRT is considered medically necessary to treat concurrently one or more tumors when there is evidence of the ability to protect an adequate volume of uninvolved liver. SBRT is considered medically necessary for unresectable localized intrahepatic bile duct cancer. SBRT is considered not medically necessary for unresectable localized extrahepatic bile duct cancer. SBRT is considered not medically necessary for unresectable localized gallbladder cancer.

Lung Cancer

SBRT (with 3D or IMRT planning) is considered medically necessary for an individual with medically inoperable Stage I or II NSCLC.

Oligometastases

SBRT for extra-cranial oligometastases is considered medically necessary in the following clinical situations:

- For an individual with NSCLC who
  - Has had or who will undergo curative treatment of the primary tumor (based on T and N stage) and
  - Has 1 to 3 metastases in the synchronous setting
- For an individual with colorectal cancer who
  - Has had or who will undergo curative treatment of the primary tumor and
  - Presents with 1 to 3 metastases in the lung or liver in the synchronous setting and
  - For whom surgical resection is not possible
- For an individual with
  - A clinical presentation of one 1 to 3 adrenal gland, lung, liver or bone metastases in the metachronous setting when all the following criteria are met:
    - Histology is non-small cell lung, colon, breast, sarcoma, renal cell, or melanoma
    - Disease free interval of > 1 year from the initial diagnosis
    - Primary tumor received curative therapy and is controlled
    - No prior evidence of metastatic disease (cranial or extracranial)

SBRT is considered medically necessary in an individual with NSCLC who presents in the synchronous or metachronous setting, has 1 to 3 sites of disease, and good performance status, assuming SBRT can be delivered safely to the involved sites.

SBRT is considered medically necessary in an individual with colorectal cancer who presents in the synchronous or metachronous setting, has 1 to 3 sites of disease limited to the lung or liver, and good performance status, assuming surgical resection is not feasible.

SBRT is considered medically necessary in an individual with breast cancer who presents in the metachronous setting; has 1 to 3 sites of disease limited to the lung, liver, or bone, has a disease free interval of > 1 year; and received curative therapy to the primary tumor.

SBRT is considered medically necessary in an individual with sarcoma, renal, or melanoma metastasis who meets the following criteria: disease free interval of > 1 year from the initial diagnosis, primary tumor received curative therapy and is controlled, and no prior evidence of metastatic disease.

SBRT to > 3 sites or non-hematogenous sites of spread such as lymphatic regions is considered experimental/investigational.

SBRT used to stimulate the abscopal effect is considered not medically necessary.

SBRT is not routinely medically necessary in an individual with oligoprogressive disease.

Pancreatic Cancer

SBRT is considered medically necessary for either of the following:

- Definitive treatment for medically or surgically inoperable or locally advanced cases following a minimum of 2 cycles of chemotherapy and restaging in which there is no evidence of tumor progression and the disease volume can be entirely encompassed in the radiation treatment volume
- Postoperative (adjuvant) cases in which there is residual gross disease or positive microscopic margins that can be entirely encompassed in the radiation treatment volume

The use of SBRT as planned neoadjuvant treatment is considered experimental, investigational and unproven.

SBRT using up to 5 radiation treatment fractions will be considered for the following:

- Preoperative (neoadjuvant resectable or borderline resectable) cases following a minimum of 2 cycles of chemotherapy and restaging in which there is no evidence of tumor progression
- Definitive treatment for medically inoperable or locally advanced cases following a minimum of 2 cycles chemotherapy and restaging in which there is no evidence of tumor progression and the disease volume can be entirely encompassed in the radiation treatment volume

SBRT is not considered medically necessary in palliative situations.

Prostate

SBRT alone is medically necessary for:

- Low-, intermediate-, and high-risk prostate cancer
- Negative bone scan within the past 6 months, where applicable

Skin Cancer

SBRT to treat melanoma metastases, require individual review and must also satisfy criteria set forth in the guideline on Radiation Therapy for Oligometastases.

Soft tissues sarcomas

Palliative use of SBRT requires medical review.

SBRT is considered medically necessary to treat a locally recurrent soft tissue sarcoma that is within or immediately adjacent to an area that has received radiation treatments as part of the primary management.

Benign conditions

Surgery remains the standard treatment for acoustic neuroma (vestibular schwannoma). However, the use of single-fraction SRS and fractionated SRS is medically necessary for those cases in which surgery is declined or not indicated.

SRS is considered medically necessary for the treatment of the following benign conditions:

- Benign brain tumor including any of the following:
  - Craniopharyngioma

- Glomus tumor
- Hemangioblastoma
- Meningioma
- Pineocytoma
- Pituitary adenoma
- Schwannomas

Regence

The following text is directly excerpted from the Regence policy on SRS and SBRT.[167]

SRS, SBRT, and SABR may be considered medically necessary for initial treatment or treatment of recurrence for any of the following indications:

- Intracranial sites:
  - Primary neoplasms of the CNS, including but not limited to low grade gliomas and high-grade gliomas
  - Metastatic lesion(s) to the CNS (solitary or multiple) in patients with a current Karnofsky performance score ≥ 60 or a current ECOG score ≤ 2
  - Acoustic neuromas (vestibular schwannomas)
  - Chordomas and chondrosarcomas of the skull base
  - Craniopharyngiomas
  - Hemangioblastoma
  - Hemangiopericytoma
  - Glomus jugulare and Glomus tympanicum tumors
  - Meningiomas, benign, atypical, or malignant
  - Pituitary adenomas
  - Spinal or paraspinal tumors (primary or metastatic)
  - Uveal melanoma
- Extracranial sites:
  - Hepatic tumor (primary or metastatic) as palliative or curative treatment when both of the following are met:
    - Absence or minimal extra hepatic disease
    - Karnofsky performance score ≥ 60 or an ECOG score ≤ 2
  - Hepatocellular carcinoma when all of the following criteria are met:
    - Five or fewer hepatic lesions
    - Size of largest lesion ≤ 6 cm diameter
    - Karnofsky performance score ≥ 60 or an ECOG score ≤ 2
  - Lung metastases when both of the following criteria are met:

        - Five or fewer metastatic lung lesions
        - Karnofsky performance score ≥ 60 or an ECOG score ≤ 2
    - Primary NSCLC (node negative, tumor stage T1a, T1b, T2a, T2b)
    - Osteosarcoma, metastatic when all of the following criteria are met:
        - Five or fewer metastatic lesions
        - Karnofsky performance score ≥ 60 or an ECOG score ≤ 2
    - Prostate cancer, low- to intermediate-risk when all of the following criteria are met:
        - Stage < than T3a
        - PSA ≤ 20
        - Gleason Score < 8
    - Spinal or paraspinal tumors (primary or metastatic)

SRS, SBRT, and SABR are considered investigational for all other indications including but not limited to:

- Cavernous malformations
- Choroidal neovascularization
- Chronic pain
- Epilepsy
- Functional disorders other than trigeminal neuralgia
- Refractory symptoms of essential tremor or Parkinson's disease
- Seizures
- Primary tumors of the following sites or metastatic to the following sites:
    - Cervix
    - Endometrium
    - Esophagus
    - Hemangiomas
    - Kidney
    - Large bowel
    - Ovaries
    - Pancreas
    - Rectum
    - Small bowel

Appendix C. Studies Registered at ClincalTrials.gov: Phase 3 and 4 Trials

NCT Number Location	Title	Status	Completion Date
NCT00003916 Australia, France Germany, Netherlands	Standard Radiation Therapy With or Without Stereotactic Radiation Therapy in Treating Patients With Glioma	Completed	December 2001
NCT00002708 U.S.	Radiation Therapy With or Without Radiosurgery in Treating Patients With Brain Metastases	Completed	December 2004
NCT00075166 U.S.	Surgery Versus Radiosurgery to Treat Metastatic Brain Tumors	Completed	November 2005
NCT00460395 U.S.	Surgery Versus Stereotactic Radiosurgery in the Treatment of Single Brain Metastasis: A Randomized Trial	Completed	December 2005
NCT00268684 Israel	Comparison Study of WBRT and SRS Alone Versus With Temozolomide or Erlotinib in Patients With Brain Metastases of NSCLC	Unknown status	February 2006
NCT00104936 Germany, Netherlands, Switzerland	Radiotherapy or Radiosurgery Compared With Observation Alone in Treating Patients With Newly Diagnosed, Benign Meningioma That Has Been Partially Removed by Surgery	Terminated	November 2006
NCT00181350 Netherlands	Serial CT Scans in Fractionated Stereotactic Radiotherapy	Completed	July 2007
NCT00002899 Belgium, Finland	Adjuvant Radiation Therapy in Treating Patients With Brain Metastases	Terminated	November 2007
NCT00581113 U.S.	Neural Stem Cell Preserving Brain Radiation Therapy & Stereotactic Radiosurgery in Patients With 1-6 Brain Metastases	Terminated	June 2009
NCT00328510 U.S.	Comparing Two Forms of Head Immobilization for Stereotactic Radiotherapy	Completed	September 2009
NCT01169129 Brazil	Surgery and Whole Brain Radiotherapy (RT) Versus Whole Brain Radiotherapy (RT) and Radiosurgery for 1-3 Resectable Brain Metastases	Withdrawn	July 2010
NCT01130766 Korea	Asymptomatic Brain Metastasis in Non-small Cell Lung Cancer (NSCLC)	Unknown status	May 2011
NCT00096265 U.S.	Radiation Therapy and Stereotactic Radiosurgery With or Without Temozolomide or Erlotinib in Treating Patients With Brain Metastases Secondary to Non-Small Cell Lung Cancer	Terminated	April 2012

NCT Number Location	Title	Status	Completion Date
NCT00280475 Japan	A Trial of Postoperative Whole Brain Radiation Therapy vs. Salvage Stereotactic Radiosurgery Therapy for Metastasis	Completed	January 2013
NCT00840749 U.S.	Randomized Study to Compare CyberKnife to Surgical Resection In Stage I Non-small Cell Lung Cancer	Terminated	March 2013
NCT01301560 Korea	Chemotherapy With or Without Radiosurgery for Asymptomatic Oligo Brain Metastasis	Unknown status	May 2013
NCT01449604 Thailand	Stereotactic Radiation in Vestibular Schwannoma	Unknown status	October 2013
NCT01233544 Denmark, Sweden	Radiofrequency Ablation Versus Stereotactic Radiotherapy in Colorectal Liver Metastases	Terminated	December 2014
NCT01535209 Poland	Stereotactic Radiotherapy of Resection Cavity For Single Brain Metastasis Versus Whole-Brain Radiotherapy After Resection	Unknown status	December 2014
NCT01364259 U.S.	A Study of Amifostine for Prevention of Facial Numbness in Radiosurgery Treatment of Trigeminal Neuralgia	Terminated	January 2015
NCT01429493 Belgium	Biological Image Guided Antalgic Stereotactic Body Radiotherapy of Bone Metastases	Unknown status	December 2015
NCT00687986 Netherlands	Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer	Terminated	December 2015
NCT01318200 U.S.	Transarterial Chemoembolization (TACE) vs. CyberKnife for Recurrent Hepatocellular Carcinoma (HCC)	Withdrawn	February 2016
NCT01336894 U.S.	Surgery With or Without Internal Radiation Therapy Compared With Stereotactic Body Radiation Therapy in Treating Patients With High-Risk Stage I Non-Small Cell Lung Cancer	Terminated	March 2017
NCT02729558 Netherlands	Local Radiotherapy Following Complete Resection of a Brain Metastasis	Unknown status	May 2017
NCT00517959 India	SCRT Versus Conventional RT in Children and Young Adults With Low Grade and Benign Brain Tumors	Unknown status	June 2017
NCT01344356 U.S.	Stereotactic Body Radiotherapy for Head and Neck Tumors	Unknown status	July 2017
NCT02323360 Italy	A Trial on SBRT After Incomplete TAE or TACE Versus Exclusive TAE or TACE For Treatment of Inoperable HCC	Unknown status	May 2018
NCT01352598 U.S.	Stereotactic Body Radiotherapy for Prostate Cancer	Recruiting	June 2018

NCT Number Location	Title	Status	Completion Date
NCT02320825 U.S.	Randomized Study Comparing Local Tumor Control After Post-Operative Single-Fraction or Hypofractionated Stereotactic Radiosurgery in the Treatment of Spinal Metastases	Completed	August 2018
NCT01839994 Poland	Conformal Radiotherapy (CRT) Alone Versus CRT Combined With HDR BT or Stereotactic Body Radiotherapy for Prostate Cancer	Unknown status	December 2018
NCT02162537 France	Therapeutic Strategies in Patients With Non-squamous Non-small Cell Lung Cancer With Brain Metastases	Recruiting	January 2019
NCT02791503 Netherlands	CROSSFIRE Trial: Comparing the Efficacy of Irreversible Electroporation With Radiotherapy	Recruiting	May 2019
NCT01592968 U.S.	A Prospective Phase III Trial to Compare Stereotactic Radiosurgery Versus Whole Brain Radiation Therapy	Recruiting	August 2019
NCT01926197 U.S.	Phase III FOLFIRINOX (mFFX) +/- SBRT in Locally Advanced Pancreatic Cancer	Recruiting	September 2019
NCT02512965 Australia	Study Comparing Stereotactic Body Radiotherapy vs Conventional Palliative Radiotherapy (CRT) for Spinal Metastases	Recruiting	December 2019
NCT03056638 U.S.	Trial of ADT and SBRT Versus SBRT for Intermediate Prostate Cancer	Recruiting	February 2020
NCT00950001 U.S.	Resection Bed Post-Surgical Stereotactic Radiosurgery (SRS)	Active, not recruiting	August 2020
NCT01372774 U.S.	Stereotactic Radiosurgery or Whole-Brain Radiation Therapy in Treating Patients With Brain Metastases That Have Been Removed By Surgery	Active, not recruiting	November 2020
NCT02882984 China	Hypofractionated Brain Radiation In EGFR Mutated Adenocarcinoma Cranial Disease (Hybrid)	Recruiting	December 2020
NCT01014130 Australia	Hypofractionated Radiotherapy (Stereotactic) Versus Conventional Radiotherapy for Inoperable Early Stage I Non-small Cell Lung Cancer (NSCLC)	Active, not recruiting	December 2020
NCT02893332 China	Stereotactic Body Radiation Therapy (SBRT) in Newly Diagnosed Advanced Staged Lung Adenocarcinoma (Sindas)	Recruiting	December 2020
NCT02820194 Italy	A Trial on SBRT Versus MWA for Inoperable Colorectal Liver Metastases (CLM)	Recruiting	February 2021
NCT02762266 U.S.	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	Recruiting	February 2021

NCT Number Location	Title	Status	Completion Date
NCT02759783 England	Conventional Care Versus Radioablation (Stereotactic Body Radiotherapy) for Extracranial Oligometastases	Recruiting	October 2021
NCT02055859 Italy	Cyberknife Radiosurgery for Patients With Neurinomas	Recruiting	November 2021
NCT01968941 Canada	Stereotactic Body Radiotherapy Versus Conventional Radiotherapy in Medically-Inoperable Non-Small Lung Cancer Patients	Recruiting	November 2021
NCT03256981 England	Stereotactic Body Radiotherapy for the Treatment of OPD	Recruiting	November 2021
NCT00922974 U.S.	Image-Guided Radiosurgery or Stereotactic Body Radiation Therapy in Treating Patients With Localized Spine Metastasis	Active, not recruiting	January 2022
NCT02794337 India	TACE vs TACE+SBRT for Unresectable Hepatocellular Cancer	Recruiting	January 2022
NCT03075072 U.S.	Whole Brain Radiation Versus Stereotactic Radiation (SRS) in Patients With 5-20 Brain Metastases: A Phase III, Randomized Clinical Trial	Recruiting	March 2022
NCT03727867 China	Efficacy of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Combined With Early Stereotactic Body Radiation Therapy to the Primary Tumor in Advanced Non-small Cell Lung Cancer	Not yet recruiting	June 2022
NCT03550391 Canada	Stereotactic Radiosurgery Compared With Whole Brain Radiotherapy (WBRT) for 5-15 Brain Metastases	Recruiting	June 2022
NCT03741673 U.S.	Pre-operative SRS or Post-operative SRS in Treating Cancer Patients With Brain Metastases	Recruiting	July 2022
NCT01581749 U.S.	Evaluation of Truebeam for Low-Intermediate Risk Prostate Cancer	Recruiting	December 2022
NCT03338647 India	SBRT or TACE for Advanced HCC	Recruiting	December 2022
NCT02089100 France	Trial of Superiority of Stereotactic Body Radiation Therapy in Patients With Breast Cancer	Recruiting	February 2023
NCT03697343 Germany	Fractionated Stereotactic Radiotherapy vs. Single Session Radiosurgery in Patients With Larger Brain Metastases	Not yet recruiting	January 2024
NCT02468024 U.S.	JoLT-Ca Sublobar Resection (SR) Versus Stereotactic Ablative Radiotherapy (SAbR) for Lung Cancer	Recruiting	December 2024
NCT02685397 Canada	Management of Castration-Resistant Prostate Cancer With Oligometastases	Recruiting	April 2025

NCT Number Location	Title	Status	Completion Date
NCT01730937 U.S.	Sorafenib Tosylate With or Without Stereotactic Body Radiation Therapy in Treating Patients With Liver Cancer	Recruiting	June 2025
NCT03750227 U.S.	Pre-Operative or Post-Operative Stereotactic Radiosurgery in Treating Patients With Operative Metastatic Brain Tumors	Recruiting	November 2025
NCT01584258 England	Prostate Advances in Comparative Evidence	Recruiting	September 2026
NCT02364557 U.S.	Standard of Care Therapy With or Without Stereotactic Radiosurgery and/or Surgery in Treating Patients With Limited Metastatic Breast Cancer	Recruiting	December 2027
NCT03367702 U.S.	Stereotactic Body Radiation Therapy or Intensity-Modulated Radiation Therapy in Treating Patients With Stage IIA-B Prostate Cancer	Recruiting	December 2028
NCT03721341 Canada	Stereotactic Ablative Radiotherapy for Comprehensive Treatment of 4-10 Oligometastatic Tumors	Not yet recruiting	January 2029

Appendix D. Studies Excluded After Full-Text Review

Abdulkarim BS, Joseph K, Vos L, et al. A phase III randomized control trial comparing skin-sparing helical tomotherapy versus 3D-conformal radiation therapy in early-stage breast cancer: acute and late skin toxicity outcomes. International journal of radiation oncology. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(2 Supplement 1):S6. Exclusion reason: Publication type

Alghamdi M, Tseng CL, Myrehaug S, et al. Postoperative stereotactic body radiotherapy for spinal metastases. Chinese Clinical Oncology. 2017;6(Suppl 2):S18. Exclusion reason: Not appropriate comparator

Anderson ES, Postow MA, Young R, Chan TA, Yamada Y, Beal K. Initial report on safety and lesion response of melanoma brain metastases after stereotactic radiosurgery or hypofractionated radiation therapy in patients receiving concurrent pembrolizumab. International journal of radiation oncology biology physics. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(2 Supplement 1):E132. Exclusion reason: Publication type

Aouadi S, Vasic A, Paloor S, et al. Generation of synthetic CT using multi-scale and dual-contrast patches for brain MRI-only external beam radiotherapy. Physica Medica. 2017;42:174-184. Exclusion reason: Not intervention of interest

Astradsson A, Munck Af Rosenschold P, Feldt-Rasmussen U, et al. Visual outcome, endocrine function and tumor control after fractionated stereotactic radiation therapy of craniopharyngiomas in adults: findings in a prospective cohort. Acta Oncologica. 2017;56(3):415-421. Exclusion reason: Sample size insufficient

Badellino S, Muzio JD, Schivazappa G, et al. No differences in radiological changes after 3D conformal vs VMAT-based stereotactic radiotherapy for early stage non-small cell lung cancer. British Journal of Radiology. 2017;90(1078):20170143. Exclusion reason: Not intervention of interest

Baker S, Lim G, Nordal R, Surgeoner B, Kostaras X, Roa W. Provincial clinical practice guidelines for patients with 1-3 brain metastases. Radiotherapy and oncology Conference: CARO. 2016;120. Exclusion reason: Publication type

Ball D, Mai T, Vinod S, et al. A randomized trial of SABR vs conventional radiotherapy for inoperable stage I non-small cell lung cancer: tROG09.02 (CHISEL). Journal of thoracic oncology. 2017;Conference: 18th world conference on lung cancer of the international association for the study of lung cancer, IASLC. 2017. Japan 12(11 Supplement 2):S1853. Exclusion reason: Publication type

Ball D, Mai T, Vinod S, et al. A randomized trial of SABR vs conventional radiotherapy for inoperable stage I non-small cell lung cancer: TROG 09.02 (CHISEL). Journal of medical imaging and radiation oncology. 2017;Conference: 68th annual scientific meeting of the Royal Australian and New Zealand College of Radiologists, RANZCR. 2017. Australia 61(Supplement 1):33-34. Exclusion reason: Publication type

Bi N, Shedden K, Zheng X, Kong FS. Comparison of the Effectiveness of Radiofrequency Ablation With Stereotactic Body Radiation Therapy in Inoperable Stage I Non-Small Cell Lung Cancer: A Systemic Review and Pooled Analysis. International Journal of Radiation Oncology, Biology, Physics. 2016;95(5):1378-1390. Exclusion reason: Not appropriate comparator

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. International journal of radiation oncology biology physics. 2017(pagination). Exclusion reason: Not intervention of interest

Blanchard P, Foulon S, Louvel G, Habibian M, Fizazi K. A randomized controlled trial of metastases-directed treatment in patients with metastatic prostate cancer using stereotactic body irradiation: a GETUG-AFU trial. Cancer/radiotherapie. 2017;21(6-7):491-494. Exclusion reason: Not in English

Borghetti P, Bonu ML, Roca E, et al. Radiotherapy and Tyrosine Kinase Inhibitors in Stage IV Non-small Cell Lung Cancer: Real-life Experience. In Vivo. 2018;32(1):159-164. Exclusion reason: Outcome data cannot be abstracted

Bosshard R, O'Reilly K, Ralston S, Chadda S, Cork D. Systematic reviews of economic burden and health-related quality of life in patients with acute myeloid leukemia. Cancer Treatment Reviews. 2018;69:224-232. Exclusion reason: Not intervention of interest

Bridges KJ, Jaboin JJ, Kubicky CD, Than KD. Stereotactic radiosurgery versus surgical resection for spinal hemangioblastoma: A systematic review. Clinical Neurology & Neurosurgery. 2017;154:59-66. Exclusion reason: Not appropriate comparator

Brown PD, Ballman KV, Cerhan J, et al. N107C/CEC.3: a phase III trial of post-operative stereotactic radiosurgery (SRS) compared with whole brain radiotherapy (WBRT) for resected metastatic brain disease. International journal of radiation oncology biology physics. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(5):937. Exclusion reason: Publication type

Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet oncology. 2017;18(8):1049-1060. Exclusion reason: Included in a systematic review

Bryant AK, Mundt R, Sandhu APS, et al. Stereotactic body radiation therapy versus surgery for early non-small-cell lung cancer in the veterans affairs system. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):S7. Exclusion reason: Publication type

Chan OSH, Lee VHF, Mok TSK, Mo F, Chang ATY, Yeung RMW. The Role of Radiotherapy in Epidermal Growth Factor Receptor Mutation-positive Patients with Oligoprogression: A Matched-cohort Analysis. Clinical Oncology (Royal College of Radiologists). 2017;29(9):568-575. Exclusion reason: Not appropriate comparator

Chang JH, Shin JH, Yamada YJ, et al. Stereotactic Body Radiotherapy for Spinal Metastases: What are the Risks and How Do We Minimize Them? Spine. 2016;41 Suppl 20:S238-S245. Exclusion reason: Not appropriate comparator

Chapet O, De Laroche G, Dorel SB, et al. Prostate hypofractionated radiation therapy with a rectal spacer comparing moderate hypofractionation (62 Gy at 3.1 Gy per fraction) versus stereotactic irradiation (37.5 Gy at 7.5 Gy per fraction): acute toxicities from the rpah2 randomized trial. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):E218-E219. Exclusion reason: Publication type

Chaudhuri AA, Binkley MS, Rigdon J, et al. Pre-treatment non-target lung FDG-PET uptake predicts symptomatic radiation pneumonitis following Stereotactic Ablative Radiotherapy (SABR). Radiotherapy & Oncology. 2016;119(3):454-460. Exclusion reason: Not appropriate comparator

Chen H, Louie A, Boldt RG, Palma D, Nossent E, Senan S. Risks of SABR for early-stage non-small cell lung cancer with co-existing interstitial lung disease: a systematic review of literature. Radiotherapy and oncology Conference: CARO. 2016;120:S86-S87. Exclusion reason: Publication type

Chen H, Louie AV, Boldt RG, Rodrigues GB, Palma DA, Senan S. Quality of Life After Stereotactic Ablative Radiotherapy for Early-Stage Lung Cancer: A Systematic Review. Clinical Lung Cancer. 2016;17(5):e141-e149. Exclusion reason: Not appropriate comparator

Chen W, Lin Q, Sun X, et al. A propensity-matched analysis of stereotactic body radiotherapy and sublobar resection for stage I non-small cell lung cancer in patients at high risk for lobectomy. Journal of clinical oncology Conference. 2017;35(15 Supplement 1). Exclusion reason: Publication type

Chi A, Chen H, Wen S, Yan H, Liao Z. Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: A systematic review and hypothesis-

generating meta-analysis. Radiotherapy & Oncology. 2017;123(3):346-354. Exclusion reason: Not appropriate comparator

Chi A, Wen S, Monga M, et al. Definitive Upfront Stereotactic Ablative Radiotherapy Combined with Image-Guided, Intensity Modulated Radiotherapy (IG-IMRT) or IG-IMRT Alone for Locally Advanced Non-Small Cell Lung Cancer. PLoS ONE [Electronic Resource]. 2016;11(9):e0162453. Exclusion reason: Sample size insufficient

Chin V, Nagrial A, Sjoquist K, et al. Chemotherapy and radiotherapy for advanced pancreatic cancer. Cochrane Database of Systematic Reviews. 2018(3). Exclusion reason: Not intervention of interest

Chmura SJ, Winter KA, Salama JK, et al. NRGBR002: a phase IIR/III trial of standard of care therapy with or without stereotactic body radiotherapy (SBRT) &/or surgical ablation for newly oligo-metastatic breast cancer. Cancer research Conference: 39th annual CTRC AACR san antonio breast cancer symposium United States. 2017;77(4 Supplement 1). Exclusion reason: Publication type

Cho WK, Noh JM, Ahn YC, Oh D, Pyo H. Radiation Therapy Alone in cT1-3N0 Non-small Cell Lung Cancer Patients Who Are Unfit for Surgical Resection or Stereotactic Radiation Therapy: Comparison of Risk-Adaptive Dose Schedules. Cancer Research & Treatment. 2016;48(4):1187-1195. Exclusion reason: Not intervention of interest

Choi J, Park SH, Khang SK, et al. Hemangiopericytomas in the Central Nervous System: a Multicenter Study of Korean Cases with Validation of the Usage of STAT6 Immunohistochemistry for Diagnosis of Disease. Annals of surgical oncology. 2016;23:954-961. Exclusion reason: Not intervention of interest

Choi JW, Kong DS, Seol HJ, et al. Outcomes of Gamma Knife Radiosurgery in Combination with Crizotinib for Patients with Brain Metastasis from Non-Small Cell Lung Cancer. World Neurosurgery. 2016;95:399-405. Exclusion reason: Sample size insufficient

Chung LK, Nguyen TP, Sheppard JP, et al. A Systematic Review of Radiosurgery Versus Surgery for Neurofibromatosis Type 2 Vestibular Schwannomas. World Neurosurgery. 2018;109:47-58. Exclusion reason: Not appropriate comparator

Churilla TM, Chowdhury I, Handorf E, et al. Comparison of local control of brain metastasis with stereotactic radiosurgery versus surgical resection: a secondary analysis of EORTC 22952-26001. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):S158-S159. Exclusion reason: Publication type

Conde-Moreno AJ, Herrando-Parreno G, Muelas-Soria R, et al. Whole-body diffusion-weighted magnetic resonance imaging (WB-DW-MRI) vs choline-positron emission tomography-

computed tomography (choline-PET/CT) for selecting treatments in recurrent prostate cancer. Clinical & translational oncology. 2017;19(5):553-561. Exclusion reason: Not intervention of interest

Cozzarini C, Noris Chiorda B, Sini C, et al. Hematologic Toxicity in Patients Treated With Postprostatectomy Whole-Pelvis Irradiation With Different Intensity Modulated Radiation Therapy Techniques Is Not Negligible and Is Prolonged: Preliminary Results of a Longitudinal, Observational Study. International Journal of Radiation Oncology, Biology, Physics. 2016;95(2):690-695. Exclusion reason: Not intervention of interest

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